University of Nottingham

School of Medicine

Division of Psychiatry and Applied Psychology

Investigating profiles of attention and arousal in Autism Spectrum Condition (ASC)

Iti Arora

Thesis submitted for the degree of Doctor of Philosophy
November 2020

Abstract

The present doctoral project aimed to investigate profiles of arousal and attention in autistic individuals and identify how atypicalities in these relate with specific clinical symptoms of autism. I recruited children and young people between the ages of 7 and 15 years who were either neurotypical (n= 31) or had autism (n= 18). I included a clinical control group of children and young people with ADHD (n= 24) as well as those who had comorbid autism and ADHD (n= 33). I collected indices of arousal and attention by measuring heart rate, brain activity (using electrophysiology) and eye movements in response to experimental tasks requiring involuntary orienting of attention to auditory and visual stimuli, and also systematically manipulated characteristics of the stimuli used.

I found that there were no group-level differences in arousal profiles related to autism; but rather, that participants with ADHD (with or without autism) exhibited profiles of sympathetic underarousal. Given the heterogeneity in arousal profiles due to presence of ADHD in autistic participants, and due to heterogeneity apparent in the arousal literature in autism, I investigated the presence of subgroups with different arousal profiles in the autistic sample. This revealed that autistic participants could be stratified into distinct subgroups who showed tonic hyper- and hypo-arousal. These subgroups presented with different clinical profiles, such that the hyper-aroused subgroup showed worse autism symptom severity and higher rates of anxiety and sensory avoidance behaviours; while the hypo-aroused subgroup showed higher rates of hyperactive and impulsive behaviours as well as more sensory-seeking behaviours. I also found that autistic participants demonstrated intact abilities to orient to and habituate to simple auditory and visual stimuli. However, autistic participants (without ADHD) showed atypicalities in their profile of orienting to stimuli with higher complexity. These atypicalities in attention were related with social interaction symptoms of autism. Further, these atypicalities appeared to relate with presence of tonic hyperarousal. I verified the atypicalities observed in orienting to more complex visual stimuli in an independent sample of neurotypical children (n= 64) and found that neurotypical children with higher levels of subclinical autistic traits showed similar atypicalities in orienting attention to more complex stimuli.

The implications of these findings within the context of the literature on arousal and attention and recommendations for future research are discussed.

Acknowledgments

This doctoral thesis could not have been completed if not for the contribution of many people.

First and foremost, I would like to express my gratitude to Dr. Maddie Groom. Her support and guidance throughout this project, and her thoughtful supervision enabled me to develop my own voice as an independent researcher.

I also would like to thank Dr. Dani Ropar, conversations with whom about autism and its various idiosyncracies always made me think more about what I was measuring and how it all fit in the context of the experiences of autistic people. She always took the time to be kind and encouraging during each of our interactions over the last four years.

I would like to thank Professor Chris Hollis, conversations with whom pushed me to think clinically and made me always look further and think deeper. I would like to thank Dr. Puja Kochhar, I really appreciate her contribution to the project, and to my professional development. Her ideas, thoughts and suggestions always helped improve my work.

An extremely important person to highlight here is Dr. Teea Gliga, who took me under her wing at Birkbeck and gave me the confidence and tools to start this academic journey. I always marvel at her ability to quantify complex and abstract behaviours, and working with her transformed the way I approach psychology and neuroscience.

The most important people at the root of my professional journey are my parents, Kalpana and Indrajeet Arora. Their own ethics of hard work, honesty and integrity inspire me and guide my own principles, personally and professionally. My brother Aadi, a constant companion, has always been and will always be my pillar of support. My family's encouragement and belief in me has always motivated me to do my best in anything I take on.

To the most important person in my life, Alex, you are the light in the storm for me. You have seen me through the most difficult and stressful moments of the last few years. Thank you for your calm presence, your eternal optimism and your ability to bring out the humour in any situation. I look forward to our next adventures together.

I would also like to thank Dr. Alessio Bellato. I could not have asked for a better person to do this project with. I would like to thank Dr. Jack Tomlin, Stephanie Sampson and Aline Cavalcanti Barroso for the time we spent together. Conversations with them at the IMH helped me to grow as a researcher but also as a person.

Finally, I would like to thank the most important people in this project, the young people who took part in these studies, and their parents. They made this project feasible by giving up their time to help push the boundaries of our knowledge about autism and ADHD.

Contribution of the Author

The doctoral work presented in this thesis uses data collected from a larger project, the SAAND Study (Studying Attention and Arousal in Neurodevelopmental Disorders). The SAAND study was carried out at the University of Nottingham by Dr. Maddie Groom, Dr. Danielle Ropar, Dr. Puja Kochhar, Professor Chris Hollis, Dr. Alessio Bellato and Iti Arora.

I (Iti Arora) contributed to the documents prepared to obtain ethical approval for the SAAND Study. I designed some of the experimental paradigms in the SAAND Study (to investigate my hypotheses) and informed the designs of the other experimental paradigms (this is further specified in Section 2.8). I had a primary role in recruitment of participants to the study, obtaining informed consent, providing information and instructions to parents, teachers and children and young people who took part in the SAAND Study. I carried out cognitive assessments, and collected data for the SAAND study, and also conducted ADOS assessments on clinical participants who took part in the SAAND study. I wrote ADOS reports for all ADOS assessments carried out, which were provided to participants in the study. I scored questionnaires and contributed to the creation of the final database of clinical and demographic data of the study. I analysed the measures from the study to investigate my hypotheses towards this doctoral thesis. In addition, I conducted piloting work on one of the tasks I designed at Summer Scientist Week (2017) at the School of Psychology, University of Nottingham (a science engagement event for children in the local community). This piloting work is presented in Appendix F. After piloting work was complete, I also collected and analysed further data on the same task (presented in Chapter 5) at Summer Scientist Week in 2018.

I was supervised in this doctoral project by Dr. Maddie Groom (MG), Dr. Danielle Ropar (DR) and Professor Chris Hollis (CH).

Dr. Alessio Bellato (AB) is a fellow colleague (previously doctoral student) who also had a primary role in the SAAND study. His doctoral work was supervised by MG and CH. He was responsible for

preparing the documents in acquiring ethical approval for the study. He also designed some tasks in the SAAND study to investigate his own hypotheses towards his doctoral work. He contributed to recruitment, obtaining informed consent from participants, collecting data for the SAAND study and carrying out cognitive assessments. We worked together in scoring questionnaires, and creating the database of the clinical and demographic data from the project.

Dr. Puja Kochhar (PK), alongside CH, was responsible for clinical classification of participants, and confirming clinical diagnoses of autism and/or ADHD in the clinical participants in the SAAND study. PK and CH used all clinical data collected by myself and AB to classify participants into clinical groups, and this classification was used in data analysis in this study. PK also contributed to decisions around exclusion/inclusion of participants in the study. PK carried out some ADOS assessments and contributed to consensus rating for ADOS assessments.

Dr. Teodora Gliga (from the University of East Anglia) contributed ideas to design of some tasks in the SAAND study. She has also generally been a person, discussions with whom, over the course of this doctoral thesis, have helped me refine my ideas and hypotheses in my doctoral work.

Further, studying within the Institute of Mental Health (IMH) provided a learning environment where the focus was on finding innovative solutions to complex problems, and where service user involvement and bridging the gaps between research and application were considered essential. Doing my doctoral work at the IMH, alongside conversations and discussions with people mentioned above, colleagues at the IMH and colleagues at national and international conferences, all influenced my ideas.

While I worked within various research groups and as part of a brilliant team behind the SAAND study, I confirm that the work presented here is my own, containing my ideas and is original. Any ideas or thoughts belonging to someone else are appropriately acknowledged.

A Note on Language and Terminology

In this thesis, I will compare autistic individuals with neurotypical individuals to identify atypicalities in their functioning that might underlie clinical symptoms of autism. In doing so, I recognize and am sensitive to the stigma and prejudice that can come from such comparisons since it is implied that neurotypical individuals present the 'normal' frame of reference against which pathology is measured. I am a strong advocate for the neurodiversity movement as a professional within the field of autism. The neurodiversity movement argues that there is not just one "healthy" type of brain, or a "right" style of thinking or being, and that neurodivergence is another form of human diversity, just like diversity in race, culture and gender. Being neurodivergent comes with its own strengths. Within the neurodiversity framework, autism is considered to be one form of diversity in neurocognitive functioning, and by adopting this framework, interventions to support autistic people should not try to correct or cure autism, but rather to help individuals thrive in a way that is compatible with their natural predispositions (Kapp, Gillespie-Lynch, Sherman, & Hutman, 2013).

In this thesis, I will still compare autistic people with neurotypical people to identify atypicalities in their attention. The intention here is to identify the areas that autistic individuals struggle in so that we can find the right support for them, so that they can indeed achieve the same opportunities and thrive in this world. Everyone (autistic or not) struggles with certain things and should be supported with those things. Research can help identify aspects of life that groups of individuals (who are similar in certain ways) may find challenging and this can inform strategies and interventions to support them. The human society is inherently dependent on social interaction and communication. If there are fundamental skills that autistic individuals struggle to develop that impact their ability to navigate the human society and access various opportunities, identifying such differences between autistic and neurotypical individuals will help us address these challenges and support autistic people. Importantly, I will not use stigmatizing words when identifying these differences between autistic and neurotypical individuals that are typically used in scientific research that follows the medical model, such as 'deficit'. Instead, I will strive to use less stigmatizing language (for example, atypicalities, difficulties) to the best of my ability

and simply describe the differences between neurotypical and autistic individuals and explore how these relate with various domains of functioning that are adversely affected in autism.

A second thing to note is that there is an on-going debate for professionals in the field of autism (autistic individuals, parents of autistic children, researchers, clinicians, educators) on whether to use person-first (person with autism) or identity-first (autistic person) language when referring to autistic individuals. This is an important conversation with implications for societal perceptions, and policies for people with disabilities. Having worked clinically and in research with autistic children and their parents, as well as through exposure to conversations within support groups for autistic individuals, I am also acutely aware of how passionate autistic people are about embracing their identity of being autistic, and recognizing the strengths that come with being autistic.

Research has found that autistic people themselves as well as parents of autistic children prefer identity first language and they find it empowering to embrace these differences. They view autism as a natural part of themselves and person-first language can be disempowering, with the focus more on autism as a disability that somehow holds the individual back (Kapp et al., 2013; Kenny et al., 2016; Sinclair, 2013). Limitations in these accounts include the fact that that they tend to be representative only of autistic people who may be more able, and therefore less affected by autism. It is indeed possible that those who are lower functioning may prefer person-first language; more research is required to address these limitations. However, I choose in this thesis to follow the research that has directly asked autistic people themselves how they prefer to be addressed. In this thesis, therefore, I will use identity-first language. I use person-first language in this thesis only to refer to specific samples, as a way to clearly define the different clinical symptoms within my study samples. However, when referring to the population, I will use identity-first language throughout this thesis.

Table of Contents

Chapter 1. INTRODUCTION

1.1. Introduction to Autism Spectrum Condition

Autism Spectrum Condition (from hereon, autism) is a lifelong, heterogeneous neurodevelopmental condition that affects the way individuals experience and interact with the social and non-social environments around them (Happe & Frith, 2020). The clinical profile of autism is characterized by impairments in social communication and social interaction (such as difficulties integrating verbal with non-verbal communication, understanding others' intent, or initiating or responding to social interactions), and repetitive or restricted behaviours (RRBs) (such as repetitive motor movements, repetitive play, insistence on sameness or difficulties with change in routines) (American Psychiatric Association, 2013). Autistic individuals vary in their ability to independently adapt to daily living situations (Szatmari et al., 2015; Visser et al., 2017). Therefore, while the core symptoms specific to autism are defined in American Psychiatric Association (2013) as social interaction and communication atypicalities and presence of restricted, repetitive behaviours; further specifiers with respect to difficulties in day-to-day functioning and level of support needed are determined to assess need (Lord et al., 2020).

In DSM-5, for the first time, American Psychiatric Association (2013) added sensory symptoms to the diagnostic criteria, such that hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment were understood to be characteristic of autistic people. It has now become evident that while sensory processing abnormalities are also present in other neurodevelopmental conditions such as Attention-Deficit Hyperactivity Disorder (ADHD) or Learning Disabilities (LD), these are particularly prevalent in autism (Baranek, David, Poe, Stone, & Watson, 2006; Ben-Sasson et al., 2009; Leekam, Nieto, Libby, Wing, & Gould, 2007). Autistic persons themselves highlight differences in perception, information processing and sensory experiences as being core to their experience of the condition (Chamak, Bonniau, Jaunay, & Cohen, 2008). Further, atypicalities in sensory responsivity have been found to relate with individual differences in adaptive functioning and participation in family life (Dellapiazza, 2018; Schaaf, Toth-Cohen, Johnson, Outten, & Benevides, 2011; Suarez, 2012).

Global estimates suggest that at least one in 100 individuals has autism (Laurie & Border, 2020). Population-wide studies in the UK have pinned the prevalence of autism to 1.6% in children (Taylor, Jick, & Maclaughlin, 2013). Autism is three times more common in males than females, although it is likely to be under-diagnosed in females (Loomes, Hull, & Mandy, 2017). Autism causes high economic costs, particularly with regard to children's special education needs and parental productivity losses (Buescher, Cidav, Knapp, & Mandell, 2014; Knapp, Romeo, & Beecham, 2009) and thus, finding effective ways to support autistic individuals is important at the societal, as well as individual, level.

Autism is diagnosed through taking a detailed developmental history from caregivers of autistic individuals as well as direct observation of the person in social interaction with others (Constantino & Charman, 2016). The average age of diagnosis in the UK is 4.5 years (Brett, Warnell, McConachie, & Parr, 2016), although the earliest behavioural signs of autism have been reported as early as the first two years of life (Elsabbagh & Johnson, 2016; Zwaigenbaum et al., 2005). There exist no independent biological markers or tests that can reliably assist clinicians in diagnosing autism, although large-scale efforts are underway to identify biomarkers during infancy or toddlerhood that could predict development of this condition (Murphy & Spooren, 2012).

Importantly, autism is a spectrum condition (American Psychiatric Association, 2013), with subclinical traits (in each symptom domain) extending into the general population, termed the broad autism phenotype (Piven, 2001). Subclinical traits of autism are present in not just those at familial risk of autism but also in community samples (Gokcen, Frederickson, & Petrides, 2016); and molecular and behavioural genetic studies have found that genetic influences on subclinical autistic traits overlap with those with diagnosed autism (Massrali et al., 2019; Robinson et al., 2011). Autism is not a linear spectrum, in that presence of higher traits or symptoms of autism does not in itself mean greater difficulties or reduced adaptive functioning. Rather, autistic people have various combinations of features of autism which differ from individual to individual and across the lifespan, leading to high phenotypic heterogeneity (Happe & Frith, 2020).

Autism is a highly heritable condition (Colvert et al., 2015). Early research in autism assumed that the three symptom domains of autism (social communication, social interaction and RRBs) are caused by unitary genetic and/or cognitive risk factors (Happe, Ronald, & Plomin, 2006). Much research suggested unitary causes for autism at a cognitive level (Baron-Cohen, 2000; Happé & Frith, 2006; Mottron, Dawson, Soulières, Hubert, & Burack, 2006); yet evidence has shown that such accounts have not proven sufficient in understanding autism (Happe & Ronald, 2008). Further, evidence shows that heritability of different autism symptom domains is predicted by distinct genetic influences (Robinson et al., 2011). 10% of children in the general population have been found to have symptoms from only one of the three domains, without co-occurring difficulties in other symptom domains (Ronald et al., 2006); and the relationships between these symptom domains in autistic individuals are only moderate-to-low (Dworzynski, Happé, Bolton, & Ronald, 2009). This is an important finding, because it suggests that autism cannot be understood using monolithic explanations, and rather, that it must be understood through the lens of individual variation along (at least) three symptom domains which for some individuals result in co-occurring symptoms of all three domains, classified as autism. This means that risk factors for the three domains may be different and should be separately measured. This also means that single treatments cannot address all difficulties in autism and each of these domains might require different types of treatments.

In addition to phenotypic heterogeneity (due to high individual variability in severity of different symptom domains), studying autism is made more complex due to high co-occurrence of other pathophysiological and psychiatric conditions. Autistic individuals have a high prevalence of epilepsy and seizure disorders, metabolic disorders, immune disorders and gastrointestinal disorders (Frye & Rossignol, 2016). Further, studies have shown higher rates of co-occurring psychiatric conditions in autistic individuals such as anxiety disorders, depressive disorders, oppositional defiant and conduct disorders, attention-deficit hyperactivity disorder, tic disorders and more (Simonoff et al., 2008). 25-30% of autistic individuals are minimally verbal and rates of co-occurring intellectual disabilities are around 30% (Jack & Pelphrey, 2017; Stedman, Taylor, Erard, Peura, & Siegel, 2018); it is unclear how much intellectual disability and language difficulties overlap in the same individuals. In DSM-5

(American Psychiatric Association, 2013), for the first time, multiple diagnoses were permitted alongside autism. Since then, studies have documented elevated rates of psychiatric conditions in autistic individuals, with the most common being ADHD (28%) and anxiety disorders (20%); alongside high rates of sleep disorders, depressive disorders, obsessive-compulsive disorders, conduct disorders and schizophrenia (Lai et al., 2019). It is recommended that research not exclude autistic individuals with such co-occurring mental health conditions (Happe & Frith, 2020), particularly since in clinical samples, it is hard to find a 'pure' case of autism without any co-occurring conditions, and even so, such cases would not be representative of the rest of the autistic population. Importantly though, it is often these co-occurring conditions that further impact upon quality of life and adaptive functioning and intervention approaches that address these conditions have been identified as one of the top research priorities by autistic individuals and parents of autistic children (Autistica, n.d.).

1.1.1. **Approaches to research in autism**

Traditionally, autism researchers focused on the social and communication impairments and many of the early models of autism posited that impairments in parts of the brain specific to processing social information were responsible for symptoms associated with autism (Baron-Cohen, 1989; Chevallier, Kohls, Troiani, Brodkin, & Schultz, 2012; Schultz, 2005). However, such a 'core-deficit' model is not supported by the empirical literature (Bedford et al., 2014; Happe & Frith, 2020). Further, recognition of sensory processing differences in autism as a core diagnostic criterion encouraged thinking about autism as a condition that impacts large-scale networks in the brain, and not just social brain networks (Elsabbagh & Johnson, 2016). More recent theories of autism focus on differences in perceptual, attentional and information processing systems and consider how these atypicalities might have arisen from various early risk factors impacting brain development (Mottron et al., 2006; Pellicano & Burr, 2012; Van de Cruys et al., 2014).

While there was an earlier drive towards finding diagnostic biomarkers in autism, that is, early risk factors that predict development of autism, these have largely not been successful, partly due to the high phenotypic heterogeneity on the autistic spectrum (Feczko et al., 2019). It is now recognized that many

different causal mechanisms might lead to the ultimate behavioural phenotype that is typically diagnosed as autism (Wolfers et al., 2019). Therefore, now, the field is moving towards stratification, with the focus being on trying to find markers that can meaningfully predict variation in adaptive functioning, prognosis and treatment response within autistic individuals (Wolfers et al., 2019).

Relevant to this, the Research Domain Criteria (RDoC) is a research framework that suggests that characterization of individuals with psychiatric and neurodevelopmental conditions on dimensions of behaviour that are rooted in neurobiology might improve understanding of psychopathology (Cuthbert & Insel, 2013). RDoC considers psychopathology as being rooted in dysfunctions of particular neurobiological systems that can be studied at various (genetic, cognitive, behavioural) levels. RDoC frameworks encourage research in psychopathology and neuroscience to look beyond diagnostic symptoms to identify intermediate phenotypes (i.e. quantifiable processes interposed between genetics and behaviour, but rooted in neurobiology) of neurobiological systems that might contribute to the development of neurodevelopmental or psychiatric conditions. An important aspect of this framework is thus to investigate impact of differences in functioning of fundamental neurobiological processes on higher-level behavioural skills, in a transdiagnostic manner.

Another relevant framework that informs this thesis is the cross-syndrome approach from developmental neuroconstructivism pioneered by Karmiloff-Smith (Karmiloff-Smith, 1998). Neuroconstructivistic approaches propose that different cognitive and neurodevelopmental disorders might each lie on a continuum from typical to atypical rather than be truly specific categories. Using this approach, we could consider the ultimate phenotype labelled as autism to be the end result of an altered organization and development of the brain, a result of compensation and adaptation in the face of early environmental and intrinsic insults (as suggested by Johnson, Jones, & Gliga, 2015). Importantly, within this framework, cross-syndrome comparisons help identify mechanisms that are condition-specific, as well as risk factors that if present, converge into certain behavioural phenotypes that overlap across conditions. Such cross-syndrome comparisons can enhance understanding of typical and atypical developmental trajectories.

Using the RDoC framework and developmental neuroconstructivistic approaches, this thesis aims to identify features rooted in neurobiological systems of attention and arousal (described more specifically in Section 1.1.2, 1.3 and 1.4) that might be atypical in autistic individuals. Further, we will investigate whether these features meaningfully relate with individual differences in autistic symptoms, presence of co-occurring conditions, and adaptive functioning. This could prove more fruitful when researching such a heterogeneous condition, in helping shed light on neurobiological processes that underlie autism.

1.1.2. **Why focus on Arousal and Attention when studying autism?**

Arousal refers to one's state of readiness to engage with or take in information from the environment. Regulation of arousal in a manner that is sensitive to the current demands of the environment is crucial to be able to effectively register and respond to different stimuli. Attention is the primary method through which we sample and process information from the dynamic and complex world around us. Rapid information sampling and processing is crucial to environmental navigation, learning and development.

Autistic individuals exhibit differences in their alertness and responsivity to the environment, suggestive of atypicalities in regulation of arousal (Benevides & Lane, 2015; Orekhova & Stroganova, 2014). There are indirect and direct sources of evidence for differences in arousal in autism. Sleep disturbances are one of the most commonly reported daily-life disruptions by parents of autistic individuals (Cohen, Conduit, Lockley, Rajaratnam, & Cornish, 2014), indicative of differences in regulation of diurnal cycles. Autistic individuals exhibit insensitivity to novel information in both visual and auditory modalities (Orekhova et al., 2009), as well as reduced responsivity to unexpected stimuli (Baranek et al., 2013; Keehn, Lincoln, Müller, & Townsend, 2010; Mutreja, Craig, & O'Boyle, 2016), suggesting that their alertness to changes in the environment is atypical. Impairments in modulating sensory input and differences in regulation of autonomic response to various types of stimuli have also been noted in autistic people (Lydon et al., 2016; Orekhova & Stroganova, 2014). These atypicalities might indicate that physiological responses to attending to a stimulus in the environment are atypical in autism. Difficulties in maintaining a stable level of alertness or in recruiting arousal regulation systems

effectively to respond optimally to the environment might lead to profiles of sensory over- and under-reactivity (Rogers & Ozonoff, 2005). Notably, the direction of causality could be the other way round, with differences in information processing underlying differences in physiological responsivity.

Autistic individuals also exhibit atypical profiles of attention to the environment. For example, some of the earliest behavioural features of autism are that autistic individuals may not respond to someone calling their name, or that when playing with a toy, they may not show triadic joint attention with a caregiver or a sibling, looking to-and-fro between the toy and another social agent (Baranek, 1999; Dawson et al., 2004; Leekam, López, & Moore, 2000; Osterling & Dawson, 1994; Werner, Dawson, Osterling, & Dinno, 2000). Other general atypicalities in profiles of attention in autistic individuals have been documented; autistic individuals show shorter fixation durations, slower latencies to first orient to a scene, and slower latencies to reorient once engaged in an activity (Elsabbagh et al., 2013a; Elsabbagh et al., 2009; Freeth, Chapman, Ropar, & Mitchell, 2010; Liss, Saulnier, Fein, & Kinsbourne, 2006; Wass et al., 2015b). Recent investigations in autism, particularly longitudinal investigations which follow babies at elevated familial risk of autism, have revealed that the earliest reliable indicators of autism are atypicalities in attention (Elsabbagh et al., 2013b; Elsabbagh et al., 2009; Gliga et al., 2015; Gliga, Smith, Likely, Charman, & Johnson, 2018).

Models of information foraging posit that a balance between exploitation (of the known) and exploration (of the unknown) is essential for optimal adaptation to the environment so that one is alert to pertinent new information but at the same time can focus on a task at hand (Cohen, McClure, & Yu, 2007). A bias against exploration or towards exploitation could impact optimal foraging, and therefore, learning and adaptive functioning (Gliga et al., 2018). Core symptoms of autism such as avoidance of social interaction (which is by nature constantly changing), repetitive behaviours and preference of sameness might reflect an attentional style that is biased towards exploitation or against exploration. Indeed, attention in autistic individuals is characterized as being perseverative, detail-focused, with a bias against exploration. For example, Sasson, Turner-Brown, Holtzclaw, Lam, and Bodfish (2008) reported that across social and non-social visual arrays, autistic individuals tended to explore fewer

images and fixate more and for longer on previously explored images. In another study where visual scenes were presented with or without a face, autistic individuals showed reduced exploration of new areas with a tendency to persist in areas closer to current fixation, across scene types (Heaton & Freeth, 2016). Other studies have corroborated the above with findings of reduced exploration of new information and increased re-visitation to previously explored information in experimental settings (Elison, Sasson, Turner-Brown, Dichter, & Bodfish, 2012; Gliga et al., 2018; Pellicano et al., 2011).

Given evidence of attention atypicalities that might precede social symptoms (Elison et al., 2013; Zwaigenbaum et al., 2005), some have suggested that differences in attention and/or arousal might play a causal role in the socio-cognitive development in autism (Keehn, Müller, & Townsend, 2013; Klusek, Roberts, & Losh, 2015). Indeed, early differences in arousal and/or attention might impact autistic individuals' abilities to effectively engage with and learn from their environment. Impairments in these fundamental skills of attention and arousal regulation thus have far-reaching implications not just for learning in a classroom but also for development of social and cognitive skills. Early atypicalities in attention and arousal might underlie the symptoms associated with autism, such as difficulties with dynamic social information processing; and a repetitive, rigid way of exploring the world with highly selective focus. However, the links between atypicalities in domains of attention, arousal and socio-cognitive skills are unclear.

Given the pervasive manner in which atypicalities in attention and arousal might impact development of social, cognitive and adaptive functioning in autistic individuals, these are important to understand. A better understanding of the nature of these atypicalities could contribute to better interventions as well as inform how various learning environments could be adapted to be more accessible for autistic individuals in terms of their ability to engage with them. For example, if autistic children find it difficult to distribute their attention to multiple things flexibly, they may benefit from interventions that help develop their attentional skills more broadly. If autistic children struggle with arousal regulation, they may benefit from arousal regulatory strategies being applied particularly in environments rich in stimulation such as classrooms or a playground. There are many strategies that autistic children and

their families use already (for example, use of headphones because their child is sensitive to sound when they go to crowded places, Pfeiffer, Erb, & Slugg, 2019). If there is a better understanding of these profiles, such strategies could be provided to parents and teachers so that different children and their families do not have to figure these things out on their own. In addition, a better understanding of such atypicalities might also contribute to development of objective diagnostic markers that can pick up features predictive of autism early in life, thus enabling early intervention to bridge crucial developmental gaps. Finally, improved understanding of why autistic children attend to the world differently might promote a kinder, less punitive approach towards autistic children and might help inform parents and teachers in the way they interact with autistic children.

A thorough investigation of impairments in attention and arousal in autism has not been conducted. This is the focus of the present thesis. Specifically, I aim to improve understanding of profiles of attention and arousal in autistic individuals and investigate how atypicalities within the domains of attention and arousal relate with different symptom domains of autism. I anticipate that my findings will be relevant for informing the design of educational and clinical interventions in autism and rehabilitative practices.

1.2. **Summary and General Aims of this thesis**

In this thesis, I will characterize autistic individuals on features of attention and arousal and identify aspects that are atypical in autistic individuals compared with neurotypical individuals. Further, I will examine the relationships between these features and clinical symptoms of autism. My focus will be on the cognitive mechanisms themselves rather than on localization of those mechanisms in the brain. In addition, I will investigate whether profiles of arousal can be useful towards stratification of autistic individuals to find meaningful substructures within the autistic phenotype. So far, stratification attempts in autism have been based primarily on cognitive and behavioural symptoms (Wolfers et al., 2019). I will investigate the utility of arousal profiles towards stratification of autistic individuals into subgroups that may show more homogeneous cognitive and behavioural functioning.

Importantly, I will utilize a cross-syndrome comparison approach. While I will include a neurotypical comparison group, I will also include comparison groups of individuals with ADHD and those with co-occurring autism and ADHD. Often, studies in autism do not characterize their sample on co-occurring conditions that might influence the constructs of interest. By including cross-syndromic comparisons in this way, I will be able to tap into attentional atypicalities that are specific to autism and those that might represent trans-diagnostic factors that influence general functioning.

The studies in this thesis primarily involve a sample of children and adolescents (7-15 years old) who are either neurotypical, or have autism, ADHD or both autism and ADHD. In Chapter 5, findings are also presented on another sample that is neurotypical with varying level of autistic traits. Cross-sectional studies of this nature can help understand which features of attention in autism extend to the general population to both sides of the diagnostic boundary.

Importantly, I measure features of attention that have typically developed by 8-10 years of age. Therefore, in our sample of children and adolescents, I am measuring the outcome phenotype of autism (and ADHD), which is a result of interactions between genetic and environmental risk and resilience factors. This type of cross-sectional research can be extremely useful towards understanding links between different domains of functioning, which can lead to mechanistic hypotheses of how certain outcome phenotypes may have developed. This can then inform longitudinal research that directly tests how individual risk and resilience factors contribute towards the development of the outcome phenotypes.

In the following sections, I will first introduce core concepts of attention under investigation in this thesis, their neuroanatomy, and indices used to measure arousal and attention that are relevant to this thesis. I will then identify the gaps in the literature on these functions in autism. Lastly, I will introduce literature on comorbidity of autism and ADHD, as well as profiles of attention and arousal in ADHD. I will then describe the main research questions under investigation.

1.3. Introduction to Attention and Arousal Regulation

Attention is a domain-general cognitive function that serves to allocate cognitive resources to perceptually salient or behaviourally relevant external stimuli or ideas/thoughts in our mind or memory. Attention optimizes sampling of information from the dynamic and complex world around us for purposes of learning and memory. Rapid and flexible allocation of attentional resources and maintenance of that attention is crucial for learning and efficient information processing. Further, being able to shift and re-direct attention quickly when novel things appear in the environment is important, particularly when those new stimuli might have reward or threat values associated with them. Engagement of attention directs learning and development of social and cognitive functioning (Fischer, Koldewyn, Jiang, & Kanwisher, 2014). Given the importance of attention in everyday life, it is a widely studied domain in relation with typical and atypical development.

1.3.1. Orienting and Reorienting of Attention

Orienting of attention refers to attentional functions that serve to prioritize and select information to be processed further. This could be external sensory information or internal thoughts or ideas. Selection is guided by complex interactions between internal processes on the one hand, such as prior information (such as current goals), perception, localization, some form of processing of the stimulus; and type of external stimuli on the other hand, such as salience of the stimulus and environmental context (Colombo & Cheatham, 2006). The function of orienting serves to focus, filter other things out, and sample information due to perceptual salience or behavioural relevance (Raz & Buhle, 2006).

Orienting attention networks have been widely studied using visuospatial attention paradigms in which the target is known/expected. In the classic Posner spatial cueing paradigm (Posner, Walker, Friedrich, & Rafal, 1984), participants are asked to fixate on a central fixation cross. A cue then appears centrally on the screen before a target appears peripherally on the left or right of the screen. Participants are asked to press a button to indicate detection of the target. Cues used in this task are of various types. A directional cue typically indicates where the target will appear, and this facilitates attentional networks

that subserve orienting to bias attention endogenously towards that side of the screen (increasing neural activity in relevant visual cortices), thus facilitating subsequent target detection (Meehan et al., 2017). On the other hand, a cue could also appear to the left or the right of the central fixation cross, eliciting exogenous orienting.

Using such paradigms, two attentional networks have been found to facilitate orienting and reorienting of attention. A dorsal frontoparietal network (DAN, which includes the frontal eye fields (FEF), areas in the dorsal parietal cortex such as the intra-parietal sulcus (IPS) and superior parietal lobule, and areas in the dorsal frontal cortex along the precentral sulcus) has been implicated in endogenous forms of orienting, i.e., generating and maintaining endogenous signals that bias where attention is allocated, based on current goals, and pre-existing information about what one could expect from the environment (Corbetta, Patel, & Shulman, 2008). DAN upregulates attentional allocation by biasing sensory areas to respond to behaviourally relevant targets (Vossel, Geng, & Fink, 2014). DAN has often been suggested to be supramodal, involved in top-down endogenous orienting of attention across sensory modalities. However, there is evidence that DAN is primarily involved in visuospatial attention; and other areas such as the middle frontal gyrus and posterior middle temporal gyrus are involved in auditory non-spatial attention (Braga, Wilson, Sharp, Wise, & Leech, 2013; Vossel et al., 2014).

In comparison, exogenous orienting elicits activity in DAN and VAN (a ventral frontoparietal network which consists of the temporo-parietal junction, TPJ, an ill-defined area typically localized as the posterior sector of the superior temporal sulcus (STS) and gyrus (STG) and the ventral part of the supramarginal gyrus (SMG) and ventral frontal cortex (VFC), including parts of the middle frontal gyrus (MFG), inferior frontal gyrus (IFG), frontal operculum and anterior insula) (Corbetta et al., 2008). VAN is typically activated when behaviourally relevant targets are detected, particularly from unattended aspects of the environment (Corbetta et al., 2008). Importantly, VAN has been found to be suppressed during tasks which require endogenous attentional allocation; suppression of VAN is higher when stimulus complexity is higher or memory load is higher (Todd, Fougnie, & Marois, 2005). This has led some to suggest that VAN plays a role in reorienting to aspects of the environment outside of

current attentional focus, and its suppression facilitates filtering out of distractors to support task-focused attention (Corbetta et al., 2008). Notably, some of the areas implicated in VAN (specifically regions in the anterior insula) are also implicated in a salience network (SN) (Seeley et al., 2007). SN will be further discussed in Section 1.3.4.

The mechanisms behind orienting of attention are not fully clear, but evidence suggests that selective attention works by increasing neuronal firing rates towards specific stimuli, reducing variability of responses to repeated stimuli, enhancing synchrony among neurons encoding the attended stimulus for instance by gamma band synchronization (as reviewed by Moore & Zirnsak, 2017).

Importantly, orienting and reorienting of attention have been found to be impacted by characteristics of the stimulus and environmental context (for instance, complexity of stimuli, social-ness of stimuli, presence of distractors etc.). Stimulus characteristics such as colour, level of contrast compared to the background etc. influence orienting such that more contrast and higher complexity typically elicits quicker engagement of attention (Itti & Koch, 2001; Kwon, Setoodehnia, Baek, Luck, & Oakes, 2016). Top down goals also bias orienting of attention to stimuli that would otherwise not be relevant, and past history with particular stimuli also can selectively bias attention to those stimuli (Awh, Belopolsky, & Theeuwes, 2012; Hutchinson & Turk-Browne, 2012). In addition, stimuli categorized as social such as faces, eyes, speech also elicit quicker orienting, suggesting that they hold higher salience than non-social stimuli (Cerf, Frady, & Koch, 2009; Dawson et al., 2004; Gliga, Elsabbagh, Andravizou, & Johnson, 2009; Kwon et al., 2016). It is not clear why social stimuli hold a special status. Theories suggest that there might be early biases in orienting to social aspects of the world since they hold informative and evolutionary value; early biases may lead to specialization of areas in the brain that subserve detection of and orienting to social aspects of the world (Chevallier et al., 2012).

1.3.2. **The role of arousal in facilitating attention**

Regulation of arousal facilitates selective attention and is crucial to adaptive responsivity to the environment, both to be able to respond to important information, but also to be able to pick up on new information that comes along when one's attention is focused elsewhere. The concept of arousal is theoretically divided into tonic arousal (which refers to diurnal fluctuations in wakefulness and general alertness to the external world) and phasic arousal (which refers to temporary increases in responsivity for short periods of time that are spontaneous or in response to internal or external events) (Orekhova & Stroganova, 2014). Tonic and phasic arousal are interdependent processes, certain levels of tonic arousal allow for optimal phasic responsivity (Aston-Jones & Cohen, 2005b). Yerkes and Dodson (1908) theorized a U-shaped relationship between tonic arousal and cognitive performance. They suggested that at the lower end of tonic arousal, drowsiness and low alertness to the environment reduce phasic responsivity; and at the higher end of tonic arousal, phasic responsivity is high and non-specific such that task-focused attention is not optimal; only at moderate levels of tonic arousal, phasic responses within the context of task-focused attention are optimal. Levels of tonic alertness can be endogenously upregulated; this is termed sustained attention or vigilance and is modulated by current goals, mediated by the cingulo-opercular networks or the SN (discussed in Section 1.3.4).

Arousal is governed by interactions between the central nervous system and the peripheral nervous system. Autonomic nervous system (ANS, a branch of the peripheral nervous system) is a prominent influence on arousal and is involved in regulating involuntary functions of internal organs such as heartbeats, digestion, pupil dilation and breathing, to support adaptation to ongoing demands in the environment. The ANS consists of the sympathetic and parasympathetic nervous systems (SNS and PNS respectively). SNS is recruited to upregulate the body's response to environmental stressors or threatening situations, as well as modulate phasic responses to events (Schaaf, Benevides, Leiby, & Sendecki, 2015). When exposed to a threat, SNS increases arousal through acceleration of heart rate, elevation of blood pressure and increase of adrenaline in the system, resulting in increase of norepinephrine (Edmiston, Muscatello, & Corbett, 2017; Goodwin et al., 2006). In contrast, PNS is involved in maintaining bodily homeostasis, self-regulation and recovery from a stressor or a challenge;

it supports ‘rest and digest’ functions by slowing down heart rate and promoting bodily functions such as digestion. At times of stress, PNS withdrawal facilitates SNS activation. SNS and PNS thus work in coordination to regulate responsivity to the environment and a balance between SNS and PNS is important to respond appropriately to incoming information (Aston-Jones & Cohen, 2005b; Porges, 1992).

The ANS provides input to brainstem regions that are involved in regulating consciousness and release of neurotransmitters towards neuromodulation (Thayer & Brosschot, 2005). Specifically, the locus-coeruleus (LC) in the brainstem receives autonomic signals through the nucleus tractus solitaris (Critchley & Garfinkel, 2018) and in turn has reciprocal connections with areas in the prefrontal cortex, hypothalamus, insula and amygdala (Van Bockstaele & Aston-Jones, 1995; as reviewed by Sara & Bouret, 2012). Therefore, regulation of arousal occurs through coordinated activity of the ANS, brainstem regions such as the LC and cortical systems. Further, activity in the ANS partly reflects activity in the central nervous system and thus, peripheral indices of arousal such as heart rate or skin conductance can be used to index arousal in the central nervous system (Murphy, O'Connell, O'Sullivan, Robertson, & Balsters, 2014; Murphy, Robertson, Balsters, & O'Connell, 2011).

1.3.3. **Spotlight on the Locus-Coeruleus-Norepinephrine (LC-NE) brain system**

The LC nucleus is a collection of monoaminergic neurons located in the dorsorostral pons (Aston-Jones & Cohen, 2005b). It is the sole source of norepinephrine (NE) in the cerebral, cerebellar and hippocampal cortices, which is the neuromodulator associated with arousal and alertness functions (Aston-Jones & Cohen, 2005b; Keehn et al., 2013; Loughlin, Foote, & Grzanna, 1986). Release of NE by the LC influences the adaptive gain in synaptic signal transmission, thus facilitating sensory processing (Mather, Clewett, Sakaki, & Harley, 2016). LC-NE gives rise to diverse projections which are unmyelinated and therefore are slow conducting (Aston-Jones, Foote, & Segal, 1985). Given its role in neuro-modulation and the widespread projections from the LC to areas in the cortex, the LC has been implicated in regulating general neural processing and behaviour (Sara, 2009).

Similar to the broad classification of arousal into tonic and phasic arousal, activity in LC nuclei follows tonic and phasic patterns. Tonic LC activity varies between 0 and 5 Hz and is closely related to tonic arousal levels of an organism (Nieuwenhuis, Aston-Jones, & Cohen, 2005). Low tonic LC activity occurs during sleep; it rises to around 2 Hz during periods of drowsiness or quiet waking. At such times, vigilance to the external environment is low (Aston-Jones & Bloom, 1981a; Hobson, McCarley, & Wyzinski, 1975; Rajkowski, Kubiak, Ivanova, & Aston-Jones, 1997). During engagement with exogenous tasks, tonic LC activity is moderate (between 2-3 Hz) and this facilitates focused attention and accurate task performance. Further increases in tonic LC activity (above 3 Hz) are associated with distractibility and reduced performance accuracy (Aston-Jones & Cohen, 2005b). These fluctuations in baseline tonic activity also covary with fluctuations in cortical arousal (Howells, Stein, & Russell, 2012). Further, LC neurons exhibit phasic activity, that is, brief bursts of discharge at around 20 Hz, to salient or behaviourally relevant stimuli. This phasic activity serves to enhance signal-to-noise ratio and thus facilitates selective orienting and processing of those signals (Aston-Jones & Cohen, 2005a).

The tonic fluctuations and phasic responses follow the inverse U-shaped Yerkes Dodson curve (discussed earlier) such that at moderate levels of tonic LC, phasic responses are optimal and least variable. Phasic responses are attenuated at both high and low levels of tonic LC activity (Aston-Jones & Cohen, 2005b). Therefore, synergistic activity between tonic and phasic firing of LC neurons is required for optimal alertness and orienting of attention to the environment (See Figure 1.1).

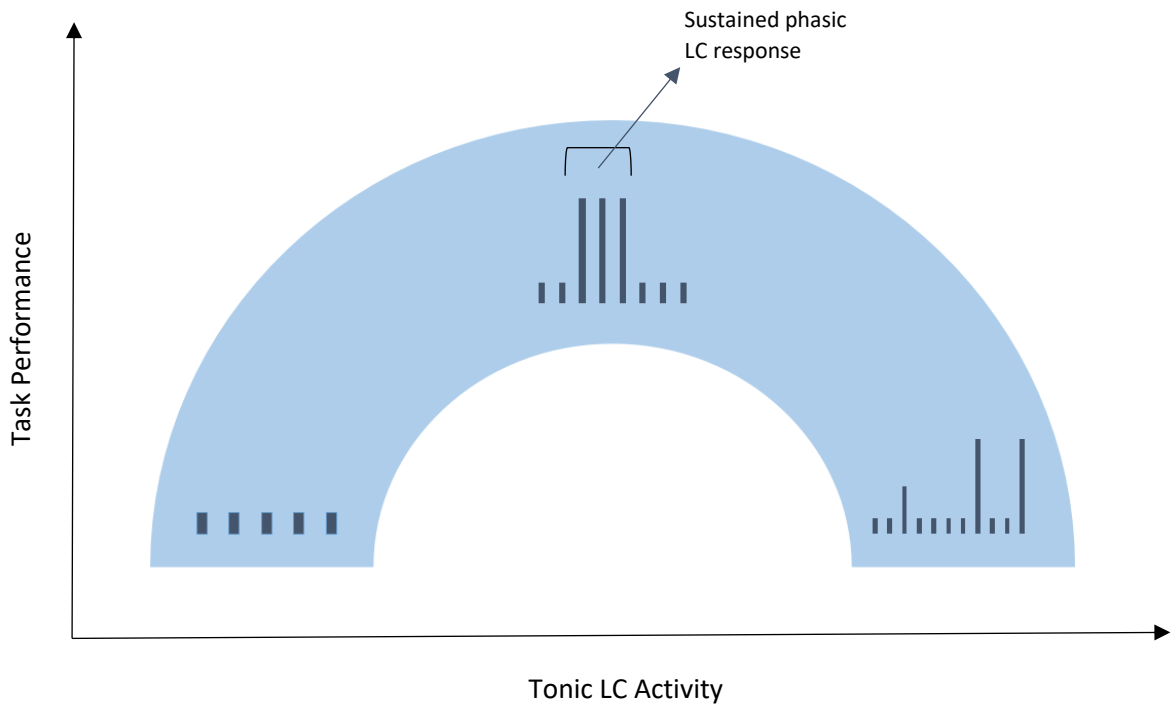


Figure 1.1. A simplified depiction of the LC-NE framework proposed by Aston-Jones and Cohen (2005b) tonic LC activity modulates phasic response within task-focused contexts, following the Yerkes-Dodson curve. X-axis represents baseline tonic-LC activity, i.e. firing rate of LC neurons. Y-axis represents task performance, with higher values on the Y-axis representing better task performance. Black bars in the figure represents activity in LC neurons; different levels of tonic LC activity results in changes in neural gain (or responsivity in widespread LC neurons) due to different levels of release of NE. At low levels of baseline tonic LC activity, neural gain is low, and phasic LC activity is not optimal, with few events eliciting a response. At high levels of tonic LC activity, neural gain is high and neurons are responsive to all stimuli regardless of their relevance, and therefore, phasic LC responses are diminished and signal to noise ratio is low. At moderate levels of tonic LC activity, phasic LC responses are optimal and increase gain in a task-relevant manner, leading to a high signal-to-noise ratio and optimal task performance.

Using information foraging frameworks, the moderate and high levels of tonic activity have been theorized to facilitate two different modes or states of attention or behaviour to the environment. When tonic LC activity is moderate and phasic responses optimal, selective orienting of attention to and processing of stimuli relevant to the current task that have high utility are facilitated; this is akin to exploitative modes of information foraging where one focuses on utilizing fully a salient stimulus, or

the focus is on efficient selection of the most salient action during a task. This mode of attentional state has been termed the 'phasic mode' (Aston-Jones & Cohen, 2005b). During phasic modes, phasic bursts of LC boost connectivity and neural gain in attention networks necessary to solve the task at hand, e.g. dorsal attention network. Changes in neural gain impact communication between neurons such that as gain increases, communication between the most excited neurons with the strongest connections increases while neurons that are inhibited or have weak connections are blocked (Mittner, Hawkins, Boekel, & Forstmann, 2016). During phasic mode therefore, task unrelated networks are also suppressed to filter out unrelated information (Mittner et al., 2016). Therefore, the phasic mode enables selective attention and enhances information processing within contexts of task-focused attention (Aston-Jones & Cohen, 2005b; Moore & Zirnsak, 2017).

On the other hand, high levels of tonic activity facilitates a widespread and indiscriminant increase in neural responsivity to sensory input, allowing the organism to respond to a broad class of events (Nieuwenhuis et al., 2005). This is related with a 'tonic' mode of attention where attention is more exploratory, and stimuli in the environment that would not normally cross threshold of activation are able to do so, allowing one to optimally explore various opportunities in the environment. In tonic mode, functional connectivity within and between task-irrelevant networks is increased, focus of attention broadens and high levels of NE lead to higher neural gain. This allows for switching of attention between different goals (Mittner et al., 2016).

Therefore, different levels of tonic activity of the LC reflect different behavioural states of attention, with the tonic mode broadening the scope or field of attention and the phasic mode reducing it and enabling filtering out of irrelevant stimuli. It has been proposed that switching from phasic to tonic mode is driven by a reorienting mechanism, paralleled by activation in VAN; in comparison, VAN is suppressed when states of attention shift from more exploratory to exploitative (Corbetta et al., 2008; Todd et al., 2005).

1.3.4. **Regulation of arousal and orienting of attention**

While arousal and alerting mechanisms are non-selective and respond homogenously across the sensory field, orienting of attention facilitates selective processing over a localized area (Keehn et al., 2013). Importantly, orienting and alertness mechanisms interact. Increasing alertness by using a non-spatial cue can facilitate orienting of attention (Callejas, Lupianez, Funes, & Tudela, 2005; Callejas, Lupiáñez, & Tudela, 2004). Similarly, orienting of attention can serve to attenuate arousal levels (Derryberry & Rothbart, 1988; as cited by Keehn et al., 2013).

The question then arises as to the mechanisms that determine which stimuli have high task utility and should be selectively attended, how waning task utility is processed and taken into account, and what triggers switching between different modes of attention, exploratory or exploitative, tonic or phasic modes of LC. Towards this, several theories have been put forward, all of which cite the LC-NE as having a key role in mediating interactions between top-down and bottom-up processes for optimal information sampling (Aston-Jones & Cohen, 2005b; Corbetta et al., 2008; Gilzenrat, Nieuwenhuis, Jepma, & Cohen, 2010; Sara & Bouret, 2012). LC increases firing rates when a novel or a salient stimulus appears. In parallel, areas in the salience network (SN), also known as the cingulo-opercular network (including the amygdala, anterior cingulate cortex and the anterior insula) (Menon & Uddin, 2010; Seeley et al., 2007) evaluate the salience of the incoming sensory information within the first 150 ms (Joshi, Li, Kalwani, & Gold, 2016). Major hubs of salience network (anterior insula, amygdala and anterior cingulate cortex) are considered to function as an integrated system that combines affect and attention to encode sensory stimuli (Touroutoglou et al., 2016). In addition, the anterior insula is implicated in integrating autonomic signals with sensory information and mediating internally and externally oriented attention, facilitating reorganization of brain networks and initiating control signals to allocate attentional resources appropriately, as well as modulating autonomic reactivity to salient stimuli. Further, the AI and the ACC couple together to facilitate rapid motor responsivity to salient events (Menon & Uddin, 2010).

Within the first 150 ms of sensory input, salience evaluations have occurred (Joshi et al., 2016; Pissiota et al., 2003) and reward values are also computed by the ventral striatum (Schultz, 2010). Top-down signals from the salience networks to brainstem regions including the LC then upregulate NE release for salient stimuli and increase phasic bursts of LC activity (Cho et al., 2013; Joshi et al., 2016; Kalwani, Joshi, & Gold, 2014; Robinson et al., 2012; as reviewed by Bast, Poustka, & Freitag, 2018). Phasic responses by the LC-NE facilitate adaptive gain in sensory processing of salient stimuli and hence facilitate more rapid responses. Concurrent activation in DAN enables maintenance of selective attention to salient/ task-relevant stimuli, or exploitative information foraging in the phasic mode of the LC. Since these responses occur after salience evaluations are completed, these are relatively late signals (Corbetta et al., 2008) and are paralleled by activation of peripheral ANS responses such as heart rate accelerations or decelerations, changes in electrodermal activity or pupil dilations or constrictions (Sara & Bouret, 2012). These changes in heart rate and pupil size likely reflect the integrated response between pre-frontal cortices and ACC and LC, in response to current environmental demands (related to attention, task performance etc.) and changes in arousal support behaviour in response to these demands (Critchley & Garfinkel, 2018; Samuels & Szabadi, 2008; Sara & Bouret, 2012; Wang, Piñol, Byrne, & Mendelowitz, 2014). For example, changes in heart rate variability (HRV) have been implicated in emotional regulation (Gentzler, Santucci, Kovacs, & Fox, 2009), behavioural inhibition (Porges, 2007; Porges, 2009) and reward responsiveness (Garland, Froeliger, & Howard, 2015). Event-related changes in heart rate variability are implicated in better learning and sustained attention (Linnemeyer & Porges, 1986; Porges, 2007; Richards, 1997, 2011; as reviewed by Wass, de Barbaro, & Clackson, 2015a). Similarly, changes in pupil dilation are associated with sustained attention, memory and cognitive effort (as reviewed by van der Wel & van Steenbergen, 2018).

Salient or task-relevant stimuli typically elicit a sympathetic response, inducing heart rate accelerations and pupil dilations (Wass et al., 2015a). In comparison, heart rate decelerations promote sustained attention, enabling us to stop and focus, in contexts of task-relevant or threatening stimuli, promoting sensory processing and decision making (Blanchard, Griebel, Pobbe, & Blanchard, 2011; Gladwin, Hashemi, van Ast, & Roelofs, 2016; Lojowska, Gladwin, Hermans, & Roelofs, 2015; Roelofs, 2017;

as reviewed by Ribeiro & Castelo-Branco, 2019). Event-related HRV is also related with reaction times, with findings that stronger heart rate decelerations occur when participants are required to respond slower (Jennings & Wood, 1977). This suggest that these changes in arousal modulated by higher order brain systems support flexible and dynamic contextually-appropriate responses. Changes in autonomic arousal are related to and predicted by electrophysiological indices of information processing (in frontal systems); for instance, more marked ERPs predict higher HR deceleration, in response to task-relevant sensory stimuli; and these are related to more accurate and less variable subsequent task performance (Ribeiro & Castelo-Branco, 2019).

If the stimulus does not have high reward value or does not have high positive or negative valence associated with it, phasic response of the LC habituates rapidly, that is, decreases with consecutive presentations of the stimulus. On the other hand, if the stimulus has high reward utility, is task-relevant, has characteristics associated which increase its salience (such as a social as compared to a non-social stimulus), the phasic response does not disintegrate as quickly (Sara & Bouret, 2012). When task utility wanes, reward value decreases, or other salient stimuli are detected, similar top-down signals initiate an increase in tonic LC activity, and concurrent activation in the TPJ or the VAN, which facilitates disengagement from the current task and switching to an exploratory, 'tonic' mode of the LC. This allows for a broader field of attention to identify salient events and therefore reorienting to exogenous stimuli (Corbetta et al., 2008).

It becomes clear then how much attentional functions rely on flexible and dynamic interactions between the LC, fronto-parietal and salience networks and the autonomic nervous system. Given that allocation of attention appropriately forms the foundation of any skill, impairments at any level of these processes, or differences in interactions between regions or neuromodulation, particularly if present during early years of life, could have far-reaching consequences. It has been proposed that early differences in brainstem function could impact development of structural and functional interactions between brainstem, limbic and cortical systems (Geva & Feldman, 2008). Differences in maturation of these functions could adversely affect attentional regulation and social attention (Geva et al., 2017; Porges,

2003b). Indeed, there is evidence that brainstem dysfunctions at birth are associated with poorer arousal regulation, hyper-responsivity to arousing stimuli and less regulated inhibitory control (Gardner, Karmel, & Flory, 2003; Karmel, Gardner, & Freeland, 1996; as reviewed by Geva & Feldman, 2008). Geva et al. (2017) reported that at 8 years of age, children with a history of neonatal brainstem dysfunction showed profiles of visual attention resembling autism: namely, dysregulated arousal-modulated attention and difficulty in engaging with social as compared to non-social cues.

Early differences in LC function might impact attentional functions, specifically optimal arousal and affect regulation as well as exogenous orienting, phasic reactivity and engagement with social and non-social cues. These early differences could have cascading effects on social learning, and typical development of structural and functional connections between various brain regions. Atypical phasic reactivity could lead to reduced bottom-up LC-NE signalling, thus impacting top-down salience attributions. Over time, this could lead to alterations in development of salience networks, and less efficient interactions between cortico-cortical pathways; as well as lead to development of differential salience values attached to social and non-social aspects of the environment. Altered salience evaluations would also impact appropriate attentional allocation. Reduced LC-TPJ signalling could lead to an exploitation-oriented attentional profile, with reduced exploration-oriented attention, a profile that has been associated with autism (Bast et al., 2018).

Research with autistic individuals shows evidence of atypical LC-NE function, with preliminary reports of increased tonic pupil size (Anderson & Colombo, 2009; Wagner, Luyster, Tager-Flusberg, & Nelson, 2016). There is also evidence of significant differences in pupillary light reflex in autism, specifically slower constriction latencies (Fan, Miles, Takahashi, & Yao, 2009; Lynch, 2018), particularly during infancy (Nystrom et al., 2018; Nystrom, Gredeback, Bolte, & Falck-Ytter, 2015), suggestive of reduced parasympathetic response to changes in lighting.

In addition, a relatively consistently replicated finding on the neural basis of autism is that there are differences in structural and functional connectivity in autistic individuals. Specifically, MRI, EEG and

MEG studies have all provided evidence for reduced long-range functional connectivity, reduced inter-hemispheric regulation and potentially compensatory increased local connectivity (Hull et al., 2017; O'Reilly, Lewis, & Elsabbagh, 2017; Rane et al., 2015). Studies have shown that feedback (top-down) functional connectivity is reduced in autism, leading to increased localized processing that is less modulated by contextual feedback, in line with an attentional profile that is biased towards exploitation and maybe less flexible with entering exploratory modes (Khan et al., 2015; Seymour, Rippon, Gooding-Williams, Schoffelen, & Kessler, 2019). Differences in long-range functional connectivity have been shown to be associated with RRBs as well as differences in sensory responsivity (Green, Hernandez, Bookheimer, & Dapretto, 2016a, 2016b; McKinnon et al., 2019). Further, areas in the cingulo-opercular network have been implicated in autism, with evidence that the amygdala is hyper-reactive (Tottenham et al., 2013) and the insula is hypoactive (Menon & Uddin, 2010). There is further evidence that ACC, AI and TPJ demonstrate reduced activation in autistic individuals (Gomot et al., 2006; Murphy et al., 2017). Given the above evidence, it is possible that development of autism is rooted in early risk to brainstem function that then impacts engagement with the world and adversely affects typical development and specialisation of attentional functions.

These models provide important points of investigation and, also, potential hypotheses about what might be atypical in autism, particularly given profiles of sensory processing differences, a narrow focus of attention and differences in perceptual and motor systems. Next, I will briefly introduce indices of measurement of arousal and attention relevant to this thesis, before specifying gaps in the arousal and attention literature in autism.

1.3.5. **Indices of measurement of arousal and attention**

Unlike animals, invasive measures of arousal and attention cannot be used in human beings. Therefore, indirect measures are typically used to index arousal and orienting of attention. As discussed earlier, activity in the ANS is a reliable index of arousal in the central nervous system and thus, indices of the ANS are often used to measure one’s state of arousal and reactivity to the environment. Changes in

physiological arousal as measured by indices of the ANS can also index orienting responses to novel or salient information in the environment (Cuve, Gao, & Fuse, 2018).

1.3.5.1. Indices of arousal

In this thesis, arousal is indexed using heart rate and heart rate variability so this will be described in more detail than other indices.

The most common indices of ANS function are heart rate, electrodermal activity (EDA) and pupillometry (Wass et al., 2015a). EDA indexes activity of the sweat glands, which are regulated by the sympathetic nervous system. Spontaneous fluctuations in EDA as well as event-related responses in EDA (called skin conductance responses or SCRs) are therefore used to measure tonic sympathetic arousal and sympathetic responses to salient events. Pupil size on the other hand is influenced by both SNS and PNS, and also correlates with LC function; therefore, it is another valid indicator of ANS function.

Within the autism literature, cardiac indices of ANS function have been most commonly used to measure arousal at rest as well as changes in arousal in response to salient events (Benevides & Lane, 2015; Klusek et al., 2015; Lydon et al., 2016). Heart rate is a measure of the number of heartbeats in a minute. Variability in time intervals between consecutive beats (or variability in inter-beat intervals) is a commonly used measure of heart rate variability (HRV) which indexes dynamic and flexible adaptations of the ANS to the environment, as regulated by the CNS. HR is regulated by both SNS and PNS, with SNS activity being associated with accelerations in HR and PNS activity being associated with decelerations in HR. Slowing down of heart rate (mediated by the PNS) is typically associated with orienting of attention, information processing and motor preparation (Ribeiro & Castelo-Branco, 2019). On the other hand, threatening stimuli elicit heart rate accelerations (by activation of SNS) indexing bodily mobilization of resources to respond effectively to the threatening information (Wass et al., 2015a). Importantly, studies evidence influences of the LC on HR as well, with an overall excitatory effect on the heart through activation of the SNS (Wang et al., 2014) or inhibition of the PNS

(Samuels & Szabadi, 2008). Changes in HRV reflect adaption to environmental changes, with decreased HRV typically associated with limited capacity to adapt to environmental changes (Appelhans & Luecken, 2006; as reviewed by Krypotos, Jahfari, van Ast, Kindt, & Forstmann, 2011). In this thesis, I will investigate profiles of HR and HRV at rest and in response to simple auditory stimuli in autistic individuals (Chapter 3). I will also investigate whether HRV could serve as a stratification marker to parse the heterogeneity on the autistic spectrum (Chapter 3).

1.3.5.2. Indices of orienting

1.3.5.2.1. Using EEG to measure orienting of attention

Electroencephalography (EEG) is a technique that measures synchronised activity of groups of neurons through recording of electrical signals at the scalp. EEG provides high temporal resolution and has been widely used to index all stages of attention and information processing, including sensory discrimination, orienting of attention, motor preparation and conflict monitoring (Luck, Girelli, & Parasuraman, 1998). EEG has been used successfully as a technique with infants, young children and individuals with developmental disabilities by researchers (Groom et al., 2017; Kolesnik et al., 2019). A traditional EEG data analysis method is averaging of the EEG response after a specific event that is repeated several times, and this averaged event-related response is called an event-related potential (ERP) (Luck, 2014). ERPs reflect fluctuations in voltage that are time-locked to and occur in response to an external (or internal) event. Specifically, in this thesis, I will focus on the P300, which is an event-related potential first discovered by Sutton, Braren, Zubin, and John (1965). This potential was discovered within an experimental context during which participants could not predict whether an upcoming stimulus would be auditory or visual (and therefore, while participants were alert, they were not upregulating alertness in any specific sensory modality). Authors reported that when an auditory or visual stimulus occurred, the stimulus elicited a large positive component that peaked around 300 ms post-stimulus. This is called the P300 and has since been used in various paradigms to index orienting of attention (Luck, 2014). Importantly, parallels have been drawn between the P300 and the late LC phasic response, since both occur after salience evaluations have been completed (Nieuwenhuis et al.,

2005; Nieuwenhuis, De Geus, & Aston-Jones, 2011). Both the P300 and the phasic LC responses are elicited to behaviourally relevant/novel/salient events, both are supramodal, and modulated by emotional valence (as reviewed by Corbetta et al., 2008). It has been shown that P300 reflects coordinated activity in regions such as the TPJ, the LC and prefrontal cortices (Nieuwenhuis et al., 2005). In this thesis, I will investigate P300 to simple auditory stimuli in autistic individuals (Chapter 4).

1.3.5.2.2. Using eye-tracking to measure shifts of attention- orienting and reorienting

Eye-tracking is a non-invasive tool that has been utilized to study wide-ranging questions of cognition and behaviour by measuring how individuals distribute their gaze over any scene. One of the main ways we access new visual information is by making eye movements to shift from the current visual scene in focus. Corneal reflection eye tracking, one of the most commonly used methods of eye-tracking, uses infra-red light directed towards participants' eyes and records the reflection of the cornea and the pupil, thus tracking gaze behaviour (Falck-Ytter, Bölte, & Gredebäck, 2013). These methods estimate location of gaze with high accuracy and allow estimation of how individuals distribute their attention in a dynamic manner (Feng, 2011). Eye-tracking studies have shown that one's eyes are typically focused on objects that are currently in one's thoughts (as reviewed by Eckstein, Guerra-Carrillo, Miller Singley, & Bunge, 2016). This allows for questions about exogenous and endogenous attention in various experimental contexts and thus, allows individual differences to emerge. If an individual struggles to orient or reorient attention, eye-tracking can provide a powerful and remote method to measure this. The typical outcome measures one obtains from eye-tracking studies, specifically when studying orienting of attention, are measures of gaze behaviour, such as look durations, saccades or latency to look at a stimulus. In this thesis, I will use eye-tracking to investigate profiles of orienting of attention to visual stimuli in autistic individuals (Chapter 5).

To summarize, I will utilize methods including electrocardiography, electroencephalography and eye-tracking to measure arousal and orienting of attention to various visual and auditory stimuli in autistic as compared to neurotypical individuals.

1.4. Attention in autism

Next, I will review literature on tonic and phasic arousal, as well as orienting of attention to different types of stimuli in autism. I will highlight the relevant theories and gaps in the literature and discuss how the type of stimuli used influences the nature of findings.

1.4.1. Autonomic Arousal in autism

Some of the earliest and most influential theories in the field of arousal and attention in autism suggest that autistic individuals might have differences (from neurotypical individuals) in resting-state arousal and arousal regulation, which might affect subsequent attention to and processing of environmental input, leading to atypical behaviours, learning and acquisition of skills. Hutt, Hutt, Lee, and Ounsted (1964) proposed that autistic individuals might present with states of hyperarousal at rest, which may underlie sensory over-responsivity to external stimuli. Further, they suggested that states of hyperarousal might also influence habituation to repeating stimuli (leading to slower or reduced habituation) thus causing the individual to become overwhelmed in environments rich in stimulation (for example, social environments). Profiles of social avoidance and restricted, repetitive behaviours might then be coping strategies that develop over time in order to downregulate arousal (Rogers & Ozonoff, 2005). In contrast, DesLauriers and Carlson (1969) suggested that autistic individuals might present with profiles of hypoarousal, leading to reduced responsiveness to sensory and social stimuli, and RRBs might be a way to upregulate arousal (Lovaas, Newsom, & Hickman, 1987). Importantly, these two theories are not mutually exclusive; the same individuals might present with profiles of hyper- or hypo- arousal at different times; alternatively, there might be subgroups of autistic individuals who present with predominantly hyper- or hypo-aroused states during rest and task (Pellicano & Burr, 2012; Rogers & Ozonoff, 2005). Such atypicalities, if present, would impact engagement with the environment and the ability to respond to and/or learn from sources of information.

There are more recent theories that support a hyperarousal model in autism, specifically in relation to vagal tone. Porges' polyvagal theory (Porges, 1992; Porges, 2003a) proposed an evolutionary role of

the vagus nerve in social engagement and suggested that top-down regulation of the vagus nerve by cortical regions through the brainstem supports social engagement. Within this framework, Porges (2001) suggested that reduced social engagement in autistic individuals might be reflective of reduced vagal influence over the heart. Similarly, the neurovisceral integration theory (Thayer & Lane, 2000) suggested that reduced parasympathetic activation and states of hypervigilance towards the environment (resulting in reduced autonomic flexibility) are associated with anxiety and difficulties with emotional regulation (Friedman, 2007). Thayer and Lane (2000) also cited the role of cortical structures (such as PFC, ACC, insula, amygdala) in regulating the PNS. Structural and functional connectivity of these structures has been found to be atypical in autism (Kushki, Brian, Dupuis, & Anagnostou, 2014). Further, there is evidence of atypicalities in cortical arousal in autism (Wang et al., 2013). Therefore, atypical interactions between central nervous system and the autonomic nervous system might manifest in differences in tonic arousal and phasic responsivity to stimuli, as measured by ANS indices. These differences might be linked with symptom domains core to autism, such as sensory responsivity, socialization skills and development of restricted, repetitive behaviours.

Studies directly measuring tonic arousal in autism have generally led to varied results. Some studies report tonic hyper-arousal in autism (Anderson, Colombo, & Unruh, 2013; Bishop-Fitzpatrick, Minshew, Mazefsky, & Eack, 2017; Kuiper, Verhoeven, & Geurts, 2019); others report evidence of hypo-arousal in autism (Eilam-Stock et al., 2014; Mathersul, McDonald, & Rushby, 2013a; Pace & Bricout, 2015); and yet other studies report null effects (Klusek, Martin, & Losh, 2013; McCormick et al., 2014; Schaaf et al., 2015). We conducted a systematic review of autonomic arousal during resting-state in autistic individuals to fully understand this heterogeneous literature (see Appendix H). We included any studies that evaluated resting-state or pre-task baseline arousal using indices of heart rate, electrodermal activity or pupillometry. Of the 60 studies reviewed, 60.8% reported evidence of group differences on an autonomic measure during resting state measurement compared with neurotypical individuals. However, when counting each group comparison from each study (yielding 130 comparisons), null effects were more common, with 61% of the group comparisons showing null effects. Therefore, evidence for differences in profiles at rest in autistic as compared to neurotypical

individuals does not support theories of tonic hyper- or hypo-arousal as being a predominant state in autistic individuals.

Importantly, most studies that found significant group differences reported evidence in support of hyperarousal during rest, particularly using indices of parasympathetic function, but findings of hypoarousal and autonomic dysregulation were also consistently present in a minority of studies. Some studies indicated evidence for both hyperarousal (using cardiac indices) and hypoarousal (using electrodermal indices) in the same autistic individuals (Bujnakova et al., 2016; Neuhaus, Bernier, & Beauchaine, 2014; Neuhaus, Bernier, & Beauchaine, 2015), possibly indicating co-occurring underactivation of both sympathetic and parasympathetic nervous systems. This might indicate overall reduced autonomic responsivity to the environment (i.e. change in autonomic arousal in response to events in the environment) in autistic individuals. Few studies included in the review evaluated change in autonomic arousal over time by measuring it multiple times within the resting-state or baseline period (meant to reflect adaptation to the environment within the experimental context of resting-state). These studies were consistent with one another, with findings of reduced or slower adaptation of ANS response in autistic as compared to neurotypical individuals (Mathewson et al., 2011; Neuhaus et al., 2015; Zahn, Rumsey, & Van Kammen, 1987).

Further, this review revealed that studies that used a resting-state measure requiring inwardly-directed attention (such as sit down with eyes closed or relax) without something external to focus attention towards, more frequently reported evidence of group differences between autistic and neurotypical individuals. On the other hand, where group differences were found, findings of hyperarousal were more common when participants were exposed to passive stimulation of some sort (for example, a video), as compared to when they were not. Therefore, the review revealed subtle differences in the type of findings based on differences in experimental context. Importantly, we also identified other factors such as control of co-occurring symptoms (such as those of ADHD, anxiety) and exposure to medication as sources of heterogeneity in the literature of resting-state arousal in autism.

Studies measuring phasic responsivity using ANS indices in autism have, similar to literature in tonic arousal, led to varied results. Some studies support the hyperarousal profile, suggesting that autistic individuals show hyper-reactivity to certain types of information. For example, some studies have found higher skin conductance in autism in response to auditory tones (Chang et al., 2012); direct gaze stimuli (Kylliäinen & Hietanen, 2006), and in response to naturalistic play activities (Prince et al., 2017). On the other hand, studies have also reported the opposite effect; reduced electrodermal responsivity to sensory stimuli (Schoen, Miller, Brett-Green, & Nielsen, 2009), reduced heart deceleration in response to social stimuli (Helminen et al., 2017; Neuhaus, Bernier, & Beauchaine, 2016; Zantinge, van Rijn, Stockmann, & Swaab, 2017), pupillary constriction to social stimuli (Anderson, Colombo, & Shaddy, 2006), or reduced SCR in response to direct eye gaze stimuli (Kaartinen, Puura, Himanen, Nevalainen, & Hietanen, 2016). Some studies have also found no differences between autistic and neurotypical groups on arousal responses to sensory stimuli (McCormick et al., 2014), between direct and averted gaze (Nuske, Vivanti, & Dissanayake, 2015), or to emotional stimuli (Trimmer, McDonald, & Rushby, 2017).

It is possible that the inconsistency in findings is partly driven by presence of subgroups with different profiles of arousal (and hence attention) in autistic individuals, which lend heterogeneity to the literature, and possibly, to the autistic spectrum itself. Some evidence towards this suggestion was reported by Hirstein, Iversen, and Ramachandran (2001) who used electrodermal activity and found that there were subgroups of hyper- and hypo-responsive autonomic responders in their autistic sample. Similarly, using cluster analysis, Schoen, Miller, Brett-Green, and Hepburn (2008) reported that their autistic sample consisted of subgroups with higher and lower baseline EDA; the subgroup of autistic children with higher EDA showed slower habituation to repeating stimuli than those with lower EDA, suggesting differential profiles of responsivity and cognitive processing in the two subgroups. Other studies have also reported presence of such subgroups in their autistic samples (Bujnakova et al., 2017; Mathersul, McDonald, & Rushby, 2013b; Toichi & Kamio, 2003). Further, these subgroups have been reported to differ from one another in functioning in different behavioural domains relevant to autism. For instance, Mathersul et al. (2013b) reported presence of a hypoaroused subgroup in their autistic

sample while another subgroup did not differ from controls on tonic arousal. Both subgroups presented with differences in perspective taking skills, but only the hypoaroused subgroup had poorer emotion recognition and reduced affective empathy.

Overall, literature on tonic and phasic arousal in autism indicates that there is inconsistent evidence for atypical autonomic arousal and responsivity. There is some converging evidence for presence of reduced vagal tone, reduced autonomic responsivity and atypical autonomic adaptation to the environment in at least a subgroup of autistic individuals (Klusek et al., 2015; Lydon et al., 2016). Further, there is preliminary evidence for different types of autonomic responders in the autistic spectrum.

Literature suggests that autonomic regulation might be better suited as an index of ability to adapt to different environments, broadly, as opposed to an index of development and severity of autism (Klusek et al., 2015; Lory, Kadlaskar, McNally Keehn, Francis, & Keehn, 2020). In line with this, there is consistent evidence (in line with Polyvagal theory) that vagal activity is associated with social developmental outcomes such as communication abilities and socialization skills as well as presence of internalizing and externalizing symptoms (Bazelmans et al., 2019; Cai, Richdale, Dissanayake, & Uljarevic, 2019; Patriquin, Scarpa, Friedman, & Porges, 2013). This is in line with the Polyvagal and Neurovisceral integration theories that highlight the role of vagal tone in social engagement and emotional regulation (Porges, 2003b; Thayer & Lane, 2000). If present, reduced vagal tone would lead to reduced autonomic flexibility to respond to and adapt to changes in the environment (Schaaf et al., 2015).

It is important to highlight that differences in parasympathetic activation, particularly in relation with reduced vagal tone, are not specific to autism. Differences in arousal and responsivity to stimuli are linked with internalizing symptoms (such as anxiety) as well as externalizing behaviours that impact adaptive functioning and participation in daily activities (Reynolds, Bendixen, Lawrence, & Lane, 2011; Tseng, Fu, Cermak, Lu, & Shieh, 2011). Vagal tone is implicated in the neurobiology of anxiety

disorders (Friedman, 2007) and profiles of higher anxiety are associated with sensory hyper-reactivity and attentional hypervigilance (Carpenter et al., 2019; Green & Ben-Sasson, 2010; McVey, 2019). In addition, differences in autonomic arousal overall, are implicated in other developmental conditions. For instance, ADHD, which as noted previously highly co-occurs with autism, is associated with profiles of sympathetic underarousal (Bellato, Arora, Hollis, & Groom, 2020). Therefore, given differences in autonomic profiles of anxiety and ADHD, both of which highly co-occur in autism, it maybe that ANS function could serve as an index of presence/severity of these other issues and may even be a factor that contributes to the development of those symptoms in autistic individuals.

Overall, based on the above evidence, it is yet unclear whether autistic individuals demonstrate profiles of hyper- or hypo-arousal at rest, and similarly whether their ability to employ autonomic nervous system to support their responses to stimuli in their environment is typical. Individual differences in autonomic arousal at rest and in response to salient events would impact profiles of engagement with and attention to the environment. Therefore, it is important to understand whether there are consistent atypicalities in arousal in autistic individuals and how these relate with different symptom domains of autism. In this thesis, I will investigate profiles of autonomic arousal in autistic individuals as compared with neurotypical individuals during resting-state and in response to presentation of auditory stimuli (Chapter 3). Further, I will investigate whether autonomic arousal function can be used to stratify autistic individuals into subgroups with different profiles of arousal (and therefore, also, attention) (Chapter 3).

Next, I will evaluate evidence for differences in orienting of attention to different types of stimuli in autism.

1.4.2. **Orienting of Attention in Autism**

The literature on orienting of attention in autism, similar to literature described above on arousal, is heterogeneous and appears to vary depending upon experimental tasks and stimuli used. Autistic individuals have been shown to have typical, or superior, endogenous orienting as assessed through

visual search paradigms (Blaser, Eglington, Carter, & Kaldy, 2014; Gliga et al., 2015). On the other hand, evidence from Posner paradigms (where participants detect spatial targets after spatially predictive or non-predictive cues) suggests that autistic individuals demonstrate slower orienting as compared to non-autistic individuals (Landry & Parker, 2013). In addition, reports of fragmented saccadic pathways as well as slower initiation of eye movements are prevalent, especially when orienting to visual stimuli presented peripherally as compared to centrally on a screen (Keehn et al., 2013; Townsend, Courchesne, & Egaas, 1996; Wainwright & Bryson, 1996). There is consistent evidence in the literature showing that once autistic individuals focus on a stimulus, they find it difficult to widen their attentional focus (Mann & Walker, 2003; Ronconi, Devita, Molteni, Gori, & Facoetti, 2018). Specifically, Mann and Walker (2003) presented a paradigm to autistic and neurotypical participants, asking them to judge between two pairs of cross-hairs, and report which was longer. They reported that autistic participants made more errors when the previous pair of cross-hairs was smaller than the current presentation; indicating that their ability to shift attention in a contextually appropriate manner to increase the visual field being attended was impaired. In relation to this, free-viewing tasks report an image centre bias in autistic individuals (Wang et al., 2015). These studies highlight the bias towards exploitative modes of attention and/or against exploratory modes of attention, indicating that flexible shifting between these might be impaired in autism.

Further, evidence from spatial orienting and gap overlap tasks has shown that autistic individuals show slower disengagement or shifting from visual stimuli; these atypicalities are reliably apparent from as early as 12 months of age in infants at high familial risk of autism (Elsabbagh et al., 2013a), and persist into childhood and adulthood (Sacrey, Armstrong, Bryson, & Zwaigenbaum, 2014). Importantly, these differences in visual orienting have been found to relate to social symptoms of autism (Ronconi et al., 2018). In fact, one of the earliest predictors of later autism symptom severity is the latency to disengage visual attention, typically tested using the gap overlap paradigm (van der Geest, Kemner, Camfferman, Verbaten, & van Engeland, 2001). In this paradigm, a central stimulus appears on the screen, followed by a peripheral stimulus either when the central stimulus has disappeared (baseline), after a gap after the central stimulus's disappearance (gap condition) or when the central stimulus continues to be present

on the screen (overlap condition). Orienting to the peripheral stimulus during the baseline condition provides a measure of efficiency of exogenous phasic orienting. In the gap condition, the gap between the central stimulus's disappearance and the peripheral stimulus's appearance is meant to facilitate this phasic orienting process and in the overlap trials, one has to disengage from the central stimulus actively and reorient to the peripheral stimulus, thus providing a measure of volitional, endogenous reorienting. It is this latter process of disengagement and reorienting that has been found to be impacted in autistic individuals and early differences (compared to neurotypical individuals) in this process relate with later autistic symptoms (Elsabbagh et al., 2013a).

Using this paradigm, it has been found that autistic individuals show overall (compared to neurotypical individuals) differences in visual attention such as slower or faster response times in both gap and overlap trials, or other eye movement differences across trials (Goldberg et al., 2002; Schmitt, Cook, Sweeney, & Mosconi, 2014; van der Geest et al., 2001). Some studies show slower disengagement (Elsabbagh et al., 2013a; Elsabbagh et al., 2009; Kawakubo et al., 2007; Landry & Bryson, 2004) while other studies have found no differences in disengagement in autistic individuals compared to neurotypical individuals (Fischer et al., 2014; Kawakubo, Maekawa, Itoh, Hashimoto, & Iwanami, 2004; Mosconi et al., 2009).

Such variability is in line with mixed findings within the autism literature in other areas and could in part be driven by phenotypic heterogeneity on the autistic spectrum. However, a closer analysis reveals that methodological factors such as the type of stimuli used for the central and peripheral stimuli, influence the effects observed. In studies where simple stimuli of low salience (such as crosses and boxes) are used and repeated over trials, autistic individuals show either no differences or overall differences in visual attention, such as slower or faster reaction times across trials than neurotypical children (Goldberg et al., 2002; Kawakubo et al., 2004; van der Geest et al., 2001). In fact, Todd, Mills, Wilson, Plumb, and Mon-Williams (2009) found different patterns when the task was active as compared to passive, indicating that autistic children do not modulate attention to less salient stimuli

spontaneously in the same way as neurotypical children do, implying not an impairment in ability but rather in employment of the ability in response to stimuli of low salience.

In comparison, studies using stimuli of higher salience or complexity (such as static images of social or non-social things or dynamic colourful animations) reveal slower attentional disengagement and reorienting in autism (Kawakubo et al., 2007; Kleberg, Thorup, & Falck-Ytter, 2017; Landry & Bryson, 2004). This suggests an interaction between tonic arousal and type of environmental information at play, specifically; spontaneous attention might be differently affected in autistic individuals when the environment is either too boring or too complex. Few studies have directly manipulated the effect of arousal or the effect of stimulus complexity. Stimulus complexity manipulations reveal that slower reorienting is specific to conditions with higher complexity, for example, present when the central stimulus is multimodal but not unimodal (Katagiri, Miya, & Matsui, 2014; Sabatos-DeVito, Schipul, Bulluck, Belger, & Baranek, 2016). One study manipulated arousal in a gap overlap task and found that while autistic individuals showed slower disengagement and reorienting, the speed of reorienting was similarly facilitated by a non-predictive alerting cue presented before the peripheral target appeared in both autistic and non-autistic individuals (Kleberg et al., 2017). These studies highlight the importance of manipulating stimulus content to understand where atypicalities lie.

1.4.3. **Social as compared to Non-Social stimuli differently impact attention in Autism**

In the social world, we distribute attention in different ways in multiple modalities, including visual, auditory and tactile modalities. Paying attention to another person's facial expression is as important as paying attention to their speech in order to appropriately interact with them. A core aspect of attention literature in autism focuses on the type of information autistic individuals do or do not pay attention to. Given the behavioural symptoms of autism that involve reduced social communication and social interaction, and in some cases social avoidance, attention to social information in autism is a highly studied area. Many studies report that autistic individuals show reduced spontaneous attention to social information (Fletcher-Watson, Leekam, Benson, Frank, & Findlay, 2009; Franchini et al., 2017; Klin, Jones, Schultz, Volkmar, & Cohen, 2002; Unruh et al., 2016). Chita-Tegmark (2016) conducted a meta-

analysis of studies that examined visual orienting to social information and found an overall effect size of 0.55 across 38 articles which provided further evidence of reduced attention to social information in autism. Similarly, studies in the auditory modality have also shown reduced preference for social sounds as compared to non-social sounds (Čeponiene et al., 2003; Lepistö et al., 2005).

In addition, autistic individuals also show increased attention to certain types of non-social stimuli, either when they are of high-interest to autistic individuals (DiCriscio et al., 2016) or when these are repetitive geometric patterns (Moore et al., 2018). Differences in attention to social and non-social information as well as core impairments in areas of social interaction and communication led to social-domain specific theories in autism which are common in proposing that specialization of social networks in the brain is atypical in autism (Chevallier et al., 2012; Dawson, 2008; Johnson, 2005; Schultz, 2005). For example, the Social Motivation Theory posits that social attention is reduced in autism due to disruption of function in areas of the brain that compute the salience value of social informaton and prioritize information in the environment that is social in nature (Chevallier et al., 2012). Similarly, Schultz (2005) proposed that early deficits in social networks such as the amygdala and the fusiform-face area underlie the social and cognitive impairments in autism. These theories would explain reduced attention to social information as a result of atypical development of specialization of social brain networks resulting in reduced preference for social information. Increased attention to non-social information might be a method of avoiding having to pay attention to social information (Dubey, Ropar, & Hamilton, 2018). Further, these theories suggest that reduced social attention might have cascading consequences on learning and adaptation to social environments and thus might underpin impairments in social cognition. This is partially supported by evidence that reduced attention to social information is associated with worse socio-communicative abilities (Freeth, Ropar, Mitchell, Chapman, & Loher, 2011).

There are several lines of research that challenge this line of thinking. Firstly, reduced engagement with social information does not generalize across contexts. For example, Unruh et al. (2016) found that it was only when paired with high-interest non-social stimuli that autistic people were slower to orient to

social stimuli, not when they were paired with low-interest stimuli. Similarly, Magrelli et al. (2013) showed that while social orienting to a facial expression was typical in autistic individuals, it was slower when orienting to a speaking face. Hanley, McPhillips, Mulhern, and Riby (2013) reported that attention to social stimuli in autistic individuals was similar to neurotypical individuals when faces were presented in isolation, but was reduced when faces were presented as part of social scenes, suggesting that increasing complexity impacted attention. In another study, Falck-Ytter, Rehnberg, and Bölte (2013) presented upright and inverted point light displays of biological motion (representative of social and non-social stimuli respectively), to autistic and neurotypical children. In some trials, they paired one of these visual stimuli with an auditory stimulus, thus making it multimodal and hence more complex. They found that autistic children showed reduced attention for both biological motion (social information) and multimodal information (both social and non-social). Systematic reviews of eye-tracking studies of social attention in autism show atypical attention in autism is most often found in studies which have higher social complexity (Chita-Tegmark, 2016).

Given that models of autism that posit a core social brain dysfunction as underpinning autistic symptoms have not been able to account for all the empirical findings in the field (Johnson, 2014), it is clear that reducing environmental stimuli to binary categories of social and non-social is not going to help identify the mechanisms that lead to profiles of reduced social attention and social engagement in autism. Further, preliminary research in two month-old infants at elevated familial risk of autism shows that early biases to attend to social information are intact, although social orienting demonstrates decline between 2 to 6 months of age in infants who later developed autism (Jones & Klin, 2013). Thus, biases against social information might indeed develop, and it is important to understand why, so that we can intervene appropriately. Social information is inherently complex as it is dynamic and unpredictable, whereas non-social information tends to be more fixed, repetitive and with limited features which have informational value. When one enters a social environment, with several people, each of those people are engaged in activities or interactions that are not perfectly predictable. Human beings are also constantly providing new and changing information through verbal and non-verbal cues. Thus, without even interacting with human beings, the level of information available that is constantly changing is

rich and complex. On the other hand, a room without human beings, with only objects, tends to be more static and does not provide ever-changing information. A ball does not have many moving parts that each hold symbolic value. Movements of a ball are perfectly predictable. A computer on the other hand, which does have a lot of information, is still predictable and one is in control of what information appears on the screen and when. Autistic individuals' preference for non-social over social information might indicate a general difficulty with complexity and/or unpredictability. Indeed, recent theories that have been proposed in autism suggest this. For example, Pellicano and Burr (2012) suggest that sensory and cognitive differences in autism result from attenuated Bayesian priors (i.e. expectations about the world before any information is available, based on prior experiences) while Lawson, Rees, and Friston (2014) posit that sensory evidence is ascribed more precision in autism than prior beliefs. Both these accounts would predict that social environments may be particularly difficult for autistic individuals to navigate since they are overwhelming in terms of sensory evidence and levels of uncertainty and prior beliefs and expectations are more important to navigate these contexts. It is possible therefore, that an apparently greater deficit in attention to social information is reflective of a general attentional style that has developed to favour simple, repeating information over complex, dynamic information and over time autistic individuals develop biases away from exploring complex, novel, dynamic information, whether social or non-social. Few studies have investigated this systematically.

In my thesis, I will thus examine whether orienting to social and non-social stimuli is atypical in autism in visual (Chapter 5) and auditory (Chapter 4) modalities. Further, I will examine how complexity of a stimulus impacts orienting of attention (Chapter 5). Importantly, when one orients attention to a new stimulus, there is an initial increase in processing of that stimulus. However, with time, the salience of the stimulus decreases, habituation occurs and we shift our attention away from it. Flexible distribution of attention is therefore partly dependent on information processing and habituation. I will discuss briefly next, evidence for atypicalities in habituation in autism.

1.4.4. **Habituation in Autism**

The term 'habituation' refers to a form of non-associative learning that cannot be explained by sensory adaptation or motor fatigue (Rankin et al., 2009). This is a mechanism that is crucial for adaptation to any environment, and it allows an organism to ignore what is known in order to allocate attention to that which is unknown. We discussed earlier that theories of tonic hyperarousal in autism also implicate impaired habituation; they propose that states of hyperarousal lead to slower habituation. It should be noted that the relationship could be in the reverse direction; impaired information processing and habituation might maintain states of hyperarousal.

In line with theories of hyperarousal, there is some evidence that autistic individuals show differences in habituation to simple sensory stimuli from young ages up to adulthood. For instance, a study by Guiraud et al. (2011) showed decreased habituation of auditory evoked potentials in 9-month old infants at elevated familial risk for autism compared with low-risk controls. Further evidence from sensory gating paradigms reveal reduced habituation (Perry, Minassian, Lopez, Maron, & Lincoln, 2007; Takahashi, Komatsu, Nakahachi, Ogino, & Kamio, 2016; as reviewed by McDiarmid, Bernardos, & Rankin, 2017). However, the habituation literature is also heterogeneous like any other literature in autism (McDiarmid et al., 2017). It is possible that differences in profiles of tonic arousal are linked with habituation profiles. As mentioned earlier, Schoen et al. (2008) reported that habituation profiles were different for subgroups of autistic participants with different tonic arousal profiles: autistic participants with hyperarousal showed reduced habituation while those with hypoarousal showed enhanced habituation.

Habituation differences have also been found in relation to more complex stimuli such as faces. For example, Webb et al. (2010) found that 18-30 months-old autistic children and their siblings show reduced habituation to images of faces compared with neurotypical controls. In a recent study, habituation of autonomic responses to repeated facial stimuli was measured and it was discovered that among autistic children, lower levels of habituation in response to direct gaze stimuli was associated with more social impairments (Kaartinen et al., 2016). Another study by Vivanti et al. (2018) reported

that when presented with novel and repeating non-social stimuli side by side, autistic children were slower in decreasing attention to the repeating stimulus as compared to children with Williams Syndrome or neurotypical children. Interestingly, slower habituation was related to lower severity of repetitive behaviours in the autistic group. It is unclear therefore, whether autistic individuals show atypicalities in habituation and whether these relate with social symptom domains and/or with RRBs. It is also possible that the type of stimulus used impacts profiles of habituation. Indeed, some studies have reported that habituation deficits are specific to social stimuli, for example, present for repeating faces but not for repeating houses (Kleinhans, Richards, Greenson, Dawson, & Aylward, 2016; Webb et al., 2010). Importantly, in studies looking at habituation to face stimuli, specific brain regions such as the amygdala and functional connectivity between the amygdala and prefrontal cortices have been implicated (Green et al., 2019; Kleinhans et al., 2009; Swartz, Wiggins, Carrasco, Lord, & Monk, 2013). In Chapters 4 and 5, I will investigate profiles of habituation to simple sensory stimuli (auditory, Chapter 4) and more complex stimuli (visual, Chapter 5). These investigations will improve understanding of whether there are differences in basic abilities to habituate, and whether heterogeneity in the literature in habituation stems from varying complexity of the stimuli used in the experiment.

Next, I will briefly describe profiles of attention and arousal in ADHD. In my thesis, I used a clinical control group (children and young people with ADHD) to identify atypicalities specific to autism when compared with another neurodevelopmental condition. In addition, I also included a group of children and young people with co-occurring autism and ADHD to determine whether any of the atypicalities in the autistic sample also occurred in those with the co-occurring phenotype and could help explain shared risk. It is therefore important to understand how presence of ADHD impacts arousal and attention and how then this might interact with autism in those who are comorbid for the two conditions.

1.5. **Attention and Arousal in ADHD**

ADHD is a neurodevelopmental psychiatric condition characterized by symptoms of hyperactivity, inattention and impulsivity (American Psychiatric Association, 2013). Estimated worldwide prevalence for ADHD is between 3-5% (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015; Polanczyk, Willcutt,

Salum, Kieling, & Rohde, 2014) and it co-occurs with autism at a high rate with studies indicating co-occurrence rates between 37-85% (as reviewed by Leitner, 2014). Similar to autism, ADHD is more common in males than females, and like in autism, it has become apparent that girls with ADHD are likely to be underdiagnosed possibly due to differences in clinical presentation as compared to males (Mowlem et al., 2019). There are no reliable, objective biological assessments for ADHD and the condition is typically diagnosed using behavioural assessments of the child as well as through use of a developmental and familial history. Typically, this process includes use of standardised behavioural rating scales, observation of the child in multiple settings and semi-structured interviews with the child's caregivers; with pervasiveness in multiple settings being a criterion for diagnosis. Importantly, symptoms of ADHD are often managed with pharmacological treatments such as stimulants. The most common medications used to treat ADHD are stimulants such as methylphenidate and dexamfetamine, although non-stimulants such as atomoxetine and guanfacine are also used. Importantly, for those with comorbid autism and ADHD, use of stimulants is associated with more negative side effects and with exacerbation of autism symptoms (Davis & Kollins, 2012).

ADHD has a negative impact on quality of life (Danckaerts et al., 2010), academic achievement (Birchwood & Daley, 2012), employment and in social relationships (Brod, Schmitt, Goodwin, Hodgkins, & Niebler, 2012; Michielsen et al., 2013). Further, co-morbid ADHD in autism is associated with worse symptom severity (Sprenger et al., 2013), as well as worse cognitive functioning and more delays in adaptive functioning (Rao & Landa, 2014; van der Meer et al., 2012). Importantly, treatments used with ADHD and autism are less effective with individuals with comorbid autism and ADHD (Davis & Kollins, 2012; Leitner, 2014). Until DSM-5 was published (American Psychiatric Association, 2013), dual diagnosis of autism and ADHD was not permitted, which impacted research in comorbidity of the two conditions. However, since DSM-5, much research has investigated the impact of this overlap and it has become clear that autism and ADHD share overlaps but also divergences in their cognitive, clinical, attentional features. For instance, both conditions are characterised by features of inattention (Johnson, Gliga, Jones, & Charman, 2015) and difficulties with

emotion recognition (Taurines et al., 2012). However, divergences have also been reported in areas such as reward processing and theory of mind (Taurines et al., 2012).

It has been suggested that attentional atypicalities might form the link between the overlaps and divergences in these conditions, specifically because both conditions are associated with inattention from an early age (Visser, Rommelse, Greven, & Buitelaar, 2016). However, inattention is a broad domain and careful and systematic evaluation of attention and arousal profiles, with consideration of different subcomponents of attention, have only recently started to be conducted, particularly in those with co-occurring autism and ADHD. In general, ADHD is associated with profiles of attention very different from those in autism. It has been suggested that ADHD is characterized by reduced alertness and vigilance which impacts allocation of attention to the environment in a flexible and dynamic manner (Howells et al., 2012). Further, profiles of hyperactivity and sensation seeking in ADHD are proposed to arise as an upregulating mechanism to increase arousal (Geissler, Romanos, Hegerl, & Hensch, 2014; Sergeant, 2000). Attentional profiles in ADHD demonstrate deficits in sustained attention and response inhibition, as well as high levels of distractibility (American Psychiatric Association, 2013), suggestive of difficulties in entering or sustaining a phasic mode and possible predominance of tonic LC mode (Aston-Jones, Gonzalez, & Doran, 2007). We investigated this through a systematic literature review (Bellato et al., 2020) on ANS function in individuals with ADHD at rest and in response to cognitive tasks and found that presence of ADHD was associated with hypoarousal, particularly at rest and during cognitive tasks that required active responses or sustained attention. Indeed, from this review, it appears that those with ADHD might struggle to respond to sensory information or salient events, unless they are particularly engaging or rewarding (Howells et al., 2012). However, individuals with ADHD also show profiles of distractibility, indicating that they might struggle to regulate arousal optimally towards task-focused attention in the phasic mode (Aston-Jones & Cohen, 2005b; Visser et al., 2016). Behavioural evidence of hypoarousal has been reported through evidence of increased intra-individual reaction-time variability in cognitive tasks (Kofler et al., 2013), although more rewarding or engaging contexts appear to normalise these impairments (Groom et al., 2013; Groom et al., 2010; Liddle et al., 2011). ADHD is not associated with deficits in visuo-spatial orienting (Huang-Pollock & Nigg, 2003).

However, atypicalities in activation of attentional networks have been reported in association with ADHD (Hasler et al., 2016; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006). Further, there is evidence of reduced amplitude and delayed latency of the P300 in response to sensory stimuli in those with ADHD (Johnstone, Barry, & Clarke, 2013).

Given the high co-occurrence between autism and ADHD, it is important to understand how presence of ADHD impacts profiles of attention and arousal in autism. Further, by systematically characterizing symptoms of ADHD in autistic individuals, and by including a control group of individuals with ADHD, we might be able to control for some random noise brought about by individual variation in ADHD symptoms in autistic participants. In this thesis therefore, participants with ADHD and with comorbid autism and ADHD were included and a cross-syndrome comparison approach was adopted. We believe this would help shed light on atypical attentional mechanisms that are syndrome-specific or those that are common in both conditions. How these syndrome-specific or overlapping features then relate to clinical symptoms might help shed light on the mechanisms that lead to the ultimate behavioural atypicalities seen in autism and ADHD (Cornish, Scerif, & Karmiloff-Smith, 2007; Karmiloff-Smith, 1998).

1.6. **Research Questions**

In this thesis, I aim to contribute to an increased understanding of the dynamic interplay between tonic arousal and contextual influences on phasic engagement of attention and information processing, and identify where atypicalities lie in autistic children and adolescents within these domains. I aim to investigate how such atypicalities relate to individual variation in different autism symptom domains and the presence of co-occurring symptoms of other conditions. Finally, I aim to examine the utility of autonomic arousal profiles in stratification of autistic individuals into sub-groups with more homogeneous profiles of attention and symptomatic functioning.

The empirical work presented in this thesis comes from one large study that entailed recruiting and assessing children with autism, ADHD, comorbid autism and ADHD and neurotypical children, on a

range of autonomic, eye-tracking and EEG measures. The following chapters present hypothesis-driven analysis conducted on the data collected from this large study.

In Chapter 2, I will outline the methods used in this thesis, including recruitment and clinical classification, sample characteristics, experimental battery and overarching statistical approaches that have been utilized.

In Chapter 3, I will use measures of HRV to investigate individual differences in resting-state arousal and autonomic responsivity to auditory stimuli in individuals with and without autism. Further, I will investigate whether, through using measures derived from HRV, we can identify subgroups of autistic individuals with different arousal profiles, and whether these subgroups are meaningfully different from one another in their clinical profiles.

In Chapter 4, I will investigate orienting to and habituation to repeating auditory stimuli using the P300 event-related potential in individuals with and without autism.

In Chapter 5, I will utilize eye-tracking to investigate orienting of attention to different types of stimuli (that vary in complexity, novelty and social-ness) in individuals with and without autism.

Finally in Chapter 6, I will present a general discussion and discuss my findings in context of the larger literature in attention and arousal in autism.

Chapter 2. Methods

2.1. SAAND Study

The majority of the data presented here was collected as part of the SAAND Study (Studying Attention and Arousal in Neurodevelopmental Disorders). The SAAND study aimed to investigate mechanisms of attention and arousal in children and adolescents with autism, ADHD or both, in order to shed light on condition-specific impairments as well as enhance understanding of attentional and arousal profiles of those with co-occurring autism and ADHD. Further, the study aimed to investigate how atypicalities in attention and arousal related with behavioural symptoms of autism and ADHD. Given the focus of my doctoral research on autism, I designed and developed certain paradigms within the SAAND study (Resting-State measurement, Habituation Task and the Probabilistic Free-Viewing Task, listed in Table 2.2, Section 2.8) and informed the design of other experimental paradigms (Auditory oddball task, Gap Overlap task, listen in Table 2.2, Section 2.8) to address my questions around profiles of attention and arousal in autism.

2.2. Recruitment and Sample Size

Recruitment for this study took place between September 2017 to March 2019. Children and adolescents between the ages of 7-15 years of age, and their parents were recruited into the study. If parents provided consent, the child's teacher was also contacted and recruited into the study. Clinical participants (i.e., those with autism and/or ADHD) were recruited from local support groups (in Nottinghamshire, Derbyshire and Leicestershire), or were referred to the SAAND study by paediatricians, child and adolescent psychiatrists or mental health nurses in NHS paediatrics clinics and CAMHS, or local special education needs teams in schools (integrated and special schools). Neurotypical participants were recruited from local schools in Nottinghamshire and Leicestershire, and from a database of volunteers held by School of Psychology, University of Nottingham, UK. The study was advertised on social media platforms such as Facebook and Twitter and information about the study was shared on a blog in association with ACAMH (https://www.acamh.org/research-digest/saand-study/). Potential participants received information about the study through a leaflet (see Appendix B) through the various gatekeepers listed above, and if interested, could contact the research team for more information using contact details provided on the leaflet. Participants in clinical groups who took part

either already had a diagnosis of autism or ADHD, or were on the diagnostic pathway seeking assessments.

A-priori power calculations were conducted to determine sample sized required to identify autism- and ADHD- specific differences in attention and arousal profiles for the SAAND study. Previous studies in attention in autism indicate effect sizes that are small to moderate in size (Chita-Tegmark, 2016; Landry & Parker, 2013). Using GPower 3.1 (Faul, Erdfelder, Lang, & Buchner, 2007), it was determined that at least 25 participants were required in each group (Autism, ADHD, co-occurring Autism and ADHD, neurotypical) to detect medium effect sizes (considering 80% power and a significance level of 0.05). In order to account for attrition, and potential exclusion of participants due to clinical reasons or due to poor data quality, we aimed to recruit 120 participants in the study (around 30 per group).

2.3. Ethics

Ethical approval for the study was obtained from the UK National Research Ethics Committee (REC reference 17/EM/0193 and the Health Research Authority (HRA: IRAS research project ID 220158) (attached in Appendix A). Parents of children and adolescents who took part provided informed written consent before any data was collected, while the children and adolescents themselves provided informed written assent. Teachers who took part provided informed written consent before filling out any questionnaires. Teachers were only contacted if parents provided consent. All data was stored in accordance with the Data Protection Act 2018.

Children and adolescents received £15 inconvenience allowance for their time and participation and travel expenses were reimbursed for all families that took part. All participants (parents, teachers, children and adolescents) could choose to withdraw from the study at any point, without losing the inconvenience allowance or travel expenses. Children and adolescents also received a certificate for their participation (see attached in Appendix C). All parents were sent a full report of any behavioural or clinical assessments for the children and adolescents that were conducted as part of the study. At the parents' explicit request, copies of reports were also sent to the child's teachers or GP or the clinician

that referred them to the study. Parents were provided the option to ask for a copy of any videos that we took (this was done for one of the clinical assessments, the Autism Diagnostic Observation Schedule, ADOS, described in Section 2.5), and if parents wanted this, they provided their own memory sticks for the video to be transferred to them. Ethically, it is important to note that many parents were interested in taking part in the study due to a specific clinical assessment provided in the study (the ADOS, see Section 2.5). Due to long waiting lists and reduced capacity in NHS services, many young people were on long waiting lists for this assessment and were referred to our study because the assessment was being carried out as part of the study. For any family that took part in the study for this reason, researchers discussed implications of their participation, and the limitations of the researchers in helping achieve a diagnosis. It was made clear that while the assessment is being conducted by qualified researchers, and the SAAND team is happy to provide a detailed report of the assessments to the families; we cannot guarantee that this will lead to a diagnosis and the report is useful only in the context of other information used by child and adolescent mental health service (CAMHS) clinicians and paediatricians. Parents were fully aware of these aspects before they provided consent.

2.4. Inclusion/Exclusion Criteria

Henceforth, the word 'participant' will be used to refer to the children and adolescents who were the primary sample of interest in this study.

All potential participants were screened against the following inclusion/exclusion criteria before they took part in the study. All participants were between the ages of 7 to 15 years of age. Parents of all participants had to provide informed written consent in order to be included in the study and children and adolescents who took part were required to provide written assent before they were included in the study. Participants were recruited for the clinical groups if they had a clinical diagnosis or were under assessment for autism and/or ADHD. Participants were recruited for the neurotypical group if they had no history of any neurological, neurodevelopmental or psychiatric conditions.

All participants were screened for presence of any neurological conditions or genetic syndromes, and if present, were not included in the study. Further, if a potential clinical participant had a diagnosis of Tourette's syndrome, they were also excluded. If a clinical participant was taking stimulant medications, they were asked to withdraw the medication for at least 24 hours prior to the lab session. If parents of participants were not agreeable to this, those participants were not included in the study. Participants were excluded from the neurotypical group if they had a history of any neurological, neurodevelopmental or psychiatric conditions. Further, participants were excluded from the neurotypical group if they had a sibling with autism or ADHD. In order to ensure that parents providing consent were able to provide informed consent, fluency in English was used as an exclusion criterion and children whose parents did not speak fluent English were not included in the study. Further, participants who were on non-stimulant medications (e.g. atomoxetine) for ADHD were not included in the study, since it is unethical to withdraw these long-acting medications, and importantly, these medications can impact the mechanisms we aimed to capture in this study. Participants on other medications (such as SSRIs) were not required to withdraw their medication. Presence of other mental health conditions (such as anxiety disorders, depression, conduct disorder, oppositional defiant disorder, obsessive compulsive disorder etc.) were not used as exclusion criteria for participants in clinical groups. Similarly, participants were not excluded for having intellectual disability (as defined by IQ < 70). This was to ensure that the sample was clinically ecologically valid. Further, it was originally an aim of this study to evaluate the role of IQ in attention and arousal regulation in autism, potentially as a resilience factor. However, we were not able to recruit enough children with low IQ for this to be feasible.

Overall, 133 participants were recruited into the study. 27 of these participants were excluded for one of the following reasons:

a. Nine participants were excluded because during the screening process (when participants' parents filled out questionnaires), it became apparent that there was a genetic condition (previously undisclosed) or presence of significant clinical symptoms in typically developing controls, that met exclusion criteria.

b. Due to incomplete assessments, enough information was not present for the participant to be classified into one of the clinical groups (see Section 2.4. for more information on Clinical classification criteria). This resulted in exclusion of four participants.

c. Four participants were excluded because they did not provide consent to take part (after their parents had provided consent).

d. In addition, 10 participants in this study were siblings of children with autism and/ or ADHD who did not meet criteria for any of the clinical groups and could not be assigned to the neurotypical group. Their data is therefore not used in this study.

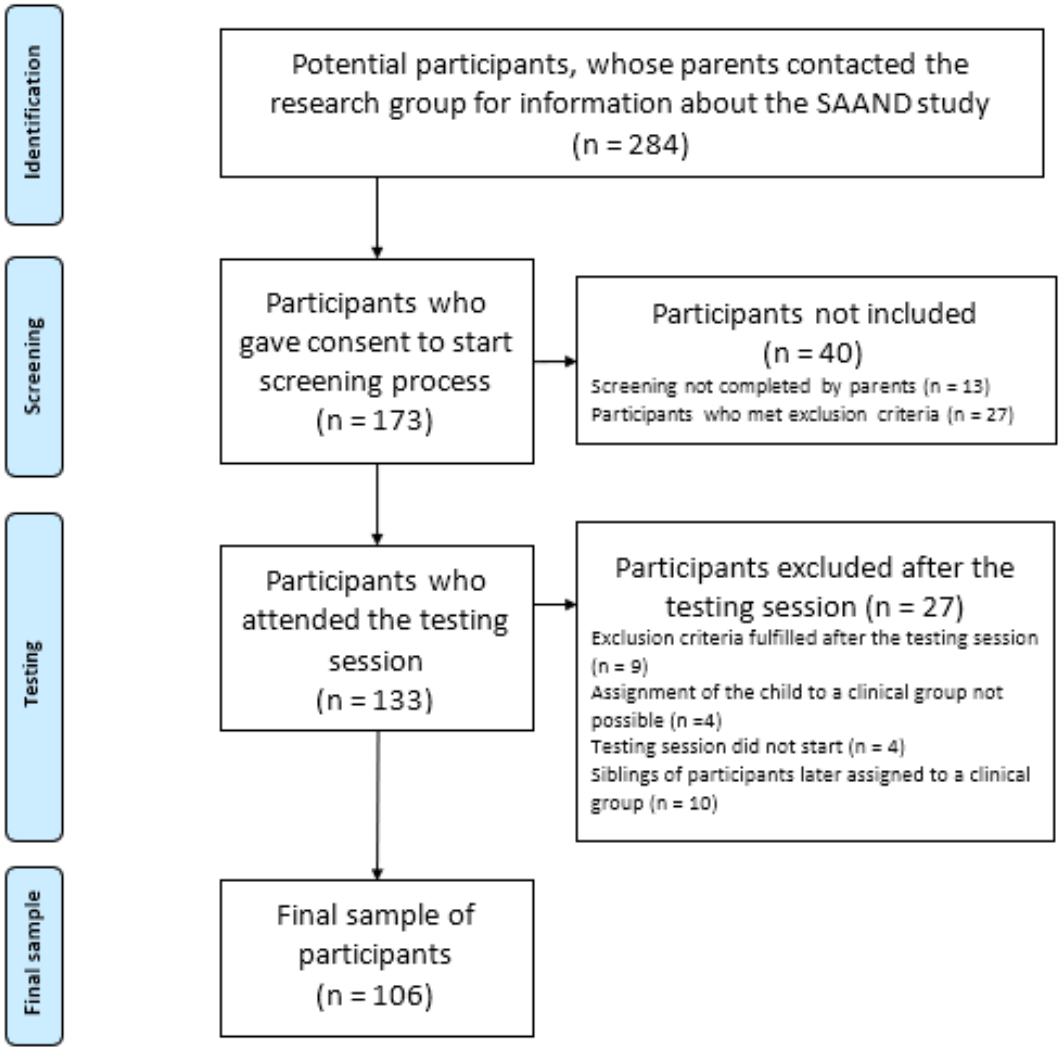


Figure 2.1. Flowchart describing recruitment of SAAND Study participants

After clinical classification, 106 participants were included in the study and the analyses presented in this thesis. This number might vary depending upon whether all participants completed the respective task or not.

2.5. Clinical Assessment and Classification

In order to assess whether participants met criteria for inclusion in one of the clinical groups (Autism-only, ADHD-only or comorbid Autism+ADHD) or the neurotypical group, the following information was collected:

2.5.1. Demographics

Parents filled out a demographics form on which the child's name, date of birth, prior diagnoses/concerns, any use of medication, as well as information about the child's teacher, school and GP were recorded.

2.5.2. Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003)

The SCQ is a parent- and teacher- report questionnaire commonly used to screen for presence of autism-related symptoms. The SCQ has two versions: the lifetime version asks questions about signs of autism during infancy and early childhood, as well as current behaviour; while the Current version asks questions about behavioural symptoms in the last 3 months. The Lifetime version was used with parents in the SAAND study, while the Current version was considered more appropriate to use with teachers in this study. The SCQ has been shown to have high sensitivity (96%) and specificity (80%) for autism, although the Lifetime version is considered to be more reliable than the current version (Chesnut, Wei, Barnard-Brak, & Richman, 2017). The scores range from 0- 39, and 15 is considered to be a cut-off separating those who are at low-risk for autism from those who are at high-risk, with higher scores indicating higher symptoms of autism. SCQ has subscales that tap into the three core domains of autism: Reciprocal Social Interaction, Social Communication, and Restricted, Repetitive and Stereotyped patterns of behaviour.

2.5.3. Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) (Lord et al., 2015)

The ADOS-2 is a semi-structured, standardised tool that uses observation and interaction-based assessment in order to evaluate presence of symptoms of autism. ADOS-2 is the gold standard when it comes to autism diagnosis, with high specificity and sensitivity (Hus & Lord, 2014; Lord et al., 2015). It is valid with individuals of all ages, with different modules used with individuals with different ages and language abilities. A Toddler module is used with toddlers who are 12 to 30 months old and do not yet consistently use phrase speech. Module 1 is used with children who are 31 months or older and do not consistently use phrased speech. Module 2 is for use with children of any age if they are not verbally fluent. Module 3 is used with children and young adolescents who are verbally fluent. Finally, Module 4 is used for older adolescents and adults who are verbally fluent. Depending upon the module, the ADOS-2 comprises of various activities, ranging from developmentally appropriate play-based activities, conversation, narrating stories or answering questions about one's understanding of social interactions and relationships as well as insight into one's own emotions. All activities are designed to evaluate individuals' abilities to engage in social interaction in a flexible and appropriate manner depending upon the social context of the activity, and to communicate their own thoughts and experiences clearly. Further, it is a long assessment that allows for RRBs to emerge, particularly with play objects; and presence of any stereotyped behaviour or speech and any repetitive behaviours is monitored. Scores on the assessment lead to classification to either 'No autism', 'autism spectrum' or 'autistic disorder' categories (ordered from low to high symptoms) depending upon the number of symptoms within each symptom domain exhibited by the participant. For the purposes of this study, if participants showed enough symptoms to be classified in 'autism spectrum' category, they were classified as having clinically significant autistic symptoms on this assessment. Dimensional measures can also be obtained from this assessment alongside subscales for core symptom domains.

I completed the qualification to conduct and rate the ADOS-2 for the SAAND study and during the course of the SAAND study, was supervised by Dr. Puja Kochhar, who is a child and adolescent psychiatrist, also qualified to do the ADOS. The behavioural assessment is typically coded by multiple

ADOS-qualified raters. In this study, a consensus rating was carried out. All ADOS assessments (where consent was given) were video-recorded. The assessments were carried out and scored by myself or Dr. Kochhar and where the scores were borderline, ratings were discussed until a consensus was reached.

In the SAAND study, primarily Modules 3 and 4 were used given that participants were 7-15 years old and most participants had average or above intellectual ability and sufficient language ability to meet requirements for these modules. For one participant, Module 2 was used. It is important to keep in mind that RRBs might not emerge or be as obvious within the context of this assessment. Further, presence of other conditions can impact behaviour on this assessment; for instance, anxiety might impact social interaction, ADHD might impact social engagement and sustained attention during this long assessment. Indeed, there is preliminary evidence that ADOS-2 scores should be interpreted with caution when using with children and adolescents with mood disorders (Colombi, Fish, & Ghaziuddin, 2019; Sikora, Hartley, McCoy, Gerrard-Morris, & Dill, 2008).

2.5.4. Conner's Rating Scales, Third Edition (CRS-3) (Conners, 2008)

CRS-3 is a parent and teacher rating scale commonly used to evaluate symptoms of ADHD. It asks questions that relate to core ADHD symptoms such as hyperactivity, impulsivity and inattention as well as asks questions about domains often affected in ADHD, such as executive functioning, peer relationships, learning and presence of aggressive behaviours. The CRS-3 uses a Likert scale ranging from 0 to 3 for each item to enquire the level of agreement participants have with the statement given; scores on each item are added up, transformed into standardised scores based on age and gender. A cut-off of standardized T-scores above 65 indicates clinically significant symptoms and dimensional scores on subscales in relation with a global ADHD index as well inattention, hyperactivity, impulsivity etc. can be obtained.

2.5.5. Development and Well-Being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)

The DAWBA is a battery of interviews and questionnaires designed to evaluate presence and likelihood of ICD-10 and DSM-5 psychiatric diagnoses in individuals between the ages of 2 and 17 years old. They can be administered as an interview or can be filled out online (or on paper) by parents, teachers and if the young person in question is 11 years or older, by the young person themselves. The assessment includes open questions (eg, 'Does he ever worry?') and invites open-text answers for examples, as well as uses closed, Likert-scale questions. In our study, parents filled out this questionnaire battery online. The reports were evaluated by and used towards clinical classification of autism or ADHD by PK (an experienced child and adolescent psychiatrist). The DAWBA is effective in discriminating between individuals who show signs of psychiatric or psychological conditions from those who do not, with high specificity and sensitivity in children and adolescents (Goodman et al., 2000). Further, it is effective in diagnosis of autism when used in combination with the ADOS (McEwen et al., 2016). Importantly, for the purposes of this study, we used two additional measures from the DAWBA to tap into aspects of adaptive functioning and impact on daily life.

Strength and Difficulties Questionnaire- Impact Supplement (Goodman, 2001) is a questionnaire that assesses psychological adjustment of children and young people using 3-point Likert scale questions. It is used as part of screening, clinical assessments as well as a treatment outcome measure and has high reliability (Goodman, 2001). The SDQ has a brief impact supplement which asks the respondent whether they think the child or young person has a problem or not, and if so, asks about distress, level of impairment, burden and chronicity. Using these answers, a score can be calculated between 0 and 10 that assesses level of impact, with higher scores representing higher impact.

Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983): CGAS is a rating scale used to assess level of global functioning at home, with friends and at school. It is an ordinal-level scale within which a single global rating is assigned to the child or young person between 0-100, with every ten points being associated with a qualitative descriptor that describes how that individual is functioning in

different areas. Importantly, CGAS measures functional competence rather than symptom severity of a given condition (Green, Shirk, Hanze, & Wanstrath, 1994). Scores are assigned based on the most impaired level of general functioning that best describes the individual's behaviour on a hypothetical continuum from health to illness, with higher scores representing less impairment. In this study, information from all the assessments conducted were used to assign a CGAS rating (done by IA). It should be noted that for parents who provided open-text comments on the DAWBA, the ratings were likely more accurate since questions about some areas of adaptive functioning were not directly asked to participants.

2.5.6. Wechsler Abbreviated Scales of Intelligence, Second Edition (WASI-II) (Wechsler, 2011)

The WASI-II is a scale that assesses cognitive ability in individuals between the ages of 6 and 90 years of age. It is composed of four subtests that measure verbal (Vocabulary and Similarities sub-tests) and perceptual reasoning (Block Design and Matrix Reasoning sub-tests) abilities. WASI-II has been reported to have high reliability and validity (McCrimmon & Smith, 2012). Three measures are obtained from the WASI-II; a measure of verbal ability (verbal comprehension index, VCI), a perceptual reasoning index (PRI) and a composite of both which is the full-scale IQ (FSIQ).

2.5.7. Child Sensory Profile, Second Edition (Dunn, 2014)

The Child Sensory Profile is a standardized measure of sensory processing behaviours in childhood and adolescence. The questionnaire uses 86 questions about the child's responses to everyday events in six sensory modalities (visual, tactile, movement, oral, auditory, body position), three behavioural domains (conduct, attention, social) and four sensory patterns (sensitivity, registration, seeking and avoiding). The responses are on a Likert scale that ask whether their child exhibits various sensory processing behaviours in a manner that is similar to their peers, or more or less than their peers, ranging from 0 (Not applicable) to 5 (Almost Always). The scale was normed for children with 3-14 years of age and has strong internal consistency (Cronbach's alpha= 0.88-0.92) and test-retest reliability (r= 0.96-0.97) (Dunn, 2014). Little, Dean, Tomchek, and Dunn (2017) used the Child Sensory Profile demonstrated

efficacy of the tool in a community sample that also included children with autism, ADHD and learning disabilities.

2.5.8. National Statistics Socio-Economic Classification (NS-SEC) (Rose, Pevalin, & O'Reilly, 2005)

Parents also provided information on their socio-economic background. This information was obtained through use of a short semi-structured interview, the NS-SEC. This questionnaire asks information about occupation (eight categories of types of occupation) and employment status (including information about whether the individual is an employer, self-employed or an employee, size of organisation, supervisory status) of the primary income earner in the family and uses this information to classify the individual/family on a Likert scale categorization where the lowest socio-economic class is one engaged in semi-routine or routine occupations (such as labourer, caretaker, driver etc.) while the highest class is engaged in managerial and professional occupations (such as an accountant, solicitor, medical practitioner, bank manager etc.). Using both these pieces of information, this questionnaire classifies individuals into 3, 5 or 7 classes of socio-economic status. In our study, we used the 5-category classification.

2.5.9. Overall clinical classification method

Using all the information collected above (except the NS-SEC), participants in the study were classified into four groups: neurotypical participants, participants with autism (labelled Autism-only), participants with ADHD (labelled ADHD-only) and participants with co-morbid autism and ADHD (labelled Autism+ADHD).

Participants were included in the Autism-only group if they showed clinically significant symptoms on the ADOS-2 (ADOS-comparison score> 4), the DAWBA (meeting DSM-5 and ICD-10 criteria), and the SCQ (raw score>15). A consensus clinical review of all available information was applied to ensure clinical rigor (McEwen et al., 2016). Participants were categorized as being in the ADHD-only group if they showed clinically significant symptoms for the ADHD combined presentation on the CRS-3 (T

scores> 65), DAWBA (meeting DSM-5 and ICD-10 criteria) and a clinical consensus of all available information. For participants who came to the study without a pre-existing diagnosis of ADHD, they were included in the ADHD groups only if teacher information was also available and converged with parent information, to ensure that the symptoms were present across different settings. Participants were included in the Autism+ADHD group if participants met research classification criteria for both conditions as described above. Importantly, where participants with Autism also showed clinically significant symptoms of ADHD-Inattentive presentation, they were not classified as having comorbid Autism and ADHD, but rather, were classified as having only Autism, since inattention is a broad domain and many symptoms of autism can be interpreted as inattention by parents/teachers. This decision was taken and implemented under the advice of Dr Puja Kochhar. Participants were classified as being in the neurotypical group if they did not present with clinically significant symptoms on any of the clinical measures (i.e., SCQ< 15, CRS T scores < 65). Further, participants were excluded from the neurotypical group if the DAWBA measure indicated significantly elevated risk (i.e., >75% probability) of presence of any ICD-10 or DSM-5 diagnoses.

2.6. SAAND Study Sample Characteristics

As can be seen in Table 2.1, there were no between-group differences on age or gender. However, there were between-group differences in IQ, such that neurotypical participants showed significantly higher IQ than the comorbid Autism+ADHD participants. On clinical measures, the pattern of group differences reflected the group allocations. Neurotypical participants had low scores on SCQ and CRS, displaying low symptoms of autism and ADHD. Participants with autism (with or without ADHD) had high scores on the SCQ and participants with ADHD-only had significantly lower SCQ symptoms as compared to participants with comorbid Autism and ADHD. Participants with ADHD (with or without autism) had high scores on the CRS and participants with Autism-only had significantly lower scores on CRS, specifically, they had significantly lower inattention scores compared to participants with ADHD-only and significantly lower scores on Hyperactivity subscale compared to all participants with ADHD.

Table 2.1. SAAND Study sample characteristics

	Neurotypical (n=31)	**Autism Only (n=18)**	**ADHD Only (n=24)**	**Autism + ADHD (n=33)**	**Group Comparisons (p-value)**
Demographics					
Age	130.71 (29.41)	130.89 (25.06)	126.88 (26.99)	130.33 (18.14)	Ns (p^w>.1)
Gender M:F	18:13	11:7	16:8	25:8	Ns (p^w>.1)
WASI					
Full-scale IQ (FSIQ)	115.94 (13.2)	104.61 (15.64)	108.13 (11.65)	101.85 (19.03)	p^w= .005[a]
Verbal Comprehension Index (VCI)	115 (12.51)	103.39 (18.48)	110.52 (10.69)	101.44 (18.81)	p^w = .007[a]
Perceptual Reasoning Index (PRI)	113.94 (14.05)	105.78 (15.43)	103.91 (14.41)	101.03 (18.36)	p = .013[a]
SCQ					
Total	3.83 (3.65)	19.11 (5.98)	15.29 (6.83)	21.06 (6.16)	
SCQ Social	1.21 (1.5)	7.56 (3.35)	5.04 (3.25)	7.53 (3.51)	
SCQ Comm	1.86 (1.48)	5.61 (2.3)	4.54 (1.98)	6.34 (2.31)	
SCQ RRB	0.55 (1.12)	4.56 (2.2)	4.08 (2.47)	5.5 (1.93)	
CPRS					

Global Index	53.14 (14.99)	79.44 (12.59)	87.96 (4.18)	87.21 (5.26)
Inattention	50.31 (9.68)	77 (12.48)	86.92 (6.53)	84.91 (6.4)
Hyperactivity	51.97 (12.84)	76.44 (13.68)	87.92 (3.84)	87.45 (5.49)

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are number of male:female.

WASI: Wechsler Abbreviated Scale of Intelligence; CPRS: Conners Parent Rating Scale (values shown are mean T-scores); SCQ: Social Communication Questionnaire

p-values in the table refer to the significance value of the main ANOVA comparing the 4 groups on respective demographic characteristics. Multiple comparisons are Bonferroni-corrected. p^{w}: Where homogeneity of variances assumption is not met, p value from Welch's F is reported. For these, post-hoc comparisons are done using Games-Howell corrections instead of Bonferroni.

[a]NT>Autism+ADHD

2.7. Procedure

If parents expressed interest in taking part in the study, after reading through all the information sheets, they were sent the demographic information sheet, SCQ, CRS-3 and DAWBA to fill out alongside consent forms before they attended any sessions. If these measures revealed that participants met any exclusion criteria, this was communicated to them, and reports provided for the assessments filled out until that point. If no exclusion criteria were met, lab sessions were scheduled at their convenience. All participants attended either one full day session in the lab (over 6 hours) or two half-day sessions (lasting 3 hours each). In these sessions, parents filled out any questionnaires that had not yet been completed, i.e., Sensory Profile, NS-SEC. The children and adolescents took part in a battery of tasks that measured their attention and arousal using eye-tracking and EEG. Further, they completed the WASI and all clinical participants underwent the ADOS-2. Appropriate breaks were provided to the families, given the long duration of the sessions. For all participants who withdrew from their stimulant medication before the session, a letter to the GP was sent advising them of this and sharing that this occurred as part of the child's participation in a research study. After completing the tasks, participants were given a participation certificate, an inconvenience allowance and parents' travel expenses were reimbursed. After the lab session was complete, if parents provided consent, the participant's teacher was contacted and provided information about the study, and if they provided consent as well, they were sent the SCQ-Current and the CRS-3 Teacher version to fill out. Parents were provided a report of all assessments carried out, and for parents who requested it, a separate, more detailed ADOS assessment report and/or the ADOS video were provided.

2.8. Experimental Task Battery and Apparatus

Given our focus on attention and arousal processes, and the gaps highlighted in spontaneous allocation of attention to different types of information, we built a battery of tasks, all of which (except the POP task, Table 2.2) measured passive attention. Where possible, we incorporated naturalistic, dynamic, multimodal stimuli, to make them more ecologically valid. This is because static, simple stimuli can often fail to capture subtle differences in autistic individuals and more naturalistic real-world stimuli

can provide a more sensitive measure to test attention and arousal (Cuve et al., 2018). Further, originally, we were interested in recruiting children and adolescents with lower intellectual ability as well, and therefore, we designed tasks that did not impose any cognitive demands or require complex verbal or written instructions.

The tasks in the EEG and eye-tracking batteries are listed below. In this thesis, results from the heart rate data collected during the Resting State and Auditory Oddball task are discussed in Chapters 3, results from EEG data collected during the Auditory Oddball task are discussed in Chapter 4, and results from the eye-tracking data collected during the habituation task are discussed in Chapter 5.

2.8.1. EEG experimental apparatus and battery

The following software programs were used to deliver tasks during the EEG session or collect/analyse EEG data:

- PsychoPy 2.5 (Peirce, 2007, 2009): design and delivery of the EEG tasks
- Biosemi® Actiview - to record EEG signals
- Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011): to pre-process and analyse EEG signals

64-channel BioSemi® headcaps with an ABC layout were used and the EEG signal was recorded at 512 Hz. The signal was amplified using Biosemi® Active Two system and saved on a University computer hard drive. Four additional electrodes were placed around the participants' eyes (one electrode each above and below the left eye, and one electrode each next to the left and right eyes) to record horizontal and vertical eye movements. Two electrodes were placed on each wrist to record heart rate. A final two electrodes were placed on the earlobes for a reference for environmental electrical noise. When electrodes and cap were being placed, participants were given an I-pad on which they watched videos of their choosing on Youtube.

Table 2.2. SAAND Data Experimental Task Battery

Battery	**Approximate battery duration**	**Task**	**Approximate task duration**	**Cognitive processes being measured**
EEG	1 hour and 45 minutes	Resting State	3 min	Autonomic and cortical arousal during resting-state
		Auditory Oddball	20 min	Orienting of attention, discrimination and habituation to auditory stimuli
		Overcoming Pre-potency (POP) task	25 min	Sustained attention, preparation and inhibition of motor responses
Eye-tracking	45 minutes	Gap Overlap task	15 min	Exogenous and endogenous orienting of attention
		Habituation task	2 min	Habituation to repeating visual stimuli varying in complexity and social-ness
		Probabilistic free-viewing task	20 min	Relationship between tonic arousal and engagement of attention and learning with visual stimuli varying in predictability and social-ness

After EEG setup, participants were moved to the EEG recording room, where all the electrodes were plugged into the BioSemi ® system. Participants continued to watch videos of their choice while final checks were made to ensure the EEG signal was clean. The participants were seated around 60cm away from a 21.5" LCD screen with a 60Hz refresh rate. A parallel port was used to send digital triggers to the recording software. After the setup was complete, a silent movie (Despicable me) was presented on a laptop provided to the participants, placed in-between them and the LCD screen (with comfort of participants ensured). They were told to relax and watch the movie, and that the researchers will be in an adjacent room. The participants could press a button in order to attract the researchers' attention if needed. Participants were told that for a few minutes, they can watch the film, after which the researcher would return to switch some sounds on (for the auditory oddball task). EEG signal was recorded for around 3 minutes (Resting-State) after which the oddball task began. Oddball paradigm is a classic experimental paradigm with a well-established evidence base for ERPs derived from the task. In an oddball paradigm, a train of repeating stimuli (standards) are presented with occasional 'deviant' stimuli interspersed that differ from the standards in some characteristics. We used a passive version of the task, wherein, we were interested in automatic and subconscious processing of simple sensory stimuli, and whether orienting of attention to these stimuli differed for the clinical participants. During the auditory oddball task, speakers were used to deliver the stimuli. The participants were told before the task that we want them to just relax, watch the movie (silent movie without subtitles), some sounds would play in the background but they do not need to pay attention to them). I will describe the task in more detail, as well as the measures derived and predictions in respective chapters. Finally, after the oddball task, the POP task was conducted, which was an active task requiring motor responses. This latter task is not included in this thesis and so will not be described further.

In this thesis, I have investigated profiles of autonomic arousal at rest and in response to auditory stimuli (in autistic as compared to neurotypical individuals, individuals with ADHD or co-ocurring autism and ADHD) using HR data collected during the Resting State and Auditory Oddball task; the results from this investigation are discussed in Chapters 3. Further, I have investigated orienting of attention and

habituation to repeating auditory stimuli by measuring and analysing event-related potentials (P3) to repeating standards during the auditory oddball task; these results are presented in Chapter 4.

2.8.2. Eye-tracking Experimental Apparatus and Battery

The following software programs were used during the eye-tracking battery:

- Eyelink® Experiment Builder (SR Research)- for design and delivery of the eye-trackign tasks
- Eyelink® Data Viewer (SR Research)- for preprocessing and exportation of eye-tracking data
- BIOPAC for acquisition of heart rate data during the eye-tracking battery (this was done during the habituation task as well as the free-viewing probabilistic task) using photoplethysmography (data from this was not analysed for this thesis)

Participants were seated on a chair in front of a 21.5" LCD screen such that participants' eyes were approximately 60 cm away from the screen. An Eyelink 100-plus eye-tracker was placed just in front of the screen and using Eyelink® 1000 (SR Research), participants' eye movements were recorded during the presentation of the tasks. Before presentation of each task, a nine points-of-gaze calibration was conducted, using a colourful stimulus. During the gap-overlap and the habituation eye-tracking tasks, a chin-rest was not used (since we were not measuring pupil and therefore, decided to prioritize participants' comfort) and a 25 mm lens was used to record eye movements at 500 Hz, with an estimated accuracy of 0.25° to 0.5°. During the free viewing probabilistic task, a chin rest was used (since in this task, we were interested in pupillometry measures, which are more reliable when the head is stabilized) with a 35 mm lens. A dimmer switch was installed in the eye-tracking room that was used to control luminance and a photometer was used to verify the luminance in the room. The screen brightness was also kept constant across participants. During the Habituation task and free-viewing probabilistic task, a clip was attached the participants' finger or ear that recorded heart rate data (using BioPac).

All the tasks used in the eye-tracking paradigm involved asking participants to look at the screen at some videos. In the gap-overlap task, we investigated spontaneous exogenous orienting and reorienting, using static and dynamic, social and non-social stimuli (indexed through measuring saccades and fixations). In the habituation eye-tracking task, we investigated orienting of attention to repeating and changing information on the screen and also manipulated complexity and social-ness of the stimuli to investigate whether this affected distribution of attention to the stimuli (indexed using number of and duration of fixations). Finally, in the probabilistic free-viewing task, spatio-temporal sequences of events took place on the screen and the predictability of these events was manipulated. Again, social-ness of these stimuli was manipulated such that there were blocks of events which differed only in whether the stimuli were social or not. We investigated whether predictability and social-ness impacted distribution of attention, engagement and learning (as measured by eye movements) and arousal (as measured by pupillometry and heart rate) in the participants.

The gap-overlap task as well as the probabilistic free-viewing task are not included in this thesis and so will not be described further.

In Chapter 5, I present results from the Habituation task. I designed this task to investigate how social-ness and complexity of visual stimuli impact distribution of attention in autistic individuals, to repeating and changing stimuli. I conducted piloting work on this task at Summer Scientist Week (described in Section 2.9 below). The results from the piloting work are provided in Appendix F. In Chapter 5, I will describe in more detail this habituation eye-tracking task, the predictions and measures and the results from this task.

2.9. Summer Scientist Week Sample

While the SAAND study sample was the main sample recruited towards this PhD thesis, some data was also collected at Summer Scientist Week, an annual science engagement event organised by the University of Nottingham where 4-11 year old children take part in science-based activities and psychology experiments. At this event, in 2017, we carried out piloting work for the Gap Overlap and

Habituation Eye-tracking tasks. In the Year 2018, more data on the final SAAND study versions of the tasks was collected. Ethical approval for these studies was granted by the School of Psychology Ethics Committee, University of Nottingham. Participants received tokens upon completion of any experiment they chose to take part in at the event and they could use these tokens to spend on games and activities at the event. The participants' parents filled out a standard battery of questionnaires, data from which was available to all the researchers who conducted experiments at the event in an anonymised form. An ID code was assigned to each participant which could be used to associate the experimental data with the questionnaire data. The equipment used and eye-tracking procedure was the same as that described for Gap Overlap and Habituation experiments in earlier sections. However, it should be noted that unlike in the lab sessions, at Summer Scientist week, lighting was not as controlled and typically participants were in a room where several other experiments were going on. I designed the Habituation eye-tracking task to investigate my own hypotheses about attention in autism, and therefore, this is the task I focus on in this doctoral thesis. In the Summer Scientist Week data therefore, I refer to the habituation task from hereon.

2.9.1. Sample Characteristics

Year 1

In 2017, 67 participants were recruited in the study (see Table 2.3 for details). The following measures were collected:

<u>British Picture Vocabulary Scale, 3rd Edition (BPVS-3) (Dunn & Dunn, 2009)</u>

The BPVS-3 was used as a measure of verbal ability. Age-adjusted standard scores (with a mean of 100 and standard deviation of 15) were available. A computerised version of this assessment was conducted during SSW, wherein four pictures were shown to participants on a laptop screen and participants were asked to point to the picture of the word spoken by the examiner. Good reliability and validity of BPVS has been reported (Dunn & Dunn, 2009).

Social Aptitude Scale (SAS) (Liddle, Batty, & Goodman, 2009)

The SAS is a parent-reported measure of social ability which requires parents to rate ten items such as "Able to compromise and be flexible", "Easy to chat with" on a 5-point Likert scale. All the items of the SAS have been shown to load onto a single factor, demonstrating high internal coherence. Further, autistic individuals show lower SAS scores than those with autism, with a cut-off score of 16 (range of scores: 0-40) reported to have high sensitivity and specificity for autism (Liddle et al., 2009).

Table 2.3. Demographic characteristics of the SSW sample from 2017

Demographic	Sample
Sample Size	67
Mean Age (in months) (SD)	101.96 (21.33)
Gender (M:F)	35 M: 32 F
Mean BPVS (Standard Score) (SD)	103.7 (12.53)
Mean SAS (SD)	26.36 (4.86)

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are number of male:female. BPVS: British Picture Vocabulary Scale, 3rd Edition; SAS: Social Aptitude Scale

Year 2

In Year 2, 52 participants took part in the Habituation task (see Table 2.4 for demographic details). The following measures were collected:

BPVS3 (as above)

Autism-Spectrum Quotient- Child's Version (AQ-Child) (Auyeung, Baron-Cohen, Wheelwright, & Allison, 2008)

The AQ-Child is a parent-report questionnaire composed of 50 items, appropriate for use with children between 4-11 years of age. Items on the AQ-Child are designed to assess five areas associated with the broad autism phenotype: social skills, attention switching, attention to detail, communication items and

imagination. Responses are on a 4-point Likert scale, where parents are asked to what extent they agree or disagree with the statement about their child, with statements used such as "Finds making up stories easy" or "Notices patterns". It has high internal consistency (overall alpha= .097) and good test-retest reliability (r= 0.85). The AQ results in scores ranging from 0-150, and a cut-off score of 76 has been shown to have high specificity and sensitivity for autism.

Table 2.4. Demographic characteristics of the SSW sample from 2018

Demographic	Sample
Sample Size	52
Mean Age (in months) (SD)	103.596 (25.23)
Gender (M:F)	27 M: 25 F
Mean BPVS (Standard Score) (SD)	106.69 (11.07)
Mean AQ (SD)	58.73 (18.995)

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are number of male:female. BPVS: British Picture Vocabulary Scale, 3rd Edition; AQ: Autism Spectrum Quotient, Child's Version

Results from the piloting work in 2017 are presented in Appendix F and combined results from the SSW data for both 2017 and 2018 for the habituation eye-tracking task are presented in Chapter 5.

2.10. Overall Approach to Statistical Analysis

As described above, we collected rich datasets (in the SAAND study) comprising of clinical information, eye-tracking, heart rate and electrophysiological data. In order to analyse this data, primarily, this thesis has employed mixed-design repeated measures analyses of variance (RMANOVA) or multivariate analyses of variance (MANOVAs) where appropriate depending upon the number and type of dependent variables. Within these analyses, Autism and ADHD were modelled as binomial between-subject factors (Autism Present: Yes, No; ADHD Present: Yes, No). This allowed us to measure the effects of either condition. Interactions between the two factors or main effects of both factors were followed up using pairwise comparisons between the four groups (Autism-only, ADHD-only, Autism+ADHD and NT) to measure whether certain effects were present in only one of the four groups. Specific hypotheses for each analyses will be presented in the respective chapter before presenting each set of results.

2.10.1. Comment on assumption testing

Assumptions of the tests were evaluated before carrying out the tests. One of the assumptions of parametric tests is that the dependent variables are normally distributed. This was evaluated by investigating the distribution of the dependent variables as well as the distribution of the standardised residuals in the models. Where deviations from normality were due to presence of outliers, consideration was given as to whether the outliers should be removed from the analysis. A conservative approach was taken in such decisions, with consideration given to the sources of extreme values, and whether there were errors in data processing leading to the extreme values. Further, since in most cases repeated-measures were taken, a case was excluded only if their values were outliers in multiple measures. If a case was removed, the analysis was run with and without the case to investigate whether the effects of interest remained with or without the case in the model. Where deviations from normality were caused by skew or kurtosis, attempts were made to correct the skew. However, as F-tests are fairly robust to deviations of normality and unbalanced sample sizes, and due to limitations of non-parametric

tests (Blanca, Alarcón, Arnau, Bono, & Bendayan, 2017; Mena et al., 2017), if residuals were non-normal, we continued to use parametric ANOVAs. In such cases, it was decided that for effects of interest, follow-up pairwise comparisons would be run parametrically and non-parametrically to investigate the equivalence of the results and investigate the reliability of the analytic results.

2.10.2. Comment on use of covariates

A covariate is a continuous variable that influences the outcome variable, but while it has been measured in an experiment, it has not been randomized or controlled. Modelling a covariate in a linear model enables controlling for such variables that might affect the main outcome measures. Typically, in clinical studies like this one, demographic variables such as gender, age or IQ, are used as covariates. Our sample included children and adolescents from a broad age range (7-15 years) who belonged to both genders. However, the four groups (Autism-only, ADHD-only, Autism+ADHD, Neurotypical) were well-matched on age and gender and therefore, these variables were not included as covariates in statistical analyses. Importantly, our groups were not well-matched on IQ. As reported in the sample descriptions in Table 2.1, our clinical groups showed lower IQ than the neurotypical group, specifically, the comorbid Autism+ADHD group presented with significantly lower IQ than the neurotypical group. However, we did not include IQ as a covariate in the main statistical analyses that compared neurotypical with clinical groups. This is because these participants were not randomly allocated to groups and so any group differences on IQ are non-random and might represent a true difference between groups. Covarying for IQ in the ANOVAs and therefore partialling out IQ effects might spuriously increase or decrease group effects on other variables, in a design where it is not possible to separate out the interaction of the clinical condition from the covariate (in this case, IQ) and how those impact performance (Miller & Chapman, 2001). However, this does mean that effects of interest might be confounded by differences in IQ between groups and might be driven by IQ rather than autism or ADHD. In order to tackle this issue, the approach we took in this thesis is that where there were differences between groups, in association with autism or ADHD, bivariate correlations and partial correlations were used to identify whether these differences were driven by differences in IQ.

Finally, for variables that were randomized experimentally, I included such variables by modelling them as covariates in the analyses. For example, in experiments with different types of stimuli (e.g., social and non-social) that were presented in blocks, I modelled the order of presentation (since we randomized or controlled this factor) as a covariate.

2.10.3. Interpretation and follow-up of main effects and interactions

With the sample we achieved, we were underpowered particularly for Autism*ADHD interactions. Frequentist approaches often set the alpha threshold at $p<.05$. However, given that we were underpowered for effects of interest, we followed up significant effects $p<.1$, instead of $p<.05$. In order to give more context to the results and also in recognition of the limitations of the frequentist approach (Hubbard & Lindsay, 2008), we evaluated the observed effect sizes, and evaluated the reliability of those effects with regard to the power we had to observe effects of different sizes.

In frequentist approaches, significant main effects and interactions are typically followed up with post-hoc pairwise comparisons to identify which groups specifically are significantly different from one another on the outcome variable of interest. Traditionally, it is considered appropriate to correct the multiple comparisons by using a more conservative alpha to reduce the risk of false positive and false negative results (Field, 2013). However, where the main effect is significant with $p < .05$, it is generally appropriate not to do so where the effects are related to predicted hypotheses and it is considered that the initial significant p protects the follow-up comparisons. For effects with $p < .05$, we did not correct for post-hoc comparisons since those comparisons are protected by the initial significant main effect. Similarly, where a planned pairwise comparison was conducted, we did not correct for that comparison since we were investigating a specific planned hypothesis. However, where the main effect was $p < .1$, we corrected for post-hoc comparisons using the Benjamini-Hochberg (BH) method to protect against a Type 1 error. This method is based on the Bonferroni method but is slightly less conservative, thus

protecting against Type II errors, and also controls for the false discovery rate (FDR), i.e. the proportion of rejected hypotheses that might be false positives (Benjamini & Hochberg, 1995).

Chapter 3. Profiles of autonomic arousal at rest and autonomic responsivity to auditory stimuli in autism

3.1. Background

As discussed in Sections 1.3.2- 1.3.4, maintenance of optimal states of arousal is essential for appropriate adaptation to changes in environmental demands. Individual differences in autonomic arousal at rest and regulation of the autonomic response to salient changes in the environment are crucial for adaptive behaviour. The sympathetic and parasympathetic nervous systems act in opposing ways to support an organism's response to environmental demands. The SNS mobilizes the organism's response to salient events in the environment (such as sudden changes in sensory stimulation) eliciting acceleration in the HR, dilations in the pupil etc. (Wass et al., 2015a). These changes are transient and are accompanied by a shift in attention towards the eliciting stimulus (Nieuwenhuis et al, 2011). The parasympathetic system on the other hand is involved in processes of sustained attention during task-focused behaviour and PNS influences deceleration in the HR, constriction of the pupil etc. (Porges, 1992). Synergistic interactions between the SNS and PNS are important for optimal arousal at rest and in response to events. An imbalance in these systems would adversely impact engagement of attention and information processing and result in reduced flexibility to adapt appropriately to a given context.

As described earlier, theories in autism cite atypicalities in arousal as underlying development of autistic symptoms. For example, hyperarousal (specifically driven by reduced PNS activation) has been suggested to underlie hyper-reactivity to sensory stimuli, social avoidance behaviours as well as repetitive behaviours (Hutt et al., 1964; Porges, 2001). On the other hand, hypoarousal profiles have been suggested to account for reduced responsivity to sensory and social stimuli as well as sensory-seeking and repetitive behaviours in autism (DesLauriers & Carlson, 1969; Lovaas et al., 1987). In this chapter, I directly tested these theories by investigating profiles of autonomic arousal at rest and changes in autonomic arousal in response to auditory stimuli (or autonomic responsivity) in autistic individuals as compared to neurotypical individuals.

3.1.1. Experimental Context: Resting State and Auditory Oddball Task

HR data collected during the 3-minute resting state and the auditory oddball task was used to investigate these questions. First, participants underwent a 3-minute long resting-state measurement, wherein they were asked to relax while sitting and watching a silent movie. After the resting-state measurement, they participated in a passive auditory oddball task. In the SAAND study, the auditory oddball task was designed to investigate auditory orienting of attention, auditory discrimination and habituation to repeating auditory stimuli. An oddball paradigm is a well-established experimental paradigm with a strong scientific background that supports its use in studying sensory encoding, discrimination and orienting of attention (Duncan et al., 2009). In an oddball paradigm, a train of repeating 'standard' stimuli are presented, with an occasional 'deviant' stimulus interspersed in the train of standard stimuli. Since we were interested in spontaneous allocation of attention, we used a passive version of the task, wherein participants watched a silent movie during the task while standard and deviant stimuli were presented in the background. Before presenting the auditory stimuli, 30-second long baseline periods were used (wherein participants continued to watch the silent movie) to record autonomic arousal at baseline and examine changes from baseline to task (see Figure 3.1 for a visual representation). Finally, we used two types of conditions in this task. Both conditions used a frequently occurring simple tone alongside an infrequent tone that in one condition was another simple non-social tone, while in the other condition was a more complex and salient social tone. Within the context of our study, participants first experienced a resting state wherein they watched a silent film, after which they experienced auditory stimuli (the standard and deviant tones) presented in the background during the task but not at rest. Therefore, the only change between resting-state and task was that auditory stimuli played in the background. Participants were asked not to pay attention to the sounds and to continue to watch the film and relax. Therefore, no demand on attention was placed on participants. The HR and HRV data collected during the resting-state and auditory oddball task were used to investigate four research questions.

3.1.2. Do autistic individuals differ from non-autistic individuals in autonomic arousal profiles at rest?

First, I investigated profiles of tonic arousal (during a 3-min resting baseline). We chose to use HR and HRV to index autonomic arousal, since, as discussed in Section 1.3.5.1, HRV allows us to index variability in the SNS and PNS separately, thus allowing us to specify where any atypicalities lie. As discussed earlier, evidence on tonic arousal in autistic individuals is inconsistent. However, where atypicalities have been reported, specifically using heart rate variability, this has been in the direction of hyperarousal (driven by reduced parasympathetic system activity). Previous literature, however, has been lacking in characterising co-occurring symptoms of ADHD in autistic individuals and controlling for these symptoms by using a control group of individuals with ADHD (without autism). Co-occurring ADHD might influence the arousal profile in autism (given that ADHD is associated with sympathetic underarousal), potentially being a source of uncontrolled noise leading to null effects. Therefore, in this study, we investigated tonic HR and HRV during the 3-minute resting-state measurement (when participants were watching a silent movie) by directly comparing Autism-only, ADHD-only and the comorbid Autism+ADHD groups with neurotypical individuals. Based on prior evidence, we predicted that as compared to neurotypical individuals, autistic individuals would exhibit profiles of tonic hyperarousal.

3.1.3. Do autistic participants show atypicalities in autonomic responsivity to auditory stimuli?

Secondly, we investigated profiles of autonomic response to auditory stimuli (during the auditory oddball task), as indexed by HR and HRV. Given evidence of sensory modulation difficulties in autism, theories of arousal in autism suggest that atypicalities in arousal regulation might underlie differences in sensory responsivity (Rogers & Ozonoff, 2005). Literature in autism on autonomic responsivity to auditory stimuli specifically is heterogeneous, with some studies finding evidence of hyper-reactivity (James & Barry, 1984; Kuiper et al., 2019; Palkovitz & Wiesenfeld, 1980), and others reporting hypo-reactivity (Stevens & Gruzelier, 1984; van Engeland, 1984). Importantly, two studies manipulated the

type of auditory stimuli being presented and investigated autonomic responsivity to these. Both studies used a simple auditory tone and the sound of a siren in their respective studies. Chang et al. (2012) reported tonic hyperarousal (using skin conductance) before the auditory stimuli were presented, and autonomic hyper-reactivity to simple tones but not to sirens in autistic individuals (they highlighted that their participants might have been familiar with sounds of siren, since they lived in urban areas, and this might underlie the effect observed). On the other hand, Kuiper et al. (2019) reported tonic hyperarousal (using HR) but no group differences in adaptation of the autonomic response (using number of trials until no SCR was observed in response to a tone) to either the tone or the siren. Atypicalities in arousal in response to sensory stimuli have been associated with sensory over-responsivity, social avoidance and RRBs in autism (Lydon et al., 2016). However, the links between these are unclear and evidence is not robust. Therefore, I used HR and HRV to investigate autonomic responsivity to simple auditory stimuli (presented during the auditory oddball task) in autistic compared to neurotypical individuals, individuals with ADHD and with comorbid Autism+ADHD. In the auditory oddball task, as mentioned earlier, participants were not asked to pay attention to the sounds being presented in the background. In such a context where sustained or focused attention is not required but salient sensory stimuli are present in the environment, we predicted that neurotypical participants would demonstrate an initial sympathetic response to the auditory stimuli, but that they would not exhibit parasympathetic activation since no demands have been placed on attention or response preparation. If autistic individuals present a profile of tonic hyperarousal, we predicted that they would subsequently demonstrate hyper-reactivity to auditory stimuli, indexed as higher HR and higher sympathetic and lower parasympathetic activation from baseline as compared to neurotypical individuals.

3.1.4. Do autistic individuals exhibit atypicalities in the adaptation of the autonomic response over time as compared to neurotypical individuals?

When salient sensory stimuli are present in the environment, the typical response is an initial sympathetic activation, which, with repeated exposure to the same stimulus and in absence of any demands on sustained attention to the repeating stimulus, decreases over time due to habituation to the

stimulus. This adaptation of the autonomic response is essential for optimal distribution of attention and flexible adaptation to dynamically changing environments, where novel and/or task-relevant stimuli may present themselves at any moment. Atypicalities in tonic arousal (hyper- or hypo-arousal) and/or atypical initial responses to new stimuli may adversely impact adaptation of the autonomic response to a given environmental context. Reduced autonomic adaptation would subsequently impact engagement of attention and learning and therefore is important to investigate, if it is atypical in autistic individuals. There is some evidence for slower adaptation of the autonomic response to a given environmental context in autistic individuals, specifically associated with the hyperarousal profile (Mathewson et al., 2011; Neuhaus et al., 2014; Neuhaus et al., 2015; Schoen et al., 2008). In comparison, some studies have also found no differences in adaptation of autonomic arousal to an environmental context between autistic and neurotypical individuals (Chang et al., 2012; Kuiper et al., 2019; Lory et al., 2020; McCormick et al., 2014; van Engeland, 1984). The heterogeneity in findings is likely influenced by differences in study methodologies and may also reflect a lack of control of co-occurring symptoms. Controlling for co-occurring symptoms of ADHD may reveal autism-specific atypicalities in adaptation of the autonomic response, if present. Therefore, we investigated adaptation of the autonomic response over time to repeating auditory stimuli, using HR and HRV and compared this response in autistic, ADHD and comorbid Autism+ADHD participants and neurotypical individuals. We predicted that neurotypical participants would exhibit an initial increase in autonomic arousal (driven by sympathetic activation) to support orienting to and processing of the auditory stimuli, and that arousal would then reduce over time as habituation to repeating stimuli occurs and this would manifest in an adaptation (decrease) in autonomic arousal (seen in slowing down of HR and reduced sympathetic activation over time). We thus analysed changes in autonomic arousal in response to auditory stimuli temporally, to analyse adaptation of the autonomic response. We predicted that if autistic individuals show a profile of hyperarousal and hyper-reactivity to auditory stimuli, this would also be associated with slower/reduced autonomic adaptation (as compared to neurotypical participants).

3.1.5. Does type of stimulus (social or non-social) influence the autonomic response differently in autistic individuals as compared to neurotypical individuals?

Salience of stimuli has been shown to impact the autonomic response, such that more salient stimuli, such as social as compared to non-social stimuli, typically elicit a larger autonomic response (Fitzgerald, 1968; Louwerse et al., 2014). This is reflective of integrated input between the LC and higher order brain systems which induce changes in physiological arousal to alert one to salient information and process it more efficiently (Gilzenrat et al., 2010). Here, we predicted therefore, that autonomic responsivity will be higher in the block with social deviants than the non-social deviants and we predicted that autistic individuals will not show this sensitivity to differential (social) salience, given literature indicating that autistic individuals do not show the higher preference for social information as neurotypical individuals do, (e.g., Chita-Tegmark, 2016).

In summary, in this chapter, I investigated 1) HR and HRV during resting-state measurement, 2) initial autonomic responsivity to the auditory stimuli (as compared to a baseline 30-second period before the sounds were played), 3) adaptation of the autonomic response (by modelling the arousal response temporally) and 4) autonomic response to social as compared to non-social conditions of the auditory oddball task in individuals who were neurotypical as compared to those who had clinical significant symptoms of autism and/or ADHD. We predicted that during the 3-min resting period, autistic participants (without ADHD) in the SAAND study would show hyperarousal (indexed specifically by reduced parasympathetic HRV). Further, we predicted that during the auditory oddball task, they will show hyper-reactivity to the auditory stimuli (higher sympathetic and lower parasympathetic activation as compared to neurotypical individuals) and that this autonomic response will reduce more slowly than in neurotypical individuals who will show quicker adaptation to the presence of auditory stimuli, reflecting rapid habituation. In comparison, we predicted that individuals with ADHD (without autism) will show profiles of hypoarousal (as indexed by reduced sympathetic and increased parasympathetic HRV) at rest and hypo-responsivity to auditory stimuli but that they will not show differences from the neurotypical group in adaptation of the autonomic response (in absence of any literature directly

investigating adaptation of the autonomic response in ADHD). Further, given evidence that autistic individuals do not show sensitivity to differences in salience and social-ness in the way that neurotypical individuals do (Chita-Tegmark, 2016), we predicted an effect in neurotypical individuals of higher responsivity in the social block, which will be reduced in autistic individuals. Given the lack of literature on profiles of arousal in individuals comorbid for autism and ADHD, it is difficult to predict what profile they might show. Given potentially opposing risks of hyper-arousal in autism and hypoarousal in ADHD, it is possible that these opposing risks combat each other and those who are comorbid for autism and ADHD might show neither, showing typical profiles of arousal. Alternatively, it is possible that comorbid participants would appear similar to one of the groups- autism or ADHD. Finally, it is also possible that the comorbid group might show a completely separate profile from the autistic or ADHD children, appearing to be a separate nosologic entity with regard to their arousal profiles (Rommelse, Geurts, Franke, Buitelaar, & Hartman, 2011). I modelled autism and ADHD as between-subjects' factors to assess the main effect of each and the possible interaction between them, to determine which of these theoretical models is supported by the data.

3.2. Methods

3.2.1. Participants

92 of the 106 participants included in the SAAND study took part in the auditory oddball task. However, of these, five cases were excluded due to missing data, resulting in 87 participants with HR data on the oddball task. Importantly, the initial 3-min resting baseline was not carried out with the first few participants in the study, and therefore, this data is available for 79 of the 87 participants. Sample characteristics can be found in Section 3.3.

3.2.2. Task Design

The design of the auditory oddball task was informed by guidelines produced by Duncan et al. (2009), who described characteristics of stimuli (such as volume, frequency, duration, inter-stimulus interval) which impact the ERPs elicited by the task. In our task, artificially created stimuli were used in order

to control for these factors. We created two conditions of the task, one in which the deviant was a social stimulus and one in which the deviant was non-social, in order to investigate whether lower-level attention processes (of arousal and attention) were impacted by salience of the stimuli. We were interested in whether a social deviant as compared to a non-social deviant would impact arousal differently in autistic individuals or not. Further, we were interested in whether orienting to the deviant would be different when the deviant was social as compared to non-social.

The standard stimuli used in both conditions were identical, and these were simple 500 Hz sinusoidal tones (created using an open-source and free software Audacity® version 2.2.2; https://www.audacityteam.org). The non-social deviant tones differed from the standards only in frequency; they were 450 hz sinusoidal tones and was created using this same software Audacity®. The social deviant was a natural-sounding vowel, which resembled the sound of the English vowel /e/, and it was created using the following formant frequencies: F0 150, F1 530, F2 1840, F3 2480 (Peterson & Barney, 1952). This tone was created using the online Simplified Vowel Synthesis Interface (Timothy Bunnell, http://www.asel.udel.edu/speech/tutorials/synthesis/vowels.html).

Each tone lasted 200 msec, and the inter-stimulus interval was 700 msec. We used a deviant : standard ratio of 80% : 20%, such that each block contained 640 standard tones and 160 deviants. At least two standard tones were presented before the presentation of a deviant and the order of presentation of the social and non-social conditions was randomised across participants. Each condition lasted 12 minutes. Two 30-second long intervals that were without sounds were used (as a baseline) before the beginning of each block and the entire task lasted around 26 minutes (see Figure 3.1 for a visual representation of the task).

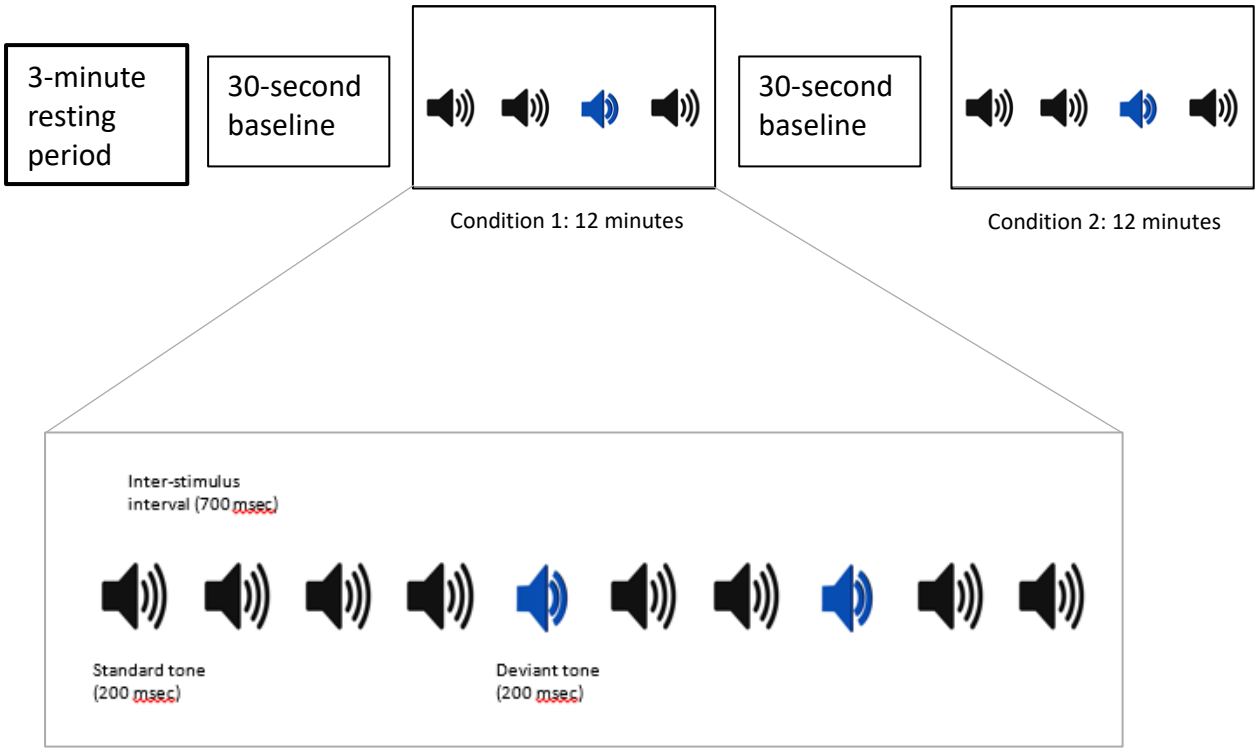


Figure 3.1. Visual representation of the auditory oddball task design.

A 3-minute resting-state measurement was carried out before the auditory oddball task. During the task, a 30-second baseline period preceded each Condition (Social, Non-Social) of the auditory oddball task. The standard tone in each condition was a non-social simple tone. In the non-social condition, the deviant stimulus was another non-social simple tone at a different frequency. In the social condition, the deviant was a social tone. The order of presentation of social and non-social conditions was randomised across participants.

3.2.3. Processing of ECG data

The raw heart rate data was recorded from two free electrodes placed on participants' wrists. The raw heart rate signal was band-pass filtered using a high-pass filter (0.5 Hz) to remove baseline fluctuations from the data and a notch filter (50 Hz) to remove sources of electrical noise. The entire dataset was resampled to 512 Hz. The raw traces from the HR electrodes were exported to Matlab in 3-minute segments. These consisted of the resting-state period (3 minutes), the two conditions of auditory stimuli exposure (12 minutes per condition, divided into four 3-min successive task blocks) and a 30-second

baseline period before each condition. In one condition, the deviants were social while in the other, they were non-social. In-house scripts were used to pre-process the signal as well as to extract the variables of interest. Using these scripts, ectopic beats were detected and noisy periods removed from the data. Manual insertion of missing beats was not carried out since this is a subjective process which can be prone to error. A record was kept that detailed how much of the signal was deleted for each participant. This ranged from 0 to 7% and thus was quite low; there were no group differences on amount of signal deleted. Thereafter, consecutive RR-intervals were extracted (i.e. time difference between consecutive heartbeats in msec). Using the RR intervals, the following indices were calculated:

- HR: Number of heartbeats per minute
- Cardiac Sympathetic Index (CSI) and Cardiac Vagal Index (CVI) (Toichi, Sugiura, Murai, & Sengoku, 1997): CSI and CVI were used to index HRV. CSI and CVI are indices of activity of the sympathetic and parasympathetic branches of the ANS respectively. These are extracted using a Poincare plot, a plot of each inter-beat interval (I_k) against its successive interval (I_{k+1}). The resulting plot is a two-dimensional ellipsoid-shaped cloud (see Figure 3.2. for a graphical representation). From this graph, two parameters can be extracted. SD1 refers to the width of the ellipse (which is the length of the transverse axis, vertical to the line $I_k = I_{k+1}$) and reflects short-term HRV. SD1 is correlated with measures of parasympathetic nervous system such as RMSSD and HF power (Shaffer & Ginsberg, 2017). SD2 represents the length of the ellipse (which is a line parallel to the line $I_k = I_{k+1}$) and reflects both short and long-term HRV and has been found to correlate with LF power (Shaffer & Ginsberg, 2017). SD1 and SD2 are calculated using the following formulas:

$$SD1 = SD(\frac{1}{\sqrt{2}} I_{(k)} - \frac{1}{\sqrt{2}} I_{(k+1)})$$

$$SD2 = SD(\frac{1}{\sqrt{2}} I_{(k)} + \frac{1}{\sqrt{2}} I_{(k+1)})$$

with $k = 1, 2, 3, \ldots, (n - 1)$; and n = number of cardiac beats within the period.

SD = standard deviation of the sample

The transverse length (T) and longitudinal length (L) of the ellipse is then obtained by multiplying SD1 and SD2 by 4. Finally, CSI and CVI are calculated as follows:

$$\text{CSI} = \frac{L}{T}$$

$$\text{CVI} = \log_{10}(L \times T)$$

with T = 4 x SD1 and L = 4 x SD2

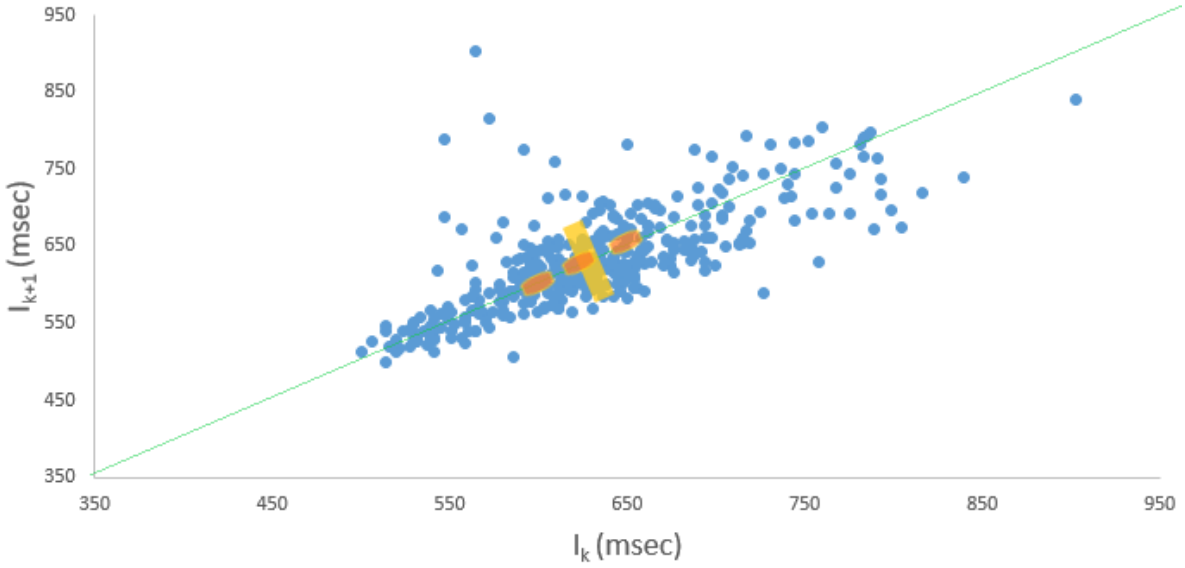


Figure 3.2. A Poincare plot made with heart data of a participant in SAAND study. Green line: Identity line. Yellow line: SD1, Orange dashes: SD2

Toichi et al. (1997) compared the effects of propanolol and atropine on CSI and CVI to validate them as indices of sympathetic and parasympathetic influences respectively. Atropine influenced CVI under various experimental conditions (sitting, standing, supine at rest and supine doing arithmetic), reducing it significantly, in healthy participants, while propranolol did not influence CVI under any experimental conditions. On the other hand, propranolol (and not atropine) significantly influenced CSI under 3 of the 4 experimental conditions (sitting, standing, supine while doing arithmetic but not

supine at rest). This supports our interpretation of CSI and CVI as measures of HRV in sympathetic and parasympathetic nervous systems, respectively.

3.2.4. Analysis Plan

3-min Resting-State: To investigate the effects of Autism and ADHD on HR and HRV during the 3-min resting-state before the auditory oddball task, a univariate ANOVA (with HR as the dependent variable) and a multivariate ANOVA (with CSI and CVI as dependent variables) were conducted with Autism and ADHD as between subject factors with two levels each (Present, Absent).

Auditory Oddball Task: To investigate the effects of Autism and ADHD on HR and HRV in the 30-second baseline periods compared with task conditions, a Condition (2 levels: Social, Non-Social) and Block (5 levels: 30-second baseline followed by 4 consecutive 3-min successive task blocks) repeated-measures ANOVA (for HR) and repeated-measures MANOVA (for CSI, CVI) were used to assess autonomic responsivity over successive task blocks to the auditory stimuli.

Half the participants were randomly presented with the Social condition first, and the other half were presented with the Non-Social condition first. Since this was a randomised factor that was experimentally controlled, before carrying out the analysis with the clinical factors, the effect of Order of presentation of the different conditions (Social or Non-Social condition presented first) was evaluated, and if any effects were found, this was used as a control variable when analysing influence of clinical factors.

We did not control for Gender or Age since the groups were not statistically significantly different on these factors. For any clinical effects of interest, relationships with IQ, symptom severity and sensory processing were assessed, firstly to investigate the influence IQ and then, secondly, to understand relationship with clinical and behavioural features.

3.3. Results

Table 3.1. Sample Characteristics of participants who completed the Auditory Oddball Task

	Neurotypical (n=24)	Autism (n=17)	ADHD (n=20)	Autism + ADHD (n=26)	Group Comparisons (p-value)
Demographics					
Age	134.54 (6.08)	129.47 (25.07)	130.8 (26.29)	131.92 (19.13)	Ns (p^w>.1)
Gender M:F	14:10	11:6	14:6	22:4	Ns (p^w>.1)
WASI					
Full-scale IQ (FSIQ)	118.29 (12.05)	105.29 (15.84)	109.15 (10.49)	104.81 (20.14)	p^w= .007[a]
Verbal Comprehension Index (VCI)	116.25 (12.26)	104.18 (18.74)	110.68 (10.47)	105.08 (19.24)	p^w = .045[b]
Perceptual Reasoning Index (PRI)	116.42 (12.73)	106.35 (15.7)	105.74 (12.84)	102.52 (20.1)	p = .013[c]
SCQ					
Total	4.25 (3.87)	18.94 (6.12)	14.8 (7.28)	20.92 (6.64)	p^w<.001[d,e]
SCQ Social Interaction	1.33 (1.58)	7.59 (3.45)	5.05 (3.52)	7.2 (3.71)	p^w<.001[d]
SCQ Communication	2 (1.59)	5.65 (2.37)	4.5 (2.06)	6.36 (2.45)	p<.001[d,e]
SCQ RRB	0.67 (1.2)	4.35 (2.09)	3.7 (2.43)	5.52 (1.87)	p^w<.001[d,e]
CPRS					

Global Index	54.46 (14.09)	78.82 (12.69)	87.65 (4.51)	86.81 (5.64)	$p^w<.001^{d,f}$
Inattention	51.33 (9.11)	76.41 (12.6)	86.8 (7.08)	84.19 (6.73)	$p^w<.001^{d,f}$
Hyperactivity	52.54 (12.71)	75.82 (13.84)	87.65 (4.13)	86.96 (6.04)	$p^w<.001^{d,g}$

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are number of male:female.

WASI: Wechsler Abbreviated Scale of Intelligence; CPRS: Conners Parent Rating Scale (values shown are mean T-scores); SCQ: Social Communication Questionnaire

p-values in the table refer to the significance value of the main ANOVA comparing the 4 groups on respective demographic characteristics. Multiple comparisons are Bonferroni-corrected. p^w: Where homogeneity of variances assumption is not met, p value from Welch's F is reported. For these, post-hoc comparisons are done using Games-Howell corrections instead of Bonferroni.

[a]NT>Autism, ADHD, Autism+ADHD, [b]NT>Autism+ADHD (marginal), [c]NT>ADHD, Autism+ADHD, [d]NT<Autism, ADHD, Autism+ADHD; [e]ADHD< Autism+ADHD; [f]Autism<ADHD, Autism+ADHD; [g]Autism< ADHD, Autism+ADHD

3.3.1. Results from Resting Baseline (3 min)

A univariate ANOVA on HR during the resting period was carried out, to evaluate whether Autism or ADHD were associated with differences in HR. HR was normally distributed and residuals from this model were also normally distributed. There were no significant outliers for HR.

There was a significant main effect of Autism ($F(1, 75) = 4.38$, $p = .04$, $\eta^2_p = .06$) and a significant main effect of ADHD ($F(1, 75) = 6.68$, $p = .012$, $\eta^2_p = .08$). Since we found main effects of both Autism and ADHD, we conducted post-hoc pairwise comparisons between the four groups (Autism-only, ADHD-only, comorbid Autism+ADHD, Neurotypical). These comparisons revealed that the participants with ADHD-only showed significantly reduced HR as compared to neurotypical (mean difference ± S.E. = 7.4 ± 3.49, $p = .038$) and Autism-only (mean difference ± S.E. = 11.66 ± 3.81, $p = .003$) participants; ADHD-only participants showed marginally lower HR than Autism+ADHD participants (mean difference ± S.E. = 6.17 ± 3.49, $p = .08$) (see Figure 3.3).

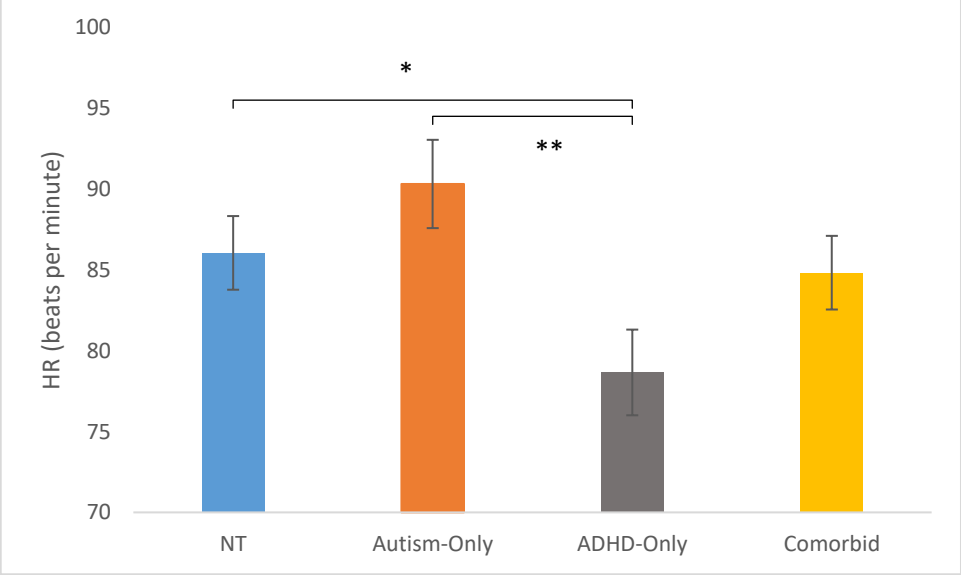


Figure 3.3. Group differences on HR during resting-state

Bars show the mean (±1 standard error) heart rate in beats per minute (plotted on the y-axis). These data are split by Group (Neurotypical, Autism-only, ADHD-only, comorbid Autism+ADHD). Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

A MANOVA on resting CSI and CVI was then carried out. Box's test of equality of covariance matrices was significant (F (9, 42752.88) = 2.44, p=.009). However, given the sample sizes in the different groups were similar (No Autism= 40, Autism= 39; No ADHD= 39, ADHD= 40), I used Pillai's statistics which are considered to be robust to violations of this assumption (Field, 2013, p. 643). While the standardised residuals for resting CVI were normally distributed, those for resting CSI were positively skewed. This skew was not due to presence of outliers. Given that ANOVAs are fairly robust to deviations from normality (Mena et al., 2017), we proceeded with a parametric ANOVA but considered effects on CSI with caution.

No effects of Autism on resting CSI or CVI were found: V= .02, F (2, 74) = .82, p = .445, η^2_p = .02. There was a significant multivariate effect of ADHD: V= .09, F (2, 74) = 3.58, p = .033, η^2_p = .09. The follow-up univariate ANOVA was not significant for CVI (F (1, 75) = .81, p = .37, η^2_p = .01) but was significant for CSI (F (1, 75) = 7.14, p = .009, η^2_p = .09) such that those who had ADHD demonstrated lower CSI (Mean ± S.E. = 1.9 ± .14) as compared to those who did not have ADHD (Mean ± S.E. = 2.44 ± .14) (see Fig. 3.4). Given that resting CSI was skewed, we also compared those with and without ADHD on baseline CSI using a non-parametric Mann Whitney U-test and found that it was consistent with the effect of the parametric statistical test (U (n_{ADHD} = 40, n_{NoADHD} = 39) = 529.00, z = -2.46, p = .014) suggesting that it was not biased by non-normality.

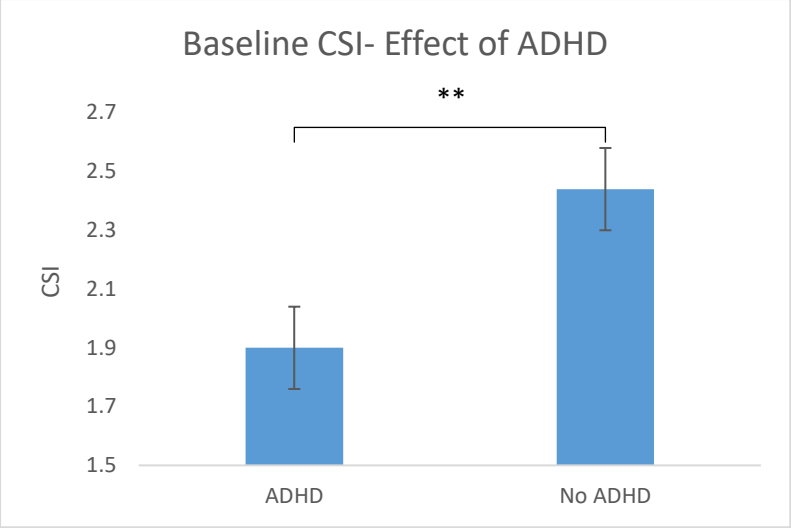


Figure 3.4 Effect of presence of ADHD on baseline CSI.

Bars show the mean (±1 standard error) Cardiac Sympathetic Index (plotted on the y-axis). These data are split by ADHD (Present, Absent). Asterisks denote statistical significance: *p < .05, **p < .01, ***p < .001

Table 3.2. Autonomic arousal during Resting-State by Clinical Group

	Neurotypical (n = 23)	**Autism-Only (n = 16)**	**ADHD-Only (n = 17)**	**Comorbid Autism+ADHD (n = 23)**
Resting State HR	86.05 (9.9)	90.31 (8.67)	78.66 (11.45)	84.83 (12.74)
Resting State CSI	2.36 (0.98)	2.52 (1.14)	1.89 (0.75)	1.92 (0.62)
Resting State CVI	4.57 (0.46)	4.39 (0.42)	4.61 (0.37)	4.53 (.51)

Data shown for all measures are mean with standard deviation in parentheses.

HR: Heart Rate; CSI: Cardiac Sympathetic Index; CVI: Cardiac Vagal Index

3.3.2. Results from Auditory Oddball task

a. Autonomic Responsivity to task indexed by HR

We ran a repeated measures ANOVA on HR with two within-subject variables: Condition (2-levels: Social, Non-Social), and Block (5-levels- the first 30 second baseline and 4 subsequent auditory exposure 3-min periods). We first considered whether Order of Presentation (a between-subjects factor indicating whether Social or Non-Social condition was presented first to the participant) influenced HR. We found that at each level of Order (Social or Non-Social condition presented first), the condition presented second elicited higher HR than the first condition, regardless of whether it was the social or the non-social condition. Arousal therefore appeared to increase with time for the participants during this task irrespective of which condition came first. These results are described more fully in Appendix D.

Next, we carried out a repeated-measures ANOVA on heart rate including two fixed factors: Autism and ADHD, each with two levels (Yes/No). We did not control for Order of presentation (Social or Non-Social condition presented first) since groups presented with social or non-social condition first did not differ from one another in the pattern of their autonomic response (as described above and detailed in Appendix D). Standardised residuals from this model were normally distributed.

There was a significant main effect of Block on HR: Greenhouse-Geisser $F(3.55, 294.64) = 26.05$, $p < .001$, $\eta^2_p = .24$. This main effect was significant at the linear ($F(1, 83) = 54.19$, $p < .001$, $\eta^2_p = .4$), cubic ($F(1, 83) = 33.77$, $p < .001$, $\eta^2_p = .29$) and Order 4 ($F(1, 83) = 6.41$, $p = .013$, $\eta^2_p = .07$) levels. Pairwise comparisons revealed significant changes at each time-point from the previous and next time-points, with an overall indication that from the baseline, there was an initial decrease at Exposure 1, and then an increase until Exposure 3 when it stabilized, there is no significant difference in HR between Exposures 3 and 4 (see Fig. 3.5).

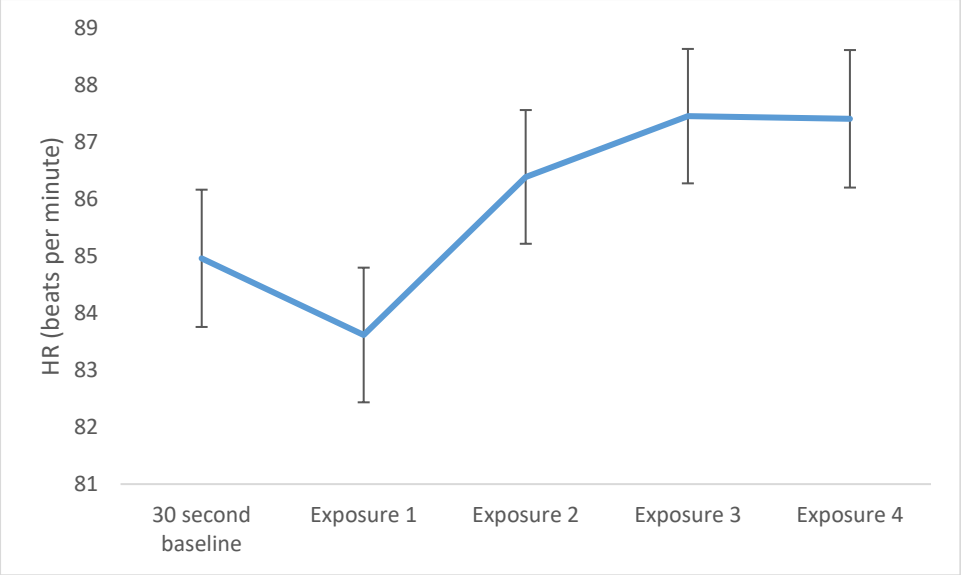


Figure 3.5. Change in HR over successive task blocks during Auditory Oddball Task

Bars show the mean (±1 standard error) average heart rate in beats per minute (plotted on the y-axis). These data are split by Block (initial 30-second baseline and 4 consecutive 3-min exposure blocks during which auditory stimuli were presented).

We evaluated whether Autism or ADHD impacted arousal during the baseline and in response to different conditions (Social, Non-Social). There was a main effect of Autism ($F (1, 80) = 4.61$, $p = .035$, $\eta^2_p = .05$). There was also a main effect of ADHD ($F (1, 80) = 4.99$, $p = .028$, $\eta^2_p = .06$). Given main effects of both Autism and ADHD, we followed these up with pairwise comparisons between the four groups (Autism-only, ADHD-only, comorbid Autism+ADHD, NT). These revealed that the ADHD-only group exhibited significantly lower HR than the Autism-only group (mean difference ± S.E. = 9.86 ± 3.37, $p = .004$), and marginally lower HR than the neurotypical (mean difference ± S.E. = 5.92 ± 3.12, $p = .06$) and the Autism+ADHD (mean difference ± S.E. = 5.71 ± 3.09, $p = .068$) groups (see Fig. 3.6).

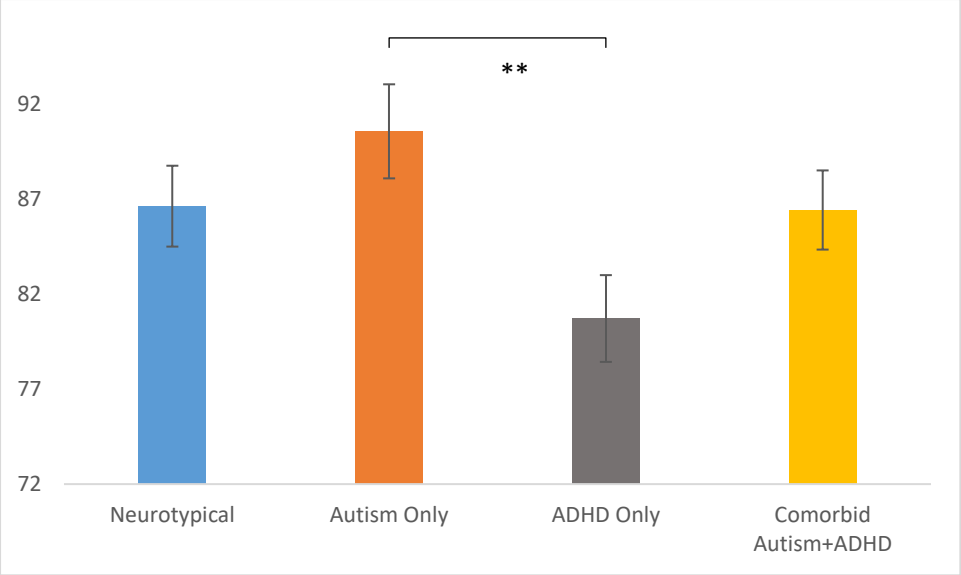


Figure 3.6. Effect of Autism on HR during auditory oddball task

Bars show the mean (±1 standard error) average heart rate in beats per minute (plotted on the y-axis). These data are split by Autism (Present, Absent). Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

The between-subjects factor of Autism did not interact with Condition ($F(1, 80) = .39$, $p = .54$, $\eta^2_p = .01$) or Block (Greenhouse-Geisser $F(3.51, 280.68) = .59$, $p = .65$, $\eta^2_p = .01$). Similarly, the between-subjects factor of ADHD did not interact with Condition ($F(1, 80) = .37$, $p = .54$, $\eta^2_p = .01$) or Block (Greenhouse-Geisser $F(3.51, 280.68) = 1.27$, $p = .28$, $\eta^2_p = .02$).

In summary, HR changed significantly during successive task blocks, with a slowing down of HR in the initial 3 minutes when the auditory stimuli began, and a subsequent increase in HR as the successive task blocks continued. ADHD was related with lower HR during the task, but no between-group differences were observed in autonomic adaptation to auditory stimuli between baseline and successive task blocks in relation to either Autism or ADHD.

b. Autonomic Responsivity to task indexed by CSI and CVI

We ran a MANOVA with 2 within-subject variables: Condition (2-levels: Social, Non-Social), and Block (five levels: the first 30-second baseline and four subsequent auditory exposure 3-min periods); with both CSI and CVI as the dependent variables. We first considered whether Order of presentation (Social or Non-Social condition presented first) had an effect. Similarly to HR, we found that at each level of Order (Social or Non-Social condition presented first), the condition presented second (regardless of whether it was Social or Non-Social) elicited higher CSI than the condition presented first. Arousal therefore appeared to increase with time for the participants during this task irrespective of which condition came first. These results are described more fully in Appendix D.

Therefore, we carried out an analysis of how Autism and ADHD impacted CSI and CVI over successive task blocks by including these as between-subject factors but did not control for Order of Presentation in the analysis. Some of the CSI variables were observed to have a significant positive skew upon inspection of the standardised residuals. Therefore, between-group effects on CSI were corroborated with non-parametric tests, if found.

There was no significant multivariate effect of Autism ($V = .04$, $F(2, 82) = 1.61$, $p = .21$, $\eta^2_p = .04$). There was a significant main effect of ADHD ($V = .08$, $F(2, 82) = 3.51$, $p = .035$, $\eta^2_p = .08$); which was significant for both CVI ($F(1, 83) = 5.25$, $p = .025$, $\eta^2_p = .06$) and CSI ($F(1, 83) = 6.72$, $p = .011$, $\eta^2_p = .08$). Participants with ADHD showed significantly higher CVI (Mean difference ± S.E.= .20 ± .09) and significantly lower CSI (Mean difference ± S.E.= .32 ± .12) as compared to participants without ADHD (see Fig. 3.7). Given deviations from normality on CSI, we averaged CSI during the task and compared those with and without ADHD using a non-parametric Mann Whitney U-test and found the same effect: $U(n_{ADHD} = 46, n_{noADHD} = 41) = 664$, $z = -2.37$, $p = .018$.

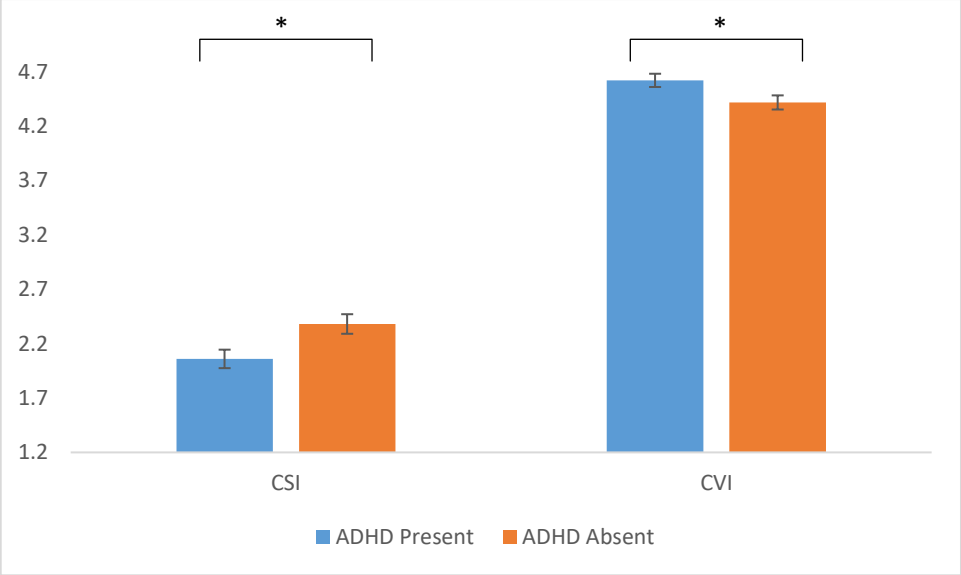


Figure 3.7. Effect of ADHD on CVI during auditory oddball task

Bars show the mean (±1 standard error) average CVI and CSI (plotted on the y-axis). These data are split by ADHD (Present, Absent). Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

Finally, there was a significant multivariate main effect of Block (as earlier) (V = .08, F (8, 664) = 3.37, p = .001, η^2_p = .04) which, at the univariate level, was significant only for CSI (F (4, 332) = 6.31, p < .001, η^2_p = .07) but not for CVI (F (4, 332) = .24, p = .92, η^2_p = .00). For CSI, this effect was defined by both a linear trend (F (1, 83) = 8.55, p = .004, η^2_p = .09) and a cubic trend (F (1, 83) = 14.98, p < .001, η^2_p = .15). As shown in Figure 3.8, the linear effect reflects a significant increase until Exposure 3 when it stabilized, there is no significant difference in CSI between Exposures 3 and 4.

We did not find any interactions between Block and Autism (V = .02, F (8, 664) = 1.02, p = .42, η^2_p = .01) or Block and ADHD (V = .03, F (8, 664) = 1.06, p = .39, η^2_p = .01) suggesting that presence of these conditions did not impact autonomic responsivity and adaptation of the autonomic response over successive task blocks to auditory stimuli.

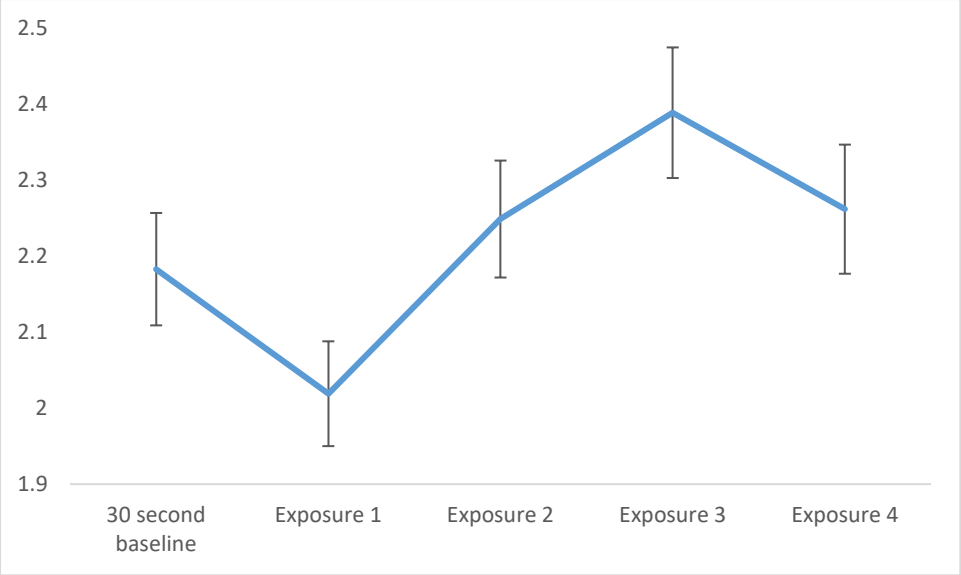


Figure 3.8. Change in CSI over successive task blocks

Bars show the mean (±1 standard error) average CSI (plotted on the y-axis). These data are split by Block (initial 30-second baseline and 4 consecutive 3-min exposure blocks during which auditory stimuli were presented).

Given that there was an effect of 'Order of Presentation' in analyses on HR, CSI and CVI such that the condition presented second elicited higher HR and CSI as compared to the condition presented first (regardless of whether the social or the non-social condition was presented first), we investigated whether there were between-group differences in this pattern. No between-group differences were found; all participants showed higher arousal (indexed by HR and CSI) in the second condition compared to the first. These results are more fully described in Appendix D.

3.3.3. Summary of Results

Overall, we found that Autism was not related to any differences in HR, CSI or CVI during either resting-state measurement or the auditory oddball task. Further, Autism was not associated with atypical autonomic reactivity to auditory stimuli (as measured by comparison between 30-second baseline and successive task blocks) or adaptation of the autonomic response to auditory stimuli over successive task blocks (as measured by HR, CSI or CVI). ADHD (with or without autism) was associated with significantly reduced CSI (during resting-state and auditory oddball task) and significantly higher CVI

(during task) and thus profiles of hypoarousal, but no differences in autonomic responsivity and adaptation of the autonomic response to auditory stimuli over successive task blocks. These atypicalities in CSI and CVI reflected in ADHD-only participants showing significantly reduced HR during resting-state (in comparison to neurotypical and autism only participants) and during the auditory oddball task (in comparison to autism only participants). The Autism+ADHD group showed a profile similar to ADHD for CSI and CVI but, with regard to HR, they were not significantly different from any of the three groups. In addition, we did not observe the predicted effect of higher autonomic response during the social as compared to the non-social block in the neurotypical or any of the clinical groups.

In order to further clarify how differences in autonomic arousal related to clinical symptoms, we took a dimensional approach next.

3.4. Can autonomic arousal profiles help parse heterogeneity on the autism spectrum?

In the first series of analyses described in Section 3.3 above, we investigated differences at a group-level and did not observe any differences in tonic arousal or autonomic responsivity in autistic participants as compared to neurotypical participants, when controlling for symptoms of ADHD. However, we found that one source of the heterogeneity in the literature on arousal in autism could be presence of co-occurring symptoms of another condition that impacts profiles of autonomic arousal differently than autism, such as ADHD. As seen in the results above, those with ADHD (with or without autism) showed profiles of hypoarousal as compared to neurotypical and Autism-only participants. Autistic participants with comorbid ADHD were more similar to ADHD individuals in demonstrating sympathetic hypoarousal (as indexed by reduced CSI). While presence of ADHD might be one source of the heterogeneity in the literature on arousal in autism, the above analyses do not allow us to take into account other layers of variability, such as possible heterogeneity in profiles of arousal within autism itself. As discussed in Chapter 1, autism is a highly heterogeneous condition and levels of heterogeneity have adversely impacted progress in theoretical, diagnostic and intervention research in autism. Discrepancies in previous research could be due to lack of a closer consideration of the

variability in autistic symptoms and arousal profiles. A dimensional approach might reveal more nuanced atypicalities. I tackled this issue in two ways.

First, I investigated dimensional relationships between different autistic symptom domains and autonomic arousal. There is some evidence to suggest that reduced vagal tone is associated with higher social symptom severity (Cai et al., 2019; Edmiston, Jones, & Corbett, 2016; Matsushima et al., 2016; Van Hecke et al., 2009). However, these studies are inconsistent with regard to which specific autistic social symptom domains are affected by reduced parasympathetic function. We therefore investigated, dimensionally, which specific symptoms of autism do individual differences in autonomic arousal relate with. Given the above evidence, we predicted that reduced CVI (but not CSI) would be associated with more SCQ social interaction and communication difficulties. This would indicate that the autistic symptoms are related with atypicalities in the activity of the parasympathetic system, rather than the sympathetic nervous system. Theoretical frameworks implicate both hyper- and hypo-arousal as being linked with RRBs; these theories propose that RRBs serve the function of downregulating arousal in hyperaroused autistic individuals, and upregulate arousal in hypoaroused autistic individuals (Hutt et al., 1964; Kinsbourne, 2011). There however is no experimental evidence to support these links. Therefore, we also directly investigated relationships between SCQ RRB subscale and arousal variables, to examine these theoretical proposals.

Second, I investigated the utility of measures that index arousal regulation towards stratification of autistic individuals into subgroups with more homogeneous clinical profiles (following the RDoC framework). Research in autism is generally shifting in the direction of stratification of autistic individuals into subgroups that maybe more homogeneous in their phenotypic profile or the risk factors that lead to autism (Wolfers et al., 2019). There is evidence of subgroups of different types of autonomic responders in autistic individuals (Hirstein et al., 2001; Schoen et al., 2008). Hyper- and hypo-aroused subgroups might show very different profiles of sensory processing, engagement and distribution of attention to the environment, autism symptom severity, and adaptive functioning (e.g. Mathersul et al., 2013b; Schoen et al., 2008). For example, autistic individuals with tonic hyperarousal might show

behavioural profiles of sensory over-responsivity, whereas those with tonic underarousal might show sensory under-responsivity (Rogers & Ozonoff, 2005). We wanted to know whether autonomic arousal profiles could index a neurobiological intermediate phenotype, to stratify autistic individuals into subgroups with more homogenous profiles of autism symptoms, adaptive functioning and sensory processing.

In the last part of this chapter, therefore, I investigated the utility of profiles of autonomic arousal (tonic arousal and autonomic responsivity to simple auditory stimuli) in identifying these subgroups, and further, whether this then helps explain some of the heterogeneity in the clinical profiles of autism, including sensory processing differences, as well as variation in symptom severity and adaptive functioning. In addition, I investigated whether such subgroups differ from one another in co-occurring symptoms of other conditions (specifically, ADHD and anxiety). As discussed earlier, profiles of autonomic hypoarousal characterise individuals with ADHD. On the other hand, those with anxiety show autonomic hyperarousal (Howells et al., 2012), avoidance behaviours (Mineka & Zinbarg, 2006), attentional hypervigilance and hyper-reactivity to stimuli (McVey, 2019; Richards, Benson, Donnelly, & Hadwin, 2014). Therefore, it is expected that subgroups of autistic individuals with hyper- or hypo-arousal will be differentially characterised by symptoms of ADHD and anxiety. Given that both of these conditions highly co-occur in autism, it might be that different autonomic arousal profiles underlie development of these symptoms in autistic individuals.

3.4.1. Dimensional relationships between arousal variables and autistic symptoms

Bivariate correlations were conducted to test the dimensional relationships between arousal variables (during the 3-minute resting state and during the auditory oddball task) and autistic symptoms, corrected for multiple comparisons by dividing the alpha level (0.05) with the number of correlations run. In the Table 3.2 below, the p values represent the actual p values from the correlations, but the relationships that survived correction for multiple comparisons have been highlighted in bold. Since there were no group differences on change in arousal over time during the auditory oddball task, we averaged HR,

CSI and CVI over the two 12-minute long conditions (social and non-social conditions) during which participants were presented with auditory stimuli in the oddball task.

As can be seen in Table 3.3, SCQ social symptoms were highly significantly correlated with HR and CVI such that higher HR and lower CVI during resting-state and task were correlated with higher scores on the social interaction subscale of the SCQ. This suggests that in our sample, a hyperarousal profile, specifically driven by reduced activity in the PNS, was associated with more social interaction difficulties. This was partly seen also in the SCQ communication subscale scores, in relation with CVI and HR (but not CSI); however, these relationships did not survive correction for multiple comparisons. RRB symptoms were not associated with any arousal variables.

Importantly, the arousal variables were, as expected, also highly correlated with each other. From Table 3.4, it can be seen that all HR and CSI variables were highly positively correlated with each other, while CVI variables were negatively correlated with HR and CSI. This substantiates our interpretation of CSI and CVI as measures of SNS and PNS respectively.

Table 3.3. Correlations of arousal variables with clinical symptoms of autism

	Pearson's r	**p**	**Lower 95% C.I.**	**Upper 95% C.I.**
SCQ Soc				
Rest CVI	-27*	.048	-.52	.04
Task CVI	**-.48*** **	**<.001**	**-.66**	**-.24**
Rest CSI	.27*	.044	.08	.50
Task CSI	.26	.055	-.08	.54
Rest HR	**.47*** **	**<.001**	**.20**	**.67**
Task HR	.29**	.007	.06	.49
SCQ Comm				
Rest CVI	-.27*	.047	-.52	-.01
Task CVI	-.37**	.006	-.58	-.15
Rest CSI	.19	.16	-.04	.48
Task CSI	.17	.23	-.14	.47
RestHR	.38**	.005	.13	.598
TaskHR	.22*	.04	-.02	.42
SCQ RRB				
Rest CVI	-.098	.48	-.39	.22
Task CVI	-.06	.67	-.32	.22
Rest CSI	.12	.38	-.12	.33
Task CSI	.04	.77	-.30	.34
RestHR	.24	.088	-.05	.49
TaskHR	.06	.61	-.17	.28

SCQ Soc: Social Communication Questionnaire- Social Interaction Subscale. SCQ Comm: Social Communication Questionnaire- Social Communication Subscale. SCQ-RRB: Social Communication Questionnaire- Restricted and repetitive behaviours subscale. CVI: Cardiac vagal index. CSI: Cardiac sympathetic index. HR: Heart rate. Rest variables represent arousal indices calculated over the 3-minute resting-state period.

Task variables represent arousal indices averaged over the auditory oddball task during exposure to auditory stimuli. Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001.

Correlations that survived correction for multiple comparisons are highlighted in bold.

Table 3.4. Correlations between Arousal variables

	Pearson's r	**p**	**Lower95% C.I.**	**Upper 95% C.I.**
Rest HR				
RestCVI	-.74***	<.001	-.84	-.60
TaskCVI	-.79***	<.001	-.87	-.69
RestCSI	.61***	<.001	.49	.73
TaskCSI	.62***	<.001	.48	.74
Task HR				
RestCVI	-.72***	<.001	-.82	-.59
TaskCVI	-.84***	<.001	-.89	-.78
RestCSI	.44***	<.001	.26	.62
Task CSI	.64***	<.001	.5	.76
Rest CVI				
RestCSI	-.46***	<.001	-.65	-.25
TaskCSI	-.67***	<.001	-.78	-.54
Task CVI				
RestCSI	-.57***	<.001	-.74	-.38
TaskCSI	-.698***	<.001	-.81	-.56

CVI: Cardiac vagal index. CSI: Cardiac sympathetic index. HR: Heart rate. Rest variables represent arousal indices calculated over the 3-minute resting-state period. Task variables represent arousal indices averaged over the auditory oddball task during exposure to auditory stimuli. Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

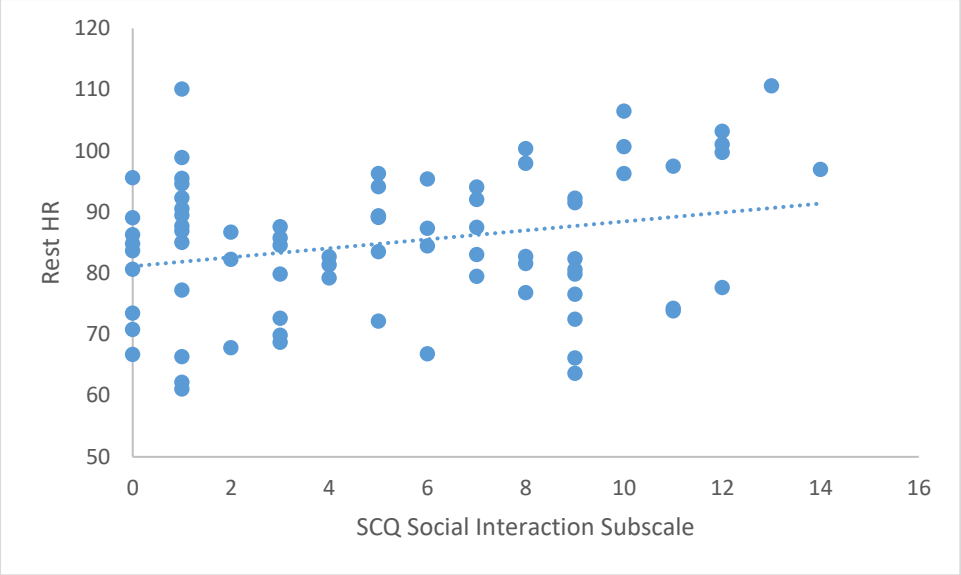


Figure 3.9. Relationship between SCQ-Social Interaction subscale scores and Heart Rate during 3-minute Resting-State period.

Scatterplot of scores on Social Communication Questionnaire (SCQ) Reciprocal Social Interaction Subscale (plotted on the x-axis) with the Average Heart Rate calculated over the 3-minute resting state period (plotted on the y-axis) for participants (represented by blue dots).

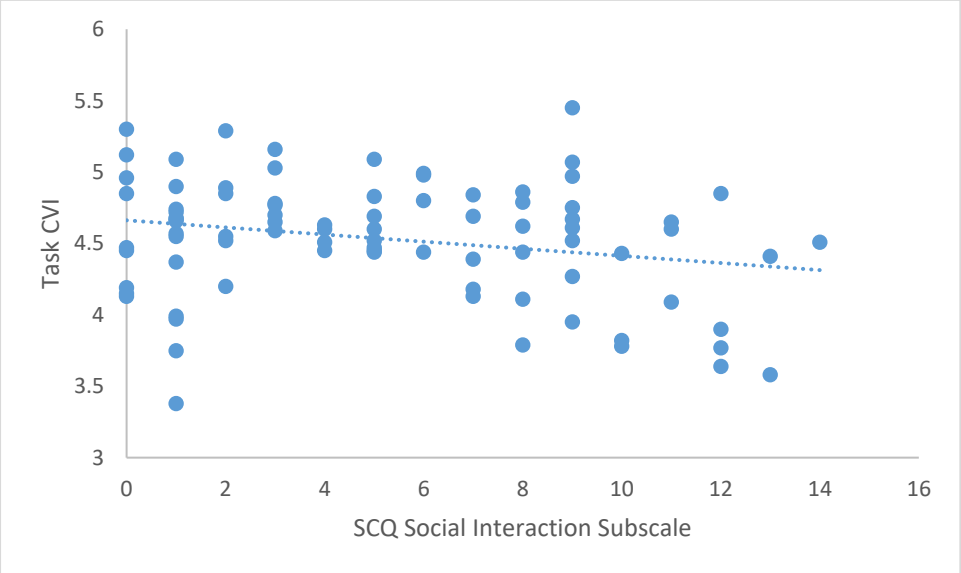


Figure 3.10. Relationship between SCQ-Social Interaction subscale scores and Cardiac Vagal Index during Auditory Oddball Task.

Scatterplot of scores on Social Communication Questionnaire (SCQ) Reciprocal Social Interaction Subscale (plotted on the x-axis) with the Cardiac Vagal Index averaged over the auditory oddball task during exposure to auditory stimuli (plotted on the y-axis) for participants (represented by blue dots).

3.4.2. Autonomic arousal profiles as a neurobiological phenotype to stratify autistic individuals into homogeneous subgroups

We investigated whether autonomic arousal profiles (during resting-state and in response to auditory stimuli) can be used to stratify autistic individuals into subgroups with more homogenous profiles of symptomatology and adaptive functioning. I carried out a cluster analysis on the autonomic arousal variables, on autistic participants only (that is, neurotypical and ADHD-only participants were excluded from the cluster analysis) since I was interested in parsing the heterogeneity within the autistic sample. Since HR is a variable representing the autonomic balance between SNS and PNS, while CVI and CSI represent variability of activity in SNS and PNS respectively, we decided to use CVI and CSI to investigate profiles of sympathetic and parasympathetic activation separately. Based on the literature, we predicted that there would be a subgroup of autistic individuals with significantly reduced CVI (thus exhibiting a hyperaroused profile), and this subgroup would have higher social symptom severity, higher presence of anxiety disorders, profiles of sensory over-responsivity and worse adaptive functioning. Further, we predicted that if present, a hypoaroused autistic subgroup would have higher symptoms of ADHD, specifically hyperactivity/impulsivity and possibly profiles of sensory under-responsivity.

We investigated this with a two-step cluster analysis in autistic participants (with or without ADHD) on the following CSI and CVI measures. Since there were no group differences in adaptation of the autonomic response over successive task blocks, we decided to average the autonomic arousal variables across task blocks in the auditory oddball task when auditory stimuli were presented.

- Resting CVI- initial 3-minute resting state measurement
- Resting CSI- initial 3-minute resting state measurement
- Average CVI across the 8 blocks of sound exposure (4 social and 4 non-social- each block is a 3-minute period)
- Average CSI across the 8 blocks of sound exposure (4 social and 4 non-social- each block is a 3-minute period)

Two-step cluster analysis models different cluster solutions and provides the best solution with clusters that are reliably distinct. Within this method, I used log-likelihood as the measure of distances and BIC criteria, and standardization of the variables was conducted as part of the cluster analysis. This led to a two-cluster solution with a Silhouette index just above 0.6 (silhouette index values range from -1 to +1 and values above 0.5 would be considered as representing good separation between clusters (Rousseeuw, 1987)). A two-step cluster with a three-cluster solution was investigated but the silhouette value was lower and the clusters were less distinct from one another.

The cluster analysis divided the autistic sample (n= 39) into two clusters such that Cluster 1 had 13 (33.3%) participants while Cluster 2 had 26 (66.7%) participants. The separation of the clusters on the main arousal variables was good, with highly significant differences on all arousal variables (HR, CVI, CSI) during resting-state and task (see Table 3.5 for descriptive statistics on arousal variables and bootstrapped t-tests examining the distinction on arousal variables for the two clusters) such that Cluster 1 represented a reduced arousal profile with lower HR, lower CSI values and higher CVI values as compared to Cluster 2. Therefore, Cluster 1 was labelled 'hypoaroused' while Cluster 2 was labelled 'hyperaroused' (see Figures 3.9- 3.10 for graphical representations of HR, CVI and CSI in the two autism sub-clusters compared to neurotypical participants). Further, the clusters were distributed such that most of the hypoaroused participants (n = 11/13) were in the comorbid Autism+ADHD group, while the hyperaroused cluster was evenly distributed between the Autism-only (n = 14/ 26) and the comorbid Autism+ADHD groups (n = 12/ 26)) (see Figure 3.11 for a visual representation).

Table 3.5. Bootstrapped independent sample t-tests and descriptive statistics on arousal variables for the two clusters

	Hypoaroused (n= 13)	**Hyperaroused (n = 26)**	**Mean difference**	**95% confidence interval around Effect size (Cohen's d)**
RestHR	75.53 (6.38)	92.85 (8.7)	-18.14	2.16 [1.32, 2.98]
TaskHR	77.78 (5.58)	94.66 (8.41)	-16.88	2.21 [1.36, 3.04]
RestCVI	4.97 (.28)	4.23 (.34)	.75	2.32 [1.46, 3.16]
TaskCVI	4.86 (.25	4.25 (.37)	.63	2.05 [1.23, 2.85]
RestCSI	1.45 (.28)	2.52 (.9)	-1.13	1.42 [.67, 2.15]
TaskCSI	1.66 (.27)	2.59 (.47)	-.94	2.67 [1.76, 3.56]

CVI: Cardiac vagal index. CSI: Cardiac sympathetic index. HR: Heart rate. Rest variables represent arousal indices calculated over the 3-minute resting-state measurement. Task variables represent arousal indices averaged over the auditory oddball task during exposure to auditory stimuli.

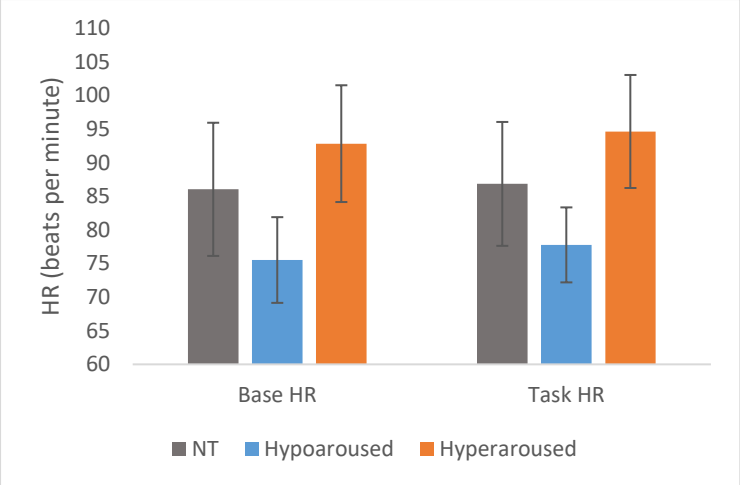


Fig 3.11. Distribution of HR scores during resting state measurement and auditory oddball task for hyperaroused and hypoaroused subgroups of autistic participants in comparison with neurotypical (NT) participants. Error bars represent +/- 1 SD. Cluster analysis did not include neurotypical or ADHD-only participants and thus the two clusters (hyperaroused, hypoaroused) consist of only autistic participants (with or without ADHD), labelled in this way based on their profile on autonomic arousal variables as described above.

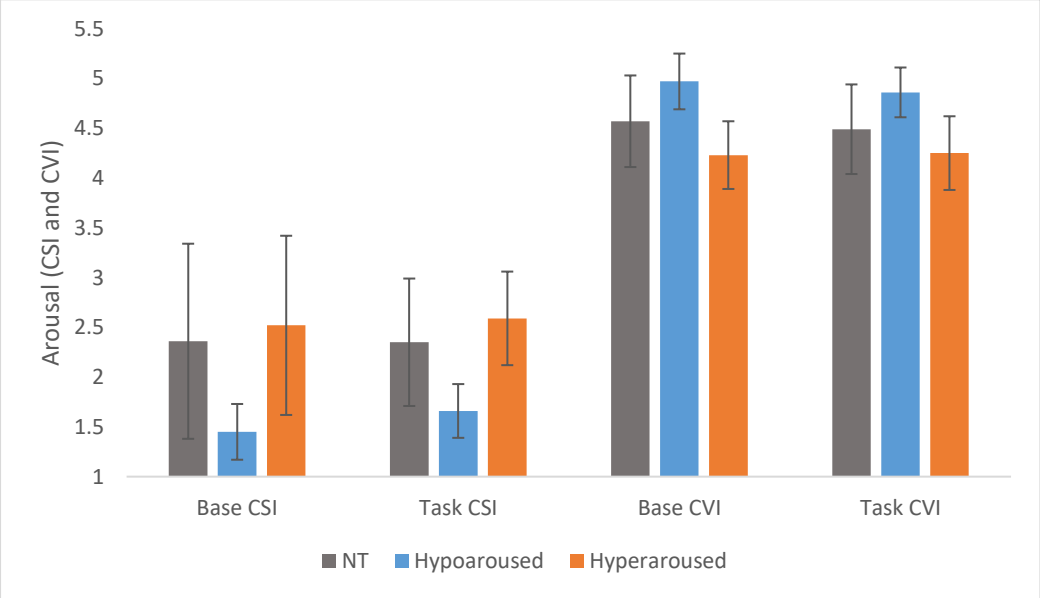


Fig 3.12. Distribution of CVI and CSI scores during resting state measurement and auditory oddball task for hyperaroused and hypoaroused subgroups of autistic participants in comparison with neurotypical participants. Y-axis represents values on CSI and CVI. Error bars represent +/- 1 SD

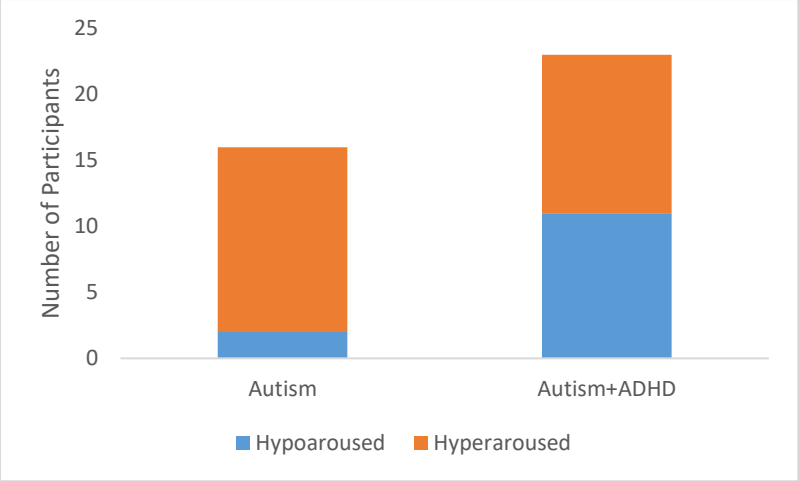


Figure 3.13. Distribution of autistic participants in the hyper- and hypo-aroused subgroups with regard to presence of ADHD.

3.4.3. Profiles of the subgroups

We then investigated the clinical profiles of these clusters with regard to autism symptomatology, ADHD symptomatology (hyperactivity/inattention), anxiety symptoms, sensory processing and intellectual ability; we also investigated gender distributions.

In Table 3.6, we present mean differences and effect sizes of these differences between the hyper- and hypo-aroused clusters on these clinical and behavioural features. Hyperaroused subgroup demonstrated higher SCQ social interaction and social communication symptoms (with differences between hyperaroused and hypoaroused subgroups being of a small effect size). The hypoaroused subgroup showed higher hyperactivity-impulsivity symptoms, as measured by the Conners (with medium effect size difference) as well as higher scores on the SDQ Impact subscale (medium effect size). A higher proportion of the hyperaroused subgroup (15/26, 57%) showed significant symptoms of anxiety as compared to the hypoaroused subgroup (5/13, 38%). Further, the hyperaroused subgroup showed less sensory-seeking (small-to-medium effect size) and more sensory-avoidance behaviours (small effect size) and more atypical bodily behaviours (small-to-medium effect size) as compared to the hypoaroused subgroup.

Table 3.6. Profiles of hyper- and hypo-aroused autistic participants on demographic and clinical variables

	Hypoaroused Autism (n= 13)	**Hyperaroused Autism (n= 26)**	**95% confidence interval around Effect size (Cohen's d)**
Age (in months)	131.15 (25.27)	129.27 (19.61)	0.09 [-.58, .75]
Gender M: F	12:1	18:8	
WASI			
FSIQ	105.69 (18.11)	103.77 (19.97)	0.1 [-.57, .76]
VIQ	105.46 (16.04)	105.19 (21.03)	0.01 [-.57, .58]
PIQ	104.62 (19.25)	101.65 (18.04)	0.16 [-.51, .83]
SCQ			
Total	19.31 (5.44)	20.85 (6.81)	0.24 [-.43, .91]
Social Interaction	6.85 (3.51)	7.72 (3.51)	0.25 [-.43, .92]
Communication	5.69 (2.59)	6.4 (2.45)	0.28 [-.39, .95]
RRB	5.08 (2.25)	5.08 (2.02)	0.00 [-.06, .06]
CPRS			
GI	86.46 (5.62)	82.65 (10.04)	0.52 [-.16, 1.19]
IN	82 (7.58)	80.35 (11.07)	0.16 [-.5, .83]
HI	86.92 (5.79)	80.35 (12.4)	0.76 [.07, 1.45]
SDQ Impact	7.77 (1.59)	6.65 (2.76)	0.46 [-.22, 1.13]
CGAS	38.54 (7.74)	38.85 (12.09)	0.03 [-.64, .69]
Anxiety (yes:no)	5:8	15:11	
Sensory Profile			
Seeking	59.92 (16.57)	51.56 (21.24)	0.42 [-.26, 1.1]
Avoidance	72.62 (13.73)	75.2 (13.71)	0.19 [-.48, .86]

Sensitivity	64.15 (14.97)	62.88 (15.5)	0.08 [-.59, .75]
Registration	67.23 (12.84)	65.72 (18.68)	0.09 [-.58, .76]
Auditory	29.85 (7.97)	29.92 (4.92)	0.01 [-.49, .5]
Visual	16.85 (5.11)	16.12 (5.72)	0.13 [-.54, .8]
Touch	32.62 (7.5)	31.76 (9.6)	0.095 [-.58, .76]
Movement	23.77 (4.69)	21.36 (9.1)	0.37 [-.31, 1.04]
Body	19.85 (8.99)	22.84 (10.19)	0.31 [-.37, .98]
Oral	28.08 (10.78)	28.32 (13.17)	0.02 [-.65, .69]

Data shown for all measures except Gender and Anxiety are mean with standard deviation in parentheses. Data for gender are n male:female. Data for Anxiety are Yes: No (Present: Absent). WASI: Wechsler Abbreviated Scale of Intelligence; FSIQ: WASI Full Scale Intelligence Quotient (standard score); VIQ: WASI Verbal IQ (standard score); PIQ: WASI Perceptual Reasoning IQ (standard score); SCQ: Social Communication Questionnaire; Total: SCQ Total Raw Score; Social Interaction: SCQ Social Interaction Subscale Raw Score; Communication: SCQ Communication Subscale Raw Score; RRB: SCQ Restricted Repetitive Behaviour Subscale Raw Score; CPRS: Conners Parent Rating Scale; GI: CPRS Global Index T-scores; HI: CPRS Hyperactivity Impulsivity Subscale T-scores; IN: CPRS Inattention Subscale T-scores; SDQ Impact: Strengths and Difficulties Questionnaire Impact Supplement Raw Scores; CGAS: Children's Global Assessment Scale Raw Scores; Sensory Profile: Child Sensory Profile 2 with subscales: Seeking, Avoidance, Sensitivity, Registration, Auditory, Visual, Touch, Movement, Body, Oral (values presented are raw scores).

3.4.4. Summary of Results

In these latter exploratory analyses, we examined how individual differences in tonic autonomic arousal related with autistic symptoms and whether autonomic arousal profiles could be useful in parsing the heterogeneity in the autistic spectrum. We found that reduced CVI and increased HR (during the resting state measurement and averaged over each block of the auditory oddball task during presentation of auditory stimuli) were associated with higher SCQ social interaction symptoms. A cluster analysis revealed presence of subgroups within autistic participants (with or without ADHD), such that there

was a subgroup that was significantly hyperaroused (with higher HR, CSI and lower CVI) as compared to the other subgroup. These subgroups differed from one another on various clinical and behavioural features, such that the hyperaroused subgroup demonstrated higher social interaction symptoms on the SCQ, more sensory-avoidance and atypical bodily behaviours and a higher number of hyperaroused autistic participants showed clinically significant symptoms of anxiety. On the other hand, the hypoaroused subgroup showed higher scores on Conners Hyperactivity Impulsivity subscale and more sensory-seeking behaviours. Further, the hypoaroused subgroup was reported to be more impacted on the SDQ Impact subscale as compared to the hyperaroused subgroup.

3.5. Discussion

In this chapter, we compared profiles of tonic HRV during resting-state and changes in autonomic arousal in response to auditory stimuli over successive task blocks between Autism-only, ADHD-only, Autism+ADHD and neurotypical participants.

All participants first watched a silent movie for 3 minutes as part of a resting-state measurement. Auditory stimuli were then played in the background as the participants continued to watch the silent movie as part of a passive auditory oddball task. The addition of auditory stimuli was observed to alter arousal in all participants (with no differences between groups on this change in autonomic response over successive task blocks), such that all participants demonstrated an increase in arousal from baseline, as measured by HR and CSI. Therefore, activity in the SNS increased with sensory stimulation, paralleled by increasing HR in response to auditory stimuli. This is in line with the literature, which suggests that salient events in the environment lead to SNS activation, with HR accelerations (Wass et al., 2015a). Importantly, over the 12 minutes of each condition (social, non-social) of the auditory oddball task (3-minutes per block), the sympathetic response did not decrease as predicted, instead it continued to increase and then stabilized. This suggests that the SNS was consistently active over the course of the auditory oddball task. In line with our predictions, we did not find any changes with time in activity in the parasympathetic nervous system as indexed by CVI. Given

that this was a passive task, without any demands placed on sustained attention or response preparation, parasympathetic input was not elicited (Porges, 1992). However, it is possible that since PNS affects short-term HRV, and we averaged over consecutive segments of 3-minutes each, our index of parasympathetic activity (CVI measured over 3-minute segments) was not sensitive to shorter-term changes in PNS activity. Importantly, in contrast to our prediction, we did not find any differences in autonomic response to social as compared to non-social blocks; rather, arousal was higher in the second as compared to the first block of the task regardless of condition. In our task, the social stimuli were deviants, rather than standards, and thus occurred rarely. Given time limitations, we did not implement a balanced design by manipulating the social-ness of the standard stimuli as well as the social-ness of deviant stimuli. It is possible therefore that order effects obscured any condition-specific effects of the social-ness of the deviant stimuli. It is also possible that any autonomic response specifically to the deviants might also not have been captured in our tonic measures averaged over 3-minute periods. Future research should use a more balanced design, manipulating the social-ness of standards as well as deviants, and investigate the autonomic response to both stimulus types in autistic and neurotypical individuals to more robustly evaluate these functions.

We did not find evidence in support of theories of arousal in autism that propose a predominantly hyper- or hypo- aroused state at rest (DesLauriers & Carlson, 1969; Hutt et al., 1964). This is in line with the generally inconsistent pattern in the literature (Klusek et al., 2015; Lydon et al., 2016). In comparison, we found evidence in support of profiles of tonic hypoarousal (driven by sympathetic underarousal) in ADHD. This accords with our review of the literature where we found that at rest and during less stimulating tasks, ADHD is associated with underarousal (Bellato et al., 2020). Interestingly, in the present study, autistic participants with comorbid ADHD showed profiles similar to ADHD individuals, particularly on HRV (CSI and CVI), showing reduced activity in the sympathetic and increased activity in the parasympathetic nervous systems. This is an important effect that contributes to our understanding of profiles of autonomic function in autism, since it shows that at least some individuals with autism (i.e., those who have co-occurring ADHD) might show autonomic underarousal. It appears

then that autistic individuals should not be considered as a homogeneous group with regard to profiles of arousal; that they might consist of subgroups with different autonomic profiles (Schoen et al., 2008).

Indeed, our cluster analytic approach revealed presence of subgroups in autistic participants (with or without ADHD) that showed opposite autonomic profiles. One subgroup showed a hyperaroused profile with increased CSI and decreased CVI, indicating reduced variability in activity of the PNS and increased variability in activity of the SNS. In contrast, the hypoaroused subgroup showed the opposite profile, with increased variability in the PNS and reduced variability in the SNS. Reduced variability in SNS activity would impact the ability to quickly mobilize resources to respond to salient or threatening events. On the other hand, reduced variability in the PNS might impact one's ability to downregulate arousal to support rest and digest functions, or sustained attention. Reduced variability in either SNS or PNS would thus generally impact flexibility to adapt to changing environments. Our findings are in line with other literature that shows presence of subgroups of different types of autonomic responders (Hirstein et al., 2001; Schoen et al., 2008) and suggest that stratification of autistic individuals on autonomic arousal profiles might be clinically meaningful.

Indeed, the hyper- and hypo- aroused subgroups showed different clinical profiles. The hyper-aroused subgroup was found to have worse social interaction abilities (as measured by the SCQ Social Interaction Subscale), and this subgroup demonstrated more sensory avoidance behaviours as well as higher prevalence of anxiety. This is in line with our predictions, and also in line with theories of reduced vagal tone impacting profiles of socialization and anxiety (Porges, 2001; Thayer & Lane, 2000). Further, we also found dimensional relationships in the entire sample such that reduced CVI was associated with worse social interaction skills, consistent with Porges' polyvagal theory (Porges, 2001). In comparison, the hypo-aroused subgroup showed higher sensory-seeking behaviours, higher hyperactivity and impulsivity symptoms and higher scores on the SDQ Impact subscale (suggestive of worse adaptive functioning), consistent with profiles of those with ADHD. These observations are preliminary, given the small sample sizes and we did not have sufficient power to evaluate these effects using inferential statistics. However, the differences between the subgroups were small to medium in

size and are worth exploring in studies with larger sample sizes since they indicate that autonomic arousal could serve effectively as a neurobiological phenotype that can serve to parse the heterogeneity on the autistic spectrum in a meaningful manner.

A final observation was that autonomic arousal measures related specifically with the social interaction symptoms (as measured by the SCQ social interaction subscale) and with the SCQ social communication subscale, albeit at a reduced level of significance. However, autonomic arousal measures did not relate with RRBs and the hyper- and hypo-aroused subgroups were not numerically different from one another in severity of RRBs as measured by the SCQ RRB subscale. Theories of arousal suggest that both hyper- and hypo- arousal would be related with higher RRBs, with RRBs serving to down- and up- regulate arousal respectively in those profiles (Kinsbourne, 2011). Given that RRBs are predicted at either end of the spectrum of tonic arousal profiles, it is possible that this is why we did not see any dimensional relationships; that both hyper- and hypo-aroused subgroups might show RRBs, just qualitatively different from one another and serving different functions. Future research should look at these in a more nuanced manner, using scales of RRBs that capture the different types of RRBs and investigate whether autistic subgroups that are hyper- and hypo-aroused show different types of RRBs.

Overall, in this chapter, we observed that autistic individuals were heterogeneous in profiles of autonomic arousal, with subgroups that showed hyper- and hypo- arousal respectively. These differences in arousal were related meaningfully with clinical symptoms and sensory behaviours and might underlie the development of those symptoms.

Next, I investigated orienting of attention to the repeating standards in the auditory oddball task and habituation of attention to repetition of the standards in autism. My aim was to measure differences in orienting of attention and habituation to auditory stimuli the stimuli in autism, and to determine whether the hyper- or hypo-aroused subgroups showed differences in these profiles from one another.

Chapter 4. Orienting and habituation to repeating standards in an auditory oddball task

4.1. Background

In this chapter, I applied a different method (event-related potentials) to investigate another aspect of orienting of attention and habituation to repeating auditory stimuli in autism. Day-to-day life requires quick orienting of attention to sounds within and outside our current focus of attention, and indeed, auditory information can often be the aspect of a stimulus that brings our attention to that stimulus in the first place. The clinical profile of autism is associated with reduced response to their name being called (Baranek, 1999; Dawson et al., 2004), atypical responses to various auditory stimuli (Baranek et al., 2013; Thye, Bednarz, Herringshaw, Sartin, & Kana, 2018) as well as reduced sensitivity to novel sounds in the environment (Orekhova & Stroganova, 2014; Orekhova et al., 2009). As reviewed in Sections 1.4.2- 1.4.3., stimuli varying in salience might impact attention differently in autistic as compared to neurotypical individuals (e.g., Chita-Tegmark, 2016). Further, many frameworks have highlighted that atypicalities in habituation might underlie the atypical sensory responses and differences in attention seen in autism (Dawson & Lewy, 1989; Hutt et al., 1964; Ramaswami, 2014), although empirical evidence towards this is limited. Spontaneous orienting of attention to novel stimuli of different types in the environment, as well as habituation to repeating stimuli are important and fundamental functions, atypicalities in which could have far-reaching implications for how autistic individuals navigate day-to-day environments. These functions are the focus of this chapter.

In Chapter 3, where I investigated autonomic response to stimuli in the auditory oddball task, the autonomic response was not specific to individual auditory stimuli, but rather, I measured changes in tonic autonomic arousal profiles in response to presentation of auditory stimuli over 3-minute long task blocks. These changes in tonic autonomic arousal reflect a cumulative effect of orienting of attention, sensory processing of stimuli, salience attributions given to standard and deviant stimuli and regulation of arousal in response to attention distributed to the sounds. In this chapter, instead, I use event-related potentials to measure orienting of attention to specific auditory stimuli, in this case repeating standards. The reason I focused on the repeating standards is because it provides an opportunity to evaluate both the initial orienting of attention to presentation of the first standard (after a deviant), eliciting detection

of novelty/change, and since the standards repeat, it elicits habituation of the orienting response (Polich, 2007). Specifically, I measured the P3a to four consecutively repeating standards and compared this between groups with Autism-only, ADHD-only, Autism+ADHD and neurotypical participants.

The P3 is a broad positive wave potential that typically occurs between 300- 400 ms following presentation of a stimulus in any sensory modality (Nieuwenhuis et al., 2005; Sutton et al., 1965). The P3 does not reflect a single cognitive process, and instead, reflects an information processing cascade wherein attentional and memory processes are engaged. Repetition of the standard stimulus leads to the formation of a memory trace for that stimulus, resulting in habituation to the standard, and reduction over time in the response to the standard (Polich, 2007). This habituation is quite quick, with studies showing that the biggest reduction in response to the standard occurs between the first two presentations of the standard, with further smaller reductions in the response until it reaches an asymptote (Rosburg, Zimmerer, & Huonker, 2010). When a deviant stimulus occurs, the stimulus is compared to the memory trace of the standard and thus elicits a larger electrophysiological response, since it is different from the standard, reflecting change detection and an involuntary orienting of attention (Duncan et al., 2009). Typically, the average ERP response indexing discrimination of the deviant from the standard stimuli is calculated by subtracting the response to the standards from the response to the deviants, since it is expected that the ERP response to the deviants would be larger in amplitude than to the standards. This distinctive brain response is called the mis-match negativity (MMN) and it reflects a sensory response to the mismatch between the memory trace of the standard and the deviant stimulus (Naatanen, Paavilainen, Rinne, & Alho, 2007). These processes are thought to support adaptive behaviour, are called upon in every environment. Importantly, these processes (and the ERPs that reflect them) are reliably elicited whether participants are actively attending to the task or not (Duncan et al., 2009).

The P3 is comprised of an early P3a potential, associated with novelty and motivational salience, which is a fronto-central component; and a later P3b, a potential in centro-parietal regions implicated in context updating (Polich, 2007). It has been proposed that the P3a represents initial engagement of fronto-central regions to evaluate the novelty of a stimulus, and stimuli that elicit enough attention (due

to their novelty or salience) elicit the later P3b which reflects updating memory representations of a given context (Polich, 2007). Stimulus characteristics and attentional resource allocation have been found to influence both P3a and P3b (Duncan et al., 2009; Naatanen et al., 2007). While P3 activity reflects broad activity of a broadly distributed neural system, the lateral prefrontal cortex is implicated in generation of the P3a and the temporo-parietal junction (TPJ) has been shown to have involvement in the generation of both P3a and P3b (Halgren et al., 1995; Kiss, Dashieff, & Lordeon, 1989; as reviewed by Nieuwenhuis et al., 2005). Nieuwenhuis et al. (2005) suggested that the P3 (P3a and P3b) could be the electrophysiological correlate of the LC phasic response. This is because the timing and distribution of the P3 is similar to that of the late LC phasic response; further, both P3a and the late LC phasic response are preferentially elicited by salient, novel or relevant stimuli and habituate rapidly with repeated presentations of the stimuli (Aston-Jones & Bloom, 1981b). Lesion studies and pharmacological studies of the LC have implicated the LC in generation of the P3 (as reviewed by Nieuwenhuis et al., 2005). Finally, the time course of the impact of the LC phasic response on cortical processing (with initial LC phasic response occurring around 150-200 ms post- stimulus and conduction latency of NE fibers around 150 ms) and the anatomy of NE fibers innervating cortical regions (with innervations from LC reaching frontal cortex first and posterior areas later) are in line with the latency and anatomical origins of the P3a and P3b (as reviewed by Nieuwenhuis et al., 2005). If tonic LC activity is atypical in autistic individuals, or if top-down evaluations of salience and top-down modulation of LC in response to salience attributions are inefficient in autism (due to reduced functional connectivity), this might manifest in not just atypical orienting to auditory stimuli, but also reduced habituation to repeating stimuli. In this chapter therefore, I evaluated orienting and habituation to repeating standards (as indexed by the P3a) in autistic as compared to neurotypical individuals.

There is evidence of atypical P3a to auditory stimuli in autism, albeit the findings are heterogeneous. Findings of reduced P3a amplitudes in response to speech stimuli (Čeponiene et al., 2003; Lepistö et al., 2005) and increased P3a amplitudes to non-speech stimuli (Gomot et al., 2011; Gomot, Giard, Adrien, Barthelemy, & Bruneau, 2002) in autism indicate that the orienting response in autism is modulated by social-ness of stimuli. However, one study indicated that these differences might be

driven by a top-down reduced attentiveness to streams of speech rather than the ability to orient to speech versus non-speech. Whitehouse and Bishop (2008) presented autistic and neurotypical individuals with active and passive versions of an oddball paradigm; they manipulated whether infrequent (social or non-social) deviants were provided in a stream of social or non-social standards. In the passive oddball condition, autistic participants showed atypically reduced P3a to non-social novel sounds when the standards were social, but P3a was not reduced to social novel sounds, when the standards were non-social; suggestive of an overall reduced attentiveness when the stream was social. In the active version of the task, no such differences were captured. Their interpretation was further supported by analyses on P3a to the standards, where the authors reported that autistic participants showed generally reduced P3a in the passive speech condition and generally larger P3a in the passive non-speech condition as compared to neurotypical participants. This suggests that autistic individuals may be atypical in the way their attention is modulated spontaneously by stimuli varying in their salience. There is further converging evidence that would imply an atypical P3a in autism. Reorienting networks in autistic individuals show significantly reduced activation (specifically in the TPJ) in response to novel stimuli in a passive oddball task (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Gomot et al., 2006). In an active version of the oddball task, activation in TPJ was significantly higher in autistic than neurotypical individuals; this increased activation was associated with quicker responses suggesting that this was adaptive. Overall, evidence from these studies that investigate orienting to simple auditory stimuli suggests that autistic individuals are able to detect, discriminate and orient to auditory stimuli in their environment endogenously in the context of an active task, but exogenous orienting of attention (during passive tasks) may be affected differentially by different types of stimuli. Salience of information might impact reorienting, with social stimuli having differential salience than non-social stimuli.

With regard to habituation, there is preliminary evidence for reduced habituation to sensory stimuli in autism, specifically using early ERPs that reflect early encoding and discrimination processes. Ruiz-Martinez et al. (2020) provided evidence of reduced habituation of the P1 to repeating standards during a passive oddball paradigm to human and electronic sounds in 5-11 year old children. They analysed

the P1 to the first two standards and found that autistic children did not show the reduction from the first to the second standard shown by neurotypical participants; this profile was found irrespective of the type of sounds used. Hudac et al. (2018) also provided evidence of slower attenuation of N1 and P3a, but they analysed this response to the deviants in their auditory oddball task, over time on task. Carter Leno et al. (2018) analysed the N2 component in response to three repeating standards and found that higher responsivity to the first standard was associated with higher levels of emotional problems; however, they did not have a neurotypical comparison group, and therefore, from their study it is difficult to comment on whether there were differences in habituation in autistic adolescents. Two studies have investigated habituation to auditory stimuli in infants at elevated familial risk of autism. These studies reported evidence of reduced habituation in infants at elevated risk of autism as compared to low risk for autism (Guiraud et al., 2011; Kolesnik et al., 2019). While these results are fairly consistent, these tap into early cortical reactivity to sensory stimuli, reflected in early ERPs such as the P1 and N1, which maybe heightened and show reduced habituation in autism. However, we were interested in whether there are atypicalities in habituation of the later orienting of attention, as indexed by the P3a, which (as discussed earlier) might be related to the late phasic LC response, guided by top-down information from anterior insula and anterior cingulate cortex of the salience of that stimulus (Menon & Uddin, 2010; Orekhova & Stroganova, 2014).

To our knowledge, habituation of the P3a to repeating standards has not been evaluated in autism before. Therefore, in this chapter, we directly investigated habituation of the P3a to repeating standards in autistic individuals as compared to neurotypical, ADHD and comorbid autism+ADHD individuals. Importantly, based on theories of arousal, it is possible that reduced habituation does not characterise all autistic individuals, but only those who have profiles of hyperarousal (Hutt et al., 1964). We investigated this idea as an additional exploratory investigation.

In individuals with ADHD, profiles of visuospatial orienting are considered to be typical (Huang-Pollock & Nigg, 2003). While there is evidence of reduced P3b amplitudes to auditory stimuli in those with ADHD, however, the P3a appears unaltered in individuals with ADHD (Duncan et al., 2009).

Various studies have reported typical, enhanced and reduced habituation in ADHD; however, habituation of the P3a to repeating auditory stimuli in a passive task has not been directly investigated in ADHD (McDiarmid et al., 2017).

Therefore, in this study, we investigated initial orienting (to the first standard after a deviant) and habituation (to repeating standards) in the auditory oddball task in the SAAND study using the P3a. We expected that the P3a would show quick habituation as standards were repeated, with the decrease in amplitude being the most significant between the 1st and 2nd repetition of the standard. We expected this effect to be attenuated in those with Autism-only, but unaffected in those with ADHD-only. We also expected that based on the evidence on the P3a in autism for there to be some atypicalities in amplitudes of the P3a in Autism-only individuals modulated by task condition (Social or Non-Social), we expected that they might show reduced P3a in the social as compared to the non-social condition. Given absence of any evidence of reduced P3a in those with ADHD, we predicted to find typical P3a in ADHD-only individuals in this study. For comorbid Autism+ADHD participants, our hypotheses were again more tentative since this has not been studied before. We predicted that the comorbid group might show P3a and habituation of the P3a similar to those with Autism-only, ADHD-only, or that the comorbid group might show a completely different profile from the pure condition groups.

We also conducted a follow-up analysis to investigate initial orienting and habituation within the two autism subgroups (hyper- and hypo- aroused) observed in Chapter 3. We predicted that profiles of initial hyper-responsivity to the standards and reduced habituation might be specific to the hyperaroused subgroup.

If present, we expected that a profile of reduced habituation to the standards would be related to higher RRBs, more social avoidance (or more severe SCQ social) symptoms and higher scores on the sensory profile, particularly in the auditory and avoidance domains.

4.2. Methods

4.2.1. Sample

The data in this chapter is from the same 87 participants as in Chapter 3.

4.2.2. Pre-processing of ERP data

The pre-processing of the EEG data was carried out in Brainstorm (Tadel et al., 2011). First, the data was band-pass filtered (0.05-30 Hz). Then, for each subject, the data was visually inspected to identify any temporal segments of noisy data, which were manually marked for exclusion. A power spectral density (PSD) was then used to identify and reject noisy or flat channels, based on the power spectrum of the EEG signal for each electrode. Next, we conducted an Independent Components Analysis (ICA) to identify and remove other sources of noise, such as ocular movements, muscular activity and other acute sources of noise that did not reflect brain activity. At this stage, I applied an average reference to the EEG signal, such that each electrode was re-referenced to the average of the signal of all the remaining channels.

Event markers were recoded to represent the first presentation of a standard stimulus, then the second repetition, third repetition and so on until the fifth repetition of a standard stimulus. In order to have sufficient data for each participant, we chose to focus on the first four repetitions of the standard stimulus. The continuous data was then epoched for each type of standard tone (1^{st} repetition, 2^{nd} repetition, 3^{rd} repetition and 4^{th} repetition) for each Condition separately (Social and Non-Social) and each epoch was 800 msec long, including a 100 ms pre-stimulus window and 700 ms post-stimulus window. Each epoch was baseline normalized using the 100 ms pre-stimulus window. Epochs were then marked for further processing if electrical activity in channels of interest (central, frontal and parietal electrodes in the midline, left and right hemispheres) did not cross ±100μV. Number of epochs for the 1^{st} and 2^{nd} repetition were the same, but this number reduced for the 3^{rd} and 4^{th} repetition of the

standard stimulus. Therefore, to maintain uniformity in number of epochs used per type of repetition within each Condition, the same minimum number of trials (based on the 4th repetition epoch availability) were randomly selected for each repetition for each Condition. This minimum number ranged between 64 to 82 across participants, with an average of 75. Grand averages for each Repetition and each Condition were then created and explored topographically and temporally to identify channels and periods of interest. This indicated that activity was greatest around centro-parietal electrodes. In the subsequent analysis, we chose to focus on FC_z and for each participant, the P3a peak was manually identified between 250-400 ms (although sometimes this could be slightly earlier or later) for each Condition (social, non-social) and each standard repetition (1st, 2nd, 3rd, 4th). The preceding trough was also identified and the amplitude at the trough was subtracted from the amplitude at the peak in order to extract the positive change in amplitude attributable to the P3a. This change in amplitude in microvolts is used here as the dependent variable and is referred henceforth as the P3a amplitude.

4.2.3. Analysis Plan

The P3a amplitude was the dependent variable in this analysis. First, I conducted a repeated-measures ANOVA on the P3a amplitude only to the first standard presentation, to analyse whether this initial response to the standard tone was different in those with Autism or ADHD. Next, a repeated-measures analysis of variance was used with two within-subject factors: Condition (Social or Non-Social), Repetition (1st, 2nd, 3rd, 4th). This analysis evaluated whether profiles of habituation to the standards were different in those with autism. Two between-subject factors were modelled in (Autism and ADHD), each with two levels (Yes, No). Before these main analyses, the effect of Order of presentation (Social or Non-Social condition presented first) was evaluated without inclusion of the clinical factors. This was done to ensure that the order of presentation did not impact P3a and habituation of the P3a.

4.3. Results

*4.3.1. P3a response to the first standard (*initial orienting responses*)*

First, a repeated-measures ANOVA with Condition (Social, Non-Social) was run with only Order of Presentation (Social or Non-Social condition presented first) as a between-subjects factor. There was a main effect of Condition ($F(1, 85) = 7.26$, $p = .009$, $\eta^2_p = .08$). This was driven by the social condition eliciting higher P3a than the non-social condition (Mean difference ± S.E. = .39 ± .15) (see Fig 4.1).

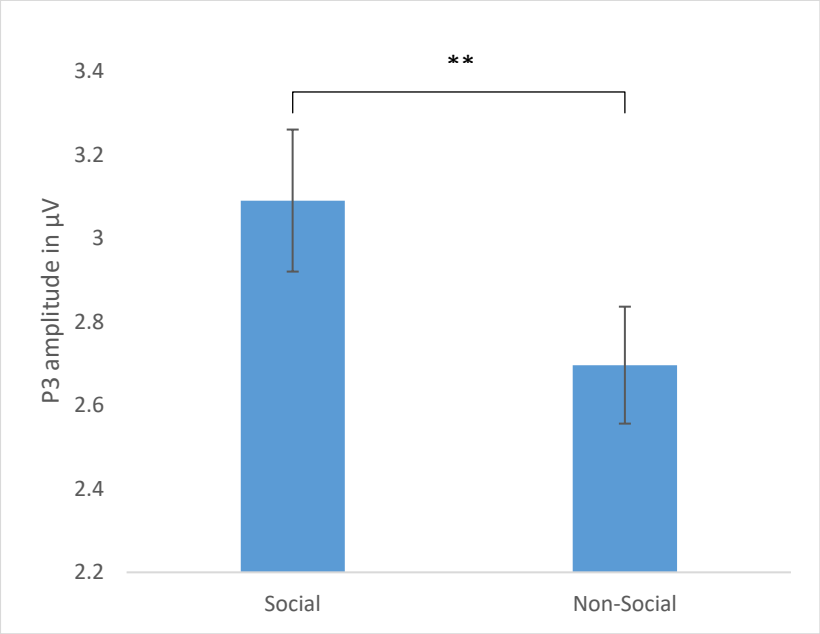


Figure 4.1. Averaged P3a amplitudes (in µV) to the 1st standard.

Bars show the mean (±1 standard error) average P3a amplitudes (plotted on the y-axis). These data are split by Condition (Social, Non-Social). Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

There was no main effect of Order of Presentation ($F(1, 85) = 1.38$, $p = .24$, $\eta^2_p = .02$) and Order of Presentation did not interact with Condition ($F(1, 85) = .24$, $p = .63$, $\eta^2_p = .00$). Therefore, in subsequent analysis of clinical effects, Order of Presentation was not included as a covariate.

Next, Autism and ADHD were modelled into the repeated-measures ANOVA. In this model, the residuals demonstrated a positive skew, due to the presence of two outliers. The results did not change when these outliers were excluded, and therefore we did not exclude them. We tested any significant between-group differences using follow-up non parametric pairwise comparisons.

The main effect of Condition continued to be present in this model ($F (1, 83) = 8.28$, $p = .005$, $\eta^2_p = .09$). There was no main effect of Autism ($F (1, 83) = .14$, $p = .71$, $\eta^2_p = .00$) and Autism did not interact with Condition ($F (1, 83) = .87$, $p = .35$, $\eta^2_p = .01$). There was no main effect of ADHD ($F (1, 83) = .62$, $p = .43$, $\eta^2_p = .01$) but there was an interaction between ADHD and Condition ($F (1, 83) = 6.98$, $p = .01$, $\eta^2_p = .08$). The three-way interaction between Condition*Autism*ADHD was non-significant ($F (1, 83) = .00$, $p = .99$, $\eta^2_p = .00$). The interaction between ADHD and Condition was driven by the main effect of Condition being present only for those without ADHD (who showed significantly higher P3a in the social as compared to the non-social condition) while those with ADHD did not show this difference in P3a between conditions. Given the focus of this thesis on autism, these effects are described more fully in Appendix E.

4.3.2. P3a habituation to repetition of standard

A RM ANOVA was conducted using Repetition (4 levels: Standard 1, 2, 3, 4) and Condition (2 levels: Social, Non-Social) as within-subjects factors and Order of Presentation (Social or Non-Social condition presented first) as a between-subjects factor. Order of Presentation did not interact with Repetition (this analysis is more fully provided in Appendix E), and thus did not influence the habituation response (which was the primary focus of interest in this analysis); therefore, it was removed from all subsequent analyses. In order to test whether profiles of habituation were different in participants with Autism or ADHD, I ran the model with clinical between-subject factors included. Residuals in this model were normally distributed.

There was a main effect of Repetition (Greenhouse-Geisser F (2.75, 228.62) = 2.75, p = .048, η^2_p = .032). There was no main effect of Condition (F (1, 83) = .48, p = .49, η^2_p = .01) but the main effect of Repetition was modulated by Condition: Condition*Repetition F (3, 249) = 3.79, p = .01, η^2_p = .04. Follow-up pairwise comparisons revealed that the main effect of Repetition was elicited by the first standard eliciting significantly higher P3a amplitude as compared to the 2nd (p = .005), 3rd (p = .057) and 4th (p = .04) standards, thus, there was quick habituation. However, this effect of Repetition was present only in the Social condition (where the 1st standard was significantly different than the 2nd (p < .001), 3rd (p = .014) and 4th (p < .001) standards), but not in the non-Social condition (where the differences between the 1st and subsequent standards were non-significant (2nd: p = .761; 3rd: p = .6; 4th: p = .79) (see Fig 4.2).

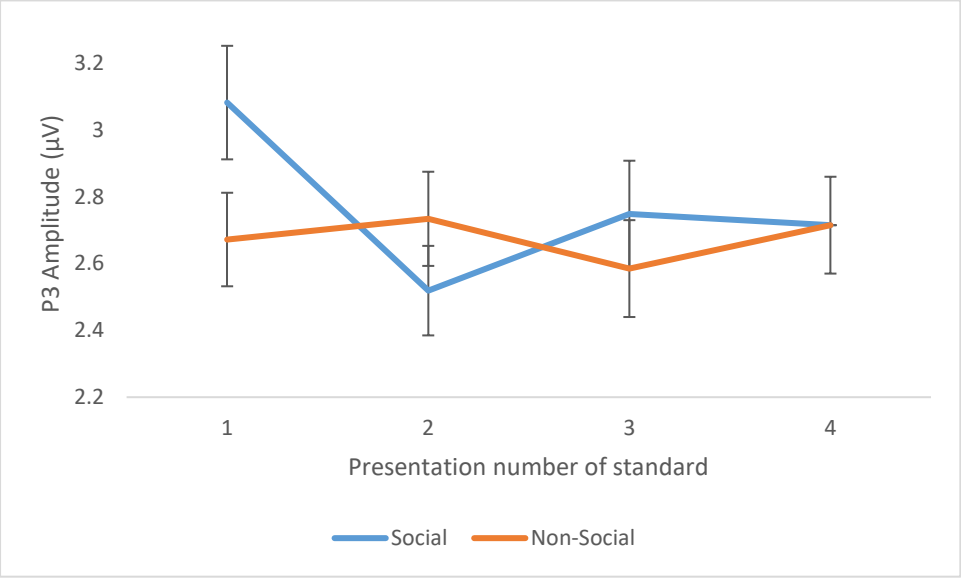


Figure 4.2. Main effect of Repetition

Bars show the mean (±1 standard error) average P3a amplitudes (in µV) (plotted on the y-axis). These data are split over the standard presentation (4 repetitions of standards) and condition (social, non-social). For the social condition, the difference between the 1st standard and all subsequent standards is significant; this is not the case for the non-social condition.

There was no main effect of Autism (F (1, 83) = .05, p = .82, η^2_p = .00), and no interaction between Repetition and Autism (Greenhouse-Geisser F (2.75, 228.62) = .17, p = .90, η^2_p = .00). There was no main effect of ADHD (F (1, 83) = .00, p = .97, η^2_p = .00), and no interaction between Repetition and ADHD (Greenhouse-Geisser F (2.75, 228.62) = 1.37, p = .25, η^2_p = .02). There was a significant three-way interaction between Condition, Repetition and ADHD (F (3, 249) = 3.54, p = .015, η^2_p = .04). This is more fully described in Appendix E since it is not relevant to research questions being addressed in this analysis. There was no such three-way interaction between Condition, Repetition and Autism (F (3, 249) = .72, p = .54, η^2_p = .01) and no four-way interaction between Condition, Repetition, Autism and ADHD (F (3, 249) = .42, p = .74, η^2_p = .01).

There was a trend towards significance in the interaction between Condition, Autism and ADHD (F (1, 83) = 3.07, p = .08, η^2_p = .04). I investigated this interaction at each level of Autism and found no significant interaction between Condition and ADHD at either level of Autism: Autism Present F (1, 41) = .66, BH-corrected p = .56 η^2_p = .02; Autism Absent F (1, 42) = 3.04, BH-corrected p = .178, η^2_p = .07. I then investigated this interaction at each level of ADHD and found that this interaction was not significant for participants with ADHD: F (1, 44) = .07, BH-corrected p = .786, η^2_p = .00. However, I found a significant interaction between Condition and Autism for participants without ADHD: F (1, 39) = 5.51, BH-corrected p = .096 η^2_p = .12. While this was a trend-level interaction, given that this is related to an a-priori hypothesis based on prior literature, we followed it up with pairwise comparisons. The interaction was driven by neurotypical participants showing a significant difference in P3a amplitude with higher P3a to the social as compared to the non-social condition (Mean difference ± S.E. = .32 ± .13, BH-corrected p = .03). Participants with Autism-only did not show this difference in P3a amplitudes to the social as compared to the non-social condition (Mean difference ± S.E. = .18 ± .16, BH-corrected p = .355) (see Fig. 4.3).

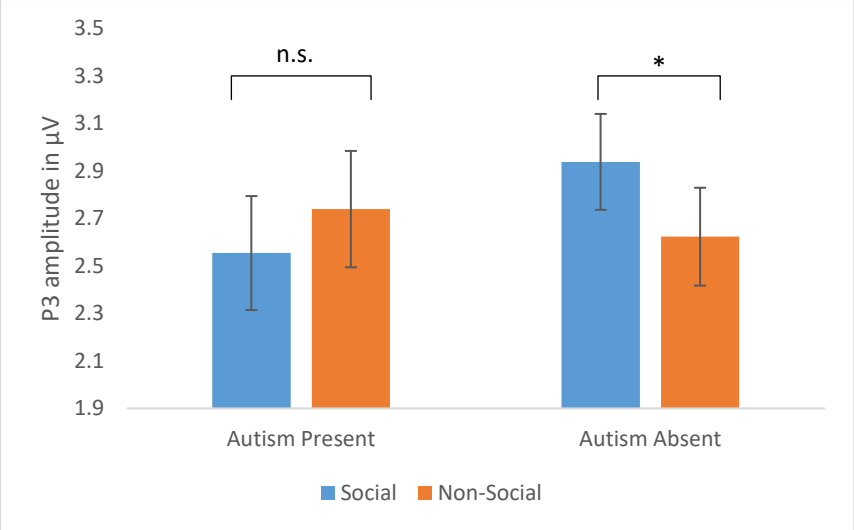


Figure 4.3. Condition*Autism interaction in neurotypical and Autism-only participants

Averaged P3a amplitudes (in µV)

Bars show the mean (±1 standard error) average P3a amplitudes (plotted on the y-axis). These data are split by Condition (Social, Non-Social) and Autism (Present, Absent). Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

In order to understand which autistic symptoms this above effect (absence of increased P3a to social condition in relation with autism) relates to, I investigated relationships between the averaged P3a (across repetitions) separately in the social and the non-social conditions with autistic symptoms as measured by the SCQ Social, Communication and RRB subscales. P3a in the Social condition was negatively correlated with SCQ Social Interaction symptoms: r = -.22, p= .04, [-.41, -.06]. P3a in the Social condition did not relate with SCQ Communication (r = -.09, p = .39, [-.297, .075]) or SCQ RRB (r = .05, p = .62, [-.27, .28]) scores. Finally, P3a in the Non-Social condition were not related with SCQ Social Interaction (r = -.18, p = .098, [-.37, .01]), SCQ Communication (r = -.02, p = .85, [-.23, .19]) or SCQ RRB (r = .11, p = .295, [-.14, .32]) scores. Given the significant difference in IQ between the comorbid and NT group, I conducted additional analysis of the correlation between the P3a in the Social condition and SCQ Social Interaction symptoms, to ensure these findings were not influence by group differences in IQ. IQ was not related to P3a in the Social condition (FSIQ: r = -.04, p = .73, [-.23, .21]; VIQ: r = -.07, p = .51, [-.26, .14]; PIQ: r = .01, p = .92, [-

.19, .29]) and partial correlations controlling for FSIQ did not impact the relationship between SCQ Social Interaction symptoms and P3a in the Social condition (r = -.23, p = .03, [-.4, -.07]).

4.3.3. Secondary Analyses on Autism Arousal Subgroups

I investigated whether the autistic subgroup with a hyperaroused profile (as defined in Chapter 3) demonstrated reduced habituation of the P3a to repeating standards, as compared to the hypoaroused subgroup. Therefore, in this analysis, I conducted a repeated measures ANOVA with Condition (Social, Non-Social), Repetition (Standard 1, 2, 3, 4) as within-subjects factor and Autism Subgroup (Hyperaroused, Hypoaroused) as a between-subjects factor.

Autism Subgroup did not have a main effect in this analysis: F (1, 37) = .01, p = .95, η^2_p = .00. There was no significant interaction between Repetition*Autism Subgroup found: F (3, 111) = .41, p = .74, η^2_p = .01. Further, there was no Condition*Autism Subgroup interaction : F (1, 37) = .19, p = .67, η^2_p = .00; or a Condition*Repetition*Autism Subgroup interaction: F (3, 111) = .07, p = .98, η^2_p = .00.

In Table 4.1, the mean P3a for the Social condition (since the main effect of Repetition was specific to the Social condition) as well as the effect sizes of the differences in the means between conditions within each autism subgroup (hyperaroused and hypoaroused) are provided. As can be seen, a habituation effect was seen with the P3a being larger to the first standard than the second, and differences in means of P3a between the first and the second standard appear to be small to medium in size. The subgroups do not differ in this and appear to show a similar effect, with the hyperaroused group showing a slightly larger habituation response than the hypoaroused subgroup (this is in a direction opposite to our prediction, we expected the hyperaroused subgroup to show less habituation). Further, P3a amplitudes appear to be numerically larger to both the first and the second standards in the hyperaroused as compared to hypoaroused subgroups, suggesting heightened orienting/processing of the stimuli.

Table 4.1. Mean P3a (in μV) to the 1st and 2nd Standards in Hyper and Hypo aroused subgroups of autistic participants

Autism Subgroup	**P3a to the 1st Standard**	**P3a to the 2nd Standard**	**Between-groups Effect Size Cohen's d**
Hyperaroused	3.08 (2.06)	2.45 (1.37)	0.19
Hypoaroused	2.75 (1.38)	2.30 (1.19)	0.12
Within-groups Effect Size Cohen's d	0.39	0.32	

Data shown for all measures except Effect Size are mean P3a amplitudes with standard deviation in parentheses. These are split by the Presentation number of the Standard- 1st or 2nd. Effect sizes are Cohen's d values.

4.4. Discussion

In this chapter I investigated profiles of orienting to and habituation to repeating standards in the auditory oddball task using the P3a. We were interested in profiles of exogenous orienting of attention to simple sensory (auditory) stimuli and habituation to repetition of these stimuli. Atypicalities in these fundamental abilities would have far-reaching consequences for flexible distribution of attention and adaptive functioning (McDiarmid et al., 2017; Ramaswami, 2014).

First, we found subtle differences in orienting of attention to the standards, as indexed by the P3a, in the Autism-only group. There was no main effect of Autism; therefore, P3a was not generally atypical throughout the task in autistic individuals as compared to neurotypical individuals. When analysing P3a to four repeating standards in the social and the non-social blocks of auditory stimuli, neurotypical individuals showed increased P3a amplitudes in the social as compared to the non-social conditions.

However, Autism-only participants did not show this effect, showing similar P3a amplitudes in each condition. However, we note that this was a trend-level effect. We were underpowered for three-way interactions and given that this was an a-priori hypothesis, we decided that it would be useful to investigate the direction of the effect, which was in line with our hypothesis. The finding is in line with other reports of reduced P3a amplitude to speech as compared to non-speech stimuli in autism (Čeponiene et al., 2003; Lepistö et al., 2005). It is important to note here that the standards in either condition were non-social simple tones, so this effect appears to be driven by the presence of social as compared to non-social deviants, which might increase orienting broadly to the standards as well. A possible interpretation of this effect could be that the higher salience of the social deviants increased tonic arousal thus facilitating phasic processing of the standards as well; this interpretation is partially supported by evidence that social information elicits higher autonomic arousal responses as compared to non-social information (Louwerse et al., 2014). However, we saw no differences in tonic autonomic arousal modulated by social or non-social conditions in Chapter 3, and therefore our data does not support this interpretation. It is important to understand these subtle differences, because they point towards atypicalities in attention within autism-only individuals where neurotypical individuals show sensitivity to changes in context, that autistic individuals do not and this might be relevant to how they respond to real-life daily-living contexts.

Importantly, we found that across the sample of SAAND participants, the P3a to the social tones was inversely related with SCQ Social Interaction Subscale scores, such that increased P3a in the social block was associated with lower symptoms of social interaction difficulties. This was a reliable correlation, with confidence intervals not crossing zero, and it remained after controlling for IQ as well, suggesting that it was specific to autistic symptoms. Importantly, there was no such relationship found for P3a in the non-social condition, and P3a in the social condition was not related to SCQ Social Communication or SCQ RRB subscale scores. This analysis provides some confidence for the above interaction that we were underpowered for and suggests that autistic symptoms (specifically of social interaction) are associated with reduced orienting to non-social simple tones, in the context of social deviants, suggesting that context modulates attention differently in autism.

Importantly, while this above effect was specific to autistic individuals without ADHD in our sample, when analysing P3a to the presentation of the first standard only, we found a similar effect in association with ADHD. Specifically, P3a amplitude only to the first standard tone was higher for those without ADHD (i.e. neurotypical and autism only participants) in the social as compared to the non-social condition but those with ADHD (i.e. ADHD only and comorbid Autism and ADHD) did not show this effect. This has not been reported in the literature previously to my knowledge, and it may be linked to subtle differences in initial responsivity to social as compared to non-social stimuli in ADHD which normalizes with repetition, possibly driven by the profile of hypoarousal seen earlier in Chapter 3. It is interesting to note that autistic individuals with co-occurring ADHD were similar to individuals with ADHD-only, showing an absence of increased orienting to the first standard in the social condition. When analysing P3a amplitude to all four standards, comorbid individuals were again similar to ADHD individuals and neurotypical participants in showing higher P3a to social as compared to non-social conditions. In comparison, autistic participants (without ADHD) diverged from the neurotypical profile when their response to all the repeating standards was analysed, exhibiting an absence of this preferential orienting to standards in the social condition (as indexed by P3a amplitude). These effects reveal a complex story, in that; it is unclear why the pattern is different when looking only at the first standard versus to repeating standards. It appears that ADHD and autism are both then associated with differential effects of stimulus salience. Importantly, in this analysis (similar to Chapter 3), comorbid autism and ADHD participants showed profiles similar to ADHD- only participants in this task, rather than autistic participants (without ADHD).

We did not observe clear differences in habituating to repeating standards in Autism or ADHD participants. While this is in line with the limited literature in ADHD (McDiarmid et al., 2017), our findings do not support theories of reduced habituation in autism (Hutt et al., 1964; Ramaswami, 2014; Rubenstein & Merzenich, 2003). This contrasts with evidence showing reduced or slower habituation to simple sensory stimuli when measured using earlier ERPs such as the P1 (Kolesnik et al., 2019; Ruiz-Martinez et al., 2020). Interestingly, it appears that these early differences do not impact subsequent

habituation of attention to repeating standards. This is a useful distinction to make, since it suggests that while there may be atypicalities in habituation at the level of sensory discrimination, the later orienting of attention may still be typical. This is a new finding in the literature, which requires replication with larger sample sizes and a fuller analysis of all (early and late) ERPs in the same group, which has not been carried out to my knowledge. When interpreting this in light of the LC model, it suggests that despite differences in tonic arousal, the late phasic LC response shows typical habituation to repeating stimuli, but it might be atypical in how it is modulated by top-down input with regard to salience attributions, with social information not eliciting a preferentially larger orienting response (Nieuwenhuis et al., 2005).

Finally, we found no evidence for the hypothesis that atypicalities in habituation would be linked to a hyperarousal profile (Hutt et al., 1964). We compared the hyper- and hypo-aroused subgroups of autistic participants in their orienting and habituation responses to the repeating standards in the social condition. We did not compare them in the non-social condition, since the non-social condition did not reliably elicit a habituation response overall in all participants. Within the social condition, the hyper- and hypo-aroused subgroups did not differ from one another in their habituation profile. The hyperaroused subgroup did appear to show a numerically larger P3a to both the first and the second standards, indicating hyper-reactivity; but they habituated quickly similar to neurotypical participants and showed a numerically larger reduction than the hypoaroused subgroup between the first and the second standards. This is in line with the literature, where autonomic hyperarousal is linked with sensory over-responsivity (Green et al., 2015) and it is interesting to note that in line with this, we also found that the hyperaroused group shows more sensory avoidance behaviours (on the Sensory Profile as discussed in Chapter 3), possibly as a coping mechanism for this sensory hyper-reactivity. However, our findings are not in line with evidence that then suggests that hyperarousal would result in reduced habituation (Schoen et al., 2008). This is an important distinction and profiles of habituation in relation with arousal have not been systematically investigated. Further research is needed to clarify the links between arousal, cognition, habituation and sensory processing profiles.

In this chapter therefore, we found that exogenous orienting of attention and habituation to repeating stimuli was typical in autistic participants. Autistic participants without ADHD did not show larger P3a in the social as compared to non-social condition, as was observed in the neurotypical participants. Thus, stimulus salience appears to impact autistic participants with and without ADHD differently. Finally, a hyperaroused autism subgroup showed larger P3a to the auditory stimuli than the hypoaroused subgroups, suggesting a difference in orienting but no differences in habituation.

In the next chapter, I tackled this issue of reduced salience of social information in autism more directly. I investigated habituation of attention to repeating stimuli that were more complex. Since salience of stimuli appears to modulate attention differently in autistic participants, I manipulated salience in various ways to identify whether it is the social-ness of stimuli or their complexity that drives the effects.

The next chapter is an article that has been currently submitted to a journal to consider for publication. Results from piloting of task used in this chapter can be found in Appendix F.

Chapter 5. What is the effect of stimulus complexity on attention to repeating and changing information in Autism?

Abstract

Slower habituation to repeating stimuli characterises Autism, but it is not known whether this is driven by difficulties with information processing or an attentional bias towards sameness. We conducted eye-tracking and presented looming geometrical shapes, clocks with moving arms and smiling faces, as two separate streams of stimuli (one repeating and one changing), to 7-15 years old children and adolescents (n=103) with Autism, ADHD or co-occurring Autism+ADHD, and neurotypical children (Study-1); and to neurotypical children (n=64) with varying levels of subclinical autistic traits (Study-2). Across both studies, autistic features were associated with longer looks to the repeating stimulus, and shorter looks to the changing stimulus, but only for more complex stimuli, indicating greater difficulty in processing complex or unpredictable information.

What is the effect of stimulus complexity on attention to repeating and changing information in Autism?

Autism Spectrum Disorder (hereafter referred to as autism) affects an estimated 1% of the population in the UK (Laurie & Border, 2020) and is characterised by impairments in social communication and interaction and presence of repetitive and restricted behaviours (American Psychiatric Association, 2013). Autistic individuals show atypical attention to the world, for example, in the form of reduced spontaneous attention to social information (Fletcher-Watson et al., 2009; Franchini et al., 2017), an intense focus on specific aspects of the world (American Psychiatric Association., 2013), and a preference for repetition and sameness (Pierce, Conant, Hazin, Stoner, & Desmond, 2011). However, the exact nature of attentional differences, and what processes or impairments underlie them, remains unclear. It has been suggested that early differences in the ability to habituate might contribute to some of the above attentional features (McDiarmid et al., 2017; Ramaswami, 2014).

Habituation refers to a cognitive process by which attention to a repeating stimulus decreases over time (Groves & Thompson, 1970; Schmid, Wilson, & Rankin, 2014). Traditionally, habituation has been studied through preferential-looking paradigms in which look durations are measured to repeated presentations of a stimulus (Csibra, Hernik, Mascaro, Tatone, & Lengyel, 2016). Look durations (i.e. durations of time that the participant orients their eyes to fixate upon a stimulus) in such paradigms measure the balance between a drive to look and a competing drive to look away (Schoner & Thelen, 2006). Widely accepted models of habituation (Groves & Thompson, 1970) suggest that look durations to a repeating stimulus increase until an internal representation has been formed that matches the stimulus (and thus, the stimulus has been 'learnt'), after which, look durations decrease until they reach an asymptotic level. Look durations in these paradigms have been reliably linked with information processing and learning, such that higher rates of decrease in look durations (or quicker habituation) are associated with better long term outcomes on standardized measures of intelligence (Colombo &

Mitchell, 2009); and individual differences in habituation during the first year of life predict later cognitive functioning (McCall & Carriger, 1993).

It is also theorized that the drive to look away from an already processed stimulus within such habituation paradigms represents a novelty bias; a pervasive information foraging tendency in all animals that serves an adaptive function of drawing attention away from what is known, towards what is novel, unknown and potentially informative (Cohen et al., 2007; Laucht, Becker, & Schmidt, 2006; Schoner & Thelen, 2006). Indeed, from infancy onwards, a balance between exploitation (of the known) and exploration (of the unknown) is essential for optimal adaptation to the environment so that one is alert to pertinent new information but at the same time can focus on a given task (Cohen et al., 2007). If there is a bias towards exploitation or exploration, this could impact optimal foraging and, consequently, learning and adaptive functioning (Gliga et al., 2018).

There is evidence for reduced habituation in autistic individuals for both simple stimuli (e.g., tones and naturalistic sounds (Guiraud et al., 2011; Hudac et al., 2018)) and more complex stimuli such as faces (Kleinhans et al., 2016; Webb et al., 2010). However, it is unclear whether atypical habituation in autism is driven by impaired information processing, leading to slower learning/acquisition of knowledge about the repeating stimulus, or an information foraging style that biases against novelty and change in favour of sameness and predictability. Evidence that habituation deficits in autism are specific to certain stimuli (present for faces but not for houses) (Kleinhans et al., 2016; Webb et al., 2010) implicates slower processing of a repeated stimulus rather than biases against novelty, because complex stimuli, such as dynamic, multimodal and social stimuli, are more difficult to process and would therefore challenge these basic learning processes more extensively. On the other hand, there is evidence of an attentional bias away from novelty, and towards attending to previously explored information at the cost of attending to unknown information (Elison et al., 2012; Pellicano et al., 2011; Sasson et al., 2008). Currently, it remains unknown whether looking longer at a repeating stimulus reflects impaired learning of the stimulus or a preference for repetition. In the habituation literature, it is not possible to disentangle

these competing accounts because only a single, repeating stimulus is usually presented and therefore an attentional bias towards repetition over novelty cannot be measured.

To separate out these competing accounts we adapted an eye-tracking paradigm that was first published by Vivanti et al. (2018), in which two competing stimuli are presented simultaneously in the left and right parts of a screen, one of which remains constant while the other one changes. The advantage of this paradigm (instead of traditional paradigms that present only a repeating stimulus) is that one can capture competing drives to look at the repeating versus novel stimuli. In the first few trials, preference for either stimuli is likely to not be evident. However, over trials, habituation should occur to the repeating stimulus and preferential looking towards the changing stimulus should increase. The novelty bias, i.e., increased attention to the changing stimulus, thus becomes more prominent after successful learning or processing of the repeating stimulus (Fantz, 1964). Using this paradigm, Vivanti et al. (2018) reported that autistic pre-schoolers required more trials than neurotypical controls to meet habituation criterion, thus exhibiting slower habituation. Using rates of change in total fixation durations per trial to the repeating and changing stimuli, they also reported that while the autistic children (similarly to neurotypical toddlers) showed reduced looking to the repeating information over successive trials, they also showed reduced looking to the changing stimulus over time, whereas neurotypical toddlers increased looking to the changing stimulus. The authors interpreted this to reflect a reduced bias to attend to novelty in autistic participants, rather than an effect of slower learning. However, one could argue that if autistic children were slower to process the repeating stimulus as evidenced by slower habituation, they would then also have been slower to show preference for the changing stimuli. Therefore, this effect (reduced looking to the changing stimulus) could be driven by slower habituation rather than reduced preference for novelty. Further work is needed therefore to fully characterise profiles of habituation and novelty biases in autism.

One way to directly address the role of information processing is by manipulating stimulus complexity. Simpler stimuli elicit quicker habituation than complex stimuli (Schoner & Thelen, 2006). We reasoned that if autistic people tend to spend longer looking at a repeating stimulus because they are slower to

habituate, more complex stimuli, which require more processing, should elicit a greater differential between repeating and changing stimuli. Conversely, if the findings are driven by information foraging differences in autistic individuals that bias them against attending to novel or changing information, this will be reflected in a significantly greater proportion of time looking towards the repeating stimulus than the changing stimulus and this effect will occur irrespective of the complexity of the stimulus. To investigate these alternative predictions, we adapted the task used by Vivanti et al. (2018), which comprised one stimulus condition with simple shapes that rotated and zoomed towards the participants. We added two conditions: one consisted of complex stimuli (clocks with moving arms); another used social (smiling faces) stimuli (as shown in Figure 5.1). These manipulations allowed us to test whether differences in attention to repeating and changing stimuli were more pronounced for complex than simple stimuli and also allowed us to test whether these effects were more pronounced for social stimuli, given the large literature suggesting greater impairments in the social domain in the autistic population (Chita-Tegmark, 2016; Dawson, Bernier, & Ring, 2012). We reasoned that if social stimuli are one example of complex stimuli, the faces and clocks stimuli used in our adapted habituation paradigm should yield similar effects to one another, and larger effects than the simple shapes condition. If, however, autistic individuals show a unique difficulty with social stimuli, the effects would be specific to this condition, over and above those for the non-social simple (shapes) and non-social complex (clocks) conditions. Faces and clocks were selected as social and non-social examples of more complex stimuli because they have a higher number of features to process, that hold informative value compared to the geometric shapes.

In addition, we developed a more sensitive measure to capture habituation. Vivanti et al. (2018) used a total fixation duration measure; however, in a two-stimulus habituation paradigm, this measure might also capture other processes apart from information processing, such as revisits to the repeating stimulus to ensure that it has not changed, or even a preference for repetition. We therefore chose to use the longest look duration per trial (comprised of one or more fixations within a stimulus) to each stimulus (repeating and changing). This is more likely to reflect looks made for the purpose of information processing and learning in a given trial (Colombo & Mitchell, 2009). We summarised the pattern of

change in look durations over trials by using a slope coefficient, with decreases in look durations reflected in a negative coefficient and increases in a positive coefficient. At the beginning of the task, we expected to observe equally long look durations to both the repeating and changing stimuli. If a person is habituating, then over time, the trial-by-trial longest look durations should decrease for the repeating stimuli and increase for the changing stimuli, since the latter hold novel information. If there is a bias for either the repeating or changing stimulus, this will emerge as an increase in look durations towards that stimulus over time.

In neurotypical individuals we predicted a rapid decrease in longest look durations to the repeating stimulus over time and an increase in longest look durations to the changing stimulus over time, reflecting rapid habituation and then an information foraging drive towards the novel stimulus. This would be reflected in a negative slope coefficient of look durations to the repeating stimulus and a positive slope coefficient to the changing stimulus. In autism, we predicted that if the tendency to spend longer looking at a repeating stimulus is driven by slower information processing (and therefore slower habituation), there will be a reduction in look durations over time to the repeating stimulus and an increase to the changing stimulus, but the slopes will be flatter than in neurotypical individuals, reflecting slower change over time. This effect will be more pronounced in the conditions with higher stimulus complexity due to the greater difficulty processing these stimuli. Conversely, if driven by a bias against novelty towards sameness, the effect will not vary by stimulus complexity and will manifest in a significant positive slope to the repeating stimulus and a flat or negative slope to the changing stimulus, i.e. a reversal of the neurotypical effect. We also explored whether these atypical features of autism are specific to social stimuli or whether they also occur when presented with non-social stimuli that have a similar level of featural complexity.

We used this task with two populations. In Study 1, we compared children with and without clinically diagnosed autism and we also compared autism with another neurodevelopmental disorder, attention deficit hyperactivity disorder (ADHD). In Study 2 we recruited a general population sample of children with varying levels of autistic traits.

5.1. Study 1

The aim of the first study was to determine whether differences in attention to repeating vs changing stimuli reflect slower processing of a repeated stimulus or atypical biases away from novelty in autistic children, by manipulating stimulus complexity. Therefore, in this study, we included children with a clinical diagnosis of Autism Spectrum Disorder and neurotypical children. In addition, we included a group of children with ADHD and a group of children with co-occurring Autism and ADHD.

ADHD is highly co-occurrent with autism (Leitner, 2014) but this is often not addressed in research. There is inconsistent evidence for atypical habituation in ADHD; with preliminary evidence for quicker habituation to rewards in those with ADHD (McDiarmid et al., 2017). ADHD is also tentatively associated with biases towards novelty-seeking and exploration (Gliga et al., 2018) and could therefore be linked with information foraging biases opposite to the ones associated with autism. Given the high comorbidity between these conditions, investigating how these potentially opposing biases are manifest in those with comorbidity might illuminate shared mechanisms between autism and ADHD. Therefore, the aim of our first study was to determine how attention to repeating vs changing information is influenced by stimulus complexity and whether any unique attentional patterns are evident within different clinical groups with a diagnosis of autism, ADHD, or both.

Specifically, we predicted a profile of relatively greater attention to the repeating stimulus over the changing stimulus in children and adolescents with autism, as outlined in the general introduction above. For children with ADHD, our hypotheses were more tentative, given that such tasks have not been used with this population before. We expected them to show a bias towards novelty, to the extent that they will look more often at the changing stimulus (Sethi, Voon, Critchley, Cercignani, & Harrison, 2018). We also expected, given profiles of hyperactivity and inattention (American Psychiatric Association, 2013), that they might be slower to reduce their attention to repeating information due to inefficient processing and therefore, flatter slopes of change in attention towards both stimuli. Again, given lack of research in the area, we anticipated different possible effects for children with co-occurring autism and ADHD. Given evidence of opposing information foraging biases in autistic and

ADHD populations (towards novelty in ADHD and against novelty or towards sameness in autism), we anticipated that comorbid children might show neither, with the two opposing risks combating each other. Alternatively, the group with co-occurring autism and ADHD might be more similar to the autistic children, or to the ADHD children, reflecting that on these measures they share the profile of one of these populations. Finally, the comorbid group might be a separate nosologic entity and thus might show a completely distinct profile (Rommelse et al., 2011) from the other children. We tested these predictions in a factorial design where ADHD and ASD were modelled as two between-subjects' factors.

5.2.Methods

5.2.1. *Sample*

The present work is based on data collected for the SAAND Study (Studying Attention and Arousal in children and adolescents with Neurodevelopmental Disorders). 103 participants aged 7-15 years took part, including 30 neurotypical participants, 18 with Autism, 23 with ADHD and 32 with both Autism and ADHD ('Autism+ADHD'). Participant demographic characteristics are presented in Table 5.1.

Participants completed a battery of EEG and eye-tracking tasks, including the task presented here. Study procedures were approved by the UK National Research Ethics Committee (REC reference 17/EM/0193 and the Health Research Authority (HRA; IRAS research project ID 220158). Clinical participants were recruited through local support groups or were referred to the study by paediatricians, child and adolescent psychiatrists or mental health nurses in local Child and Adolescent Mental Health Services (CAMHS) or the special needs departments of local schools. Neurotypical participants were recruited from local schools and from a database of volunteers held by the School of Psychology, University of Nottingham, UK. Participants in the clinical groups either already had a clinical diagnosis or were referred to the study by clinicians because of suspected ADHD or autism. Consensus research diagnoses were made in consultation with two experienced child and adolescent psychiatrists (PK and

CH). The measures used to inform research diagnoses were: Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000), Social Communication Questionnaire (SCQ) (Rutter et al., 2003), Conners' Rating Scales (CRS-3) (Conners, 2008), the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) (Lord et al., 2015) (completed by IA and PK who have research accreditation for the tool) and the Wechsler Abbreviated Scales of Intelligence (WASI-II) (Wechsler, 2011) to obtain a measure of verbal and non-verbal cognitive functioning for all participants. Parent and teacher data were available for the participants on the SCQ and CRS-3. Due to missing data on the teacher measure, in this study we report the parent CRS and SCQ scores. In this study, we used parent-reported SCQ (Total score and social communication, social interaction and restricted and repetitive behaviours subscale scores) and CRS (Hyperactivity-Impulsivity and Inattention subscales) scores as indices of symptom severity of Autism and ADHD respectively. Further information about inclusion/exclusion criteria as well as allocation of participants into clinical groups is available in Appendix G.

5.2.2. *Eye-Tracking Task*

We adapted the novelty versus repetition task from Vivanti et al. (2018). In this task, two streams of dynamic stimuli are presented adjacent to one another, one each in the left and right sides of the screen, on a computer screen. In one stream, a repeating stimulus is presented and in the other, a changing stimulus is presented. In the original task (Vivanti et al. 2018), the stimuli were dynamic shapes, rotating and looming towards the viewer. We adapted these original stimuli but retained the timing and display parameters of the original study.

In addition, we added two conditions to enable us to measure the effects of social-ness and complexity of stimuli (see Figure 5.1). We added a social condition in which the stimuli consisted of movies of faces breaking into smiles taken from the UvA-NEMO Smile Database (Dibeklioğlu, Salah, & Gevers, 2015). The videos are shot under controlled illumination conditions and are in RGB colour. We cropped the videos to size them similarly to the stimuli from other conditions.

We also created a non-social condition in which we used animations of clocks with moving arms as stimuli. Clocks were sized similarly to the faces in the social condition. Clocks were of different colours (similar to non-social simple condition), and the arms moved from different starting points to different endpoints. The clocks were designed to be more complex than the shapes since there was more information within them to process. Clocks have multiple features that have informative value and the movement of internal features changes the meaning to be drawn from the stimulus, similar to facial features. Importantly, the faces and clocks differ primarily in their social status but are approximately equivalent in global and featural complexity (see Fig 5.1). Further information about task design is available in Appendix G.

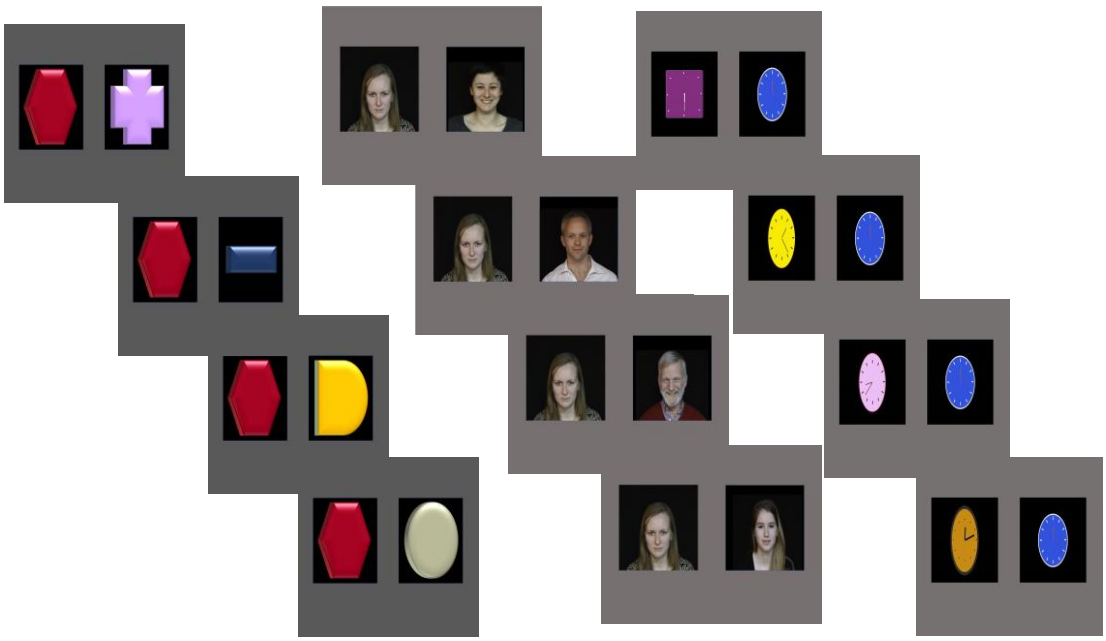


Figure 5.1. Examples of stimuli used.

From left to right, examples of stimuli from Non-Social Simple Condition, Social Condition and Non-Social Complex Condition.

5.2.3. *Procedure*

The task was delivered on Eyelink 1000 Plus after a 9-point gaze calibration was completed. Eye movements from both eyes were recorded without a chin-rest and children were seated approximately 60 cm from the screen. Eye movements were recorded at 500 Hz through a 25 mm lens, with an estimated accuracy of 0.25° to 0.5°. The task was presented on a 21.5'' LCD screen with a refresh rate of 60 Hz, placed immediately behind the eye-tracker.

This task lasted approximately 2 minutes, including calibration. It was a part of a 15-minute eye-tracking battery and was presented mid-way through another eye-tracking task. Participants were asked to pay attention to what was happening on the screen but were given no other instructions.

5.2.4. *Analysis Plan*

We extracted two measures from the task. The first, number of fixations to the screen, was a measure of task engagement, compared between groups to ensure that analysis of other measures was not influenced by any between-subject differences in task engagement. The second measure of interest was the rate of change in look durations to the repeating and changing stimulus over time. Interest areas were drawn around stimuli to capture any fixations falling within the area of the stimuli. A 'look duration' was defined as cumulative duration of consecutive fixations in the same interest area in a trial without shifting to another interest area. Therefore, for each trial, the longest look to the repeating and changing stimulus was extracted. We then computed the coefficients of the linear slope of the rate of change in these look durations to the repeating and changing stimulus in each condition (Non-Social Simple, Non-Social Complex, Social) separately. We expected a negative slope to the repeating stimulus across conditions, representing reduced looking to repeating information over time, and a positive slope to the changing stimulus, driven by longer looking to the changing information over time representing a novelty bias.

To analyse the engagement variable (number of fixations), we used repeated measures analyses of variance (ANOVA) with one within-subject factor: Condition with three levels (Non-Social Simple, Non-Social Complex, Social). Autism and ADHD were modelled as two between-subject factors with two levels each, 'Present' and 'Absent'. In our analysis of this variable we focussed on checking individual differences in task engagement. We therefore only report main effects of Autism or ADHD or interactions between these and the within-subjects Condition factor. For our main analysis on the Rate of change in Look durations, we included a second within-subjects factor Stimulus with two levels (Repeating, Changing).

For each dependent variable, we assessed common assumptions before testing hypotheses. Based on evidence that repeated measures ANOVAs are robust to assumptions of normality we carried out ANOVA with normal and non-normal dependent variables (Field, 2013). Mauchly's tests of sphericity was evaluated and where violated, we report Greenhouse-Geisser adjusted degrees of freedom. Interactions and main effects were followed up with appropriate analysis to characterise the simple effects.

Given differences between clinical groups on IQ, we used partial correlations to evaluate whether differences in IQ were associated with any effects of interest.

5.3. Results

Overall, the pattern of group differences reflected the group allocations, showing greater CRS scores in the ADHD and Autism+ADHD groups and greater SCQ scores in the Autism and Autism+ADHD groups. The clinical groups had lower IQ than the neurotypical group; however, this difference was statistically significant only between NT and Autism + ADHD group (see Table 5.1).

Table 5.1

Sample characteristics for Study 1

	Neurotypical (n=30)	**Autism (n=18)**	**ADHD (n=23)**	**Autism + ADHD (n=32)**	**Group Comparisons (p-value)**
Demographics					
Age	129.63 (29.29)	130.89 (25.05)	127.87 (27.14)	130.06 (18.36)	Ns (p^w>.1)
Gender M:F	17:13	11:7	15:8	24:8	Ns (p^w>.1)
WASI Full-scale IQ	116.2 (13.34)	104.61 (15.64)	108.61 (11.67)	102.06 (19.29)	p^w= .006[a]
SCQ					
Total	3.79 (3.71)	19.11 (5.98)	15.17 (6.96)	21.16 (6.23)	p^w<.001[b,c]
SCQ Social Interaction	1.25 (1.5)	7.56 (3.34)	4.91 (3.26)	7.68 (3.47)	p^w<.001[b,c]
SCQ Communication	1.82 (1.49)	5.61 (2.3)	4.61 (1.99)	6.39 (2.33)	p^w<.001[b,c]
SCQ RRB	0.5 (1.1)	4.56 (2.2)	4.04 (2.51)	5.42 (2.76)	p^w<.001[b]

CPRS					
Global Index	51.82 (13.45)	79.44 (12.59)	87.87 (4.25)	87.13 (5.32)	$p^w<.001^b$
Inattention	50.57 (9.75)	77 (12.48)	86.78 (6.64)	85.09 (6.41)	$p^w<.001^{b, d}$
Hyperactivity	52.32 (12.93)	76.44 (13.68)	87.83 (3.9)	87.38 (5.56)	$p^w<.001^{b,e}$

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are n male:female. WASI: Wechsler Abbreviated Scale of Intelligence; CPRS: Conners Parent Rating Scale (values shown are mean T-scores); SCQ: Social Communication Questionnaire

p-values in the table refer to the significance value of the main ANOVA, comparing the 4 groups on respective demographic characteristics; multiple comparisons for these variables are Bonferroni-corrected. p^w refers to the p value of Welch's F test carried out where homogeneity of variances assumption was violated; for these variables, post-hoc comparisons are corrected using Games-Howell method.

[a]NT>Autism+ADHD, [b]NT<Autism, ADHD, Autism+ADHD; [c]ADHD< Autism+ADHD; [d]Autism<ADHD, [e]Autism< ADHD, Autism+ADHD

5.3.1. *Number of fixations (control variable measuring task engagement)*

First, we analysed participants' number of fixations to the screen to ensure that all participants were attentive to the task at all levels of Condition. The between-subjects factor of Autism interacted significantly with Condition: F (2, 198) = 3.03, p = .05, η^2_p = .03. However, follow up pairwise comparisons comparing groups (Autism-Present, Autism-Absent) within each condition yielded no significant differences (all p>.1) (descriptive statistics provided in Appendix G). Main effects of Autism and ADHD were not significant: Autism: F (1, 99) = .008, p = .93, η^2_p = .00; ADHD: F (1,99) = .009, p = .92, η^2_p = .00.

5.3.2. *Rate of change in look durations*

We predicted that all participants would show reduced look durations over time to the repeating stimulus (indexed by a negative slope) and increased look durations over time to the changing stimulus (indexed by a positive slope). There was a main effect of Stimulus (F (1, 99) = 52.78, p = .000, η^2_p = .35). As predicted, this was driven by a significantly more positive slope for the changing stimulus (Mean ± S.E. = 40.04 ± 4.84) as compared to the repeating stimulus (Mean ± S.E. = -10.84 ± 3.68). There was also a main effect of Autism (F (1, 99) = 4.74, p = .032, η^2_p = .046). This was driven by those without Autism (neurotypical and ADHD-only: Mean ± S.E. = 20.03 ± 3.42) showing steeper slopes than those with Autism (Autism-only and Autism+ADHD: Mean ± S.E. = 9.17 ± 3.63).

There was an interaction between Condition and Stimulus (F (1.87, 185.25) = 8.74, p < .001, η^2_p = .08) driven by a significant main effect of Stimulus for the Non-Social Simple (Mean difference Repeating vs Changing = -82.38 ± 11.16, p < .001) and Social (Mean difference = -53.74 ± 9.93, p < .001) conditions, which was non-significant in the Non-Social Complex condition (Mean difference= -16.51 ± 13.18, p= .213). This two-way interaction was moderated by a 4-way interaction between

Condition*Stimulus*Autism*ADHD: $F (1.87, 185.25) = 3.82$, $p = .026$, $\eta^2_p = .037$. We broke this interaction down by running two repeated-measures ANOVAs, separately within each level of Autism and within each level of ADHD. At each level of Autism (Absent, Present), the three-way Condition*Stimulus*ADHD interaction was not significant: Autism-Absent: $F (2, 102) = 1.49$, $p = .23$, $\eta^2_p = .028$; Autism-Present: $F (1.78, 85.55) = 2.39$, $p = .103$, $\eta^2_p = .047$. The equivalent analysis at each level of the ADHD factor showed that the three-way Condition*Stimulus*Autism interaction was not significant at 'ADHD-Present': $F (2, 106) = 1.18$, $p = .308$, $\eta^2_p = .022$; but, in the groups without ADHD (that is in the neurotypical (NT) and Autism-only groups), there was a three-way interaction of Condition*Stimulus*Autism ($F (2, 92) = 4.375$, $p = .015$, $\eta^2_p = .087$). Follow-up comparisons were conducted to test the Condition*Stimulus interaction in each of these groups (NT, Autism-only). These analyses showed a significant main effect of Stimulus in Neurotypical children ($p < .0001$, $\eta^2_p = .447$), with shorter looks to repeating stimuli (Mean ± S.E. = -9.03 ± 5.5) and longer looks to changing stimuli (Mean ± S.E.= 46.49 ± 7.74) over time across conditions (see Figure 5.2a); the Condition*Stimulus interaction was not statistically significant in this group ($F (2, 58) = .29$, $p = .75$). On the other hand, the Condition*Stimulus interaction was significant in the Autism-only group ($F (2, 34) = 5.50$, $p = .009$, $\eta^2_p = .24$) with shorter look durations over time to the repeating stimulus and longer look durations over time to the changing stimulus in the Non-Social Simple (repeating vs changing Mean ± S.E.: -31.39 ± 7.03 vs 54.64 ± 16.48) and Social conditions (repeating vs changing Mean ± S.E.: -8.68 ± 9.53 vs 33.77 ± 12.52) but a numerical difference in the opposite direction in the Non-Social Complex condition which did not reach statistical significance (repeating vs changing Mean ± S.E.: 27.79 ± 23.96 vs -19.88 ± 20.41) (as shown in Figure 5.2b).

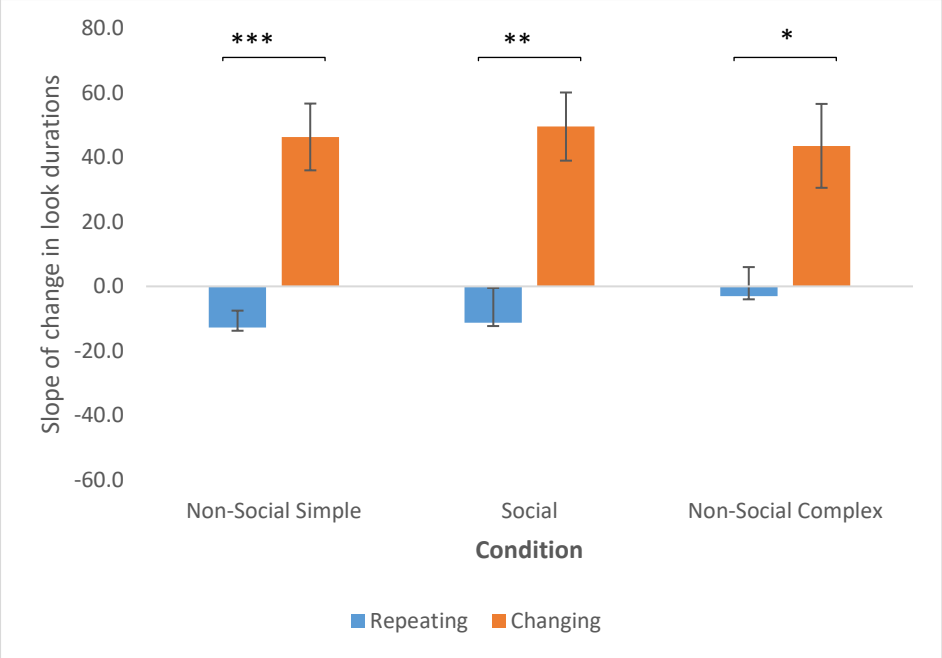


Figure 5.2a. The main effect of Stimulus in Neurotypical participants.

Bars show the mean (±1 standard error) coefficient of the slope for the rate of change in look durations over trials (plotted on the y-axis). These data are split by stimulus type and condition. Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001. The interaction between Condition*Stimulus is non-significant but shown here for the purpose of visualization of differences from the Autism-only group shown in Figure 5.2b.

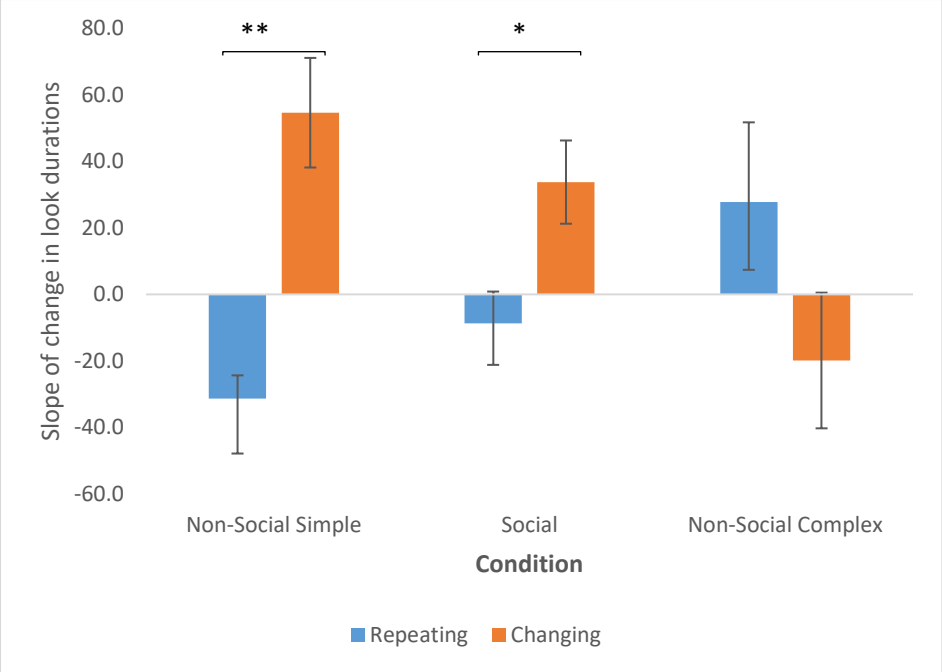


Figure 5.2b. Condition*Stimulus Interaction in the Autism-Only Group

Bars show the mean (±1 standard error) coefficient of the slope for the rate of change in look durations over trials (plotted on the y-axis). These data are split by stimulus type and condition. Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

5.3.3. *Correlations with SCQ*

Bootstrapped bivariate correlations were computed between number of fixations to repeating and background stimuli (across conditions) and rate of change of attention to the repeating and changing stimuli in the non-social complex condition) and the SCQ subscales of social, communication and RRB symptoms. A greater reduction in look durations to the changing stimulus over time in the Non-Social Complex condition was associated with higher SCQ Social symptoms (r= -.198, p= .05, [-.365, -.032]) (See Figure 5.3), suggesting that those with higher symptom severity on this scale showed a bias against attending to the changing stimulus over time, in this condition. To evaluate the role of IQ, we computed partial correlations between SCQ Social symptoms and Rate of change of attention to the changing stimulus in the Non-Social Complex Condition, whilst controlling IQ. The correlation became nonsignificant (r = -.161, p = .112, [-.326, -.007]).

Given the finding of flatter slopes for the rate of change in look durations overall in autistic individuals as compared to non-autistic individuals in our sample, we also ran a correlation between IQ and the average rate of change of look durations over time with data collapsed across conditions and stimuli. The correlation was not statistically significant (r = -.111, p= .264, [-.282, .079]).

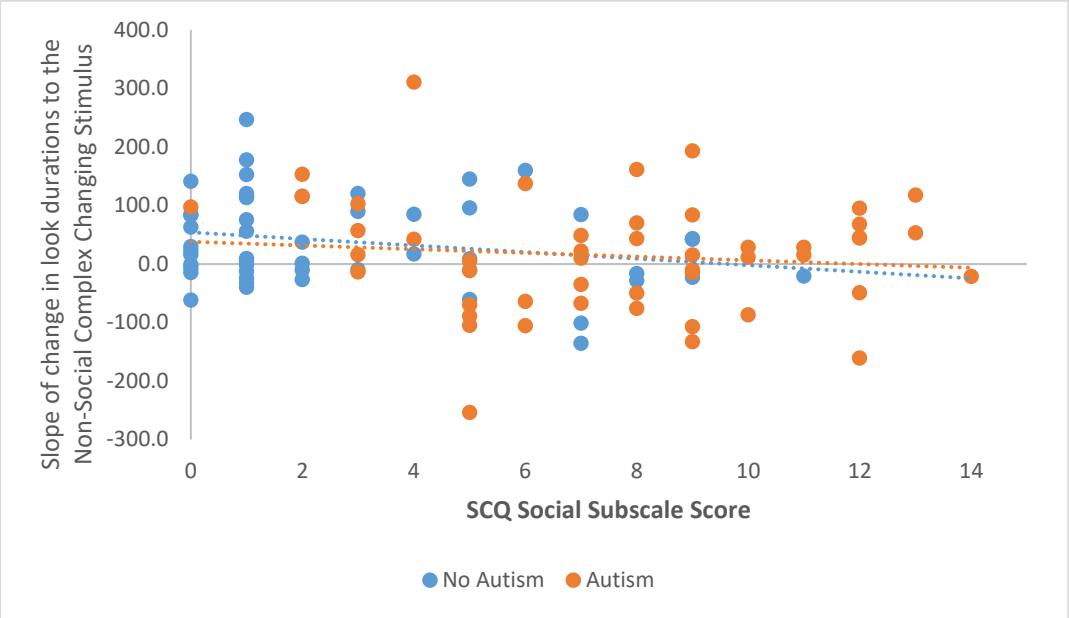


Figure 5.3. Relationship between SCQ-Social scores and Rate of change measure in Non-Social Complex condition

Scatterplot of scores on Social Communication Questionnaire (SCQ) Reciprocal Social Interaction Subscale (plotted on the x-axis) with the coefficient of the slope for the rate of change in look durations over trials to the Non-Social Complex Changing Stimulus (plotted on the y-axis) for participants with and without Autism (represented by orange and blue dots respectively. Dotted orange and blue lines represents the trend lines for the participants with and without Autism respectively.

5.4. Summary and Discussion of Study 1

In this study, we set out to identify whether differences in attention to repeating versus changing information in autism are present across stimulus contexts, suggesting a bias away from novelty towards repetition and predictability; or if they are dependent upon stimulus complexity, indicating slower information processing which is exacerbated when stimuli are complex. Further, we investigated whether this attention profile was specific to children with autism when compared with a group of children with ADHD. Finally, we also included a group of children with co-occurring autism and ADHD to investigate what profile of information foraging biases they show.

Analysis of the rate of change in look durations to the repeating versus changing stimuli revealed that autistic participants (with or without ADHD) showed flatter slopes of change in look durations to repeating and changing stimuli across conditions of stimulus complexity, suggesting that they were slower to shift attention, possibly due to slower information processing. Further, autistic children (without co-occurring ADHD) showed a neurotypical profile of reduced attention over time to the repeating stimulus and increased attention over time to the novel stimulus in the Non-Social Simple (shapes) and Social conditions. However, they did not show this effect in the Non-Social Complex (clocks) condition, in which they showed prolonged attention to the repeating over the changing stimulus. This is a reversal of the neurotypical effect and indicates that autistic children are not just defined by reduced habituation to a repeating stimulus but, when presented with visually complex stimuli, they show a bias towards repetition and away from novelty. This effect is more complex than we predicted as it suggests both slower information processing, reflected in flatter slopes to the repeating and changing stimuli (compared with neurotypical participants) with a preservation of the changing>repeating pattern to Social and Non-Social Simple stimuli, and a bias for repetition over novelty (reflected in a reversal of the changing>repeating effect) to Non-Social Complex stimuli. This is an important effect, which suggests that attentional biases in favour of exploring known over unknown information (Elison et al., 2012; Pellicano et al., 2011; Sasson et al., 2008) might partly be

driven by a response to stimulus complexity such that greater complexity elicits this bias towards sameness and predictability, away from novelty (Hanley et al., 2013; Kawa & Pisula, 2010).

Interestingly, although this effect of a bias towards repetition did not occur in the Social condition, the effect in the Non-Social Complex condition was associated with social impairments in our sample, such that those with more parent-reported social interaction difficulties showed an atypical bias away from the changing stimulus in the Non-Social Complex condition. It is interesting that the autistic sample showed a neurotypical profile in the Social condition, albeit with flatter slopes for look durations than the NT group. One possibility is that the social stimuli used here were not complex enough; further work is needed to determine whether more socially complex stimuli (for example multimodal stimuli combining faces with speech) would also elicit the effect found here in the Non-Social Complex clocks condition.

ADHD was not related to any predicted effects. Further, while autistic participants (with or without ADHD) showed flatter slopes of rate of change in attention to both stimuli overall, only those with autism without ADHD showed an additional bias against novelty when stimuli were particularly complex. This suggests that the co-occurring presence of ADHD benefited those with autism, protecting them from biases against novelty in the Non-Social Simple and Social conditions, possibly through a compensatory effect of an opposing bias towards novelty, as suggested by Gliga et al. (2018), who reported that infants at elevated likelihood of both autism and ADHD did not show exploitative biases. However, in our study, given that ADHD was not a main effect in these analyses, we cannot call this an additive effect because we did not find evidence of opposing biases being nulled in the comorbid group.

To summarize, Study 1 found that autistic participants (with and without ADHD) exhibited a slower rate of change in look durations over time as evidenced by flatter slopes, possibly due to slower processing of information. Autistic children (without ADHD) showed a profile of prolonged attention to repetition and reduced attention to the changing stimulus over time, but only in the Non-Social

Complex condition. Biases against exploration of new information in complex conditions were associated with higher social impairments in our sample, across autistic and non-autistic participants.

5.5. Study 2

The aim of the second study was to determine whether the effect found in Study 1 (wherein autistic participants' attention to changing information is reduced only in contexts of higher stimulus complexity) extends into the general population in individuals with high autistic traits. The behavioural profile associated with autism has been found to be present sub-clinically in those at increased familial risk of autism, termed the Broad Autism Phenotype (BAP), (Piven, 2001; Robinson et al., 2011). Further, the autistic traits that comprise the BAP, such as reduced social skills and impaired social cognitive abilities, as well as restrictive and repetitive behaviours, have been found to extend into the general population, suggesting that they lie on a continuum between individuals meeting diagnostic criteria and those in the general population (Constantino & Todd, 2003; Ingersoll, 2010; Ronald et al., 2006; Sasson, Nowlin, & Pinkham, 2013). Therefore, when teasing apart mechanisms underlying specific features, studying individuals on different sides of the diagnostic boundary may prove fruitful in enhancing our understanding of the autistic spectrum.

We hypothesised that if higher autistic traits are associated with similar risks to information processing, children in our sample with higher autistic traits would orient their attention more towards the repeating stimulus stream over trials, and show reduced attention to the novel stimulus stream; but that this will be specific to conditions where the stimuli are more complex.

5.6.Methods

5.6.1. *Participants*

Sixty-four children between the ages of 4 -12 years took part in this study (see Table 5.2 for demographic and behavioural characteristics). Participants were recruited during a local science engagement event (Summer Scientist Week; SSW) organised by the University of Nottingham in 2017 and 2018. Three children were reported to have a pre-existing diagnosis of autism, and one had a pre-existing diagnosis of ADHD. These children were not excluded from analysis as it was considered advantageous to include children on the extreme end of the autism continuum. One child used hearing aids but was not an outlier on any measure so they were included in the analyses.

5.6.2. *Measures*

The British Picture Vocabulary Scale (BPVS3) (Dunn & Dunn, 2009): age-adjusted standard scores (with a mean of 100 and standard deviation of 15) were used as a proxy for mental age. Autistic traits were measured using the Autism Spectrum Quotient- Child's Version (AQ-Child) (Auyeung et al., 2008), a parent-report questionnaire with high internal consistency (overall alpha= 0.97) and good test-retest reliability (r= 0.85). The AQ-Child has a range of scores from 0-150, with a cut-off score of 76 showing high sensitivity and specificity for Autism.

5.6.3. *Procedure*

Ethical approval for the study was granted by the School of Psychology Ethics Committee, University of Nottingham. The eye-tracking task presented to participants was identical to the task described in Study 1 except that, due to time constraints within the SSW experimental set-up, and because the participant sample was recruited from a younger age range, nine trials were presented per condition (similar to the original study by Vivanti et al. (2018)). In the analysis reported here, 13 participants' data is from 2017, while 51 participants were tested in 2018. Participants received tokens upon

completion of the experiment which they could use to spend on games and activities at the event. The equipment used and eye-tracking procedure was the same as that described in Study 1.

5.6.4. *Analysis Plan*

We extracted the same two measures as Study 1: Engagement (measured by number of fixations to the screen in different conditions) and the rate of change of cumulative look durations to the repeating and changing stimuli over time in each Condition. The within-subject factors (Stimulus, Condition) were the same as in Study 1.

Here we report the results from our main model testing our hypotheses with AQ score included as a linear predictor. To account for potential effects of factors such as age and mental ability, we ran separate correlations with age and BPVS to assess whether these were related to scores on the AQ-Child and/or task effects of interest.

5.7. Results

5.7.1. *Engagement*

First, we analysed participants' number of fixations to the screen at different levels of Condition (Non-Social Simple, Non-Social Complex, Social) to ensure participants were attentive throughout. AQ did not interact with Condition: Greenhouse-Geisser F (1.77, 109.55) = .73, p = .47, η^2_p = .01. There was also no main effect of AQ scores: F (1, 62) = .213, p = .65, η^2_p = .00.

Table 5.2

Demographic characteristics of the sample in Study 2

Demographic	Sample
Sample Size	64
Mean Age (in months) (SD)	101.797 (23.997)
Gender (M:F)	34 M: 30 F
Mean BPVS (Standard Score) (SD)	105.16 (11.785)
Mean AQ (SD)	58.33 (18.12)

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are n male:female. BPVS: British Picture Vocabulary Scale, 3rd Edition; AQ: Autism Spectrum Quotient-Child's Version

5.7.2. *Rate of change in look durations*

There was a main effect of Stimulus (F (1, 62) = 8.16, p = .006, η^2_p = .116); with the slope to the repeating stimuli being more negative (Mean ± S.E.= -.89 ± 6.59) than the slope to the changing stimuli (Mean ± S.E.= 54.13 ± 7.7). This was modulated by a Condition*Stimulus interaction (Greenhouse-Geisser F (1.8, 111.675) = 4.504, p = .013, η^2_p = .068). The main effect of Stimulus was present within each condition (See Figure 5.4a): Simple (Mean difference (Repeating vs Changing) = -64.13 ± 22.73, p = .006); Complex (Mean difference = -65.46 ± 27.99, p < .023); Social (Mean difference = -59.56 ± 13.74, p < .001). This interaction was further moderated by a 3-way interaction with AQ (F (1.8, 111.675) = 4.96, p = .011, η^2_p = .074). As can be seen below in Figure 5.4b, in both the Non-Social Complex and Social conditions, the main effect of Stimulus reversed, such that in the Non-Social Complex and Social conditions, those with higher AQ scores (i.e., higher levels of autistic traits) showed longer look durations to the repeating stimuli over time and reduced look durations to the changing stimuli over time.

5.7.3. *Correlations between AQ and slope of attention to repeating and changing information*

We ran correlations between AQ scores and the slopes of attention to repeating and changing information in the Non-Social Complex and Social conditions. AQ scores correlated positively with the slope of change in longest look durations to the repeating stimulus in the Social condition (r = .257, p = .044, [.001, .502]) and negatively related to the slope to the changing stimulus in the Social condition (r = -.295, p = .02, [-.48, -.07]). Thus, higher autistic traits were related to prolonged attention to the repeating stimulus and reduced attention to the changing stimulus in the Social condition.

We then assessed whether any demographic characteristics were related to AQ. Neither BPVS scores nor Age correlated significantly with AQ or with the rate of change in look durations to repeating or changing stimuli in either the Non-Social Complex or Social conditions (all p>.1, full correlation values provided in Appendix G).

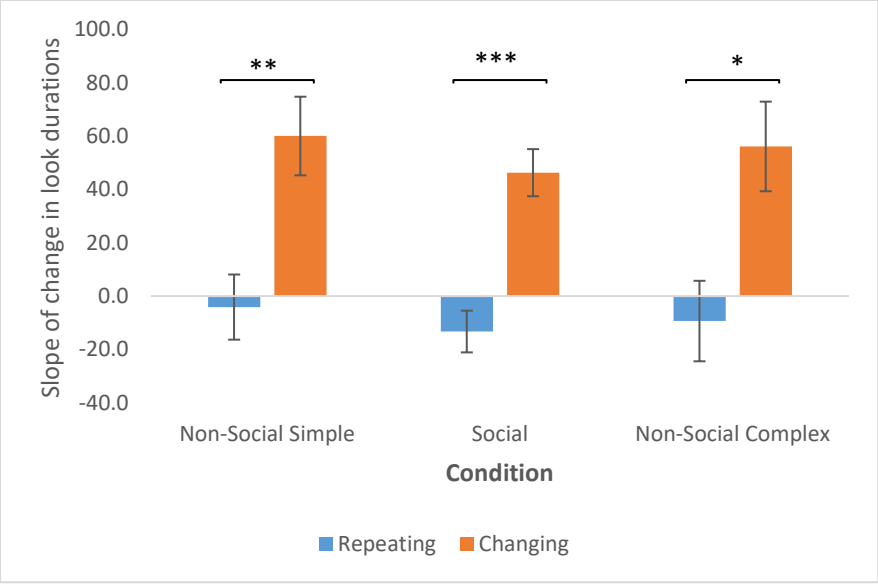


Figure 5.4a. Interaction between Condition and Stimulus on rate of change in look durations

Bars show the mean (±1 standard error) coefficient of the slope for the rate of change in look durations over trials (plotted on the y-axis). These data are split by stimulus type and condition. Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

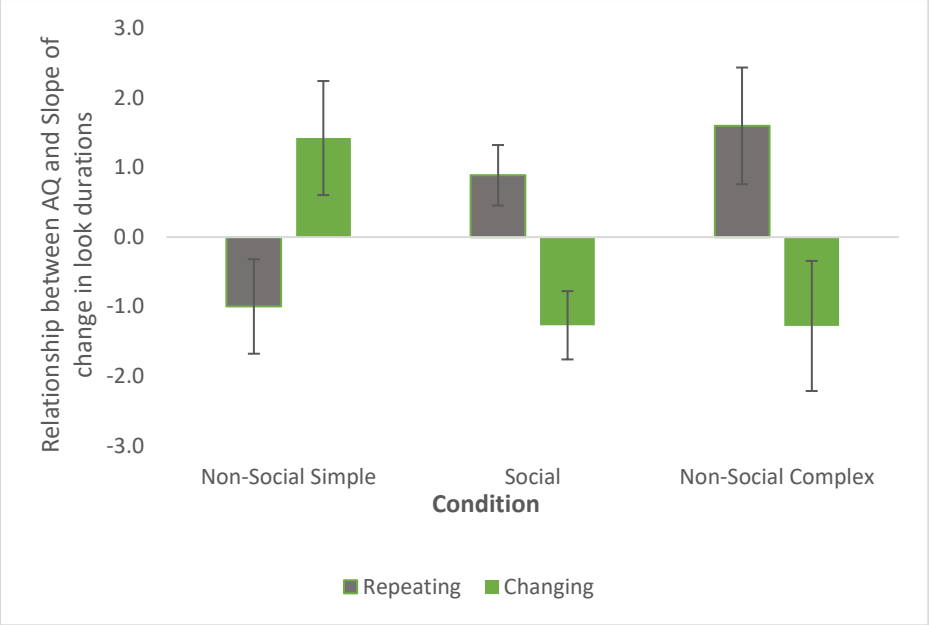


Figure 5.4b. Interaction between Condition, Stimulus and AQ on rate of change in look durations

Bars show the mean (±1 standard error) coefficient of the linear relationship between scores on the Autism Spectrum Quotient- Child Version (AQ-Child) and the rate of change in look durations over trials (plotted on the y-axis). These data are split by stimulus type and condition.

5.8.Summary and Discussion of Study 2

We aimed to identify whether biases found in our clinical sample of autistic children against attending to changing information when stimuli were more complex are related to subclinical autistic traits in a general population sample. Indeed, this is what we found. In the Non-Social Simple (shapes) condition, traits of AQ did not impact information foraging, all children showed the expected profile of reducing attention over time to the repeating stimulus and increasing attention over time to the changing stimulus. However, in the Social (faces) and Non-Social Complex (clocks) conditions, higher traits of AQ were related to reduced look durations to changing stimuli over time and increased look durations to repeating stimuli over time. The presence of this effect for both Social and Non-Social Complex stimuli suggests that, in this study, the two types of stimuli elicit equivalent effects on attention, suggesting that an atypical attentional style to social stimuli may at least partly be explained by the complexity of those

stimuli. Our findings are in line with other studies that have investigated social abilities and attention in association with subclinical traits of autism (Ingersoll, 2010; Sasson et al., 2013) which have also found that higher sub-clinical traits are associated with similar profiles of social abilities as those seen in clinical diagnosis of autism.

5.9. General Discussion

In the present study, we aimed to disentangle whether differences in habituation or biases against novelty drive differences in attention to repeating vs changing information in autistic individuals. We investigated these questions by manipulating stimulus complexity and extracting a measure of information processing and learning, indexed through the longest look duration to each stimulus per trial, to assess how this changed over time to the repeating and changing stimuli. We found that across two independent samples of children, traits and clinical symptoms of autism were related with prolonged attention to repetition and reduced attention to novelty, but only in contexts of higher stimulus complexity (in Non-Social Complex condition in Study 1, and in both Social and Non-Social Complex conditions in Study 2). This suggests that there might be two processes at play: differences in habituation due to difficulties processing more complex stimuli and a bias against novelty in favour of repetition which is elicited by complex stimuli (at least in this paradigm) in individuals with clinical symptoms or higher traits of autism. Our findings are partly in line with Vivanti et al.'s (2018) report of slower habituation and attentional biases against novelty; however, our findings extend this work by showing that these attention profiles seem to be partly driven by slower learning or processing of stimuli.

Our findings suggest that differences in habituation to repeating stimuli emerge when stimuli are more complex. Importantly, we also found this effect to be specific to children with autism without comorbid ADHD. These are important factors that have previously not been considered in the literature. Studies on habituation mechanisms in autism have yielded heterogeneous findings, with some studies reporting differences in habituation to be only present when using social stimuli (such as faces) but not when

using non-social stimuli (Kleinhans et al., 2016; Webb et al., 2010), and interpreting those effects to be related to difficulties in social information processing in autism. Our findings challenge this interpretation: using non-social stimuli with high level of featural complexity (clocks with moving parts) as well as social stimuli with similar featural complexity allowed us to test whether there is anything unique to processing of social stimuli when they are compared with complex non-social stimuli. We found that autistic traits and symptoms are associated with atypical processing of complex information, not specifically social information. Our findings therefore suggest that this heterogeneity might be at least partly driven by stimulus complexity. Slower learning might be captured more fully in experimental paradigms that use more complex stimuli and thus differences in habituation findings in the literature might be partly explained by this. Further, studies in habituation in autism have sometimes found null effects and they usually do not take into consideration the presence of co-occurring difficulties and conditions. In our study, autistic children (with and without autism) showed slower rates of change in look durations to both repeating and changing stimuli, irrespective of the type of stimulus. However, only autistic participants without ADHD showed prolonged attention to repetition reflecting a bias against novelty in contexts of higher stimulus complexity. Participants with autism with comorbid ADHD did not show this profile. This again implies that heterogeneous findings in the habituation literature in autism might be partly driven by lack of proper characterization of the co-occurring conditions in autistic participants. In our study, presence of ADHD appears to benefit autistic individuals by combating the biases against novelty that emerge when processing more complex stimuli.

Previous research has also shown that autistic children demonstrate an attentional preference towards revisiting previously explored regions at the cost of exploring new information (Elison et al., 2012; Gliga et al., 2018; Pellicano et al., 2011). These studies have used paradigms very different to ours, with multiple static objects present on the screen at once, both social and non-social. While our study does not refute those findings, we do question whether presence of information foraging biases of exploitation over exploration characterize autistic individuals in all contexts. In future studies, it would

be important to manipulate stimulus complexity to assess whether the attentional biases reported in autism might be partly driven by slower processing of stimuli.

Given the cross-sectional nature of our study and the age groups we focused on (children and adolescents), we are limited in being able to shed light on specific mechanisms behind the differences observed in processing more complex stimuli and whether such differences are a consequence or a cause of autism. It has been suggested that habituation differences in autism might lead to an exaggerated perception of change, and that restricted and repetitive behaviors might be a resultant coping mechanism (Dawson & Lewy, 1989; Vivanti et al., 2018). Contrary to this, we found that differences in attention to changing stimuli in the Non-Social Complex condition (in Study 1) were associated with more social interaction impairments in children but were not related with restrictive, repetitive behaviours on the SCQ. Other studies have also found evidence for reduced habituation to complex stimuli to be linked with higher severity of social impairments (Kleinhans et al., 2009; Webb et al., 2010). This suggests that these differences in processing more complex stimuli are related to skills involved in social interaction, rather than RRBs. Social interaction is dependent on processing complex and ever-changing information in real time. Thus, development of social interaction differences might well be rooted in early differences in being able to process complex information. Further, Vivanti et al. (2018) found a similar bias against attending to changing information in preschoolers with autism, therefore these differences in attention and information processing might emerge quite early.

Importantly, given that biases against novelty were found in relation with stimulus complexity regardless of the social-ness of the information, it appears that domain-general models of mechanisms in autism rather than domain-specific models, such as those that focus on social processing atypicalities as a core mechanism in autism, are likely to hold more value. Further research, particularly using longitudinal designs from an early age, is crucial to identify the precise mechanisms that drive such differences.

There were some differences between the findings from our two studies. In the clinical study, prolonged attention to repetition and biases against attending to novelty were present only in the Non-Social Complex condition. In comparison, in the second study, we found this effect in both the Non-Social Complex and Social Conditions. In comparison, Vivanti et al. (2018) found similar differences in a younger sample with stimuli from the Non-Social Simple condition (the only condition they used). Many factors could have led to these discrepant findings. Firstly, we did not match the stimuli between conditions. Like most developmental studies, this is a difficult task to accomplish while trying to retain the natural-ness of stimuli. Rather, we manipulated complexity and social-ness of stimuli. Secondly, the children in Study 2 (Age range- 4-12 years, Mean Age: 101.8 months) were younger than Study 1 (Age range- 7-15 years, Mean Age: 129.6 months); both of whom were older than Vivanti et al. (2018)'s sample (Mean Age calculated for Autistic and neurotypical participants from their study: 46.78 months). Thirdly, Study 1 included clinical participants, children diagnosed with autism, while Study 2 included children with varying levels of subclinical traits of autism. Any of these factors could have led to the differences in our findings. Further research using big samples at different developmental time-points and including participants on either side of the diagnostic boundary is required to understand these subtle differences.

There were some limitations of the current study. Sample sizes in both Study 1 and Study 2 were modest. However, the samples were carefully characterized which removes sources of noise and thus improves statistical power. In Study 1, we also included children from another clinical group (ADHD) and found the results to be specific to children with autism, which makes the finding more robust. The replication of the main effects in samples of children with clinically significant symptoms of autism and children with higher traits of autism further improves confidence in our findings. Regardless, our findings warrant replication in larger and more representative samples.

Importantly, we found that differences in attention to changing information were related to context and the type of information being presented, and thus might be partly influenced by IQ. Our sample in Study 1 was unbalanced with regard to IQ, with clinical participants showing lower IQ than neurotypical

participants. However, while IQ was partly associated with the main clinical effect, it did not explain completely the relationship between SCQ scores and differences in looking to changing stimuli in the Non-Social Complex condition (the partial correlation did not reach statistical significance but the correlation was still present and indicated an effect size of similar magnitude). Further, the autistic participants with co-occurring ADHD had lower IQ than those without; yet the pattern of differences was specific to autistic children without co-occurring ADHD. In Study 2, we did not find any relationship between BPVS scores and looking to more complex repeating or changing stimuli. Therefore, while IQ might contribute to these differences in processing more complex stimuli, from our data it appears that IQ does not fully explain these differences. Other studies in the literature have also found information foraging biases such as in our study not to be associated with IQ (Elison et al., 2012; Pellicano et al., 2011). Therefore, information foraging biases might be independent of IQ in these populations. Another possible limitation of this study is the nature of stimuli used, particularly in the non-social complex condition. The clocks we used were not naturalistic and it is possible that given the prevalence of digital clocks these days, the effects we saw are driven partly by lack of familiarity with these stimuli. However, this is still important to further investigate since lack of familiarity might influence foraging differently in autistic individuals than non-autistic individuals. Importantly, clocks contain many small features each of which have symbolic meanings and they are typically processed by paying closer attention to these local features. On the other hand, faces are typically processed more globally (Gao, Flevaris, Robertson, & Bentin, 2011). It is possible that the pattern of differences is related to this, given that there are differences in local versus global processing in autism (Koldewyn, Jiang, Weigelt, & Kanwisher, 2013). However, if this were the case, those with autism would have shown better processing of the clocks instead of the other two conditions so we do not believe this to be the case. Future studies should use different types of complex non-social and social stimuli to investigate these effects further, using designs which balance social-ness and complexity for both social and non-social stimuli (for example, static and dynamic social and non-social stimuli, unimodal and multimodal social and non-social stimuli, etc.).

In conclusion, our research demonstrated that reduced attention to changing information might emerge only in conditions with higher stimulus complexity in autistic individuals and in typically developing children with high autistic traits (regardless of the stimuli being social or non-social). This is an important finding and future research should look at when such differences first emerge and how they develop over time in interaction with symptoms of autism.

5.10. Profiles of autistic subgroups in eye-tracking task

We observed in the analysis on SAAND study data in this eye-tracking task (Chapter 5, Study 1), that autistic children (without ADHD) showed an atypicality in their attention profile such that only in the conditions with higher complexity (specifically, the Non-Social Complex condition), look durations increased over trials to the repeating stimuli and decreased over trials to the changing stimuli.

Such profiles of 'slower habituation' or 'preference for repetition' or 'biases against novelty' have been linked in the literature to profiles of arousal such that hyperarousal has been suggested to elicit avoidance of novel information, and preference for repetitive behaviours (Green et al., 2019; McCormick et al., 2014; McDiarmid et al., 2017). We wanted to explore this further.

We hypothesised that if preference for repetition or biases against novelty are driven by arousal, then in our SAAND study sample, this profile of higher complexity eliciting longer look durations over trials to repeating stimuli and shorter look durations over trials to changing stimuli, would be specific to the hyperaroused autistic subgroup, and the hypoaroused autistic subgroup would show profiles similar to neurotypical participants. If so, this would provide support for arousal theories that suggest that hyperarousal elicits avoidance behaviours in order to manage arousal (here represented by avoidance of novelty in the context of higher complexity of stimuli).

In order to investigate this, we looked descriptively at the slopes to repeating and changing stimuli in the various conditions split by autistic subgroups (See Table 5.3).

Table 5.3

Slope	**Hypoaroused (n= 13)**	**Hyperaroused (n= 25)**	**Between-groups Cohen's d**
Non-Social Simple Repeating	-35.57 (41.51)	-37.7 (34.3)	0.06
Non-Social Simple Changing	43.08 (49.98)	64.18 (96.41)	0.27
Within-group Cohen's d	1.28	0.86	
Social Simple Repeating	-27.69 (47.04)	-5.37 (56.24)	0.43
Social Simple Changing	30.76 (91.25)	31.78 (59.26)	0.01
Within-group Cohen's d	0.25	0.04	
Non-Social Complex Repeating	-13.16 (96.79)	3.21 (80.61)	0.18
Non-Social Complex Changing	33.36 (105.87)	9.47 (92.65)	0.24
Within-group Cohen's d	0.61	0.37	

All values (except for Cohen's d) represent group means of rate of change in look durations to respective stimuli in respective conditions. Parentheses provide standard deviation of the mean. Between groups Cohen's d values represent the effect size of the between-group difference on slope. Within-groups Cohen's d represents the within-group difference between the slopes to the repeating and changing stimuli for each Condition.

As can be seen in Table 5.3 above, for the hypoaroused subgroup, the slope of change in look durations over successive trials was negative for repeating stimuli across conditions (and thus, look durations to repeating stimuli decreased over trials) while for the changing stimuli, these were positive across conditions (and thus, look durations to changing stimuli increased over trials). In contrast, for the hyperaroused subgroup, while the look durations to repeating stimuli decreased over trials in the Non-Social Simple and Social conditions, these increased to repeating stimuli in the Non-Social Complex condition. In addition, the slope was flatter (albeit negative) to the Social repeating stimuli as compared to the Non-Social Simple repeating stimuli, suggesting that habituation might have been slower with higher complexity. For the changing stimuli, the look durations in the hyper-aroused subgroup increased

over trials across conditions, but this slope was flatter for the Non-Social Complex condition as compared to the Non-Social Simple and Social conditions.

It appears therefore, that the atypicality observed in which higher complexity elicits a preference for repetition and a tendency to shift attention away from novelty might be specific to autistic children who have a predominantly hyperaroused profile. Overall, this is in line with our hypothesis that profiles of arousal might drive this difference in attention. Given the small sample sizes, we did not conduct statistical tests to compare the subgroups on these profiles. However, the direction of the effects are consistent with our predictions and provide tentative evidence for these hypotheses, which warrant further exploration.

Chapter 6. Final Discussion and Conclusions

6.1. Summary and Discussion of general results

In this thesis, I systematically investigated profiles of arousal and attention in response to various types of stimuli and different experimental contexts. I also investigated how these profiles relate with clinical symptoms of autism and other conditions. Further, I investigated attention in autistic individuals; more specifically, whether autistic individuals show atypicalities in orienting of attention and habituation to auditory and visual stimuli, and the factors that might drive these differences. Finally, I investigated the role arousal might play in atypicalities in attention.

My approach to investigating these questions was informed by neuroconstructivistic and developmental psychological frameworks (Karmiloff-Smith, 1998), such that I looked beyond diagnostic labels at various dimensions of functioning and focused on functional interactions between these dimensions. I recruited a heterogeneous clinical sample, in that autistic individuals in my sample were not "pure" cases of the condition, but rather also had co-occurring symptoms of other conditions (in this case, ADHD, mood disorders or other psychiatric conditions). I carefully characterised participants in the study on these symptoms and controlled specifically for ADHD by including a clinical control group of participants with ADHD without autism. Further, I utilized both between-group comparisons and dimensional analyses to identify whether atypicalities in attention or arousal were specific to autism (or ADHD) or shared across conditions as well as investigated which specific symptom domains of autism (social interaction, social communication or restricted and repetitive behaviours) the atypicalities were related with.

Overall, I found that as a group, autistic children and young people were not different from neurotypical participants in their tonic arousal profiles. Further, I did not observe any differences between autistic and neurotypical groups on changes in autonomic arousal in response to presentation of auditory tones (Chapter 3). Dimensional analyses revealed that autistic children and young people in my sample were heterogeneous in their tonic arousal profiles, that some of them may present with tonic hyperarousal driven by parasympathetic under-activation; while others may present with tonic under-arousal, driven

by sympathetic under-activation. Further, autistic individuals demonstrated intact abilities to orient to and habituate to simple auditory (Chapter 4) and visual (Chapter 5) stimuli, but they showed atypicalities in the way these abilities were employed in response to certain types of stimuli, particularly more complex or social stimuli (Chapter 5). These atypicalities in attention were related with the social interaction symptoms of autism, but not with social communication symptoms or RRBs. I will discuss these findings and their implications below.

6.1.1. The role of tonic arousal in autistic individuals

My review of the resting state literature (Appendix H) and other reviews of arousal in the autism literature (Klusek et al., 2015; Lydon et al., 2016) have found that evidence for atypicalities in autonomic arousal in autistic individuals at resting state and in response to various types of stimuli is not robust. However, most studies in the literature treat autistic individuals as a homogeneous group of individuals. Including a clinical control group of ADHD-only individuals in my study revealed that at least a subgroup of autistic individuals who had comorbid ADHD were similar in their tonic arousal profile to individuals with ADHD without autism (rather than autistic individuals), in showing sympathetic underarousal. This suggests that autistic individuals might be heterogeneous in their tonic arousal profiles, and that such atypicalities may not be autism-specific but rather, shared across other developmental conditions. Indeed, a dimensional cluster analysis revealed presence of subgroups of autistic individuals that were hyper- and hypo-aroused respectively. The hypoaroused subgroup showed profiles of reduced HR and reduced CSI during both resting state and the auditory oddball tasks. The hyperaroused subgroup showed profiles of increased HR and reduced CVI during both tasks. This is important and my findings take the literature forward. While subgroups have been reported in previous autism literature (Hirstein et al., 2001; Schoen et al., 2008), their clinical profiles have not been investigated properly and my findings revealed that these subgroups may be clinically different from one another in their symptomatic profiles of autism, as well as in their sensory processing profiles and co-occurring symptoms of ADHD and anxiety. In line with the literature and our predictions, the hyperaroused subgroup showed higher autism symptom severity (specifically in domains of social

interaction and social communication), and more sensory avoidance behaviours, and higher rates of anxiety as compare to hypoaroused individuals (Cai et al., 2019; Howells et al., 2012; Mineka & Zinbarg, 2006; Rogers & Ozonoff, 2005). On the other hand, the hypoaroused subgroup showed more hyperactive-impulsive symptoms and more sensory-seeking behaviours (Howells et al., 2012; Rogers & Ozonoff, 2005). These findings provide some evidence that tonic arousal profiles might help explain some of the heterogeneity on the autistic spectrum in a meaningful manner. Further, this provides some support for theories that suggest that sensory processing profiles and some symptoms of autism (e.g., avoidance behaviours) and ADHD (hyperactivity-impulsivity) might reflect functional coping strategies in response to atypicalities in being able to regulate and maintain optimal arousal (Hutt et al., 1964; Kuntsi & Klein, 2012; Porges, 1992, 2001; Porges, 2009; Sergeant, 2000). In future research, it would be important to replicate these effects and identify how these subgroups differ from neurotypical individuals, as we did not have sufficient power to quantitatively compare the subgroups from neurotypical individuals. Further, it will be important to verify whether differences in tonic arousal do indeed relate with sensory seeking and avoidance behaviours, by measuring sensory processing directly alongside autonomic arousal.

The LC-NE framework (Aston-Jones & Cohen, 2005a; Aston-Jones et al., 2007; Howells et al., 2012) suggests that if LC neurons' tonic firing is at lower frequencies than typical, this would adversely influence phasic LC function; phasic firing of the LC would be achieved only for extremely novel or salient events, and maintenance of attention even for these events may be insufficient and lead to inattention. Sensory-seeking behaviours could develop in such individuals in an effort to upregulate arousal. Our data partially support these predictions. Participants with ADHD and some autistic participants (those with co-occurring ADHD or those categorized in the hypoaroused subgroup) in our sample exhibited profiles of sympathetic underarousal and this was linked with higher sensory-seeking and hyperactive-impulsive behaviours in our data. In contrast, the LC-NE frameworks also predict that profiles of hyperarousal (due to LC neurons tonically firing at an atypically increased rate, such that it is not held within 1-3 Hz) would be linked with atypicalities in phasic responses to salient or target events due to a suboptimal signal-to-noise ratio, with LC neurons also firing in response to irrelevant

or distracting events. This could again lead to inattention and avoidant behaviours that serve to downregulate arousal due to a processing system that is overwhelmed by being responsive to everything (Howells et al., 2012). Within the LC-NE model of arousal regulation and behaviour (Aston-Jones & Cohen, 2005b), tonic LC hyperarousal can arise from reduced top-down regulation of parasympathetic nervous system. According to Porges' polyvagal theory, this would impact social engagement and social interaction (Porges, 2001), due to increased release of norepinephrine and higher levels of stress. In our data, a subgroup of autistic participants (the hyperaroused subgroup) exhibited profiles of reduced parasympathetic activation (as indexed by reduced CVI) and tonic hyperarousal (as indexed by high HR and low CVI) was indeed linked with worse social interaction symptoms as well as more sensory avoidance symptoms, and higher prevalence of anxiety. Our data did not find evidence in support of suboptimal phasic responses linked with profiles of tonic hyper- or hypo-arousal as predicted by the LC-NE framework described above. All participants (including ADHD and autistic participants) demonstrated typical autonomic responsivity (as indexed by changes in HR and HRV) to auditory stimuli, although here we measured changes in tonic arousal rather than phasic responses specifically. There were subtle atypicalities in P3a (proposed to be an index of late phasic LC response, Nieuwenhuis et al. (2005)) associated with both ADHD and autism in our sample (discussed further in Section 6.1.2.) which might be related to atypicalities in tonic and phasic LC function; however, this requires further research with direct measurement of LC-NE function itself. Future research should directly investigate longitudinally whether early atypicalities in brainstem systems such as the LC relate with atypical autonomic arousal profiles and how these are developmentally related to symptoms of autism and adaptive functioning, as well as sensory processing behaviours. Overall, we found that tonic arousal could be a candidate for a stratification biomarker in autistic individuals and that stratifying autistic individuals along this neurobiological phenotype is clinically meaningful.

An important factor to consider in future research is the degree to which an individual's baseline level of HR is high or low. If HR is low, strategies to upregulate it may be more effective, since there is more scope for change; however, for hyperaroused individuals, who are already at the ceiling with regard to their arousal, it may be harder to regulate and it may impact their ability to adapt and be flexible to

situational demands more. In our study, we were not able to directly investigate whether adaptive functioning to different contexts is worse for individuals that are hyper- vs hypo-aroused. However, symptomatic severity of autism was higher in hyperaroused than hypoaroused autistic individuals and so it could be clinically important to investigate the limits of this system within individual participants, before testing the adaptation of the system under different conditions.

6.1.2. Orienting and Habituation of attention in autistic individuals

Across the auditory oddball and the eye-tracking tasks, autistic individuals showed typical profiles of orienting and habituating to simple auditory and visual stimuli. In the auditory oddball task (Chapter 4), autistic individuals (with or without ADHD) showed orienting and habituation to repeating non-social tones (as measured by P3a amplitudes) similarly to neurotypical participants. In the eye-tracking task (Chapter 5), autistic individuals (with or without ADHD) showed habituation to repeating stimuli and increased orienting (as measured by longest look durations per trial) to changing stimuli over trials in the Non-Social Simple and Social conditions. This suggests that these basic abilities to orient and habituate are intact in autistic individuals. However, there were subtle differences observed in orienting of attention that were dependent on stimulus complexity and salience.

In the auditory oddball task, we presented two conditions of stimuli to participants, one in which non-social standard tones were interspersed with non-social deviant tones (Non-Social condition), and one in which non-social standard tones were interspersed with social deviant tones (Social condition). Neurotypical individuals exhibited increased orienting (as measured by P3a amplitudes) to non-social standards in the social condition (i.e., in the context of presence of social deviants) as compared to the non-social standards in the non-social condition. However, we found that autistic individuals without ADHD did not show this preferential orienting (as indexed by P3a amplitudes) to non-social tones in the social condition, instead showing similar levels of orienting (or P3a amplitudes) to non-social standards in both the social and non-social conditions. This indicates that while for neurotypical individuals, presence of social deviants (which were more salient and complex than the non-social

deviants) increased orienting of attention broadly even to the non-social standards, autistic individuals (without ADHD) were not sensitive to these differences in experimental context. Further, reduced P3a in the social condition in the oddball task was associated with worse social interaction symptoms as measured by SCQ.

Similarly, in the eye-tracking task, autistic individuals (without ADHD) showed a typical profile of attention in the Non-Social Simple and Social conditions. However, they exhibited an atypical profile in the Non-Social Complex condition such that they showed increased look durations over trials to the repeating stimuli and decreased look durations over trials to the changing stimuli, thus showing preference for repetition and a bias against attending to novelty. Again, decreasing look durations over trials to the non-social complex changing stimuli was associated with worse social interaction symptoms on the SCQ subscale. Therefore, across visual (Chapter 5) and auditory (Chapter 4) modalities, autistic individuals (without ADHD) appeared to show a drive away from attending to complexity as compared to neurotypical individuals or individuals with ADHD and this was associated with only the social interaction autism symptom domain. This suggests that social interaction difficulties in autistic individuals in autistic individuals maybe rooted in underlying differences in processing complex information. Social interactions are heavily dependent on attending to and processing complex information in real time that is multi-sensory and unpredictable. Our findings are in line with the attention literature in autism that reports specific differences in attending to social information in autism (Chita-Tegmark, 2016; Dawson et al., 2012). However, our findings extend this literature further by highlighting that difficulties in attending to social information might be rooted in their complexity and these differences relate with only the social interaction domain in autism and not the social communication or RRB domains. Further, it is interesting to note that autistic individuals with ADHD did not show these atypicalities in attending to more complex information. It is possible that individuals with ADHD have a drive towards novelty (Gliga et al., 2018; Sethi et al., 2018) which compensates for biases away from novelty in autism; alternatively, a hypoarousal profile in ADHD might benefit autistic individuals in attending to more complex information. This will be discussed more in Section 6.1.3.

Importantly, our findings on habituation are not in line with the wider literature that has reported reduced habituation in autistic individuals (McDiarmid et al., 2017). Previous literature has used measures different than ours to tap into habituation to auditory stimuli, using ERPs that that capture early sensory processing (Kolesnik et al., 2019; Ruiz-Martinez et al., 2020). We measured habituation to auditory stimuli using the P3a which taps into a later stage of orienting of attention and information processing and is a putative marker of the LC phasic response (Nieuwenhuis et al., 2005), and our findings suggest that at this later stage of information processing, abilities to habituate are not impaired in autistic (or ADHD) individuals. This effect requires replication. Further, previous literature in habituation has not manipulated the stimuli along various dimensions to investigate whether differences in habituation reflect a true impairment in the ability to habituate or other atypicalities such as a preference for repetition in the context of complexity, or an over-responsivity to stimuli due to hyperarousal. We manipulated the stimuli more systematically in the eye-tracking study (Chapter 5) and observed that autistic individuals showed intact abilities to habituate, but atypicalities in distribution of their attention were elicited by stimuli with higher complexity. Further, we found this profile also in neurotypical individuals with high levels of subclinical traits of autism, highlighting that we were able to capture an autism-specific effect. Future research should manipulate stimuli along other dimensions, for example using multimodal stimuli, and investigate developmentally when these atypicalities arise.

6.1.3. The interaction of arousal and attention in autistic individuals

A final thread of investigation in my thesis was comparing the arousal subgroups of autistic participants on their attention profiles. Importantly, we found that the subgroups were different from one another in the way they paid attention to the stimuli in our tasks. In the auditory oddball task, we found that the hyperaroused autistic individuals showed numerically larger P3a to the auditory tones as compared to the hypoaroused subgroups (Chapter 4), with between-group effect sizes being small (e.g., Cohen's d comparing hyper- and hypo- aroused subgroups = 0.19 for the P3a to the first standard), This is line with our predictions that autistic individuals who are hyperaroused would be hyper-responsive to sensory stimuli (Rogers & Ozonoff, 2005). Further, in the eye-tracking task (Chapter 5), the profile of

atypicality in looking at repeating and changing stimuli over trials in conditions with higher stimulus complexity was specific to the hyperaroused subgroup. The hypoaroused subgroup was similar to neurotypical individuals, showing more looking to the changing stimuli than the repeating stimuli over time while the hyperaroused subgroup showed a flat/positive change in look durations to the repeating stimuli over time in the Non-Social Complex and Social conditions. These findings, although tentative given the sample sizes, point towards important differences in attention driven by arousal, such that in the social condition in the auditory oddball task and in the more complex conditions in the eye-tracking tasks, the hyper-aroused subgroup responded with larger P3a amplitudes to the first stimuli and exhibited a preference for repetition or avoidance of novelty. This highlights an important area for further investigation and suggests that some of the differences in attention may indeed be driven by arousal.

An additional aspect to consider is that autistic individuals with and without ADHD showed different attentional profiles. One possibility is that this is due to different arousal profiles in individuals with ADHD which then impact attention differently. Profiles of hyper-responsivity to repeating stimuli and an avoidance of novelty might be specific to those autistic individuals who have hyperarousal, as noted above; and presence of hypoarousal (which appears related with ADHD in our sample) might combat some of the autism-specific risks as complexity might not overwhelm processing capacity if one is not hyperaroused. These are areas that require further investigation and it appears important based on our findings, that co-occurring symptoms of ADHD (as well as anxiety) are carefully characterised in autistic individuals to understand the directions of these relationships between profiles of arousal, attention and development of symptoms of ADHD and/or anxiety in autistic individuals.

6.2. Implications

6.2.1. Scientific Impact

Implications for theoretical and neurobiological frameworks in autism

Our findings are in agreement with the wider autism literature that core-deficit models that place social information processing at the root of all autistic symptoms are unlikely to suffice. Rather, system-wide models might be more useful. For instance, Lawson et al. (2014) posit that sensory information might be prescribed more weight/precision than prior beliefs. Similarly, the enhanced perceptual functioning model of autism suggests that superior perceptual functioning with atypical higher-order modulation of lower-order cognitive processes might lead to the cognitive differences in autism, wherein perceptual processes are disruptive to other behaviours (Mottron et al., 2006). These models would predict reduced adaptation to and habituation to simple sensory stimuli, due to reduced top-down modulation of sensory information. Our data do not support these predictions. In our participants, we observed typical adaptation of autonomic responses (Chapter 3) and typical habituation of the P3a (Chapter 4) to auditory stimuli. These models would also indicate that autistic individuals may demonstrate profiles of perceptual functioning that is insensitive to contextual differences. Our data on reduced P3a to non-social standards in the context of social deviants provides partial support for this idea (Chapter 4). In contrast, Pellicano and Burr (2012) suggest that attenuated priors (expectations about the world based on prior experiences) underlie sensory and cognitive differences in autism. Our data from Chapter 5 partially supports this model as well as Lawson et al.'s (2014) model; more complex information might overwhelm an information processing system that is more reliant on sensory signals and less modulated by prior beliefs. Indeed, this might impact learning and the ability to predict change, leading to the development of a profile that prefers sameness and repetition, the attentive profile we observed in autistic participants as complexity of stimuli increased. Domain-general theories such as those described above deserve further investigation and direct evaluation. Importantly, while all the above theories appear to be possible candidates in explaining the outcome attentional profile of autism, they may not help understand how these differences develop.

My findings have implications for the developmental and causal mechanisms that might be at the root of development of autism. Specifically, my research suggests that there may indeed be atypicalities in autism in development of brainstem regulatory systems and of salience networks. Indeed, early differences in LC function might impact the development of both local and long-range structural and functional connections, and ultimately, the development of the attentional profile wherein the balance between sensory evidence and predictions about the world is atypical. Our findings point towards atypicalities, for instance in how LC-NE may interact with and be modulated by top-down systems in response to various salient events in the environment. Salience networks have been found to be atypical in autism (Menon & Uddin, 2010) and this might impact their modulation of LC-NE in response to different types of stimuli, and also have a downstream effect on autonomic function. Further, there is evidence for reduced long-range functional connectivity, reduced inter-hemispheric regulation and increased local connectivity (Hull et al., 2017; O'Reilly et al., 2017; Rane et al., 2015). In addition, areas in the cingulo-opercular networks have been found to be implicated in autism (Gomot et al., 2006; Menon & Uddin, 2010; Murphy et al., 2017; Tottenham et al., 2013). Future research should investigate longitudinally models that theorize that early atypicalities in brainstem systems lead to atypicalities in structural and functional development of top-down regulatory systems leading to atypicalities in more complex behaviours such as social interactions (Geva & Feldman, 2008). Further, any such developmental investigations should investigate how early differences in arousal, sensory processing and cognitive abilities link with development of social and non-social symptoms of autism.

It is extremely important to note that while my findings suggest that complex information processing may be impaired in autism; this appears to be unrelated to cognitive ability. While IQ was lower in the autistic samples, differential attention to complex information in Chapter 5 was present in autism after controlling for IQ and reduced P3a amplitudes to social condition in Chapter 4 was also unrelated to IQ. Indeed, these differences, particularly in Chapter 5 appeared related to arousal and thus point towards more nuanced atypicalities in processing information when tonic arousal is higher and thus, ability to appropriately process information might be adversely affected. Other literature also shows

that autistic symptom severity is unrelated to IQ (Hoekstra, Happé, Baron-Cohen & Ronald, 2010) and indeed, our findings are in line with this.

Finally, in line with the fractionated triad model (Happe & Ronald, 2008), we found that social interaction difficulties were specifically related to profiles of hyperarousal, and difficulties in processing social and/or more complex information. We found that social communication and RRB domains were not statistically related to arousal and orienting of attention (at least on the measures we used) and this suggests that it will be useful in future research to look at these domains separately and measure them separately to identify risk factors specific to them.

Implications for methodology of research in autism

The manipulation of stimuli and experimental contexts in a controlled manner as well as the comprehensive characterization of co-occurring symptoms of other conditions and including a clinical control group proved useful in identifying the specific mechanisms that appear atypical in autism. Further, they also show the important experimental methods that are crucial to understanding autism better in future studies.

Using the RDoC framework (Cuthbert & Insel, 2013), and shifting away from the biomedical model of deficits, we found that mapping neurobiological mechanisms dimensionally can help enhance understanding of factors that might contribute to the heterogeneity of the autistic spectrum. Tonic arousal profiles, when used dimensionally, revealed functionally different and meaningful subgroups that were not specific to a diagnosis but rather, helped understand the heterogeneity within that diagnosis, thus providing useful clinical information. Further, using the neuroconstructivistic approach of cross-syndrome clinical comparisons (and not trying to study individuals who are “pure” without comorbid conditions, who tend to be the exception rather than the norm (Astle & Fletcher-Watson, 2020)) also helped identify atypicalities specific to ADHD and autism, and also identify atypicalities that might be shared between conditions. Again, this meant that we had a more representative sample

of autistic individuals as they truly exist in the population. We found that autistic children with co-occurring ADHD showed attentional profiles similar to ADHD. Presence of ADHD in autistic children compensated for some atypicalities in attention, particularly towards more complex/social stimuli. However, autistic children and young people comorbid with ADHD were not all similar to ADHD children in their arousal profile, rather some of them showed hyperarousal profiles, while others showed hypoarousal profiles. Future research should adopt these approaches, not just in research in autism, but indeed, in all developmental disorders to shed light on the nuanced ways in which risk factors for different conditions, and/or risk factors that impair certain fundamental mechanisms, interact to produce the heterogeneous phenotypes we observe at the outcome stage.

Another extremely important implication of my thesis is the importance of systematically manipulating the experimental context and the stimuli used along various dimensions. It is crucial as researchers to reflect on the specific context and experience of research participants that might then influence the results we find. In my thesis, I was keen to measure spontaneous distribution of attention, when no cognitive demands are placed on participants. Therefore, I used a resting-state (in which participants simply watched a silent movie in a dimly lit room); I then added auditory stimulation with this being the only change from the resting-state. Just this simple manipulation in a controlled manner helped reveal that autistic individuals and individuals with ADHD showed similar changes in autonomic response to auditory stimuli. This is useful because many theories in the fields of autism and ADHD posit that these basic and fundamental mechanisms are atypical in these conditions, which we did not find support for. Future research should manipulate a greater range of experimental contexts in controlled ways, for example, investigating differences in autonomic and cortical arousal within resting-state between eyes-open and eyes-closed as well as measure how increasing demand on sensory and cognitive processing impacts arousal and attention in autism. This would help us better understand the difficulties autistic individuals may face in specific environments in their lives.

Similarly, manipulating the stimuli used along multiple dimensions proved extremely useful. In Chapter 5, I manipulated visual stimuli not just in their social-ness, as is typical in autism literature, but also

their complexity. We observed atypicalities then, not in association with social-ness but in association with complexity, and this was observed not just in a clinical sample but also in a neurotypical population with varying subclinical traits of autism, thus providing more confidence that it was complexity that impacted attention in autism and this effect was specific to autism, having controlled for ADHD. This has important implications for future research in autism, which has historically focused on the assumption that social stimuli elicit a specific effect because they are social, without investigating other aspects of these stimuli that might confer a specific effect on attentional systems. Indeed, social stimuli do hold a significant place in the life of human beings, given we are a society that is highly dependent on successful social interactions for survival. Further, social stimuli elicit activity in a specific network in the brain that does not respond to non-social stimuli (Chevallier et al., 2012). Moreover, the primary difficulties in autism are reflected in social settings. However, my findings suggest that there may be factors besides social characteristics that may drive attentional differences in autism, such as familiarity/complexity/predictability of stimuli. Importantly, there is preliminary evidence that infants at elevated risk for autism show similar biases to social stimuli during infancy as neurotypical individuals, but that these biases decrease in autistic individuals with time (Jones & Klin, 2013). It is important to investigate longitudinally then, the aspects of social stimuli that impact attention negatively, so that we can work preventatively; not to change the way autistic individuals attend to the world, but to potentially prevent their experience of the social world from being aversive, and to ensure that they are able to take advantage of all learning opportunities in the world. Understanding what about social stimuli makes it difficult- complexity, predictability, etc., would go a long way in informing the types of interventions and adaptations in home and education environments that would benefit autistic individuals from an early age. Manipulating stimuli across multiple dimensions then is extremely important when studying attention in autism.

6.2.2. Impact on everyday life of autistic individuals

While my findings do not directly impact everyday life of autistic individuals, they do have implications that are relevant to everyday life for autistic individuals. Firstly, autistic individuals with and without ADHD may present different profiles of attention. This is important since this suggests that for any autistic child, careful characterisation of symptoms of other conditions (such as ADHD) may be extremely important to understand the type of things they struggle with day-to-day and to help them manage those difficulties. Further, we found that profiles of reduced parasympathetic activation were associated with more social interaction difficulties (Chapter 3) and similarly, social interaction difficulties were also associated with reduced preferential orienting to auditory stimuli (within the context of more complex/social deviants, Chapter 4) and reduced orienting to novelty (Chapter 5). These findings suggest that for autistic children and young people with more severe social interaction difficulties might find it difficult to spontaneously attend to complex information, possibly due to underlying differences in arousal regulation, and these young people may benefit from being given information in a scaffolded way so that they can engage with the environment better.

My findings also highlight that autistic children and young people that are hyper- or hypo-aroused might experience day-to-day situations very differently from one another and they might need different types of support to take advantage of learning opportunities in sensory-rich environments. Hyperaroused children or young people that are autistic might be very sensitive and possibly hypervigilant to different types of stimuli and this might impact their engagement with more complex information. In more sensory-rich environments such as typical classroom settings, they might benefit from being sheltered from any stimulation that is unnecessary, for example noise-cancelling headphones, sitting in the front of the class so that they do not see all the other children. Similarly, at home, environments with less noise might be helpful. Further, strategies that help them downregulate their arousal might be helpful to enable them to engage and information may need to be adapted in its complexity and be provided in a more piecemeal manner. On the other hand, hypoaroused autistic children and young people might benefit from strategies that enable them to upregulate their arousal,

such as sitting on bouncing balls while studying, and using rewards and reinforcers as well as more engaging tasks etc. It is important, in general, to take a more individualised approach for these children and young people and look at what each specific autistic child finds hard. Profiling their arousal might help understand the functional purpose of their avoidance or seeking sensory behaviours and thus inform the strategies that will help with any particular child.

6.2.3. Impact on Clinical Settings

An important clinical implication of this study is that all autistic individuals do not have the same profile, and some autistic individuals present at least with regard to orienting of attention etc. like individuals with ADHD. Autistic individuals with ADHD might need different kinds of support than autistic people without ADHD. In addition, our findings, particularly with regard to arousal also highlight why some comorbid autistic individuals with ADHD might not do well with medication for ADHD (Davis & Kollins, 2012), possibly because they have a different arousal profile than ADHD, hyper- rather than hypo- aroused. Typical medication for ADHD impacts arousal and this may actually make things worse for hyperaroused autistic individuals. Measurement of arousal using ECG or wearable devices that measure physiological arousal in daily living environments might aid identification of autistic individuals who might need support with hyperarousal than hypoarousal. This could inform which medications are appropriate for which autistic children. Further, hyperaroused individuals in our sample showed worse autistic social interaction symptoms and higher anxiety, which would be useful information for clinicians trying to formulate care plans for autistic individuals. Further research replicating our findings with larger sample sizes is needed to inform such clinical approaches.

Additionally, it is important to remember that diagnostic boundaries are arbitrary. Autistic individuals with inattention in our sample were not classified in the comorbid group because inattention is a broad domain associated with both autism and ADHD. While inattention in ADHD is typically associated with distractibility, in autism it may be linked to atypical distribution of attention to different types of information in the environment. When measuring inattentive features, we measure behaviours rather

than factors driving those behaviours. Clinically, when engaging in a differential diagnosis, it is important to keep in mind then that the same feature could be indicative of different conditions depending upon when and why the behaviour arises. Similarly, there were individuals with ADHD who had autistic traits but these were just below threshold for them to be categorized in the comorbid group. Again, this is important to recognise and track longitudinally, as sometimes, for such young people, as they grow older and social demands increase, they may struggle to cope and the autistic traits may underlie continued or worse difficulties in adapting to the world. Therefore, clinical work might need to shift from the traditional medical models of diagnosing an illness and then treating it to a more developmental approach that addresses the various areas that an individual child is struggling in and addressing those needs and trying to bridge specific developmental gaps. A comprehensive and systematic approach during assessment and a nuanced approach when formulating treatment and care/support strategies is ultimately important for clinical care as well as educational settings.

Finally, if social interaction difficulties are driven by the complexity of social interactions, it may be important for early intervention programmes in autism to develop interventions and adaptations in various settings to enable autistic children to process complex social and non-social information better. Scaffolding their social interactions with support and slowing down the pace as well as reducing the sensory load within such interactions at an early age may prevent autistic children from becoming avoidant of social interactions later on.

6.3. Limitations

One main limitation in this study was sample size and power. We recruited 106 children and young people in the SAAND study who were either neurotypical, or with autism and/or ADHD. However, not all participants completed all the tasks in the experimental battery. Our a-priori power analyses showed that we needed at least 25 participants per group (NT, Autism-only, ADHD-only and Autism+ADHD) to achieve 80% power. While we had sufficient power to identify main effects (of medium size) in our analyses of autism or ADHD, we were underpowered for autism and ADHD interactions. Therefore,

we were cautious in interpreting such interaction effects and where the interaction was marginal (between $p < 0.05$ and $p < 0.1$), we corrected following pairwise comparisons using Benjamini-Hochberg corrections (Benjamini & Hochberg, 1995). Nonetheless, replication in new samples is essential given the multi-factorial design of many of the ANOVAs and the potential for Type II errors arising from this. Further, we were underpowered in comparing the arousal subgroups within the autistic participants and therefore we did not compare them using statistical tests, and rather used effect sizes which were consistently in the small-to-medium range. Most of these effects were in line with our a-priori predictions and in agreement with the wider literature and this provides confidence towards the reliability of these effects. However, these do require replication using larger samples. Importantly, we used bootstrapped confidence intervals in correlational analyses to check whether the correlation crossed zero. Our main correlations of interest (which investigated relationship between SCQ subscales and outcome measures such as P3a amplitudes or rate of change in look durations over trials) were reliable and did not cross zero after bootstrapping. Therefore, while we were underpowered for some of these effects, we utilized a careful approach, using effect sizes and confidence intervals to check reliability of the effects. Further, in Chapter 5, we also utilized a neurotypical sample to investigate whether the clinical effect was present on the other side of autistic diagnostic boundary in individuals with subclinical autistic traits.

We struggled in this study specifically to recruit autistic children and young people. Despite our best efforts at reaching out to various sources of recruitment, including special schools with autism units, support groups for autism, and clinics, this was a hard-to-recruit population for this study. We were unable to recruit autistic children who were also learning disabled. A significant proportion of the autistic participants took part in the study because they were on a waiting list for the ADOS assessment and participating in this study helped them circumvent that waiting list and get an ADOS assessment sooner. This meant that our autistic participants were not representative of autistic people who have a classic autism presentation that is typically diagnosed in early childhood. Indeed, many autistic participants in our study had comorbid conditions such as anxiety disorders, or ADHD, which had been identified earlier and were possibly more prominent in these children, meaning that traits of autism were

masked initially and only detected at a later stage. This introduces a sampling bias in our study and it is possible that the general trend in my results of autistic individuals with ADHD showing profiles of attention more similar to ADHD-only participants is partially due to this sampling bias. While this means that our autistic sample was not representative of the whole autistic population, we were able to tap into a part of the autistic population that is under-researched, that is, those with comorbid ADHD and/or with other emotional/mental health/psychiatric conditions. Further, recognizing that our recruitment efforts were not sufficient in engaging the whole autistic population, I started a qualitative study alongside my supervisor (Dr. Groom) in which I interviewed parents of autistic children about barriers to participation in neuroscientific research. This study is still ongoing, but already, interviews conducted thus far have revealed important aspects of the recruitment process that discouraged some families from taking part, and these are practical things we can change in the future to increase the representativeness of autistic samples in neuroscientific research.

Finally, when we started this study, we did not have specific questions around anxiety or adaptive functioning. As our knowledge and understanding grew and our thinking developed, we recognized the importance of characterising adaptive functioning and anxiety in our participants. Therefore, we used all information collected to rate CGAS (Shaffer et al., 1983) on adaptive functioning as well as utilized the SDQ Impact subscale (Goodman, 2001); and used DAWBA ratings on various anxiety disorders. These efforts did prove useful in comparing the subgroups of autistic individuals on these factors. However, future research should use better measures to directly investigate anxiety and adaptive functioning in autistic individuals in association with profiles of arousal and attention. Scales such as the Vineland Adaptive Behaviour Scales for adaptive functioning (Sparrow, Cicchetti, & Balla, 1984); and other measures for anxiety, including measures that investigate anxiety that is more specific to autism, such as Intolerance of Uncertainty Scale (Carleton, Norton, & Asmundson, 2007), might be better.

We also used the Sensory Profile to measure sensory processing behaviours. This measure did not prove very useful for us with scores at ceiling across domains in all participants from clinical groups. Other

measures of sensory processing may be warranted. However, we do note that when looking at the Sensory Profile domains in association with arousal subgroups, this measure was more sensitive in showing that the hyperaroused subgroup shows more sensory avoidance behaviours while the hypoaroused subgroup shows more sensory seeking behaviours. It is possible then that when investigating sensory processing profiles, one needs to take a more functional approach, rather than a diagnostic approach, to understand the functions these behaviours serve. Depending upon the research question then, this measure may indeed be useful.

6.4. Future directions

Overall, in this thesis, we captured autism-specific atypicalities but also differences in neurobiological systems of arousal that are not autism-specific that impact attention and may underlie the development of social interaction difficulties in autism as well as contribute to the heterogeneity of the autistic spectrum. I would like to conclude the thesis with some suggestions and recommendations for future research, based on the implications of my work as discussed above:

- It will be important to investigate profiles of sympathetic and parasympathetic arousal at rest and in response to sensory stimulation and cognitive demands in neurotypical individuals, and create standardized measures (that measure traits rather than states) that can aid identification of atypically increased or decreased tonic arousal, driven by sympathetic or parasympathetic systems, at different ages. This has important implications for early identification of infants, toddlers or children who may struggle to regulate their arousal irrespective of diagnosis. Further, this would help understand clinically significant differences between groups that differ in some way, rather than just statistically significant differences.
- We found that measuring heart rate was useful in stratification of autistic individuals into empirically homogenous subgroups. It will be important to replicate this effect in larger sample sizes, and to investigate how such subgroups of hyper- and hypo- aroused individuals behave

in different environments, in response to cognitive demands, but also in day to day living environments.

- Future research should also map developmental trajectories of autonomic arousal profiles and how these associate with development of autistic symptoms in different autistic symptom domains of social interaction, social communication and restricted, repetitive behaviours. Further, sensory processing behaviours should be directly measured developmentally to identify whether some of these reflect regulatory/coping strategies due to sub-optimal states of arousal.
- Our findings suggest that profiles of tonic hyperarousal might underlie an avoidance of complexity in attention in autism. This requires further investigation with larger sample sizes and in studies that manipulate stimuli along various dimensions, including complexity but also predictability and familiarity.
- We observed that RRBs in particular (although also the social communication symptoms) were not related to profiles of arousal, which is not in line with the wider theories in autism. As an autism research community, we should develop more sensitive tools that fully tap into the multidimensional construct of RRBs. Both hyper and hypoarousal are theoretically linked with RRBs, but potentially different types of RRBs. A more nuanced approach in measurement of RRBs that measures qualitatively different types of RRBs might be important to understand whether profiles of arousal are linked with these and what function they serve, if it is to regulate arousal.
- Future studies should also investigate how arousal profiles link with other aspects of attention, such as latency of orienting to stimuli, and measure learning of information alongside attention to more directly measure information processing.
- Measuring attention and information processing to multimodal information would further help understand how information across modalities is integrated and whether autistic individuals struggle in this area.

- Finally, it is important to investigate arousal and attention using multiple types of measures simultaneously, such as using autonomic measures alongside neuroimaging measures, to identify where atypicalities lie in the brain, and how these develop over life.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (DSM-5®)*: American Psychiatric Pub.

Anderson, C., Colombo, J., & Shaddy, D. J. (2006). Visual scanning and pupillary responses in young children with Autism Spectrum Disorder. *Journal of clinical and experimental neuropsychology, 28*(7), 1238-1256. http://dx.doi.org/10.1080/13803390500376790

Anderson, C. J., & Colombo, J. (2009). Larger tonic pupil size in young children with autism spectrum disorder. *Developmental Psychobiology, 51*(2), 207-211. https://doi.org/10.1002/dev.20352

Anderson, C. J., Colombo, J., & Unruh, K. E. (2013). Pupil and salivary indicators of autonomic dysfunction in autism spectrum disorder. *Dev Psychobiol, 55*. https://doi.org/10.1002/dev.21051

Appelhans, B. M., & Luecken, L. J. (2006). Heart rate variability as an index of regulated emotional responding. *Review of general psychology, 10*(3), 229-240. https://doi.org/10.1037/1089-2680.10.3.229

Astle, D. E., & Fletcher-Watson, S. (2020). Beyond the Core-Deficit Hypothesis in Developmental Disorders. *Current Directions in Psychological Science*. https://doi.org/10.1177/0963721420925518

Aston-Jones, G., & Bloom, F. (1981a). Activity of norepinephrine-containing locus coeruleus neurons in behaving rats anticipates fluctuations in the sleep-waking cycle. *Journal of Neuroscience, 1*(8), 876-886. https://doi.org/10.1523/JNEUROSCI.01-08-00876.1981

Aston-Jones, G., & Bloom, F. (1981b). Nonrepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *Journal of Neuroscience, 1*(8), 887-900. https://doi.org/10.1523/JNEUROSCI.01-08-00887.1981

Aston-Jones, G., & Cohen, J. D. (2005a). Adaptive gain and the role of the locus coeruleus-norepinephrine system in optimal performance. *Journal of Comparative Neurology, 493*(1), 99-110. https://doi.org/10.1002/cne.20723

Aston-Jones, G., & Cohen, J. D. (2005b). An Integrative Theory of Locus Coeruleus Norepinephrine Function: Adaptive Gain and Optimal Performance. *Annual Review of Neuroscience, 28*(1), 403-450. https://doi.org/10.1146/annurev.neuro.28.061604.135709

Aston-Jones, G., Foote, S., & Segal, M. (1985). Impulse conduction properties of noradrenergic locus coeruleus axons projecting to monkey cerebrocortex. *Neuroscience, 15*(3), 765-777. https://doi.org/10.1016/0306-4522(85)90077-6

Aston-Jones, G., Gonzalez, M., & Doran, S. (2007). Role of the locus coeruleus-norepinephrine system in arousal and circadian regulation of the sleep-wake cycle. https://doi.org/10.1017/CBO9780511544156.007

Autistica. (n.d.). *Your questions: Shaping future autism research.* Retrieved August 1, 2020, from https://www.autistica.org.uk/downloads/files/Autism-Top-10-Your-Priorities-for-Autism-Research.pdf

Auyeung, B., Baron-Cohen, S., Wheelwright, S., & Allison, C. (2008). The autism spectrum quotient: Children's version (AQ-Child). *Journal of Autism and Developmental Disorders, 38*(7), 1230-1240. https://doi.org/10.1007/s10803-007-0504-z

Awh, E., Belopolsky, A. V., & Theeuwes, J. (2012). Top-down versus bottom-up attentional control: A failed theoretical dichotomy. *Trends in Cognitive Sciences, 16*(8), 437-443. https://doi.org/10.1016/j.tics.2012.06.010

Baranek, G. T. (1999). Autism during infancy: A retrospective video analysis of sensory-motor and social behaviors at 9–12 months of age. *Journal of Autism and Developmental Disorders, 29*(3), 213-224. https://doi.org/10.1023/A:1023080005650

Baranek, G. T., David, F. J., Poe, M. D., Stone, W. L., & Watson, L. R. (2006). Sensory Experiences Questionnaire: Discriminating sensory features in young children with autism, developmental delays, and typical development. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 47*(6), 591-601. https://doi.org/10.1111/j.1469-7610.2005.01546.x

Baranek, G. T., Watson, L. R., Boyd, B. A., Poe, M. D., David, F. J., & McGuire, L. (2013). Hyporesponsiveness to social and nonsocial sensory stimuli in children with autism, children

with developmental delays, and typically developing children. *Development and Psychopathology, 25*(2), 307-320. doi:10.1017/S0954579412001071

Baron-Cohen, S. (1989). The Autistic Child's Theory of Mind: a Case of Specific Developmental Delay. *Journal of Child Psychology and Psychiatry, 30*(2), 285-297. doi:10.1111/j.1469-7610.1989.tb00241.x

Baron-Cohen, S. (2000). Theory of mind and autism: A fifteen year review. *Understanding other minds: Perspectives from developmental cognitive neuroscience, 2*, 3-20.

Bast, N., Poustka, L., & Freitag, C. M. (2018). The locus coeruleus-norepinephrine system as pacemaker of attention - a developmental mechanism of derailed attentional function in autism spectrum disorder. *European Journal of Neuroscience*. doi:10.1111/ejn.13795

Bazelmans, T., Jones, E. J. H., Ghods, S., Corrigan, S., Toth, K., Charman, T., & Webb, S. J. (2019). Heart rate mean and variability as a biomarker for phenotypic variation in preschoolers with autism spectrum disorder. *Autism Research, 12*(1), 39-52. doi:10.1002/aur.1982

Bedford, R., Pickles, A., Gliga, T., Elsabbagh, M., Charman, T., Johnson, M. H., & Team, B. (2014). Additive effects of social and non-social attention during infancy relate to later autism spectrum disorder. *Dev Sci, 17*(4), 612-620. doi:10.1111/desc.12139

Bellato, A., Arora, I., Hollis, C., & Groom, M. J. (2020). Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence. *Neuroscience and biobehavioral reviews, 108*, 182-206. doi:10.1016/j.neubiorev.2019.11.001

Ben-Sasson, A., Hen, L., Fluss, R., Cermak, S. A., Engel-Yeger, B., & Gal, E. (2009). A meta-analysis of sensory modulation symptoms in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*(1), 1-11. doi:10.1007/s10803-008-0593-3

Benevides, T. W., & Lane, S. J. (2015). A Review of Cardiac Autonomic Measures: Considerations for Examination of Physiological Response in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders, 45*(2), 560-575. doi:10.1007/s10803-013-1971-z

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological), 57*(1), 289-300. doi:10.1111/j.2517-6161.1995.tb02031.x

Birchwood, J., & Daley, D. (2012). Brief report: The impact of Attention Deficit Hyperactivity Disorder (ADHD) symptoms on academic performance in an adolescent community sample. *Journal of Adolescence, 35*(1), 225-231. https://doi.org/10.1016/j.adolescence.2010.08.011

Bishop-Fitzpatrick, L., Minshew, N. J., Mazefsky, C. A., & Eack, S. M. (2017). Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 47*(1), 1-16. doi: 10.1007/s10803-016-2910-6

Blanca, M. J., Alarcón, R., Arnau, J., Bono, R., & Bendayan, R. (2017). Non-normal data: Is ANOVA still a valid option? *Psicothema, 29*(4), 552-557. doi: 10.7334/psicothema2016.383

Blanchard, D. C., Griebel, G., Pobbe, R., & Blanchard, R. J. (2011). Risk assessment as an evolved threat detection and analysis process. *Neuroscience & Biobehavioral Reviews, 35*(4), 991-998. https://doi.org/10.1016/j.neubiorev.2010.10.016

Blaser, E., Eglington, L., Carter, A. S., & Kaldy, Z. (2014). Pupillometry Reveals a Mechanism for the Autism Spectrum Disorder (ASD) Advantage in Visual Tasks. *Scientific Reports, 4*. doi:10.1038/srep04301

Braga, R. M., Wilson, L. R., Sharp, D. J., Wise, R. J., & Leech, R. (2013). Separable networks for top-down attention to auditory non-spatial and visuospatial modalities. *NeuroImage, 74*, 77-86. https://doi.org/10.1016/j.neuroimage.2013.02.023

Brett, D., Warnell, F., McConachie, H., & Parr, J. R. (2016). Factors Affecting Age at ASD Diagnosis in UK: No Evidence that Diagnosis Age has Decreased Between 2004 and 2014. *Journal of Autism and Developmental Disorders, 46*(6), 1974-1984. doi:10.1007/s10803-016-2716-6

Brod, M., Schmitt, E., Goodwin, M., Hodgkins, P., & Niebler, G. (2012). ADHD burden of illness in older adults: a life course perspective. *Quality of Life Research, 21*(5), 795-799. doi:10.1007/s11136-011-9981-9

Buescher, A. V., Cidav, Z., Knapp, M., & Mandell, D. S. (2014). Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatr, 168*(8), 721-728. doi:10.1001/jamapediatrics.2014.210

Bujnakova, I., Ondrejka, I., Mestanik, M., Fleskova, D., Sekaninova, N., Farsky, I., & Tonhajzerova, I. (2017). Potential effect of pharmacotherapy on sympathetic arousal in autism. *Acta Medica Martiniana, 17*(3), 16-23. http://dx.doi.org/10.1515/acm-2017-0013

Bujnakova, I., Ondrejka, I., Mestanik, M., Visnovcova, Z., Mestanikova, A., Hrtanek, I., . . . Tonhajzerova, I. (2016). Autism spectrum disorder is associated with autonomic underarousal. *Physiological research, 65*(Supplementum 5), S673-S682. doi: 10.33549/physiolres.933528

Cai, R. Y., Richdale, A. L., Dissanayake, C., & Uljarevic, M. (2019). Resting heart rate variability, emotion regulation, psychological wellbeing and autism symptomatology in adults with and without autism. *International Journal of Psychophysiology, 137*, 54-62. http://dx.doi.org/10.1016/j.ijpsycho.2018.12.010

Callejas, A., Lupianez, J., Funes, M. J., & Tudela, P. (2005). Modulations among the alerting, orienting and executive control networks. *Experimental Brain Research, 167*(1), 27-37. doi: 10.1007/s00221-005-2365-z

Callejas, A., Lupiáñez, J., & Tudela, P. (2004). The three attentional networks: On their independence and interactions. *Brain and Cognition, 54*(3), 225-227. https://doi.org/10.1016/j.bandc.2004.02.012

Carleton, R. N., Norton, M. P. J., & Asmundson, G. J. (2007). Fearing the unknown: A short version of the Intolerance of Uncertainty Scale. *Journal of anxiety disorders, 21*(1), 105-117. doi: 10.1016/j.janxdis.2006.03.014

Carpenter, K. L., Baranek, G. T., Copeland, W. E., Compton, S., Zucker, N., Dawson, G., & Egger, H. L. (2019). Sensory over-responsivity: an early risk factor for anxiety and behavioral challenges in young children. *Journal of Abnormal Child Psychology, 47*(6), 1075-1088. https://doi.org/10.1007/s10802-018-0502-y

Carter Leno, V., Chandler, S., White, P., Yorke, I., Charman, T., Pickles, A., & Simonoff, E. (2018). Alterations in electrophysiological indices of perceptual processing and discrimination are associated with co-occurring emotional and behavioural problems in adolescents with autism spectrum disorder. *Molecular Autism, 9*, 50. doi:10.1186/s13229-018-0236-2

Čeponiene, R., Lepistö, T., Shestakova, A., Vanhala, R., Alku, P., Näätänen, R., & Yaguchi, K. (2003). Speech-sound-selective auditory impairment in children with autism: They can perceive but do not attend. *Proceedings of the National Academy of Sciences of the United States of America, 100*(9), 5567-5572. doi:10.1073/pnas.0835631100

Cerf, M., Frady, E. P., & Koch, C. (2009). Faces and text attract gaze independent of the task: Experimental data and computer model. *Journal of Vision, 9*(12), 10-10. https://doi.org/10.1167/9.12.10

Chamak, B., Bonniau, B., Jaunay, E., & Cohen, D. (2008). What can we learn about autism from autistic persons? *Psychotherapy and Psychosomatics, 77*(5), 271-279. doi:10.1159/000140086

Chang, M. C., Parham, L. D., Blanche, E. I., Schell, A., Chou, C. P., Dawson, M., & Clark, F. (2012). Autonomic and behavioral responses of children with autism to auditory stimuli. *American Journal of Occupational Therapy, 66*(5), 567-576. doi:10.5014/ajot.2012.004242

Chesnut, S. R., Wei, T., Barnard-Brak, L., & Richman, D. M. (2017). A meta-analysis of the social communication questionnaire: Screening for autism spectrum disorder. *Autism, 21*(8), 920-928. doi:10.1177/1362361316660065

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The social motivation theory of autism. *Trends Cogn Sci, 16*(4), 231-239. doi:10.1016/j.tics.2012.02.007

Chita-Tegmark, M. (2016). Social attention in ASD: A review and meta-analysis of eye-tracking studies. *Research in Developmental Disabilities, 48*, 79-93. doi:10.1016/j.ridd.2015.10.011

Cho, Y. T., Fromm, S., Guyer, A. E., Detloff, A., Pine, D. S., Fudge, J. L., & Ernst, M. (2013). Nucleus accumbens, thalamus and insula connectivity during incentive anticipation in typical adults and adolescents. *NeuroImage, 66*, 508-521. https://doi.org/10.1016/j.neuroimage.2012.10.013

Cohen, J. D., McClure, S. M., & Yu, A. J. (2007). Should I stay or should I go? How the human brain manages the trade-off between exploitation and exploration. *Philosophical Transactions of the Royal Society B: Biological Sciences, 362*(1481), 933-942. doi:10.1098/rstb.2007.2098

Cohen, S., Conduit, R., Lockley, S. W., Rajaratnam, S. M. W., & Cornish, K. M. (2014). The relationship between sleep and behavior in autism spectrum disorder (ASD): a review. *Journal of Neurodevelopmental Disorders, 6*(1), 44. doi:10.1186/1866-1955-6-44

Colombi, C., Fish, A., & Ghaziuddin, M. (2019). Utility of the ADOS-2 in children with psychiatric disorders. *Eur Child Adolesc Psychiatry*. doi:10.1007/s00787-019-01411-8

Colombo, J., & Cheatham, C. L. (2006). The emergence and basis of endogenous attention in infancy and early childhood.

Colombo, J., & Mitchell, D. W. (2009). Infant visual habituation. *Neurobiol Learn Mem, 92*(2), 225-234. doi:10.1016/j.nlm.2008.06.002

Colvert, E., Tick, B., McEwen, F., Stewart, C., Curran, S. R., Woodhouse, E., . . . Bolton, P. (2015). Heritability of Autism Spectrum Disorder in a UK Population-Based Twin Sample. *JAMA Psychiatry, 72*(5), 415-423. doi:10.1001/jamapsychiatry.2014.3028

Conners, C. K. (2008). Conners third edition (Conners 3). *Los Angeles, CA: Western Psychological Services*.

Constantino, J. N., & Charman, T. (2016). Diagnosis of autism spectrum disorder: reconciling the syndrome, its diverse origins, and variation in expression. *The Lancet Neurology, 15*(3), 279-291. doi:10.1016/s1474-4422(15)00151-9

Constantino, J. N., & Todd, R. D. (2003). Autistic traits in the general population: a twin study. *Archives of General Psychiatry, 60*(5), 524-530. doi: 10.1001/archpsyc.60.5.524

Corbetta, M., Patel, G., & Shulman, G. L. (2008). The Reorienting System of the Human Brain: From Environment to Theory of Mind. *Neuron, 58*(3), 306-324. doi:10.1016/j.neuron.2008.04.017

Cornish, K., Scerif, G., & Karmiloff-Smith, A. (2007). Tracing Syndrome-Specific Trajectories of Attention Across the Lifespan. *Cortex, 43*(6), 672-685. doi: https://doi.org/10.1016/S0010-9452(08)70497-0

Critchley, H. D., & Garfinkel, S. N. (2018). The influence of physiological signals on cognition. *Current Opinion in Behavioral Sciences, 19*, 13-18. doi: https://doi.org/10.1016/j.cobeha.2017.08.014

Csibra, G., Hernik, M., Mascaro, O., Tatone, D., & Lengyel, M. (2016). Statistical treatment of looking-time data. *Dev Psychol, 52*(4), 521-536. doi: 10.1037/dev0000083

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Medicine, 11*(1), 126. doi: 10.1186/1741-7015-11-126

Cuve, H. C., Gao, Y., & Fuse, A. (2018). Is it avoidance or hypoarousal? A systematic review of emotion recognition, eye-tracking, and psychophysiological studies in young adults with autism spectrum conditions. *Research in Autism Spectrum Disorders, 55*, 1-13. doi:10.1016/j.rasd.2018.07.002

Danckaerts, M., Sonuga-Barke, E. J. S., Banaschewski, T., Buitelaar, J., Döpfner, M., Hollis, C., . . . Coghill, D. (2010). The quality of life of children with attention deficit/hyperactivity disorder: a systematic review. *European Child & Adolescent Psychiatry, 19*(2), 83-105. doi:10.1007/s00787-009-0046-3

Davis, N. O., & Kollins, S. H. (2012). Treatment for co-occurring attention deficit/hyperactivity disorder and autism spectrum disorder. *Neurotherapeutics, 9*(3), 518-530. doi:10.1007/s13311-012-0126-9

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology, 20*(3), 775-803. doi: 10.1017/S0954579408000370

Dawson, G., Bernier, R., & Ring, R. H. (2012). Social attention: A possible early indicator of efficacy in autism clinical trials. *Journal of Neurodevelopmental Disorders, 4*(1), 1-12. doi:10.1186/1866-1955-4-11

Dawson, G., & Lewy, A. (1989). Arousal, attention, and the socioemotional impairments of individuals with autism.

Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., & Liaw, J. (2004). Early Social Attention Impairments in Autism: Social Orienting, Joint Attention, and Attention to Distress. *Developmental Psychology, 40*(2), 271-283. doi:10.1037/0012-1649.40.2.271

Dellapiazza, F. (2018). Links between sensory processing, adaptive behaviours, and attention in children with autism spectrum disorder: A systematic review. *Psychiatry Research, 270*, 78-88. doi:10.1016/j.psychres.2018.09.023

Derryberry, D., & Rothbart, M. K. (1988). Arousal, affect, and attention as components of temperament. *Journal of Personality and Social Psychology, 55*(6), 958. doi: 10.1037//0022-3514.55.6.958

DesLauriers, A. M., & Carlson, C. F. (1969). Your child is asleep: Early infantile autism: Etiology, treatment, and parental influences.

Dibeklioğlu, H., Salah, A. A., & Gevers, T. (2015). Recognition of genuine smiles. *IEEE Transactions on Multimedia, 17*(3), 279-294.

DiCriscio, A. S., Miller, S. J., Hanna, E. K., Kovac, M., Turner-Brown, L., Sasson, N. J., . . . Dichter, G. S. (2016). Brief Report: Cognitive Control of Social and Nonsocial Visual Attention in Autism. *Journal of Autism and Developmental Disorders, 46*(8), 2797-2805. doi:10.1007/s10803-016-2804-7

Dubey, I., Ropar, D., & Hamilton, A. (2018). Comparison of choose-a-movie and approach–avoidance paradigms to measure social motivation. *Motivation and Emotion, 42*(2), 190-199. doi:10.1007/s11031-017-9647-1

Duncan, C. C., Barry, R. J., Connolly, J. F., Fischer, C., Michie, P. T., Naatanen, R., . . . Van Petten, C. (2009). Event-related potentials in clinical research: guidelines for eliciting, recording, and quantifying mismatch negativity, P300, and N400. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 120*(11), 1883-1908. doi:10.1016/j.clinph.2009.07.045

Dunn, L. M., & Dunn, D. M. (2009). *The British picture vocabulary scale*: GL Assessment Limited.

Dunn, W. (2014). *Sensory profile 2*: Psych Corporation.

Dworzynski, K., Happé, F., Bolton, P., & Ronald, A. (2009). Relationship between symptom domains in autism spectrum disorders: a population based twin study. *Journal of Autism and Developmental Disorders, 39*(8), 1197-1210. https://doi.org/10.1007/s10803-009-0736-1

Eckstein, M. K., Guerra-Carrillo, B., Miller Singley, A. T., & Bunge, S. A. (2016). Beyond eye gaze: What else can eyetracking reveal about cognition and cognitive development? *Developmental Cognitive Neuroscience*. doi:10.1016/j.dcn.2016.11.001

Edmiston, E. K., Jones, R. M., & Corbett, B. A. (2016). Physiological Response to Social Evaluative Threat in Adolescents with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders, 46*(9), 2992-3005. doi:10.1007/s10803-016-2842-1

Edmiston, E. K., Muscatello, R. A., & Corbett, B. A. (2017). Altered pre-ejection period response to social evaluative threat in adolescents with autism spectrum disorder. *Research in Autism Spectrum Disorders, 36*, 57-65. doi:10.1016/j.rasd.2017.01.008

Eilam-Stock, T., Xu, P., Cao, M., Gu, X., Dam, N. T., & Anagnostou, E. (2014). Abnormal autonomic and associated brain activities during rest in autism spectrum disorder. *Brain, 137*. doi:10.1093/brain/awt294

Elison, J. T., Paterson, S. J., Wolff, J. J., Reznick, J. S., Sasson, N. J., Gu, H., . . . Network, I. (2013). White matter microstructure and atypical visual orienting in 7-month-olds at risk for autism. *The American Journal of Psychiatry, 170*(8), 899-908. doi:10.1176/appi.ajp.2012.12091150

Elison, J. T., Sasson, N. J., Turner-Brown, L. M., Dichter, G. S., & Bodfish, J. W. (2012). Age trends in visual exploration of social and nonsocial information in children with autism. *Research in Autism Spectrum Disorders, 6*(2), 842-851. doi:10.1016/j.rasd.2011.11.005

Elsabbagh, M., Fernandes, J., Jane Webb, S., Dawson, G., Charman, T., & Johnson, M. H. (2013a). Disengagement of visual attention in infancy is associated with emerging autism in toddlerhood. *Biological Psychiatry, 74*(3), 189-194. doi:10.1016/j.biopsych.2012.11.030

Elsabbagh, M., Gliga, T., Pickles, A., Hudry, K., Charman, T., & Johnson, M. H. (2013b). The development of face orienting mechanisms in infants at-risk for autism. *Behavioural Brain Research, 251*, 147-154. doi:10.1016/j.bbr.2012.07.030

Elsabbagh, M., & Johnson, M. H. (2016). Autism and the Social Brain: The First-Year Puzzle. *Biol Psychiatry, 80*(2), 94-99. doi:10.1016/j.biopsych.2016.02.019

Elsabbagh, M., Volein, A., Holmboe, K., Tucker, L., Csibra, G., Baron-Cohen, S., . . . Johnson, M. H. (2009). Visual orienting in the early broader autism phenotype: Disengagement and facilitation. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 50*(5), 637-642. doi:10.1111/j.1469-7610.2008.02051.x

Falck-Ytter, T., Bölte, S., & Gredebäck, G. (2013). Eye tracking in early autism research. *Journal of Neurodevelopmental Disorders, 5*(1), 28. doi:10.1186/1866-1955-5-28

Falck-Ytter, T., Rehnberg, E., & Bölte, S. (2013). Lack of Visual Orienting to Biological Motion and Audiovisual Synchrony in 3-Year-Olds with Autism. *PLoS ONE, 8*(7), e68816. doi:10.1371/journal.pone.0068816

Fan, X., Miles, J. H., Takahashi, N., & Yao, G. (2009). Abnormal transient pupillary light reflex in individuals with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*(11), 1499-1508. doi:http://dx.doi.org/10.1007/s10803-009-0767-7

Fantz, R. L. (1964). Visual experience in infants: Decreased attention to familiar patterns relative to novel ones. *Science, 146*(3644), 668-670. https://doi.org/10.1126/science.146.3644.668

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G* Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*(2), 175-191. https://doi.org/10.3758/BF03193146

Feczko, E., Miranda-Dominguez, O., Marr, M., Graham, A. M., Nigg, J. T., & Fair, D. A. (2019). The Heterogeneity Problem: Approaches to Identify Psychiatric Subtypes. *Trends Cogn Sci, 23*(7), 584-601. doi:10.1016/j.tics.2019.03.009

Feng, G. (2011). Eye Tracking: A Brief Guide for Developmental Researchers. *Journal of Cognition and Development, 12*(1), 1-11. doi:10.1080/15248372.2011.547447

Field, A. (2013). *Discovering statistics using IBM SPSS statistics*: sage.

Fischer, J., Koldewyn, K., Jiang, Y. V., & Kanwisher, N. (2014). Unimpaired attentional disengagement and social orienting in children with autism. *Clinical Psychological Science, 2*(2), 214-223. doi:10.1177/2167702613496242

Fitzgerald, H. E. (1968). Autonomic pupillary reflex activity during early infancy and its relation to social and nonsocial visual stimuli. *Journal of Experimental Child Psychology, 6*(3), 470-482. doi:https://doi.org/10.1016/0022-0965(68)90127-6

Fletcher-Watson, S., Leekam, S. R., Benson, V., Frank, M. C., & Findlay, J. M. (2009). Eye-movements reveal attention to social information in autism spectrum disorder. *Neuropsychologia, 47*(1), 248-257. doi:10.1016/j.neuropsychologia.2008.07.016

Franchini, M., Glaser, B., Wood de Wilde, H., Gentaz, E., Eliez, S., & Schaer, M. (2017). Social orienting and joint attention in preschoolers with autism spectrum disorders. *PLoS ONE, 12*(6), e0178859. doi:10.1371/journal.pone.0178859

Freeth, M., Chapman, P., Ropar, D., & Mitchell, P. (2010). Do Gaze Cues in Complex Scenes Capture and Direct the Attention of High Functioning Adolescents with ASD? Evidence from Eye-tracking. *Journal of Autism and Developmental Disorders, 40*(5), 534-547. doi:10.1007/s10803-009-0893-2

Freeth, M., Ropar, D., Mitchell, P., Chapman, P., & Loher, S. (2011). Brief Report: How Adolescents with ASD Process Social Information in Complex Scenes. Combining Evidence from Eye Movements and Verbal Descriptions. *Journal of Autism and Developmental Disorders, 41*(3), 364-371. doi:10.1007/s10803-010-1053-4

Friedman, B. H. (2007). An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. *Biol Psychol, 74*(2), 185-199. doi:10.1016/j.biopsycho.2005.08.009

Frye, R. E., & Rossignol, D. A. (2016). Identification and treatment of pathophysiological comorbidities of autism spectrum disorder to achieve optimal outcomes. *Clinical Medicine Insights: Pediatrics, 10*, CMPed. S38337. https://doi.org/10.4137/CMPed.S38337

Gao, Z., Flevaris, A. V., Robertson, L. C., & Bentin, S. (2011). Priming global and local processing of composite faces: revisiting the processing-bias effect on face perception. *Attention, Perception & Psychophysics, 73*(5), 1477-1486. doi:10.3758/s13414-011-0109-7

Gardner, J. M., Karmel, B. Z., & Flory, M. J. (2003). Arousal modulation of neonatal visual attention: Implications for development. *Perspectives on fundamental processes in intellectual functioning, 2*, 125-153.

Garland, E. L., Froeliger, B., & Howard, M. O. (2015). Allostatic dysregulation of natural reward processing in prescription opioid misuse: autonomic and attentional evidence. *Biol Psychol, 105*, 124-129. doi:10.1016/j.biopsycho.2015.01.005

Geissler, J., Romanos, M., Hegerl, U., & Hensch, T. (2014). Hyperactivity and sensation seeking as autoregulatory attempts to stabilize brain arousal in ADHD and mania? *Atten Defic Hyperact Disord, 6*(3), 159-173. doi:10.1007/s12402-014-0144-z

Gentzler, A. L., Santucci, A. K., Kovacs, M., & Fox, N. A. (2009). Respiratory sinus arrhythmia reactivity predicts emotion regulation and depressive symptoms in at-risk and control children. *Biological Psychology, 82*(2), 156-163. https://doi.org/10.1016/j.biopsycho.2009.07.002

Geva, R., Dital, A., Ramon, D., Yarmolovsky, J., Gidron, M., & Kuint, J. (2017). Brainstem as a developmental gateway to social attention. *J Child Psychol Psychiatry*. doi:10.1111/jcpp.12746

Geva, R., & Feldman, R. (2008). A neurobiological model for the effects of early brainstem functioning on the development of behavior and emotion regulation in infants: Implications for prenatal and perinatal risk. *Journal of Child Psychology and Psychiatry, 49*(10), 1031-1041. https://doi.org/10.1111/j.1469-7610.2008.01918.x

Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective and Behavioral Neuroscience, 10*(2), 252-269. doi:10.3758/CABN.10.2.252

Gladwin, T. E., Hashemi, M. M., van Ast, V., & Roelofs, K. (2016). Ready and waiting: Freezing as active action preparation under threat. *Neuroscience Letters, 619*, 182-188. https://doi.org/10.1016/j.neulet.2016.03.027

Gliga, T., Bedford, R., Charman, T., Johnson, Mark H., Baron-Cohen, S., Bolton, P., . . . Tucker, L. (2015). Enhanced Visual Search in Infancy Predicts Emerging Autism Symptoms. *Current Biology, 25*(13), 1727-1730. doi:10.1016/j.cub.2015.05.011

Gliga, T., Elsabbagh, M., Andravizou, A., & Johnson, M. (2009). Faces attract infants' attention in complex displays. *Infancy, 14*(5), 550-562. https://doi.org/10.1080/15250000903144199

Gliga, T., Smith, T. J., Likely, N., Charman, T., & Johnson, M. H. (2018). Early Visual Foraging in Relationship to Familial Risk for Autism and Hyperactivity/Inattention. *Journal of attention disorders, 22*(9), 839-847. doi:10.1177/1087054715616490

Gokcen, E., Frederickson, N., & Petrides, K. V. (2016). Theory of Mind and Executive Control Deficits in Typically Developing Adults and Adolescents with High Levels of Autism Traits. *Journal of Autism and Developmental Disorders, 46*(6), 2072-2087. doi:10.1007/s10803-016-2735-3

Goldberg, M. C., Lasker, A. G., Zee, D. S., Garth, E., Tien, A., & Landa, R. J. (2002). Deficits in the initiation of eye movements in the absence of a visual target in adolescents with high

functioning autism. *Neuropsychologia, 40*(12), 2039-2049. https://doi.org/10.1016/S0028-3932(02)00059-3

Gomot, M., Belmonte, M. K., Bullmore, E. T., Bernard, F. A., & Baron-Cohen, S. (2008). Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. *Brain, 131*(9), 2479-2488. https://doi.org/10.1093/brain/awn172

Gomot, M., Bernard, F. A., Davis, M. H., Belmonte, M. K., Ashwin, C., Bullmore, E. T., & Baron-Cohen, S. (2006). Change detection in children with autism: an auditory event-related fMRI study. *NeuroImage*, *29*(2), 475-484. doi: 10.1016/j.neuroimage.2005.07.027

Gomot, M., Blanc, R., Clery, H., Roux, S., Barthelemy, C., & Bruneau, N. (2011). Candidate electrophysiological endophenotypes of hyper-reactivity to change in autism. *Journal of Autism and Developmental Disorders*, *41*(6), 705-714. doi: 10.1007/s10803-010-1091-y

Gomot, M., Giard, M.-H., Adrien, J.-L., Barthelemy, C., & Bruneau, N. (2002). Hypersensitivity to acoustic change in children with autism: electrophysiological evidence of left frontal cortex dysfunctioning. *Psychophysiology, 39*(5), 577-584. https://doi.org/10.1017/S0048577202394058

Goodman, R. (2001). Psychometric Properties of the Strengths and Difficulties Questionnaire. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(11), 1337-1345. doi:https://doi.org/10.1097/00004583-200111000-00015

Goodman, R., Ford, T., Richards, H., Gatward, R., & Meltzer, H. (2000). The Development and Well-Being Assessment: Description and Initial Validation of an Integrated Assessment of Child and Adolescent Psychopathology. *Journal of Child Psychology and Psychiatry, 41*(5), 645-655. doi:10.1111/j.1469-7610.2000.tb02345.x

Goodwin, M. S., Groden, J., Velicer, W. F., Lipsitt, L. P., Baron, M. G., Hofmann, S. G., & Groden, G. (2006). Cardiovascular arousal in individuals with autism. *Focus on autism and other developmental disabilities, 21*(2), 100-123. https://doi.org/10.1177/10883576060210020101

Green, B., Shirk, S., Hanze, D., & Wanstrath, J. (1994). The Children's Global Assessment Scale in Clinical Practice: An Empirical Evaluation. *Journal of the American Academy of Child &*

Adolescent Psychiatry, 33(8), 1158-1164. doi:https://doi.org/10.1097/00004583-199410000-00011

Green, S. A., & Ben-Sasson, A. (2010). Anxiety disorders and sensory over-responsivity in children with autism spectrum disorders: is there a causal relationship? *Journal of Autism and Developmental Disorders, 40*(12), 1495-1504. doi:10.1007/s10803-010-1007-x

Green, S. A., Hernandez, L., Bookheimer, S. Y., & Dapretto, M. (2016a). Reduced modulation of thalamocortical connectivity during exposure to sensory stimuli in ASD. *Autism Research*. doi:10.1002/aur.1726

Green, S. A., Hernandez, L., Bookheimer, S. Y., & Dapretto, M. (2016b). Salience Network Connectivity in Autism Is Related to Brain and Behavioral Markers of Sensory Overresponsivity. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(7), 618-626.e611. doi:10.1016/j.jaac.2016.04.013

Green, S. A., Hernandez, L., Lawrence, K. E., Liu, J., Tsang, T., Yeargin, J., . . . Bookheimer, S. Y. (2019). Distinct Patterns of Neural Habituation and Generalization in Children and Adolescents With Autism With Low and High Sensory Overresponsivity. *The American Journal of Psychiatry*(1535-7228 (Electronic)), appiajp201918121333. doi:10.1176/appi.ajp.2019.18121333

Green, S. A., Hernandez, L., Tottenham, N., Krasileva, K., Bookheimer, S. Y., & Dapretto, M. (2015). Neurobiology of Sensory Overresponsivity in Youth With Autism Spectrum Disorders. *JAMA Psychiatry, 72*(8), 778-786. doi:10.1001/jamapsychiatry.2015.0737

Groom, M. J., Kochhar, P., Hamilton, A., Liddle, E. B., Simeou, M., & Hollis, C. (2017). Atypical Processing of Gaze Cues and Faces Explains Comorbidity between Autism Spectrum Disorder (ASD) and Attention Deficit/Hyperactivity Disorder (ADHD). *Journal of Autism and Developmental Disorders*, 1-14. doi:10.1007/s10803-017-3078-4

Groom, M. J., Liddle, E. B., Scerif, G., Liddle, P. F., Batty, M. J., Liotti, M., & Hollis, C. P. (2013). Motivational incentives and methylphenidate enhance electrophysiological correlates of error monitoring in children with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, 54*(8), 836-845. doi: 10.1111/jcpp.12069

Groom, M. J., Scerif, G., Liddle, P. F., Batty, M. J., Liddle, E. B., Roberts, K. L., . . . Hollis, C. (2010). Effects of Motivation and Medication on Electrophysiological Markers of Response Inhibition in Children with Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *67*(7), 624-631. doi:http://dx.doi.org/10.1016/j.biopsych.2009.09.029

Groves, P. M., & Thompson, R. F. (1970). Habituation: a dual-process theory. *Psychological review*, *77*(5), 419. https://doi.org/10.1037/h0029810

Guiraud, J. A., Kushnerenko, E., Tomalski, P., Davies, K., Ribeiro, H., Johnson, M. H., & Team, B. (2011). Differential habituation to repeated sounds in infants at high risk for autism. *Neuroreport*, *22*(16), 845-849. doi:10.1097/WNR.0b013e32834c0bec

Halgren, E., Baudena, P., Clarke, J. M., Heit, G., Liégeois, C., Chauvel, P., & Musolino, A. (1995). Intracerebral potentials to rare target and distractor auditory and visual stimuli. I. Superior temporal plane and parietal lobe. *Electroencephalography and Clinical Neurophysiology*, *94*(3), 191-220. doi:https://doi.org/10.1016/0013-4694(94)00259-N

Hanley, M., McPhillips, M., Mulhern, G., & Riby, D. M. (2013). Spontaneous attention to faces in Asperger syndrome using ecologically valid static stimuli. *Autism*, *17*(6), 754-761. doi:10.1177/1362361312456746

Happe, F., & Frith, U. (2020). Annual Research Review: Looking back to look forward - changes in the concept of autism and implications for future research. *J Child Psychol Psychiatry*. doi:10.1111/jcpp.13176

Happé, F., & Frith, U. (2006). The weak coherence account: detail-focused cognitive style in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *36*(1), 5-25. https://doi.org/10.1007/s10803-005-0039-0

Happe, F., & Ronald, A. (2008). The 'fractionable autism triad': a review of evidence from behavioural, genetic, cognitive and neural research. *Neuropsychol Rev*, *18*(4), 287-304. doi:10.1007/s11065-008-9076-8

Happe, F., Ronald, A., & Plomin, R. (2006). Time to give up on a single explanation for autism. *Nat Neurosci*, *9*(10), 1218-1220. doi:10.1038/nn1770

Hasler, R., Perroud, N., Meziane, H. B., Herrmann, F., Prada, P., Giannakopoulos, P., & Deiber, M.-P. (2016). Attention-related EEG markers in adult ADHD. *Neuropsychologia, 87,* 120-133. doi:http://dx.doi.org/10.1016/j.neuropsychologia.2016.05.008

Heaton, T. J., & Freeth, M. (2016). Reduced visual exploration when viewing photographic scenes in individuals with autism spectrum disorder. *J Abnorm Psychol, 125*(3), 399-411. doi:10.1037/abn0000145

Helminen, T. M., Leppanen, J. M., Eriksson, K., Luoma, A., Hietanen, J. K., & Kylliainen, A. (2017). Atypical physiological orienting to direct gaze in low-functioning children with autism spectrum disorder. *Autism research : official journal of the International Society for Autism Research, 10*(5), 810-820. doi:https://dx.doi.org/10.1002/aur.1738

Hirstein, W., Iversen, P., & Ramachandran, V. S. (2001). Autonomic responses of autistic children to people and objects. *Proceedings of the Royal Society of London. Series B: Biological Sciences, 268*(1479), 1883. https://doi.org/10.1098/rspb.2001.1724

Hobson, J. A., McCarley, R. W., & Wyzinski, P. W. (1975). Sleep cycle oscillation: reciprocal discharge by two brainstem neuronal groups. *Science, 189*(4196), 55-58. doi: 10.1126/science.1094539

Hoekstra, R. A., Happé, F., Baron-Cohen, S., & Ronald, A. (2010). Limited genetic covariance between autistic traits and intelligence: findings from a longitudinal twin study. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *153*(5), 994-1007. https://doi.org/10.1002/ajmg.b.31066

Howells, F. M., Stein, D. J., & Russell, V. A. (2012). Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance. *Metab Brain Dis, 27*(3), 267-274. doi:10.1007/s11011-012-9287-9

Huang-Pollock, C. L., & Nigg, J. T. (2003). Searching for the attention deficit in attention deficit hyperactivity disorder: The case of visuospatial orienting. *Clinical Psychology Review, 23*(6), 801-830. doi:https://doi.org/10.1016/S0272-7358(03)00073-4

Hubbard, R., & Lindsay, R. M. (2008). Why P Values Are Not a Useful Measure of Evidence in Statistical Significance Testing. *Theory & Psychology, 18*(1), 69-88. doi:10.1177/0959354307086923

Hudac, C. M., DesChamps, T. D., Arnett, A. B., Cairney, B. E., Ma, R., Webb, S. J., & Bernier, R. A. (2018). Early enhanced processing and delayed habituation to deviance sounds in autism spectrum disorder. *Brain Cogn, 123*, 110-119. doi:10.1016/j.bandc.2018.03.004

Hull, J. V., Dokovna, L. B., Jacokes, Z. J., Torgerson, C. M., Irimia, A., & Van Horn, J. D. (2017). Resting-State Functional Connectivity in Autism Spectrum Disorders: A Review. *Frontiers in Psychiatry, 7*, 205. https://doi.org/10.3389/fpsyt.2016.00205

Hus, V., & Lord, C. (2014). The autism diagnostic observation schedule, module 4: revised algorithm and standardized severity scores. *Journal of Autism and Developmental Disorders, 44*(8), 1996-2012. doi:10.1007/s10803-014-2080-3

Hutchinson, J. B., & Turk-Browne, N. B. (2012). Memory-guided attention: Control from multiple memory systems. *Trends in Cognitive Sciences, 16*(12), 576-579. https://doi.org/10.1016/j.tics.2012.10.003

Hutt, C., Hutt, S., Lee, D., & Ounsted, C. (1964). Arousal and childhood autism. *Nature, 204*(4961), 908-909. https://doi.org/10.1038/204908a0

Ingersoll, B. (2010). Broader autism phenotype and nonverbal sensitivity: evidence for an association in the general population. *Journal of Autism and Developmental Disorders, 40*(5), 590-598. doi:10.1007/s10803-009-0907-0

Itti, L., & Koch, C. (2001). Computational modelling of visual attention. *Nature Reviews Neuroscience, 2*(3), 194-203. https://doi.org/10.1038/35058500

Jack, A., & Pelphrey, K. A. (2017). Annual Research Review: Understudied populations within the autism spectrum - current trends and future directions in neuroimaging research. *Journal of Child Psychology and Psychiatry*. doi:10.1111/jcpp.12687

James, A. L., & Barry, R. J. (1984). Cardiovascular and electrodermal responses to simple stimuli in autistic, retarded and normal children. *International Journal of Psychophysiology, 1*(2), 179-193. doi:http://dx.doi.org/10.1016/0167-8760%2884%2990037-0

Jennings, J. R., & Wood, C. C. (1977). Cardiac cycle time effects on performance, phasic cardiac responses, and their intercorrelation in choice reaction time. *Psychophysiology, 14*(3), 297-307. https://doi.org/10.1111/j.1469-8986.1977.tb01179.x

Johnson, M. H. (2005). Subcortical face processing. *Nature Reviews Neuroscience, 6*(10), 766-774. doi:10.1038/nrn1766

Johnson, Mark H. (2014). Autism: Demise of the Innate Social Orienting Hypothesis. *Current Biology, 24*(1), R30-R31. doi:http://dx.doi.org/10.1016/j.cub.2013.11.021

Johnson, M. H., Gliga, T., Jones, E., & Charman, T. (2015). Annual Research Review: Infant development, autism, and ADHD - early pathways to emerging disorders. *Journal of Child Psychology and Psychiatry, 56*(3), 228-247. doi:10.1111/jcpp.12328

Johnson, M. H., Jones, E. J. H., & Gliga, T. (2015). Brain adaptation and alternative developmental trajectories. *Development and Psychopathology, 27*(2), 425-442. doi:10.1017/S0954579415000073

Johnstone, S. J., Barry, R. J., & Clarke, A. R. (2013). Ten years on: a follow-up review of ERP research in attention-deficit/hyperactivity disorder. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 124*(4), 644-657. doi:10.1016/j.clinph.2012.09.006

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2-6-month-old infants later diagnosed with autism. *Nature, 504*(7480), 427-431. doi:10.1038/nature12715

http://www.nature.com/nature/journal/v504/n7480/abs/nature12715.html#supplementary-information

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between Pupil Diameter and Neuronal Activity in the Locus Coeruleus, Colliculi, and Cingulate Cortex. *Neuron, 89*(1), 221-234. doi:10.1016/j.neuron.2015.11.028

Kaartinen, M., Puura, K., Himanen, S. L., Nevalainen, J., & Hietanen, J. K. (2016). Autonomic Arousal Response Habituation to Social Stimuli Among Children with Asd. *Journal of Autism and Developmental Disorders, 46*(12), 3688-3699. doi:10.1007/s10803-016-2908-0

Kalwani, R. M., Joshi, S., & Gold, J. I. (2014). Phasic activation of individual neurons in the locus ceruleus/subceruleus complex of monkeys reflects rewarded decisions to go but not stop. *Journal of Neuroscience, 34*(41), 13656-13669. https://doi.org/10.1523/JNEUROSCI.2566-14.2014

Kapp, S. K., Gillespie-Lynch, K., Sherman, L. E., & Hutman, T. (2013). Deficit, difference, or both? Autism and neurodiversity. *Developmental Psychology, 49*(1), 59-71. doi:10.1037/a0028353

Karmel, B. Z., Gardner, J. M., & Freeland, R. L. (1996). Arousal-modulated attention at four months as a function of intrauterine cocaine exposure and central nervous system injury. *Journal of Pediatric Psychology, 21*(6), 821-832. https://doi.org/10.1093/jpepsy/21.6.821

Karmiloff-Smith, A. (1998). Development itself is the key to understanding developmental disorders. *Trends in Cognitive Sciences, 2*(10), 389-398. doi:https://doi.org/10.1016/S1364-6613(98)01230-3

Katagiri, M., Miya, K., & Matsui, M. (2014). Difficulty of crossmodal processing in individuals with autism spectrum disorders: An audio-visual gap/overlap paradigm study. *Research in Autism Spectrum Disorders, 8*(4), 424-431. doi:10.1016/j.rasd.2014.01.001

Kawa, R. l., & Pisula, E. (2010). Locomotor activity, object exploration and space preference in children with autism and Down syndrome. *Acta Neurobiol Exp, 70*, 131-140.

Kawakubo, Y., Kasai, K., Okazaki, S., Hosokawa-Kakurai, M., Watanabe, K.-i., Kuwabara, H., . . . Maekawa, H. (2007). Electrophysiological abnormalities of spatial attention in adults with autism during the gap overlap task. *Clinical Neurophysiology, 118*(7), 1464-1471. doi:http://dx.doi.org/10.1016/j.clinph.2007.04.015

Kawakubo, Y., Maekawa, H., Itoh, K., Hashimoto, O., & Iwanami, A. (2004). Spatial attention in individuals with pervasive developmental disorders using the gap overlap task. *Psychiatry Research, 125*(3), 269-275. doi:10.1016/j.psychres.2003.12.012

Keehn, B., Lincoln, A. J., Müller, R. A., & Townsend, J. (2010). Attentional networks in children and adolescents with autism spectrum disorder. *Journal of child psychology and psychiatry, and allied disciplines, 51*(11), 1251-1259. https://doi.org/10.1016/j.neubiorev.2012.11.014

Keehn, B., Müller, R. A., & Townsend, J. (2013). Atypical attentional networks and the emergence of autism. *Neuroscience and biobehavioral reviews, 37*(2), 164-183. doi:10.1016/j.neubiorev.2012.11.014

Kenny, L., Hattersley, C., Molins, B., Buckley, C., Povey, C., & Pellicano, E. (2016). Which terms should be used to describe autism? Perspectives from the UK autism community. *Autism, 20*(4), 442-462. https://doi.org/10.1177/1362361315588200

Khan, S., Michmizos, K., Tommerdahl, M., Ganesan, S., Kitzbichler, M. G., Zetino, M., . . . Kenet, T. (2015). Somatosensory cortex functional connectivity abnormalities in autism show opposite trends, depending on direction and spatial scale. *Brain, 138*(5), 1394-1409. doi:10.1093/brain/awv043

Kinsbourne, M. (2011). Repetitive movements and arousal. *The neuropsychology of autism*, 367-394.

Kiss, I., Dashieff, R. M., & Lordeon, P. (1989). A Parietooccipital Generator for P300: Evidence from Human Intracranial Recordings. *International Journal of Neuroscience, 49*(1-2), 133-139. doi:10.3109/00207458909087048

Kleberg, J. L., Thorup, E., & Falck-Ytter, T. (2017). Reduced visual disengagement but intact phasic alerting in young children with autism. *Autism Research, 10*(3), 539-545. doi:10.1002/aur.1675

Kleinhans, N. M., Johnson, L. C., Richards, T., Mahurin, R., Greenson, J., Dawson, G., & Aylward, E. (2009). Reduced Neural Habituation in the Amygdala and Social Impairments in Autism Spectrum Disorders. *American Journal of Psychiatry, 166*(4), 467-475. doi:10.1176/appi.ajp.2008.07101681

Kleinhans, N. M., Richards, T., Greenson, J., Dawson, G., & Aylward, E. (2016). Altered dynamics of the fMRI response to faces in individuals with autism. *Journal of Autism and Developmental Disorders, 46*(1), 232-241. doi: 10.1007/s10803-015-2565-8

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59*(9), 809-816. doi: 10.1001/archpsyc.59.9.809

Klusek, J., Martin, G. E., & Losh, M. (2013). Physiological arousal in autism and fragile X syndrome: group comparisons and links with pragmatic language. *American journal on intellectual and developmental disabilities, 118*(6), 475-495. doi:http://dx.doi.org/10.1352/1944.7558-118.6.475

Klusek, J., Roberts, J. E., & Losh, M. (2015). Cardiac autonomic regulation in autism and Fragile X syndrome: A review. *Psychological Bulletin, 141*(1), 141-175. doi:10.1037/a0038237

Knapp, M., Romeo, R., & Beecham, J. (2009). Economic cost of autism in the UK. *Autism, 13*(3), 317-336. doi:10.1177/1362361309104246

Kofler, M. J., Rapport, M. D., Sarver, D. E., Raiker, J. S., Orban, S. A., Friedman, L. M., & Kolomeyer, E. G. (2013). Reaction time variability in ADHD: a meta-analytic review of 319 studies. *Clinical Psychology Review, 33*(6), 795-811. https://doi.org/10.1016/j.cpr.2013.06.001

Koldewyn, K., Jiang, Y. V., Weigelt, S., & Kanwisher, N. (2013). Global/local processing in autism: not a disability, but a disinclination. *Journal of Autism and Developmental Disorders, 43*(10), 2329-2340. doi:10.1007/s10803-013-1777-z

Kolesnik, A., Begum Ali, J., Gliga, T., Guiraud, J., Charman, T., Johnson, M. H., . . . Team, B. (2019). Increased cortical reactivity to repeated tones at 8 months in infants with later ASD. *Transl Psychiatry, 9*(1), 46. doi:10.1038/s41398-019-0393-x

Konrad, K., Neufang, S., Hanisch, C., Fink, G. R., & Herpertz-Dahlmann, B. (2006). Dysfunctional Attentional Networks in Children with Attention Deficit/Hyperactivity Disorder: Evidence from an Event-Related Functional Magnetic Resonance Imaging Study. *Biological Psychiatry, 59*(7), 643-651. doi:https://doi.org/10.1016/j.biopsych.2005.08.013

Krypotos, A. M., Jahfari, S., van Ast, V. A., Kindt, M., & Forstmann, B. U. (2011). Individual Differences in Heart Rate Variability Predict the Degree of Slowing during Response Inhibition and Initiation in the Presence of Emotional Stimuli. *Front Psychol, 2*, 278. doi:10.3389/fpsyg.2011.00278

Kuiper, M. W. M., Verhoeven, E. W. M., & Geurts, H. M. (2019). Stop Making Noise! Auditory Sensitivity in Adults with an Autism Spectrum Disorder Diagnosis: Physiological Habituation and Subjective Detection Thresholds. *Journal of Autism and Developmental Disorders, 49*(5), 2116-2128. doi:http://dx.doi.org/10.1007/s10803-019-03890-9

Kuntsi, J., & Klein, C. (2012). Intraindividual Variability in ADHD and Its Implications for Research of Causal Links. In C. Stanford & R. Tannock (Eds.), *Behavioral Neuroscience of Attention*

Deficit Hyperactivity Disorder and Its Treatment (pp. 67-91). Berlin, Heidelberg: Springer Berlin Heidelberg.

Kushki, A., Brian, J., Dupuis, A., & Anagnostou, E. (2014). Functional autonomic nervous system profile in children with autism spectrum disorder. *Molecular Autism, 5*, 39. doi:10.1186/2040-2392-5-39

Kwon, M.-K., Setoodehnia, M., Baek, J., Luck, S. J., & Oakes, L. M. (2016). The development of visual search in infancy: Attention to faces versus salience. *Developmental Psychology, 52*(4), 537. doi: 10.1037/dev0000080

Kylliäinen, A., & Hietanen, J. K. (2006). Skin Conductance Responses to Another Person's Gaze in Children with Autism. *Journal of Autism and Developmental Disorders, 36*(4), 517-525. doi:10.1007/s10803-006-0091-4

Lai, M.-C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., . . . Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: a systematic review and meta-analysis. *The Lancet Psychiatry, 6*(10), 819-829. doi:10.1016/s2215-0366(19)30289-5

Landry, O., & Parker, A. (2013). A meta-analysis of visual orienting in autism. *Frontiers in Human Neuroscience, 7*, 833. doi:10.3389/fnhum.2013.00833

Landry, R., & Bryson, S. E. (2004). Impaired disengagement of attention in young children with autism. *Journal of child psychology and psychiatry, and allied disciplines, 45*(6), 1115-1122. doi:10.1111/j.1469-7610.2004.00304.x

Laucht, M., Becker, K., & Schmidt, M. H. (2006). Visual exploratory behaviour in infancy and novelty seeking in adolescence: two developmentally specific phenotypes of DRD4? *J Child Psychol Psychiatry, 47*(11), 1143-1151. doi:10.1111/j.1469-7610.2006.01627.x

Laurie, M., & Border, P. (2020). *Autism* https://post.parliament.uk/research-briefings/post-pn-0612/#fullreporthttps://post.parliament.uk/research-briefings/post-pn-0612/#fullreport.

Lawson, R. P., Rees, G., & Friston, K. J. (2014). An aberrant precision account of autism. *Frontiers in Human Neuroscience, 8*, 302. doi:10.3389/fnhum.2014.00302

Leekam, S. R., López, B., & Moore, C. (2000). Attention and joint attention in preschool children with autism. *Developmental Psychology, 36*(2), 261-273. https://doi.org/10.1037/0012-1649.36.2.261

Leekam, S. R., Nieto, C., Libby, S. J., Wing, L., & Gould, J. (2007). Describing the sensory abnormalities of children and adults with autism. *Journal of Autism and Developmental Disorders, 37*(5), 894-910. https://doi.org/10.1007/s10803-006-0218-7

Leitner, Y. (2014). The co-occurrence of autism and attention deficit hyperactivity disorder in children - what do we know? *Frontiers in Human Neuroscience, 8*, 268. doi:10.3389/fnhum.2014.00268

Lepistö, T., Kujala, T., Vanhala, R., Alku, P., Huotilainen, M., & Näätänen, R. (2005). The discrimination of and orienting to speech and non-speech sounds in children with autism. *Brain Research, 1066*(1-2), 147-157. doi:10.1016/j.brainres.2005.10.052

Liddle, E. B., Batty, M. J., & Goodman, R. (2009). The Social Aptitudes Scale: an initial validation. *Soc Psychiatry Psychiatr Epidemiol, 44*(6), 508-513. doi:10.1007/s00127-008-0456-4

Liddle, E. B., Hollis, C., Batty, M. J., Groom, M. J., Totman, J. J., Liotti, M., . . . Liddle, P. F. (2011). Task-related default mode network modulation and inhibitory control in ADHD: Effects of motivation and methylphenidate. *Journal of Child Psychology and Psychiatry, 52*(7), 761-771. https://doi.org/10.1111/j.1469-7610.2010.02333.x

Linnemeyer, S. A., & Porges, S. W. (1986). Recognition memory and cardiac vagal tone in 6-month-old infants. *Infant Behavior and Development, 9*(1), 43-56. https://doi.org/10.1016/0163-6383(86)90037-8

Liss, M., Saulnier, C., Fein, D., & Kinsbourne, M. (2006). Sensory and attention abnormalities in autistic spectrum disorders. *Autism, 10*(2), 155-172. doi:10.1177/1362361306062021

Little, L. M., Dean, E., Tomchek, S. D., & Dunn, W. (2017). Classifying sensory profiles of children in the general population. *Child: Care, Health and Development, 43*(1), 81-88. doi:10.1111/cch.12391

Lojowska, M., Gladwin, T. E., Hermans, E. J., & Roelofs, K. (2015). Freezing promotes perception of coarse visual features. *Journal of Experimental Psychology: General, 144*(6), 1080. https://doi.org/10.1037/xge0000117

Loomes, R., Hull, L., & Mandy, W. P. L. (2017). What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(6), 466-474. doi:10.1016/j.jaac.2017.03.013

Lord, C., Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., . . . Veenstra-VanderWeele, J. (2020). Autism spectrum disorder. *Nature Reviews Disease Primers, 6*(1), 5. doi:10.1038/s41572-019-0138-4

Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., & Bishop, S. (2012). Autism diagnostic observation schedule–2nd edition (ADOS-2). *Los Angeles, CA: Western Psychological Corporation*.

Lory, C., Kadlaskar, G., McNally Keehn, R., Francis, A. L., & Keehn, B. (2020). Brief Report: Reduced Heart Rate Variability in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-020-04458-8

Loughlin, S., Foote, S., & Grzanna, R. (1986). Efferent projections of nucleus locus coeruleus: morphologic subpopulations have different efferent targets. *Neuroscience, 18*(2), 307-319. https://doi.org/10.1016/0306-4522(86)90156-9

Louwerse, A., Tulen, J. H. M., van der Geest, J. N., van der Ende, J., Verhulst, F. C., & Greaves-Lord, K. (2014). Autonomic Responses to Social and Nonsocial Pictures in Adolescents With Autism Spectrum Disorder. *Autism Research, 7*(1), 17-27. doi:10.1002/aur.1327

Lovaas, I., Newsom, C., & Hickman, C. (1987). Self-stimulatory behavior and perceptual reinforcement. *Journal of applied behavior analysis, 20*(1), 45-68. https://doi.org/10.1901/jaba.1987.20-45

Luck, S., Girelli, M., & Parasuraman, R. (1998). The attentive brain.

Luck, S. J. (2014). *An introduction to the event-related potential technique*: MIT press.

Lydon, S., Healy, O., Reed, P., Mulhern, T., Hughes, B. M., & Goodwin, M. S. (2016). A systematic review of physiological reactivity to stimuli in autism. *Developmental Neurorehabilitation, 19*(6), 335-355. https://doi.org/10.3109/17518423.2014.971975

Lynch, G. (2018). Using pupillometry to assess the atypical pupillary light reflex and LC-Ne system in ASD. *Behavioral Sciences*, *8*(11). doi:10.3390/bs8110108

Magrelli, S., Jermann, P., Noris, B., Ansermet, F., Hentsch, F., Nadel, J., & Billard, A. (2013). Social orienting of children with autism to facial expressions and speech: A study with a wearable eye-tracker in naturalistic settings. *Frontiers in Psychology*, *4*(NOV). doi:10.3389/fpsyg.2013.00840

Mann, T. A., & Walker, P. (2003). Autism and a deficit in broadening the spread of visual attention. *Journal of Child Psychology and Psychiatry, 44*(2), 274-284. https://doi.org/10.1111/1469-7610.00120

Massrali, A., Brunel, H., Hannon, E., Wong, C., i, P.-M. E. G., Baron-Cohen, S., & Warrier, V. (2019). Integrated genetic and methylomic analyses identify shared biology between autism and autistic traits. *Molecular Autism*, *10*, 31. doi:10.1186/s13229-019-0279-z

Mather, M., Clewett, D., Sakaki, M., & Harley, C. W. (2016). Norepinephrine ignites local hotspots of neuronal excitation: How arousal amplifies selectivity in perception and memory. *Behav Brain Sci*, *39*, e200. doi:10.1017/S0140525X15000667

Mathersul, D., McDonald, S., & Rushby, J. A. (2013a). Automatic facial responses to affective stimuli in high-functioning adults with autism spectrum disorder. *Physiol Behav*, *109*. doi:10.1016/j.physbeh.2012.10.008

Mathersul, D., McDonald, S., & Rushby, J. A. (2013b). Autonomic arousal explains social cognitive abilities in high-functioning adults with autism spectrum disorder. *Int J Psychphysiol*, *89*. doi:10.1016/j.ijpsycho.2013.04.014

Mathewson, K. J., Drmic, I. E., Jetha, M. K., Bryson, S. E., Goldberg, J. O., Hall, G. B., . . . Schmidt, L. A. (2011). Behavioral and cardiac responses to emotional stroop in adults with autism spectrum disorders: Influence of medication. *Autism Research*, *4*(2), 98-108. doi:http://dx.doi.org/10.1002/aur.176

Matsushima, K., Matsubayashi, J., Toichi, M., Funabiki, Y., Awaya, T., & Kato, T. (2016). Unusual sensory features are related to resting-state cardiac vagus nerve activity in autism spectrum

disorders. *Research in Autism Spectrum Disorders, 25*, 37-46. doi:http://dx.doi.org/10.1016/j.rasd.2015.12.006

McCall, R. B., & Carriger, M. S. (1993). A meta-analysis of infant habituation and recognition memory performance as predictors of later IQ. *Child Development, 64*(1), 57-79. https://doi.org/10.1111/j.1467-8624.1993.tb02895.x

McCormick, C., Hessl, D., Macari, S. L., Ozonoff, S., Green, C., & Rogers, S. J. (2014). Electrodermal and behavioral responses of children with autism spectrum disorders to sensory and repetitive stimuli. *Autism Research: Official Journal of the International Society for Autism Research, 7*(4), 468-480. doi:10.1002/aur.1382

McCrimmon, A. W., & Smith, A. D. (2012). Review of the Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II). *Journal of Psychoeducational Assessment, 31*(3), 337-341. doi:10.1177/0734282912467756

McDiarmid, T. A., Bernardos, A. C., & Rankin, C. H. (2017). Habituation is altered in neuropsychiatric disorders-a comprehensive review with recommendations for experimental design and analysis. *Neuroscience and biobehavioral reviews*. doi:10.1016/j.neubiorev.2017.05.028

McEwen, F. S., Stewart, C. S., Colvert, E., Woodhouse, E., Curran, S., Gillan, N., . . . Bolton, P. (2016). Diagnosing autism spectrum disorder in community settings using the Development and Well-Being Assessment: validation in a UK population-based twin sample. *J Child Psychol Psychiatry, 57*(2), 161-170. doi:10.1111/jcpp.12447

McKinnon, C. J., Eggebrecht, A. T., Todorov, A., Wolff, J. J., Elison, J. T., Adams, C. M., . . . Pruett, J. R. (2019). Restricted and Repetitive Behavior and Brain Functional Connectivity in Infants at Risk for Developing Autism Spectrum Disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 4*(1), 50-61. doi:https://doi.org/10.1016/j.bpsc.2018.09.008

McVey, A. J. (2019). The neurobiological presentation of anxiety in autism spectrum disorder: A systematic review. *Autism Research*. doi:10.1002/aur.2063

Meehan, T. P., Bressler, S. L., Tang, W., Astafiev, S. V., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2017). Top-down cortical interactions in visuospatial attention. *Brain Structure and Function, 222*(7), 3127-3145. https://doi.org/10.1007/s00429-017-1390-6

Mena, B., José, M., Alarcón, R., Arnau Gras, J., Bono Cabré, R., & Bendayan, R. (2017). Non-normal data: Is ANOVA still a valid option? *Psicothema, 2017, vol. 29, num. 4, p. 552-557*. doi: 10.7334/psicothema2016.383

Menon, V., & Uddin, L. Q. (2010). Saliency, switching, attention and control: a network model of insula function. *Brain Struct Funct, 214*(5-6), 655-667. doi:10.1007/s00429-010-0262-0

Michielsen, M., Comijs, H. C., Aartsen, M. J., Semeijn, E. J., Beekman, A. T. F., Deeg, D. J. H., & Kooij, J. J. S. (2013). The Relationships Between ADHD and Social Functioning and Participation in Older Adults in a Population-Based Study. *Journal of attention disorders, 19*(5), 368-379. doi:10.1177/1087054713515748

Miller, G. A., & Chapman, J. P. (2001). Misunderstanding analysis of covariance. *Journal of Abnormal Psychology, 110*(1), 40. doi: 10.1037//0021-843x.110.1.40

Mineka, S., & Zinbarg, R. (2006). A contemporary learning theory perspective on the etiology of anxiety disorders: it's not what you thought it was. *American psychologist, 61*(1), 10. https://doi.org/10.1037/0003-066X.61.1.10

Mittner, M., Hawkins, G. E., Boekel, W., & Forstmann, B. U. (2016). A Neural Model of Mind Wandering. *Trends Cogn Sci, 20*(8), 570-578. doi:10.1016/j.tics.2016.06.004

Moore, A., Wozniak, M., Yousef, A., Barnes, C. C., Cha, D., Courchesne, E., & Pierce, K. (2018). The geometric preference subtype in ASD: identifying a consistent, early-emerging phenomenon through eye tracking. *Molecular Autism, 9*, 19. doi:10.1186/s13229-018-0202-z

Moore, T., & Zirnsak, M. (2017). Neural mechanisms of selective visual attention. *Annual Review of Psychology, 68*, 47-72. https://doi.org/10.1146/annurev-psych-122414-033400

Mosconi, M. W., Kay, M., D'Cruz, A. M., Seidenfeld, A., Guter, S., Stanford, L. D., & Sweeney, J. A. (2009). Impaired inhibitory control is associated with higher-order repetitive behaviors in autism spectrum disorders. *Psychological Medicine, 39*(09), 1559. doi:10.1017/S0033291708004984

Mottron, L., Dawson, M., Soulières, I., Hubert, B., & Burack, J. (2006). Enhanced Perceptual Functioning in Autism: An Update, and Eight Principles of Autistic Perception. *Journal of Autism and Developmental Disorders, 36*(1), 27-43. doi:10.1007/s10803-005-0040-7

Mowlem, F. D., Rosenqvist, M. A., Martin, J., Lichtenstein, P., Asherson, P., & Larsson, H. (2019). Sex differences in predicting ADHD clinical diagnosis and pharmacological treatment. *European Child & Adolescent Psychiatry, 28*(4), 481-489. doi:10.1007/s00787-018-1211-3

Murphy, D., & Spooren, W. (2012). EU-AIMS: a boost to autism research. *Nature Reviews Drug Discovery, 11*(11), 815-816. https://doi.org/10.1038/nrd3881

Murphy, E. R., Norr, M., Strang, J. F., Kenworthy, L., Gaillard, W. D., & Vaidya, C. J. (2017). Neural Basis of Visual Attentional Orienting in Childhood Autism Spectrum Disorders. *Journal of Autism and Developmental Disorders, 47*(1), 58-67. doi:10.1007/s10803-016-2928-9

Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. *Human Brain Mapping, 35*(8), 4140-4154. doi:10.1002/hbm.22466

Murphy, P. R., Robertson, I. H., Balsters, J. H., & O'Connell, R. G. (2011). Pupillometry and P3 index the locus coeruleus-noradrenergic arousal function in humans. *Psychophysiology, 48*(11), 1532-1543. doi:10.1111/j.1469-8986.2011.01226.x

Mutreja, R., Craig, C., & O'Boyle, M. W. (2016). Attentional network deficits in children with autism spectrum disorder. *Developmental Neurorehabilitation, 19*(6), 389-397. doi:10.3109/17518423.2015.1017663

Naatanen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118*(12), 2544-2590. doi:10.1016/j.clinph.2007.04.026

Neuhaus, E., Bernier, R., & Beauchaine, T. P. (2014). Brief report: social skills, internalizing and externalizing symptoms, and respiratory sinus arrhythmia in autism. *Journal of Autism and Developmental Disorders, 44*. doi:10.1007/s10803-013-1923-7

Neuhaus, E., Bernier, R. A., & Beauchaine, T. P. (2015). Electrodermal Response to Reward and Non-Reward Among Children With Autism. *Autism Research, 8*(4), 357-370. doi:http://dx.doi.org/10.1002/aur.1451

Neuhaus, E., Bernier, R. A., & Beauchaine, T. P. (2016). Children with Autism Show Altered Autonomic Adaptation to Novel and Familiar Social Partners. *Autism Research, 9*(5), 579-591. doi:http://dx.doi.org/10.1002/aur.1543

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus--norepinephrine system. *Psychological Bulletin, 131*(4), 510. https://doi.org/10.1037/0033-2909.131.4.510

Nieuwenhuis, S., De Geus, E. J., & Aston-Jones, G. (2011). The anatomical and functional relationship between the P3 and autonomic components of the orienting response. *Psychophysiology, 48*(2), 162-175. doi:10.1111/j.1469-8986.2010.01057.x

Nuske, H. J., Vivanti, G., & Dissanayake, C. (2015). No Evidence of Emotional Dysregulation or Aversion to Mutual Gaze in Preschoolers with Autism Spectrum Disorder: An Eye-Tracking Pupillometry Study. *Journal of Autism and Developmental Disorders, 45*(11), 3433-3445. doi:10.1007/s10803-015-2479-5

Nystrom, P., Gliga, T., Jobs, E. N., Gredeback, G., Charman, T., Johnson, M. H., . . . Falck-Ytter, T. (2018). Enhanced pupillary light reflex in infancy is associated with autism diagnosis in toddlerhood. *Nature Communications*, *9*(1), 1678. doi:http://dx.doi.org/10.1038/s41467-018-03985-4

Nystrom, P., Gredeback, G., Bolte, S., & Falck-Ytter, T. (2015). Hypersensitive pupillary light reflex in infants at risk for autism. *Molecular Autism*, *6*(1), 10. doi:http://dx.doi.org/10.1186/s13229-015-0011-6

O'Reilly, C., Lewis, J. D., & Elsabbagh, M. (2017). Is functional brain connectivity atypical in autism? A systematic review of EEG and MEG studies. *PLoS ONE, 12*(5). doi:10.1371/journal.pone.0175870

Orekhova, E. V., & Stroganova, T. A. (2014). Arousal and attention re-orienting in autism spectrum disorders: Evidence from auditory event-related potentials. *Frontiers in Human Neuroscience, 8*(1 FEB). doi:10.3389/fnhum.2014.00034

Orekhova, E. V., Stroganova, T. A., Prokofiev, A. O., Nygren, G., Gillberg, C., & Elam, M. (2009). The right hemisphere fails to respond to temporal novelty in autism: Evidence from an ERP study. *Clinical Neurophysiology, 120*(3), 520-529. doi:10.1016/j.clinph.2008.12.034

Osterling, J., & Dawson, G. (1994). Early recognition of children with autism: A study of first birthday home videotapes. *Journal of Autism and Developmental Disorders, 24*(3), 247-257. doi:10.1007/BF02172225

Pace, M., & Bricout, V.-A. (2015). Low heart rate response of children with autism spectrum disorders in comparison to controls during physical exercise. *Physiology & Behavior, 141*, 63-68. doi:http://dx.doi.org/10.1016/j.physbeh.2015.01.011

Palkovitz, R. J., & Wiesenfeld, A. R. (1980). Differential autonomic responses of autistic and normal children. *Journal of Autism and Developmental Disorders, 10*(3), 347-360. https://doi.org/10.1007/BF02408294

Patriquin, M. A., Scarpa, A., Friedman, B. H., & Porges, S. W. (2013). Respiratory sinus arrhythmia: a marker for positive social functioning and receptive language skills in children with autism spectrum disorders. *Dev Psychobiol, 55*. doi:10.1002/dev.21002

Peirce, J. W. (2007). PsychoPy—psychophysics software in Python. *Journal of Neuroscience Methods, 162*(1-2), 8-13. https://doi.org/10.1016/j.jneumeth.2006.11.017

Peirce, J. W. (2009). Generating stimuli for neuroscience using PsychoPy. *Frontiers in neuroinformatics, 2*, 10. https://doi.org/10.3389/neuro.11.010.2008

Pellicano, E., & Burr, D. (2012). When the world becomes 'too real': a Bayesian explanation of autistic perception. *Trends Cogn Sci, 16*(10), 504-510. doi:10.1016/j.tics.2012.08.009

Pellicano, E., Smith, A. D., Cristino, F., Hood, B. M., Briscoe, J., & Gilchrist, I. D. (2011). Children with autism are neither systematic nor optimal foragers. *Proceedings of the National Academy of Sciences, 108*(1), 421-426. doi:10.1073/pnas.1014076108

Perry, W., Minassian, A., Lopez, B., Maron, L., & Lincoln, A. (2007). Sensorimotor gating deficits in adults with autism. *Biol Psychiatry, 61*(4), 482-486. doi:10.1016/j.biopsych.2005.09.025

Peterson, G. E., & Barney, H. L. (1952). Control methods used in a study of the vowels. *The Journal of the acoustical society of America, 24*(2), 175-184. doi: 10.1121/1.1917300

Pfeiffer, B., Erb, S. R., & Slugg, L. (2019). Impact of noise-attenuating headphones on participation in the home, community, and school for children with autism spectrum disorder. *Physical & Occupational Therapy In Pediatrics, 39*(1), 60-76. https://doi.org/10.1080/01942638.2018.1496963

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Archives of General Psychiatry, 68*(1), 101-109. doi: 10.1001/archgenpsychiatry.2010.113

Pissiota, A., Frans, Ö., Michelgård, Å., Appel, L., Långström, B., Flaten, M. A., & Fredrikson, M. (2003). Amygdala and anterior cingulate cortex activation during affective startle modulation: a PET study of fear. *European Journal of Neuroscience, 18*(5), 1325-1331. https://doi.org/10.1046/j.1460-9568.2003.02855.x

Piven, J. (2001). The broad autism phenotype: a complementary strategy for molecular genetic studies of autism. *American journal of medical genetics, 105*(1), 34-35. https://doi.org/10.1002/1096-8628(20010108)105:1<34::AID-AJMG1052>3.0.CO;2-D

Polanczyk, G. V., Salum, G. A., Sugaya, L. S., Caye, A., & Rohde, L. A. (2015). Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry, 56*. doi:10.1111/jcpp.12381

Polanczyk, G. V., Willcutt, E. G., Salum, G. A., Kieling, C., & Rohde, L. A. (2014). ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *International Journal of Epidemiology, 43*(2), 434-442. doi:10.1093/ije/dyt261

Polich, J. (2007). Updating P300: an integrative theory of P3a and P3b. *Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology, 118*(10), 2128-2148. doi:10.1016/j.clinph.2007.04.019

Porges, S. W. (1992). Vagal tone: a physiologic marker of stress vulnerability. *Pediatrics, 90*(3 Pt 2), 498-504.

Porges, S. W. (2001). The polyvagal theory: phylogenetic substrates of a social nervous system. *International Journal of Psychophysiology, 42*(2), 123-146. https://doi.org/10.1016/S0167-8760(01)00162-3

Porges, S. W. (2003a). The Polyvagal Theory: Phylogenetic contributions to social behavior. *Physiology and Behavior, 79*(3), 503-513. doi:http://dx.doi.org/10.1016/S0031-9384%2803%2900156-2

Porges, S. W. (2003b). Social engagement and attachment: a phylogenetic perspective. *Annals of the New York Academy of Sciences, 1008*(1), 31-47. doi: 10.1196/annals.1301.004

Porges, S. W. (2007). The polyvagal perspective. *Biological Psychology, 74*(2), 116-143. https://doi.org/10.1016/j.biopsycho.2006.06.009

Porges, S. W. (2009). The polyvagal theory: new insights into adaptive reactions of the autonomic nervous system. *Cleve Clin J Med, 76 Suppl 2*, S86-90. doi:10.3949/ccjm.76.s2.17

Posner, M. I., Walker, J. A., Friedrich, F. J., & Rafal, R. D. (1984). Effects of parietal injury on covert orienting of attention. *Journal of Neuroscience, 4*(7), 1863-1874. https://doi.org/10.1523/JNEUROSCI.04-07-01863.1984

Prince, E. B., Kim, E. S., Wall, C. A., Gisin, E., Goodwin, M. S., Simmons, E. S., . . . Shic, F. (2017). The relationship between autism symptoms and arousal level in toddlers with autism spectrum disorder, as measured by electrodermal activity. *Autism, 21*(4), 504-508. doi:10.1177/1362361316648816

Rajkowski, J., Kubiak, P., Ivanova, S., & Aston-Jones, G. (1997). State-related activity, reactivity of locus ceruleus neurons in behaving monkeys. In *Advances in pharmacology* (Vol. 42, pp. 740-744): Elsevier. https://doi.org/10.1016/S1054-3589(08)60854-6

Ramaswami, M. (2014). Network plasticity in adaptive filtering and behavioral habituation. *Neuron, 82*(6), 1216-1229. doi:10.1016/j.neuron.2014.04.035

Rane, P., Cochran, D., Hodge, S. M., Haselgrove, C., Kennedy, D., & Frazier, J. A. (2015). Connectivity in autism: a review of MRI connectivity studies. *Harvard Review of Psychiatry, 23*(4), 223. doi: 10.1097/HRP.0000000000000072

Rankin, C. H., Abrams, T., Barry, R. J., Bhatnagar, S., Clayton, D. F., Colombo, J., . . . Thompson, R. F. (2009). Habituation revisited: an updated and revised description of the behavioral characteristics of habituation. *Neurobiol Learn Mem, 92*(2), 135-138. doi:10.1016/j.nlm.2008.09.012

Rao, P. A., & Landa, R. J. (2014). Association between severity of behavioral phenotype and comorbid attention deficit hyperactivity disorder symptoms in children with autism spectrum disorders. *Autism, 18*(3), 272-280. doi:10.1177/1362361312470494

Raz, A., & Buhle, J. (2006). Typologies of attentional networks. *Nature Reviews Neuroscience, 7*(5), 367-379. doi:10.1038/nrn1903

Reynolds, S., Bendixen, R. M., Lawrence, T., & Lane, S. J. (2011). A pilot study examining activity participation, sensory responsiveness, and competence in children with high functioning autism spectrum disorder. *Journal of Autism and Developmental Disorders, 41*(11), 1496-1506. doi:10.1007/s10803-010-1173-x

Ribeiro, M. J., & Castelo-Branco, M. (2019). Neural correlates of anticipatory cardiac deceleration and its association with the speed of perceptual decision-making, in young and older adults. *NeuroImage, 199*, 521-533. doi:https://doi.org/10.1016/j.neuroimage.2019.06.004

Richards, H. J., Benson, V., Donnelly, N., & Hadwin, J. A. (2014). Exploring the function of selective attention and hypervigilance for threat in anxiety. *Clinical Psychology Review, 34*(1), 1-13. https://doi.org/10.1016/j.cpr.2013.10.006

Richards, J. E. (1997). Peripheral stimulus localization by infants: Attention, age, and individual differences in heart rate variability. *Journal of Experimental Psychology: Human Perception and Performance, 23*(3), 667. https://doi.org/10.1037/0096-1523.23.3.667

Richards, J. E. (2011). *Infant attention, arousal, and the brain*: Oxford University Press, New York, NY, USA.

Robinson, E. B., Koenen, K. C., McCormick, M. C., Munir, K., Hallett, V., Happé, F., . . . Ronald, A. (2011). Evidence that autistic traits show the same etiology in the general population and at the quantitative extremes (5%, 2.5%, and 1%). *Archives of General Psychiatry, 68*(11), 1113-1121. doi: 10.1001/archgenpsychiatry.2011.119

Robinson, L. J., Stevens, L. H., Threapleton, C. J., Vainiute, J., McAllister-Williams, R. H., & Gallagher, P. (2012). Effects of intrinsic and extrinsic motivation on attention and memory. *Acta psychologica, 141*(2), 243-249. https://doi.org/10.1016/j.actpsy.2012.05.012

Roelofs, K. (2017). Freeze for action: neurobiological mechanisms in animal and human freezing. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *372*(1718), 20160206. https://doi.org/10.1098/rstb.2016.0206

Rogers, S. J., & Ozonoff, S. (2005). Annotation: what do we know about sensory dysfunction in autism? A critical review of the empirical evidence. *J Child Psychol Psychiatry*, *46*(12), 1255-1268. doi:10.1111/j.1469-7610.2005.01431.x

Rommelse, N. N. J., Geurts, H. M., Franke, B., Buitelaar, J. K., & Hartman, C. A. (2011). A review on cognitive and brain endophenotypes that may be common in autism spectrum disorder and attention-deficit/hyperactivity disorder and facilitate the search for pleiotropic genes. *Neuroscience & Biobehavioral Reviews*, *35*(6), 1363-1396. doi:10.1016/j.neubiorev.2011.02.015

Ronald, A., Happe, F., Bolton, P., Butcher, L. M., Price, T. S., Wheelwright, S., . . . Plomin, R. (2006). Genetic heterogeneity between the three components of the autism spectrum: a twin study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*(6), 691-699. doi:10.1097/01.chi.0000215325.13058.9d

Ronconi, L., Devita, M., Molteni, M., Gori, S., & Facoetti, A. (2018). Brief Report: When Large Becomes Slow: Zooming-Out Visual Attention Is Associated to Orienting Deficits in Autism. *Journal of Autism and Developmental Disorders*, *48*(7), 2577-2584. doi:10.1007/s10803-018-3506-0

Rosburg, T., Zimmerer, K., & Huonker, R. (2010). Short-term habituation of auditory evoked potential and neuromagnetic field components in dependence of the interstimulus interval. *Exp Brain Res*, *205*(4), 559-570. doi:10.1007/s00221-010-2391-3

Rose, D., Pevalin, D. J., & O'Reilly, K. (2005). *The National Statistics Socio-economic Classification: origins, development and use*: Palgrave Macmillan Basingstoke.

Rousseeuw, P. J. (1987). Silhouettes: A graphical aid to the interpretation and validation of cluster analysis. *Journal of Computational and Applied Mathematics*, *20*, 53-65. doi:https://doi.org/10.1016/0377-0427(87)90125-7

Rubenstein, J., & Merzenich, M. M. (2003). Model of autism: increased ratio of excitation/inhibition in key neural systems. *Genes, Brain and Behavior, 2*(5), 255-267. https://doi.org/10.1034/j.1601-183X.2003.00037.x

Ruiz-Martinez, F. J., Rodriguez-Martinez, E. I., Wilson, C. E., Yau, S., Saldana, D., & Gomez, C. M. (2020). Impaired P1 Habituation and Mismatch Negativity in Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders, 50*(2), 603-616. doi:10.1007/s10803-019-04299-0

Rutter, M., Bailey, A., & Lord, C. (2003). *The social communication questionnaire: Manual*: Western Psychological Services.

Sabatos-DeVito, M., Schipul, S. E., Bulluck, J. C., Belger, A., & Baranek, G. T. (2016). Eye Tracking Reveals Impaired Attentional Disengagement Associated with Sensory Response Patterns in Children with Autism. *Journal of Autism and Developmental Disorders, 46*(4), 1319-1333. doi:10.1007/s10803-015-2681-5

Sacrey, L. A. R., Armstrong, V. L., Bryson, S. E., & Zwaigenbaum, L. (2014). Impairments to visual disengagement in autism spectrum disorder: A review of experimental studies from infancy to adulthood. *Neuroscience and biobehavioral reviews, 47*, 559-577. doi:10.1016/j.neubiorev.2014.10.011

Samuels, E. R., & Szabadi, E. (2008). Functional neuroanatomy of the noradrenergic locus coeruleus: Its roles in the regulation of arousal and autonomic function part I: Principles of functional organisation. *Current Neuropharmacology, 6*(3), 235-253. doi:10.2174/157015908785777229

Sara, S. J. (2009). The locus coeruleus and noradrenergic modulation of cognition. *Nature Reviews Neuroscience, 10*(3), 211-223. doi:10.1038/nrn2573

Sara, S. J., & Bouret, S. (2012). Orienting and reorienting: the locus coeruleus mediates cognition through arousal. *Neuron, 76*(1), 130-141. doi:10.1016/j.neuron.2012.09.011

Sasson, N. J., Nowlin, R. B., & Pinkham, A. E. (2013). Social cognition, social skill, and the broad autism phenotype. *Autism, 17*(6), 655-667. doi:10.1177/1362361312455704

Sasson, N. J., Turner-Brown, L. M., Holtzclaw, T. N., Lam, K. S. L., & Bodfish, J. W. (2008). Children with autism demonstrate circumscribed attention during passive viewing of complex social and nonsocial picture arrays. *Autism Research, 1*(1), 31-42. doi:10.1002/aur.4

Schaaf, R. C., Benevides, T. W., Leiby, B. E., & Sendecki, J. A. (2015). Autonomic dysregulation during sensory stimulation in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 45*(2), 461-472. doi:10.1007/s10803-013-1924-6

Schaaf, R. C., Toth-Cohen, S., Johnson, S. L., Outten, G., & Benevides, T. W. (2011). The everyday routines of families of children with autism: Examining the impact of sensory processing difficulties on the family. *Autism, 15*(3), 373-389. doi:10.1177/1362361310386505

Schmid, S., Wilson, D. A., & Rankin, C. H. (2014). Habituation mechanisms and their importance for cognitive function. *Front Integr Neurosci, 8*, 97. doi:10.3389/fnint.2014.00097

Schmitt, L. M., Cook, E. H., Sweeney, J. A., & Mosconi, M. W. (2014). Saccadic eye movement abnormalities in autism spectrum disorder indicate dysfunctions in cerebellum and brainstem. *Molecular Autism, 5*(1). doi:10.1186/2040-2392-5-47

Schoen, S. A., Miller, L. J., Brett-Green, B., & Hepburn, S. L. (2008). Psychophysiology of children with autism spectrum disorder. *Research in Autism Spectrum Disorders, 2*(3), 417-429. doi:10.1016/j.rasd.2007.09.002

Schoen, S. A., Miller, L. J., Brett-Green, B. A., & Nielsen, D. M. (2009). Physiological and behavioral differences in sensory processing: A comparison of children with Autism Spectrum Disorder and Sensory Modulation Disorder. *Frontiers in Integrative Neuroscience, 3*(NOV). doi:10.3389/neuro.07.029.2009

Schoner, G., & Thelen, E. (2006). Using dynamic field theory to rethink infant habituation. *Psychol Rev, 113*(2), 273-299. doi:10.1037/0033-295X.113.2.273

Schultz, R. T. (2005). Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience, 23*(2), 125-141. doi:https://doi.org/10.1016/j.ijdevneu.2004.12.012

Schultz, W. (2010). Dopamine signals for reward value and risk: basic and recent data. *Behavioral and Brain Functions, 6*(1), 24. https://doi.org/10.1186/1744-9081-6-24

Seeley, W. W., Menon, V., Schatzberg, A. F., Keller, J., Glover, G. H., Kenna, H., . . . Greicius, M. D. (2007). Dissociable intrinsic connectivity networks for salience processing and executive control. *Journal of Neuroscience, 27*(9), 2349-2356. https://doi.org/10.1523/JNEUROSCI.5587-06.2007

Sergeant, J. (2000). The cognitive-energetic model: an empirical approach to Attention-Deficit Hyperactivity Disorder. *Neuroscience & Biobehavioral Reviews, 24*(1), 7-12. doi:http://dx.doi.org/10.1016/S0149-7634(99)00060-3

Sethi, A., Voon, V., Critchley, H. D., Cercignani, M., & Harrison, N. A. (2018). A neurocomputational account of reward and novelty processing and effects of psychostimulants in attention deficit hyperactivity disorder. *Brain, 141*(5), 1545-1557. doi:10.1093/brain/awy048

Seymour, R. A., Rippon, G., Gooding-Williams, G., Schoffelen, J. M., & Kessler, K. (2019). Dysregulated oscillatory connectivity in the visual system in autism spectrum disorder. *Brain, 142*(10), 3294-3305. doi:10.1093/brain/awz214

Shaffer, D., Gould, M. S., Brasic, J., Ambrosini, P., Fisher, P., Bird, H., & Aluwahlia, S. (1983). A children's global assessment scale (CGAS). *Archives of General Psychiatry, 40*(11), 1228-1231. doi: 10.1001/archpsyc.1983.01790100074010

Shaffer, F., & Ginsberg, J. P. (2017). An Overview of Heart Rate Variability Metrics and Norms. *Front Public Health, 5*, 258. doi:10.3389/fpubh.2017.00258

Sikora, D. M., Hartley, S. L., McCoy, R., Gerrard-Morris, A. E., & Dill, K. (2008). The performance of children with mental health disorders on the ADOS-G: A question of diagnostic utility. *Research in Autism Spectrum Disorders, 2*(1), 188-197. doi:10.1016/j.rasd.2007.05.003

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(8), 921-929. doi:10.1097/CHI.0b013e318179964f

Sinclair, J. (2013). Why I dislike “person first” language. *Autonomy, the Critical Journal of Interdisciplinary Autism Studies, 1*(2).

Sparrow, S. S., Cicchetti, D., & Balla, D. A. (1984). Vineland adaptive behavior scales. https://doi.org/10.1037/t15164-000

Sprenger, L., Buhler, E., Poustka, L., Bach, C., Heinzel-Gutenbrunner, M., Kamp-Becker, I., & Bachmann, C. (2013). Impact of ADHD symptoms on autism spectrum disorder symptom severity. *Research in developmental disabilities, 34*(10), 3545-3552. doi:10.1016/j.ridd.2013.07.028

Stedman, A., Taylor, B., Erard, M., Peura, C., & Siegel, M. (2018). Are Children Severely Affected by Autism Spectrum Disorder Underrepresented in Treatment Studies? An Analysis of the Literature. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-018-3844-y

Stevens, S., & Gruzelier, J. (1984). Electrodermal activity to auditory stimuli in autistic, retarded, and normal children. *Journal of Autism and Developmental Disorders, 14*(3), 245-260. https://doi.org/10.1007/BF02409577

Suarez, M. A. (2012). Sensory processing in children with autism spectrum disorders and impact on functioning. *Pediatric Clinics of North America, 59*(1), 203-214. doi:10.1016/j.pcl.2011.10.012

Sutton, S., Braren, M., Zubin, J., & John, E. (1965). Evoked-potential correlates of stimulus uncertainty. *Science, 150*(3700), 1187-1188. doi: 10.1126/science.150.3700.1187

Swartz, J. R., Wiggins, J. L., Carrasco, M., Lord, C., & Monk, C. S. (2013). Amygdala habituation and prefrontal functional connectivity in youth with autism spectrum disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(1), 84-93. doi:10.1016/j.jaac.2012.10.012

Szatmari, P., Georgiades, S., Duku, E., Bennett, T. A., Bryson, S., Fombonne, E., . . . for the Pathways in, A. S. D. S. T. (2015). Developmental Trajectories of Symptom Severity and Adaptive Functioning in an Inception Cohort of Preschool Children With Autism Spectrum Disorder. *JAMA Psychiatry, 72*(3), 276-283. doi:10.1001/jamapsychiatry.2014.2463

Tadel, F., Baillet, S., Mosher, J., Pantazis, D., & Leahy, R. (2011). Brainstorm: A User-Friendly Application for MEG/EEG Analysis Computational Intelligence and Neuroscience. *Hindawi Publishing Corporation*, 1-13. doi: 10.1155/2011/879716

Takahashi, H., Komatsu, S., Nakahachi, T., Ogino, K., & Kamio, Y. (2016). Relationship of the acoustic startle response and its modulation to emotional and behavioral problems in typical development children and those with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 46*(2), 534-543. doi: 10.1007/s10803-015-2593-4

Taurines, R., Schwenck, C., Westerwald, E., Sachse, M., Siniatchkin, M., & Freitag, C. (2012). ADHD and autism: differential diagnosis or overlapping traits? A selective review. *ADHD Attention Deficit and Hyperactivity Disorders, 4*(3), 115-139. doi:10.1007/s12402-012-0086-2

Taylor, B., Jick, H., & Maclaughlin, D. (2013). Prevalence and incidence rates of autism in the UK: time trend from 2004-2010 in children aged 8 years. *BMJ Open, 3*(10), e003219. doi:10.1136/bmjopen-2013-003219

Thayer, J. F., & Brosschot, J. F. (2005). Psychosomatics and psychopathology: looking up and down from the brain. *Psychoneuroendocrinology, 30*(10), 1050-1058. doi:https://doi.org/10.1016/j.psyneuen.2005.04.014

Thayer, J. F., & Lane, R. D. (2000). A model of neurovisceral integration in emotion regulation and dysregulation. *Journal of affective disorders, 61*(3), 201-216.

Thye, M. D., Bednarz, H. M., Herringshaw, A. J., Sartin, E. B., & Kana, R. K. (2018). The impact of atypical sensory processing on social impairments in autism spectrum disorder. *Dev Cogn Neurosci, 29*(1878-9307 (Electronic)), 151-167. doi:10.1016/j.dcn.2017.04.010

Todd, J., Mills, C., Wilson, A. D., Plumb, M. S., & Mon-Williams, M. A. (2009). Slow Motor Responses to Visual Stimuli of Low Salience in Autism. *Journal of Motor Behavior, 41*(5), 419-426. doi:10.3200/35-08-042

Todd, J. J., Fougnie, D., & Marois, R. (2005). Visual short-term memory load suppresses temporo-parietal junction activity and induces inattentional blindness. *Psychological Science, 16*(12), 965-972. https://doi.org/10.1111/j.1467-9280.2005.01645.x

Toichi, M., & Kamio, Y. (2003). Paradoxical autonomic response to mental tasks in autism. *Journal of Autism and Developmental Disorders, 33*(4), 417-426. doi:http://dx.doi.org/10.1023/A:1025062812374

Toichi, M., Sugiura, T., Murai, T., & Sengoku, A. (1997). A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of R–R interval. *Journal of the Autonomic Nervous System, 62*(1-2), 79-84. doi:10.1016/s0165-1838(96)00112-9

Tottenham, N., Hertzig, M. E., Gillespie-Lynch, K., Gilhooly, T., Millner, A. J., & Casey, B. J. (2013). Elevated amygdala response to faces and gaze aversion in autism spectrum disorder. *Social Cognitive and Affective Neuroscience, 9*(1), 106-117. doi:10.1093/scan/nst050

Touroutoglou, A., Bliss-Moreau, E., Zhang, J., Mantini, D., Vanduffel, W., Dickerson, B. C., & Barrett, L. F. (2016). A ventral salience network in the macaque brain. *NeuroImage, 132*, 190-197. https://doi.org/10.1016/j.neuroimage.2016.02.029

Townsend, J., Courchesne, E., & Egaas, B. (1996). Slowed orienting of covert visual-spatial attention in autism: Specific deficits associated with cerebellar and parietal abnormality. *Development and Psychopathology, 8*(3), 563-584. https://doi.org/10.1017/S0954579400007276

Trimmer, E., McDonald, S., & Rushby, J. A. (2017). Not knowing what i feel: Emotional empathy in autism spectrum disorders. *Autism, 21*(4), 450-457. doi:10.1177/1362361316648520

Tseng, M. H., Fu, C. P., Cermak, S. A., Lu, L., & Shieh, J. Y. (2011). Emotional and behavioral problems in preschool children with autism: Relationship with sensory processing dysfunction. *Research in Autism Spectrum Disorders, 5*(4), 1441-1450. doi:10.1016/j.rasd.2011.02.004

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W. (2016). Social orienting and attention is influenced by the presence of competing nonsocial information in adolescents with autism. *Frontiers in Neuroscience, 10*(DEC). doi:10.3389/fnins.2016.00586

Van Bockstaele, E., & Aston-Jones, G. (1995). Integration in the ventral medulla and coordination of sympathetic, pain and arousal functions. *Clinical and Experimental Hypertension, 17*(1-2), 153-165. https://doi.org/10.3109/10641969509087062

Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: Predictive coding in autism. *Psychological review, 121*(4), 649. doi: 10.1037/a0037665

van der Geest, J. N., Kemner, C., Camfferman, G., Verbaten, M. N., & van Engeland, H. (2001). Eye movements, visual attention, and autism: a saccadic reaction time study using the gap and overlap paradigm. *Biological Psychiatry, 50*(8), 614-619. https://doi.org/10.1016/S0006-3223(01)01070-8

van der Meer, J. M., Oerlemans, A. M., van Steijn, D. J., Lappenschaar, M. G., de Sonneville, L. M., Buitelaar, J. K., & Rommelse, N. N. (2012). Are autism spectrum disorder and attention-deficit/hyperactivity disorder different manifestations of one overarching disorder? Cognitive and symptom evidence from a clinical and population-based sample. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(11), 1160-1172. e1163. https://doi.org/10.1016/j.jaac.2012.08.024

van der Wel, P., & van Steenbergen, H. (2018). Pupil dilation as an index of effort in cognitive control tasks: A review. *Psychon Bull Rev, 25*(6), 2005-2015. doi:10.3758/s13423-018-1432-y

van Engeland, H. (1984). The electrodermal orienting response to auditive stimuli in autistic children, normal children, mentally retarded children, and child psychiatric patients. *Journal of Autism and Developmental Disorders, 14*(3), 261-279. https://doi.org/10.1007/BF02409578

Van Hecke, A. V., Lebow, J., Bal, E., Lamb, D., Harden, E., Kramer, A., . . . Porges, S. W. (2009). Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. *Child development, 80*(4), 1118-1133. doi:http://dx.doi.org/10.1111/j.1467-8624.2009.01320.x

Visser, J. C., Rommelse, N. N., Greven, C. U., & Buitelaar, J. K. (2016). Autism spectrum disorder and attention-deficit/hyperactivity disorder in early childhood: A review of unique and shared characteristics and developmental antecedents. *Neuroscience and biobehavioral reviews, 65*, 229-263. doi:10.1016/j.neubiorev.2016.03.019

Visser, J. C., Rommelse, N. N. J., Lappenschaar, M., Servatius-Oosterling, I. J., Greven, C. U., & Buitelaar, J. K. (2017). Variation in the Early Trajectories of Autism Symptoms Is Related to the Development of Language, Cognition, and Behavior Problems. *Journal of the American Academy of Child and Adolescent Psychiatry, 56*(8), 659-668. doi:10.1016/j.jaac.2017.05.022

Vivanti, G., Hocking, D. R., Fanning, P. A. J., Uljarevic, M., Postorino, V., Mazzone, L., & Dissanayake, C. (2018). Attention to novelty versus repetition: Contrasting habituation profiles in Autism and Williams syndrome. *Dev Cogn Neurosci, 29*, 54-60. doi:10.1016/j.dcn.2017.01.006

Vossel, S., Geng, J. J., & Fink, G. R. (2014). Dorsal and ventral attention systems: distinct neural circuits but collaborative roles. *Neuroscientist, 20*(2), 150-159. doi:10.1177/1073858413494269

Wagner, J. B., Luyster, R. J., Tager-Flusberg, H., & Nelson, C. A. (2016). Greater Pupil Size in Response to Emotional Faces as an Early Marker of Social-Communicative Difficulties in Infants at High Risk for Autism. *Infancy, 21*(5), 560-581. doi:10.1111/infa.12128

Wainwright, J. A., & Bryson, S. E. (1996). Visual-spatial orienting in autism. *Journal of Autism and Developmental Disorders, 26*(4), 423-438. doi: 10.1007/BF02172827

Wang, J., Barstein, J., Ethridge, L. E., Mosconi, M. W., Takarae, Y., & Sweeney, J. A. (2013). Resting state EEG abnormalities in autism spectrum disorders. *Journal of Neurodevelopmental Disorders, 5*(1), 24. https://doi.org/10.1186/1866-1955-5-24

Wang, S., Jiang, M., Duchesne, Xavier M., Laugeson, Elizabeth A., Kennedy, Daniel P., Adolphs, R., & Zhao, Q. (2015). Atypical Visual Saliency in Autism Spectrum Disorder Quantified through Model-Based Eye Tracking. *Neuron, 88*(3), 604-616. doi:10.1016/j.neuron.2015.09.042

Wang, X., Piñol, R. A., Byrne, P., & Mendelowitz, D. (2014). Optogenetic stimulation of locus ceruleus neurons augments inhibitory transmission to parasympathetic cardiac vagal neurons via activation of brainstem α1 and β1 receptors. *Journal of Neuroscience, 34*(18), 6182-6189. doi: 10.1523/JNEUROSCI.5093-13.2014

Wass, S. V., de Barbaro, K., & Clackson, K. (2015a). Tonic and phasic co-variation of peripheral arousal indices in infants. *Biological Psychology, 111*, 26-39. doi:10.1016/j.biopsycho.2015.08.006

Wass, S. V., Jones, E. J. H., Gliga, T., Smith, T. J., Charman, T., Johnson, M. H., . . . Volein, A. (2015b). Shorter spontaneous fixation durations in infants with later emerging autism. *Scientific Reports, 5*, 8284. doi:10.1038/srep08284

Webb, S. J., Jones, E. J., Merkle, K., Namkung, J., Toth, K., Greenson, J., . . . Dawson, G. (2010). Toddlers with elevated autism symptoms show slowed habituation to faces. *Child Neuropsychology: A Journal on Normal and Abnormal Development in Childhood and Adolescence, 16*(3), 255-278. doi:10.1080/09297041003601454

Wechsler, D. (2011). *WASI-II: Wechsler abbreviated scale of intelligence*: PsychCorp.

Werner, E., Dawson, G., Osterling, J., & Dinno, N. (2000). Brief report: Recognition of autism spectrum disorder before one year of age: A retrospective study based on home videotapes. *Journal of Autism and Developmental Disorders, 30*(2), 157. https://doi.org/10.1023/A:1005463707029

Whitehouse, A. J. O., & Bishop, D. V. M. (2008). Do children with autism 'switch off' to speech sounds? An investigation using event-related potentials. *Developmental Science, 11*(4), 516-524. doi:10.1111/j.1467-7687.2008.00697.x

Wolfers, T., Floris, D. L., Dinga, R., van Rooij, D., Isakoglou, C., Kia, S. M., . . . Beckmann, C. F. (2019). From pattern classification to stratification: towards conceptualizing the heterogeneity of Autism Spectrum Disorder. *Neuroscience and biobehavioral reviews, 104*, 240-254. doi:10.1016/j.neubiorev.2019.07.010

Yerkes, R. M., & Dodson, J. D. (1908). The relation of strength of stimulus to rapidity of habit-formation. *Journal of comparative neurology and psychology, 18*(5), 459-482. https://doi.org/10.1002/cne.920180503

Zahn, T. P., Rumsey, J. M., & Van Kammen, D. P. (1987). Autonomic nervous system activity in autistic, schizophrenic, and normal men: effects of stimulus significance. *Journal of Abnormal Psychology, 96*(2), 135-144. https://doi.org/10.1037/0021-843X.96.2.135

Zantinge, G., van Rijn, S., Stockmann, L., & Swaab, H. (2017). Psychophysiological responses to emotions of others in young children with autism spectrum disorders: Correlates of social functioning. *Autism Research*. doi:10.1002/aur.1794

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. *International Journal of Developmental Neuroscience, 23*(2-3), 143-152. doi:10.1016/j.ijdevneu.2004.05.001

Appendices

Appendix A- Ethics approval

NHS
Health Research Authority

Dr Madeleine J Groom
Division of Psychiatry & Applied Psychology
Institute of Mental Health
Triumph Road,
University of Nottingham
NG7 2TU

Email: hra.approval@nhs.net

16 August 2017

Dear Dr Groom

Letter of HRA Approval

Study title:	**The SAAND Project: Studying Attention and Arousal regulation in neurodevelopmental disorders: comparison between Attention Deficit Hyperactivity Disorder (ADHD) and Autism Spectrum Disorders (ASD)**
IRAS project ID:	**220158**
Protocol number:	**17029**
REC reference:	**17/EM/0193**
Sponsor	**University of Nottingham**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

IRAS project ID	220158

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from www.hra.nhs.uk/hra-approval.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The document *"After Ethical Review – guidance for sponsors and investigators"*, issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found at http://www.hra.nhs.uk/resources/applying-for-reviews/nhs-hsc-rd-review/.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

IRAS project ID	220158

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

Your IRAS project ID is **220158**. Please quote this on all correspondence.

Yours sincerely

Kelly Rowe
Assessor

Email: hra.approval@nhs.net

Copy to: *Ms Angela Shone, University of Nottingham, Sponsor Representative*
Mrs Shirley Mitchell, Nottinghamshire Healthcare NHS Foundation Trust, Lead NHS R&D contact

Appendix B- Recruitment Leaflet

the SAAND project

University of Nottingham
UK | CHINA | MALAYSIA

CHILDREN and ADOLESCENTS (7-15 years old)

needed for the SAAND project (University of Nottingham)

We are studying attention in children with Autism (ASD) and/or Attention Deficit Hyperactivity Disorder (ADHD), and we are looking for children to come to the University of Nottingham and help us in our research.

We will measure your eye-movements, your brain activity, while you watch some images, videos or play some games on a computer.

You can take part in this study:

- if you are between 7 and 15 years of age
- If you have Autism and/or ADHD, but also if you don't have any of these conditions

If you want more information or you would like to participate in the study, you can contact us:

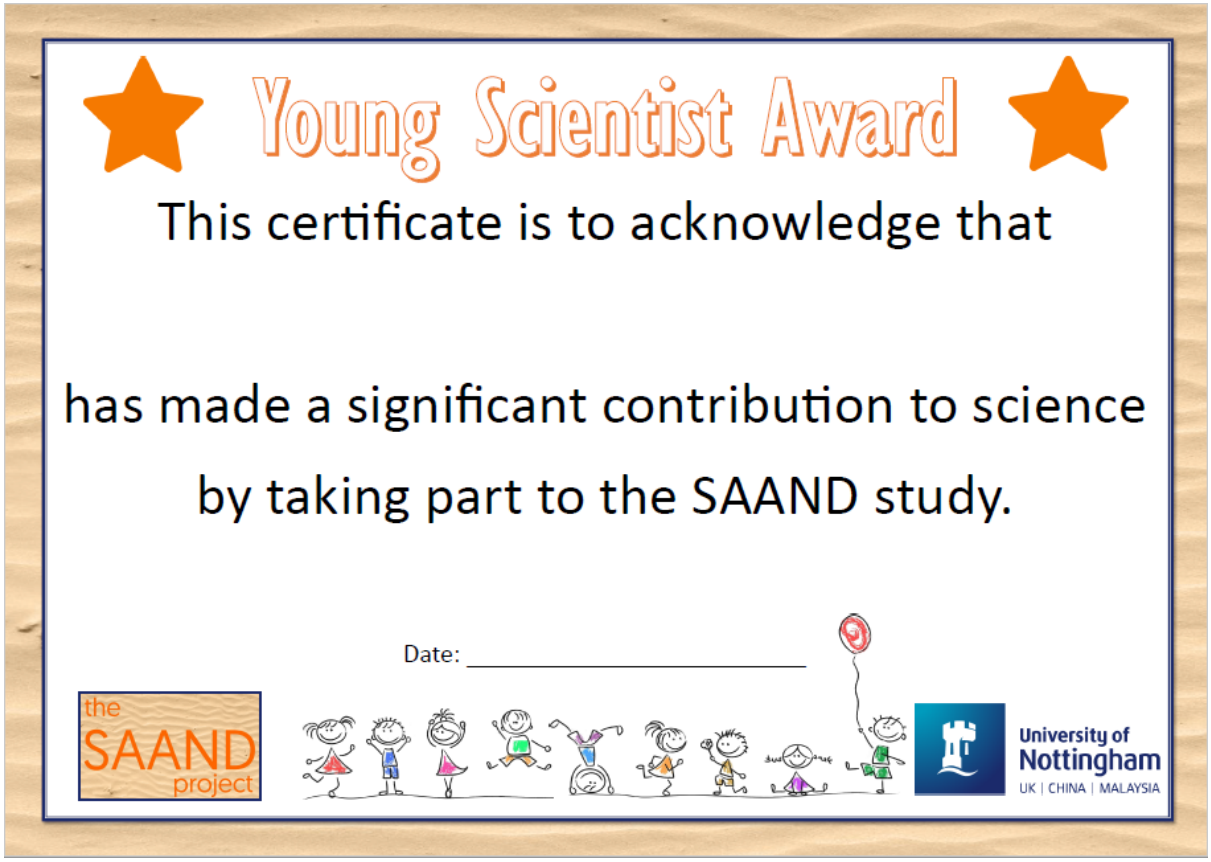
Alessio Bellato Alessio.Bellato@nottingham.ac.uk

Iti Arora Iti.Arora@nottingham.ac.uk

Mobile Number: 07806777705

Travel expenses will be paid to your parent, and an incovenience allowance will be given to you.

Appendix C- Certificate of Participation provided to participants.



Appendix D- Results from Chapter 3

Investigation of the effect of order of presentation of social and non-social conditions on autonomic arousal

1. Effect of Order of Presentation on HR

Repeated measures ANOVA were conducted, with two within-subject factors (Condition: Social, Non-Social) and Block (Baseline, Exposure Periods 1, 2, 3, 4) and a between-subject factor of Order of Presentation (2 levels: Social condition first, or, Non-Social condition first).

There was a significant main effect of Block: Greenhouse-Geisser F (3.53, 289.05) = 27.28, p <.001, η^2_p = .25. This main effect was significant at the linear (F (1, 82) = 55.94, p < .001, η^2_p = .41), cubic (F (1, 82) = 37.06, p < .001, η^2_p = .31) and Order 4 (F (1, 82) = 6.14, p = .015, η^2_p = .07) levels. Pairwise comparisons revealed significant changes at each time-point from the previous and next time-points, with an overall indication that from the baseline, there was an initial decrease over the first 3 minutes, and then an increase until Exposure 3 when it stabilized, there is no significant difference in HR between Exposures 3 and 4 (see Fig. C.1).

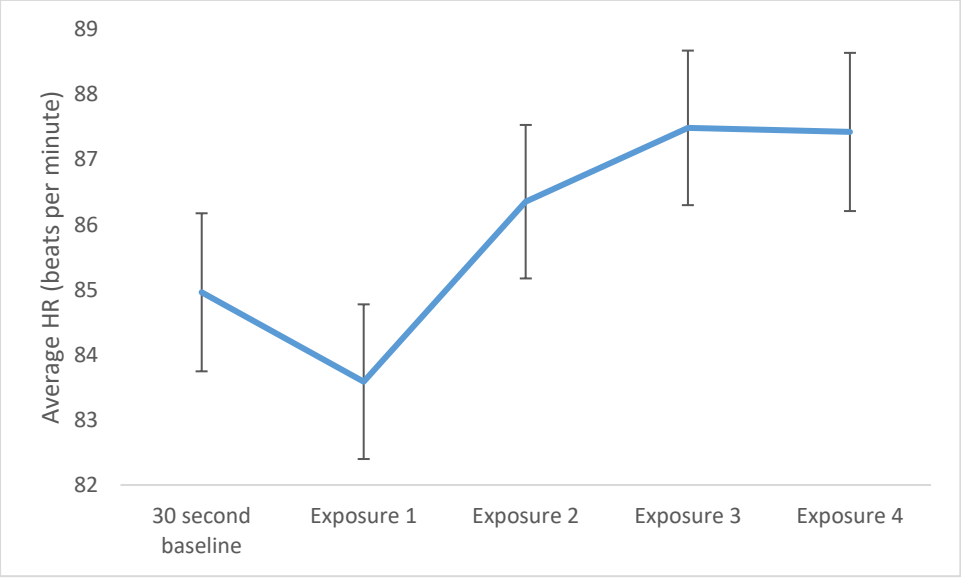


Figure C.1. Change in HR over time during Auditory Oddball Task

Bars show the mean (±1 standard error) average heart rate in beats per minute (plotted on the y-axis). These data are split over Time (initial 30-second baseline and 4 consecutive 3-min exposure blocks during which auditory stimuli were presented).

There was no significant main effect of Condition: F (1, 82) = .33, p= .57, η^2_p= .00. There was also no main effect of Order of Presentation: F (1, 82) = .02, p = .89, η^2_p = .00. However, there was a significant interaction between Condition and Order of Presentation: F (1, 82) = 18.99, p < .001, η^2_p = .19; and between Block and Order of Presentation: Greenhouse-Geisser F (3.53, 289.05) = 3.33, p = .015, η^2_p = .04. These interactions were modulated by a three-way interaction between Condition, Order of Presentation and Block: Greenhouse-Geisser F (3.36, 275.57) = 6.54, p < .001, η^2_p = .07.

In order to understand these interactions, the ANOVA was conducted at each level of Order of Presentation. Specifically, we were interested in whether order of presentation impacted autonomic responsivity over successive task blocks, differently in the social and non-social conditions. For participants who were presented with the Social condition first, followed by the Non-Social Condition, there was a significant effect of Condition: F (1, 43) = 13.43, p = .001, η^2_p = .24. This effect was driven by presence of higher HR during the Non-Social (Mean ± S.E.= 87.04 ± 1.29) as compared to the Social (Mean ± S.E. = 85.21 ± 1.36) condition.

These participants presented a significant effect of Block (Greenhouse-Geisser F (3.15, 135.3) = 9.09, p < .001, η^2_p = .17) and an interaction between Condition and Block (Greenhouse-Geisser F (3.18, 136.57) = 7.38, p < .001, η^2_p = .15). The interaction was driven by the effect of time on HR being different in the Social and Non-Social conditions. In the Social condition, the main effect of Block was similar to what was described earlier, with an initial significant decrease in HR from baseline to the first sound exposure block, and thereafter an increase in HR. On the other hand, in the Non-Social condition, the initial decrease was not present, but the increase in HR from the 1st exposure block onwards was present (see Fig. C.2).

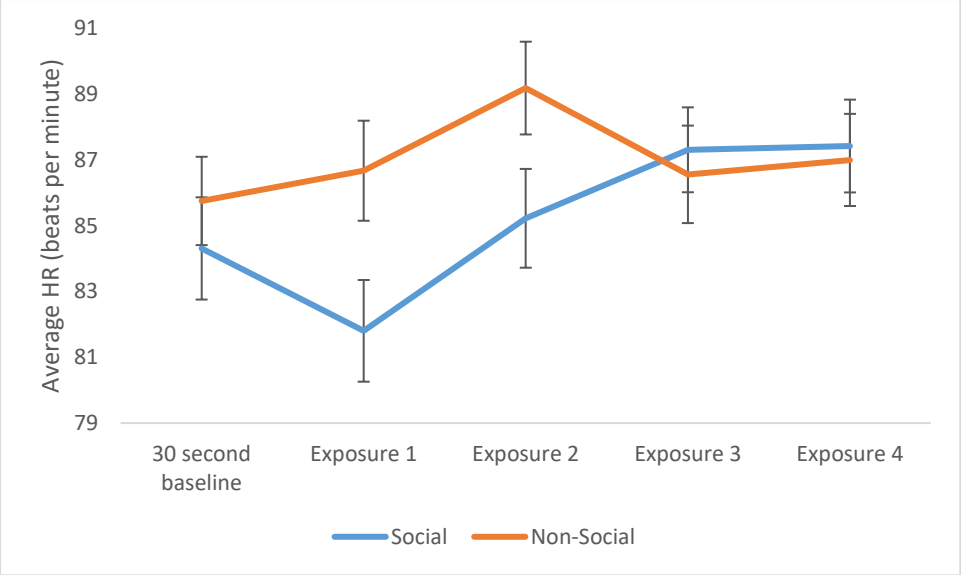


Figure C.2. Change in HR over successive task blocks for participants presented with Social Condition first

Bars show the mean (±1 standard error) average heart rate in beats per minute (plotted on the y-axis). These data are split by Block (initial 30-second baseline and 4 consecutive 3-min exposure blocks during which auditory stimuli were presented). Blue and Orange lines represent HR for social and non-social conditions respectively.

For participants who were presented with the Non-Social condition followed by the Social condition, there was also a main effect Condition ($F (1, 39) = 6.48$, $p = .015$, $\eta^2_p = .14$), a main effect of Block (Greenhouse-Geisser $F (3.36, 131.03) = 22.38$, $p < .001$, $\eta^2_p = .37$) but no interaction between Condition and Block (Greenhouse-Geisser $F (3.3, 128.78) = 1.2$, $p = .31$, $\eta^2_p = .03$). The main effect of Condition was driven by higher HR in the Social (Mean ± S.E. = 86.496 ± 2.04) as compared to the Non-Social (Mean ± S.E. = 85.101 ± 1.94) condition. The main effect of Block was similar to the main effect of Block described earlier- with an initial significant decrease in HR from baseline to the first exposure block, and then an increase in HR from the 1st to the 3rd exposure blocks until HR stabilized (see Fig C.3).

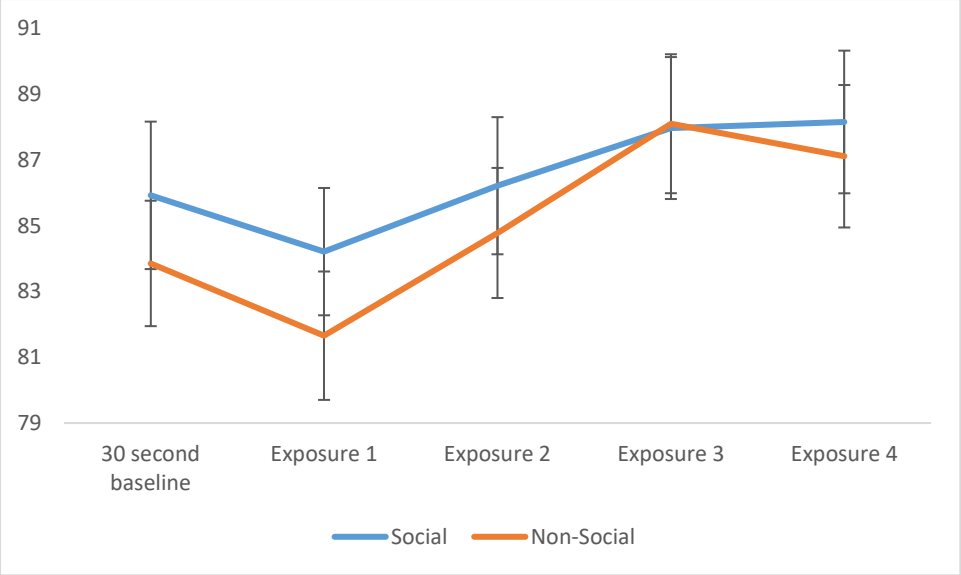


Fig C.3. Change in HR over successive task blocks for participants presented with Non-Social Condition first

Bars show the mean (±1 standard error) average heart rate in beats per minute (plotted on the y-axis). These data are split by Block (initial 30-second baseline and 4 consecutive 3-min exposure blocks during which auditory stimuli were presented). Blue and Orange lines represent HR values for social and non-social conditions respectively.

In summary, at each level of Order of Presentation, the second exposure block elicited higher HR than the first block (regardless of Condition). Arousal therefore appeared to increase with successive task blocks for the participants during this task and this did not differ based on Order of Presentation.

2. Effect of Order of Presentation on CSI and CVI

A similar repeated measures MANOVA was conducted with Condition and Block as within-subject factors (similar to the previous analysis), CSI and CVI as the dependent variables and Order of Presentation as a between-subjects factor.

There was no main effect of Order: V = .01, F (2, 84) = .29, p = .748, η^2_p = .007. There was no main effect of Condition: V= .005, F (2, 84) = .23, p = .79, η^2_p = .005. However, there was a significant multivariate effect of Condition*Order: V = .24, F (2, 84) = 13.24, p < .001, η^2_p = .24. This interaction was non-significant for CVI (F (1, 85) = .16, p = .69, η^2_p = .00). However, there was significant

Condition*Order interaction for CSI: $F(1, 85) = 26.72$, $p < .001$, $\eta^2_p = .24$. Similarly to above, this was driven by a pattern of increasing CSI throughout the task, such that regardless of Condition (Social or Non-Social) CSI was higher for the second chronological block as compared to the first chronological block: For participants who were administered the Social condition followed by the Non-Social condition, the Non-Social condition elicited higher CSI (Non-Social-Social: Mean difference ± S.E.= .30 ± .07, $p < .001$). For participants who were administered the Non-Social condition followed by the Social condition, the Social condition elicited significantly higher CSI (Social- Non-Social: Mean difference ± S.E. = .25 ± .08, $p = .002$).

There was a main multivariate effect of Block: $V = .09$, $F(8, 678) = 3.86$, $p < .001$, $\eta^2_p = .04$. Follow-up univariate ANOVAs revealed that this was not significant for CVI: Greenhouse-Geisser $F(3.6, 305.8) = .2$, $p = .94$, $\eta^2_p = .00$. There was a significant main effect for Block only for CSI ($F(4, 340) = 7.3$, $p < .001$, $\eta^2_p = .08$. This was related to both a linear ($F(1, 85) = 9.38$, $p = .003$, $\eta^2_p = .1$) and a cubic ($F(1, 85) = 17.7$, $p < .001$, $\eta^2_p = .17$) effect.

The linear effect appears to relate with an initial significant decrease in CSI when sound exposure first begins and then a subsequent significant increase until Block 3 where CSI was significantly higher than all other blocks (see Fig C.4).

Further, there was an interaction between Block*Order: $V = .05$, $F(8, 680) = 2.09$, $p = .034$, $\eta^2_p = .02$. However, this was not significant for either CVI ($F(3.6, 305.8) = 1.2$, $p = .1$, $\eta^2_p = .02$) or CSI ($F(3.66, 310.66) = 1.51$, $p = .2$, $\eta^2_p = .02$).

Overall, it appears that Order of presentation of different conditions does impact arousal, but it does not impact arousal in response to different conditions. Rather, it is a chronology effect. Regardless of which condition is presented, arousal is higher in the second half of the task than the first half.

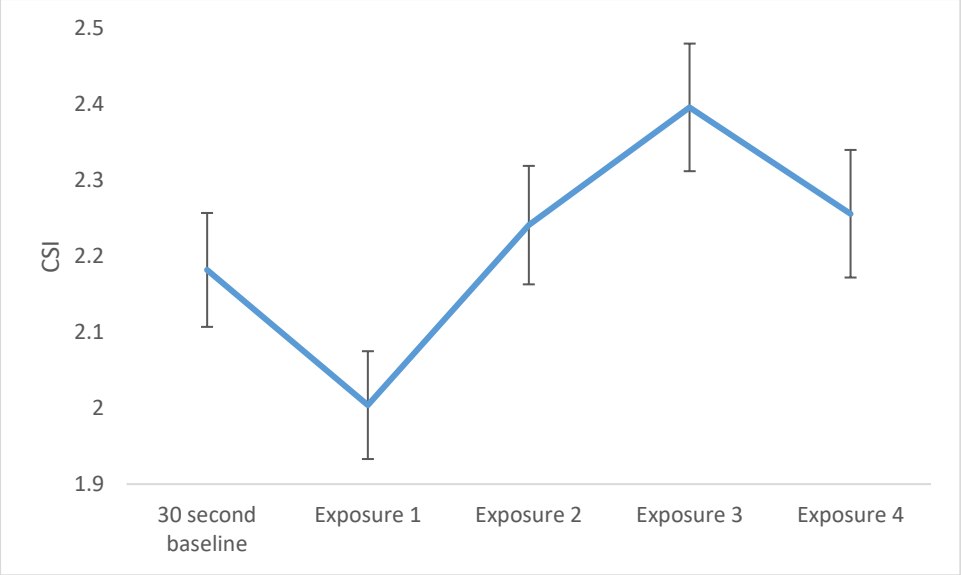


Figure C.4. Change in CSI over time

Bars show the mean (±1 standard error) average CSI (plotted on the y-axis). These data are split by Block (initial 30-second baseline and 4 consecutive 3-min exposure blocks during which auditory stimuli were presented).

3. Chronological effects

We ran another MANOVA to test the effect of Sequence (given that we did not present Social and Non-Social blocks in a fixed order) and here, we defined 2 within-subject variables: Sequence (1, 2, regardless of it being social or non-social- these were chronological), Block (5 levels, same as previously). We used Autism and ADHD as factors. We investigated using a repeated measures ANOVA whether Autism or ADHD was related to the effect of Sequence: There was a main effect of Sequence ($F(1, 83) = 21.57$, $p < .001$, $\eta^2_p = .21$). Neither Autism ($F(1, 83) = .02$, $p = .89$, $\eta^2_p = .00$) nor ADHD interacted significantly with Sequence ($F(1, 83) = 1.05$, $p = .31$, $\eta^2_p = .01$). For CSI and CVI, we conducted a similar MANOVA. There was a main effect of Sequence ($V = .24$, $F(2, 82) = 13.06$, $p < .001$, $\eta^2_p = .24$) but this did not interact with Autism ($V = .02$, $F(2, 82) = .72$, $p = .488$, $\eta^2_p = .02$) or ADHD ($V = .02$, $F(2, 82) = .65$, $p = .525$, $\eta^2_p = .02$). As reported earlier, the main effect of Sequence was significant only for CSI ($F(1, 83) = 26.28$, $p < .001$, $\eta^2_p = .24$) (and not for CVI ($F(1, 83) = .06$, $p = .805$, $\eta^2_p = .00$)) such that in the second half of the experiment, participants showed higher CSI than the first half (Mean difference ± S.E.= .28 ± .05, $p < .001$).

Appendix E- Results from Chapter 4

1. P3a to the first standard: Interaction between Condition and ADHD

The interaction between Condition and ADHD was driven by those with ADHD showing no significant difference in P3a amplitudes ($p = .86$) between the social (Mean ± S.E. = 3.00 ± .24) and the non-social (Mean ± S.E. = 2.97 ± .19) conditions; while those without ADHD showed significantly higher P3a amplitudes ($p < .001$) in the social (Mean ± S.E. = 3.16 ± .25) as compared to the non-social (Mean ± S.E. = 2.37 ± .20) conditions (see Fig D.1).

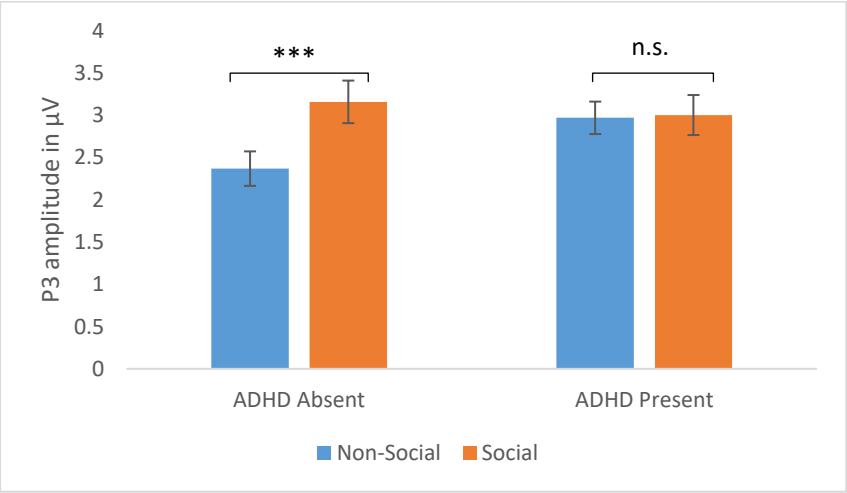


Figure D.1. Interaction between ADHD and Condition.

Bars show the mean (±1 standard error) average P3a amplitudes (in µV) (plotted on the y-axis). These data are split by Condition (Social, Non-Social) and ADHD (Present, Absent). Asterisks denote statistical significance: *p<.05, **p<.01, ***p<.001

2. Habituation of P3a to repetition of standard

2a. Effect of Order of Presentation of the Social and Non-Social Blocks

There was a main effect of Repetition (Greenhouse-Geisser $F (2.78, 235.97) = 3.14$, $p = .029$, $\eta^2_p = .04$). There was no main effect of Condition ($F (1, 85) = .72$, $p = .399$, $\eta^2_p = .01$) but the main effect of Repetition was modulated by Condition: Condition*Repetition $F (3, 255) = 3.66$, $p = .013$, $\eta^2_p = .04$.

Follow-up pairwise comparisons revealed that the main effect of Repetition was elicited by the first standard eliciting significantly higher P3a amplitude as compared to the 2nd (p = .003), 3rd (p = .04) and 4th (p = .03) standards, thus, there was quick habituation. However, this effect of Repetition was present only in the Social condition (where the 1st standard was significantly different than the 2nd (p < .001), 3rd (p = .019) and 4th (p < .001) standards), but not in the non-Social condition (where the differences between the 1st and subsequent standards were non-significant (2nd: p = .78; 3rd: p = .46; 4th: p = .87) (see Fig D.2).

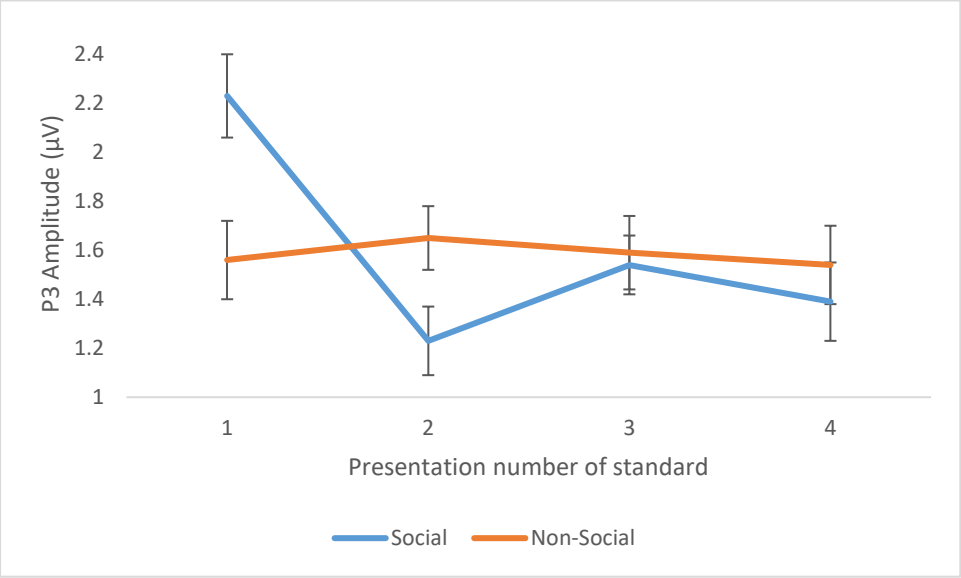


Figure D.2. Main effect of Repetition

Bars show the mean (±1 standard error) average P3 amplitudes (in µV) (plotted on the y-axis). These data are split over the standard presentation (4 repetitions of standards) and condition (social, non-social). For the social condition, the difference between the 1st standard and all subsequent standards is significant; this is not the case for the non-social condition.

There was no main effect of Order of Presentation ($F (1, 85) = 0.3$, $p = .59$, $\eta^2_p = .00$). There was a trend towards significance in the interaction between Condition and Order of Presentation ($F (1, 85) = 3.41$, $p = .068$, $\eta^2_p = .04$). However, there was no interaction between Repetition and Order of Presentation (Greenhouse-Geisser $F (2.78, 236.97) = 1.1$, $p = .35$, $\eta^2_p = .01$) and no three-way interaction between Condition, Repetition and Order of Presentation ($F (3, 255) = 1.22$, $p = .30$, $\eta^2_p = .01$).

2b. Habituation of the P3a to repetition of standards: Interaction between Condition, Repetition and ADHD

There was a significant three-way interaction between Condition, Repetition and ADHD ($F (3, 249) = 3.54$, $p = .015$, $\eta^2_p = .04$). In order to understand this effect, first, we looked at each level of ADHD to assess it using a within-subjects approach. At each level of ADHD, Condition and Repetition interacted significantly (ADHD Present: $F (3, 132) = 2.8$, $p = .04$, $\eta^2_p = .06$; ADHD Absent: $F (3, 117) = 4.27$, $p = .007$, $\eta^2_p = .099$). Therefore, we looked at each level of Condition and found that there was no significant interaction between Repetition and ADHD for the social condition ($F (3, 249) = 1.18$, $p = .32$, $\eta^2_p = .01$) but this was significant for the non-social condition (Greenhouse-Geisser $F (2.64, 219.05) = 3.69$, $p = .017$, $\eta^2_p = .04$). Follow-up pairwise comparisons show that those with ADHD showed a significant decrease in P3 amplitude from standard 1 to standard 3. However, for participants without ADHD, there was a significant increase from standard 1 to standard 2 (see Fig D.3).

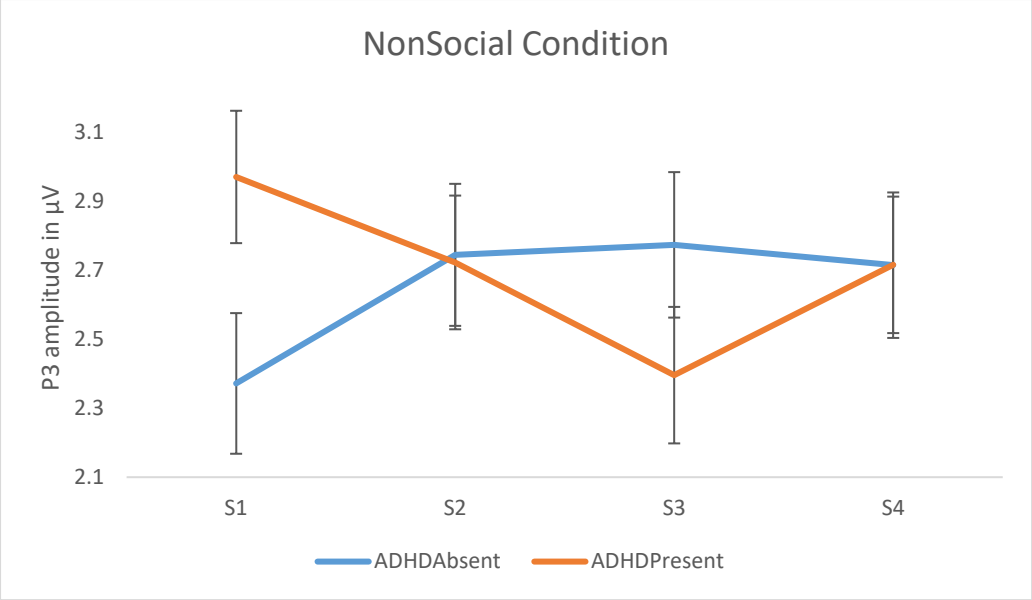


Figure D.3. Repetition*ADHD interaction in Non-Social Condition

Bars show the mean (±1 standard error) average P3 amplitudes (in µV) (plotted on the y-axis). These data are split over the standard presentation (4 repetitions of standards) and ADHD (Present, Absent).

Appendix F- Piloting of Eye-tracking Task

Here, I report results from the piloting work on the eye-tracking task.

Sample

Summer Scientist Week Year 1 (2017)

	Total	Version 1	Version 2	Version 3	Version 4
Sample Size	67	16	17	19	16
Age (in months)	107.955 (21.327)	113.6 (16.44)	106.647 (27.64)	99.105 (20.944)	114.56 (15.104)
Gender	35 M: 32 F	10M: 5F	9M: 8F	9M: 10F	7M: 9F
BPVS (Standard Score)	103.7 (12.526)	109.64 (12.18)	104.25 (10.53)	97.06 (12.86)	105.53 (12.86)
SAS	26.356 (4.856)	25.69 (5.17)	26 (3.66)	26.94 (6.07)	26.92 (4.34)

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are n male:female. BPVS: British Picture Vocabulary Scale, 3rd Edition; SAS: Social Aptitude Scale.

Methods

4 versions of the task were used. Each condition comprised of 9 trials. Each version comprised of different repeating stimuli for each condition. The repeating and changing stimuli were presented in the left and right hemifields, counterbalancing across versions for each condition. Two versions used a male repeating social stimulus while the other two used a female social repeating stimulus.

Analysis

We were interested, first, in whether regardless of task version, we elicited the effects of habituation to repeating stimuli and increased looking over time to the changing stimuli. We also wanted to ensure

that no specific stimuli in any version created any confounding effects and that main effects of the task were present regardless of the specifics of a stimulus.

We investigated these in two variables: number of fixations (control variable, to investigate engagement with the task) and rate of change in look durations over trials (to investigate habituation and novelty preference).

Investigations of main task effects

Number of fixations

In the first analysis, conducted a repeated measures ANOVA with 2 within-subject factors: Condition (Non-Social Simple, Non-Social Complex and Social) and Stimulus (Repeating, Changing and Background). We hypothesised that the changing stimulus would elicit the most number of fixations and the background the least.

There was a main effect of condition: $F(2, 134) = 11.23$, $p < .001$, $\eta^2_p = .144$. Each level of Condition was significantly different than the other (Social vs Non-Social Simple $p = .019$, Non-Social Simple vs Non-Social Complex $p = .018$, Social vs Non-Social Complex $p < .001$). This was driven by the Social condition eliciting the highest number of fixations (M ± S.E. = 23.89 ± .52), followed by the Non-Social Simple condition (M ± S.E. = 22.42 ± .59) followed by the Non-Social complex condition (M ± S.E. = 20.87 ± .56).

There was a main effect of Stimulus: $F(2, 134) = 484.53$, $p < .001$, $\eta^2_p = .88$. This was driven by the Changing stimulus (Mean ± S.E. = 35.37 ± .87) eliciting significantly higher number of fixations (all pairwise comparison $p < .001$) than the Repeating stimulus (Mean ± S.E. = 26.28 ± .71) and the Background (Mean ± S.E. = 5.53 ± .47). The Repeating Stimulus also elicited significantly higher number fixations than the Background.

Finally, there was an interaction between Condition and Stimulus: F (3.35, 224.49)= 6.43, p < .001, η^2_p = .09. The effect of Stimulus was present at each level of Condition, suggesting that the distribution of attention to repeating and changing stimuli was not impacted by the type of stimuli (social/non-social, simple/complex).

Rate of change in look durations

We then investigated the task effects for the main dependent variable of interest: Slope of change in look durations to repeating and changing stimuli. A repeated measures ANOVA with Condition (Social, Non-Social Simple, Non-Social Complex) and Stimulus (Repeating, Changing) was conducted.

There was no main effect of Condition: F (2, 130) = .68, p = .51, η^2_p = .01. There a main effect of Stimulus F (1, 65) = 41.02, p < .001, η^2_p = .39. This main effect was not modulated by a Condition*Stimulus interaction: F (2 , 130) = 1.67, p = .19, η^2_p = .03. The main effect of Stimulus was driven by the slopes of change in look durations over trials being significantly different from one another, such that the slope to the repeating stimuli (Mean ± S.E. = -15.65 ± 6.26) was negative and that to the changing stimuli (Mean ± S.E. = 56.99 ± 6.76) was positive. The repeating stimuli thus elicited decreasing look durations over trials and the changing stimuli elicited increasing look durations over trials. This confirms that the task is eliciting the desired attention behaviour.

Effects of Task Version

Number of Fixations

We repeated the RM-ANOVA on number of fixations as above, including the Task Version (with 4 levels) as a between-subjects factor). There was no between subjects effect of Task Version (F (3, 64) = 1.32, p = .28, η^2_p = .06), and Task Version did not interact with the condition (F (6, 128) = 1.2, p = .31, η^2_p = .05).

There was an interaction between Stimulus and Task Version: F (6, 128) = 2.97, p = .009, η^2_p = .12.

The main effect of Stimulus was present at each level of Task Version such that each stimulus elicited significantly different number of fixations than each other stimulus, and the changing stimulus elicited highest number of fixations, followed by the repeating stimulus and then the background.

The interaction was driven by differences between task versions, such that the changing stimulus in Task Version 4 elicited significantly higher number fixations than the changing stimuli in all other versions (1 vs 4 p = .068; 2 vs 4 p = .01, 3 vs 4 p = .035) and the repeating stimuli in versions 1 and 3 elicited a higher number of fixations than the repeating stimuli of the other task versions (1 vs 2 p = .028, 1 vs 4 p = .035; 3 vs 2 p = .051, 3 vs 4 p = .064). Numerically these differences were small and the main effect of Stimulus was not affected.

Based on this analysis, it appeared that stimuli used in different conditions elicit more or less engagement than one another, but it does not appear to impact the main effect of Stimulus (which is the main effect of interest).

Rate of change in look durations

The model was then run to evaluate the main variable of interest: Slope of change in look durations to Stimulus (Repeating, Changing) in different Conditions (Non-Social Simple, Non-Social Complex and Social). Task Version was included as a between-subjects factor.

There was no main effect of Task Version : F (3, 62) = .66, p = .58, η^2_p = .03. Task Version did not interact with Condition (F (6, 124) = 1.11, p = .36, η^2_p = .05). However, there was a significant interaction between Stimulus and Task Version (F (3, 62) = 7.39, p < .001, η^2_p = .26). The main effect of Stimulus was observed in all versions of the task except for Version 1 where the slopes to repeating and changing stimuli were not significantly different from one another (p = .68).

Based on these results, it appeared that the stimuli used in Task Version 1 were not appropriate for the task.

Effect of autistic traits on looking at repeating and changing stimuli over trials

Social Aptitude Scale Scores were used as a measure of autistic traits. We evaluated whether SAS groups (split on SAS scores by median score) were different from one another on the slopes of change in look durations over trials. Task Version was modelled in as a covariate in this analysis given differences between versions. Further, we controlled for Age, Gender and BPVS in this analysis. There was no main effect of SAS group: $F(1, 37) = .62$, $p = .44$, $\eta^2_p = .02$. SASGroup also did not interact with Stimulus ($F(1, 37) = .11$, $p = .07$, $\eta^2_p = .00$) or Condition ($F(2, 74) = .63$, $p = .54$, $\eta^2_p = .02$).

Summary

In light of this, we made some changes to the task:

- Changes were made to the task versions and only 2 versions kept, stimuli chosen that were not particularly attractive, eliciting higher fixations than others. 2 versions were different from one another in the repeating stimuli, such that for the social condition, one version had a male repeating stimulus and the other version had a female repeating stimulus. The repeating stimuli for the non-social simple and complex conditions were also different. Further, side of presentation of repeating and changing stimuli were alternated for each condition between versions.
- We decided to add Autism Spectrum Quotient to the battery of measures to be done with parents, since it was decided that this was more sensitive to autistic traits than SAS.
- 2 additional trials were added to each condition, in order to ensure any subtle differences in habituation and learning are captured, particularly since the plan was to use the task with clinical populations

Year 2- Summer Scientist Week 2018

Sample

	Total	Version 1	Version 2
Sample Size	52	25	27
Age (in months)	103.596 (25.23)	98.48 (22.01)	108.33 (27.44)
Gender	27M: 25F	14M: 11F	13M: 14F
BPVS (Standard Score)	106.69 (11.07)	107.08 (11.28)	106.33 (11.08)
AQ	58.73 (18.995)	64.63 (20.42)	53.48 (16.26)

Data shown for all measures except Gender are mean with standard deviation in parentheses. Data for gender are n male:female. BPVS: British Picture Vocabulary Scale, 3rd Edition; AQ: Autism Spectrum Quotient- Child's Version

Effect of Task Version on Number of Fixations

There was no main effect of Task Version: $F(1, 50) = .87$, $p = .36$, $\eta^2_p = .02$.

Task Version did not interact with Condition ($F(2, 100) = .28$, $p = .76$, $\eta^2_p = .01$) or Stimulus ($F(2, 100) = 1.29$, $p = .28$, $\eta^2_p = .03$).

Effect of Rate of change in look durations

Then we investigated the effect of Task Version on rate of change in look durations over trials:

There was no main effect of Task Version: $F(1, 50) = 65$, $p = .42$, $\eta^2_p = .01$.

Task Version did not interact with Condition ($F(2, 100) = 1.23$, $p = .297$, $\eta^2_p = .02$) or with Stimulus ($F(1, 50) = .42$, $p = .52$, $\eta^2_p = .01$). Therefore, the two task versions used in Year 2 did not elicit different effects from one another.

Appendix G- Supplementary Materials from Chapter 5

Task Information

We created two versions of the task: in one version of the task, the repeating stimulus in the social condition was male and in the other, it was female, in case stimuli of different genders elicited different attentional effects depending on the gender of the participant. Each participant did one version of the task, and we presented the version with the male repeating social stimulus to half the participants and the version with the female social repeating stimulus to the other half. Analyses on the main dependent task variables confirmed no significant differences between task versions and so we collapsed across the versions in all analyses. Order of presentation of conditions and stimuli within conditions were both randomized. Further, we counterbalanced the visual hemifield in which the repeating stimulus was presented in each condition and between the two versions. In Vivanti's study, nine trials were presented. We added two trials (to each condition) to ensure that there were sufficient trials to capture changes in looking patterns given the older age of our participants.

Study 1

Sample Characteristics and Study Procedure

Participants were included in the Autism group if they presented with clinically significant symptoms of autism on the ADOS-2 (ADOS comparison scores > 4), the DAWBA (meeting DSM-5 and ICD-10 criteria) (American Psychiatric Association 2013; World Health Organization 1993) and SCQ (raw score > 15) and a consensus clinical review of all available information applied to ensure diagnostic rigor (McEwen et al. 2016).

Participants were included in the ADHD group if they presented with clinically significant symptoms of ADHD combined presentation on DAWBA (meeting DSM-5 criteria) (American Psychiatric Association 2013) and the CRS (T scores > 65) and a consensus clinical review of all available information. Importantly, where we did not have teacher CRS on a child and the child did not have a

pre-existing diagnosis of ADHD, they were not included in the study since presence of these symptoms across different settings is important for a diagnosis.

Participants were included in the comorbid Autism + ADHD group if they met research diagnostic criteria for both autism and ADHD as defined above.

Participants were excluded from the neurotypical group if any of these measures revealed clinically significant symptoms (as defined above), or significantly elevated risk (i.e., >75% probability) of presence of any DSM-5 or ICD-10 diagnoses as predicted by DAWBA, or there was family history of ADHD or autism. Children with ADHD were excluded if they were on non-stimulant medications or if their parents did not wish to remove them from stimulant medications for 24 hours before the study.

Other exclusion criteria were neurological disorders including epilepsy and Tourette's syndrome and non-fluent English in the child or parent. Other mental health conditions (anxiety, depression, obsessive-compulsive disorder, conduct disorder, oppositional defiant disorder etc.) and intellectual disability were not excluded. Another aim of this research study, not covered within this paper, was to investigate the role of IQ (intelligence quotient, as measured by WASI) in attention in Autism and ADHD. Therefore, participants were not excluded for having intellectual disability. None of the participants included in the present paper had IQ below 70, 3 participants had IQ below 80.

After providing informed consent, parents completed DAWBA, SCQ and CRS-3 as well as demographic and medical information. Participants with ADHD who were taking stimulants were asked to withdraw from medication for at least 24 hours prior to the laboratory session. Participants completed the ADOS and WASI-II and those who met the inclusion criteria then completed the eye-tracking and EEG batteries. At the end of the study, participants were given a certificate and a £15 voucher. Parents' travel expenses were reimbursed.

Number of fixations (control variable measuring task engagement)

Follow-up pairwise comparisons were conducted to evaluate the interaction of Condition*Autism, to identify whether within Condition (Non-Social Simple, Non-Social Complex, Social), there were differences between groups with and without Autism in number of fixations to the screen. At each level of Condition, there were no significant differences between groups on this variable:

Non-Social Simple Condition: Groups with Autism (Mean ± S.E. = 79.09 ± 2.71) demonstrated similar number of fixations to the screen as those without Autism (Mean ± S.E. = 81.52 ± 2.55); p= .52.

Non-Social Complex Condition: Groups with Autism (Mean ± S.E. = 73.63 ± 3.11) demonstrated similar number of fixations to the screen as those without Autism (Mean ± S.E. = 76.64 ± 2.92); p= .48.

Social Condition: Groups with Autism (Mean ± S.E. = 88.95 ± 2.86) demonstrated similar number of fixations to the screen as those without Autism (Mean ± S.E. = 82.66 ± 2.69); p= .11.

Study 2

Bias-corrected and accelerated bootstrapped correlations of BPVS and Age with AQ and Rate of change in look durations to repeating and changing stimuli in Non-SocialComplex and Social Conditions

	AQ-Child	**Rate of Change in Look Durations over Trials**			
		Non-Social Complex Repeating Stimulus	Non-Social Complex Changing Stimulus	Social Repeating Stimulus	Social Changing Stimulus
BPVS standard score	r = -.02, p = .88, [-.28, .25]	r = -.08, p = .55, [-.37, .24]	r = .16, p = .21, [-.08, .38]	r = -.02, p = .87, [-.2, .15]	r = -.02, p = .89, [-.26, .23]
Age (in months)	r = -.12, p = .35, [-.39, .19]	r = -.09, p = .51, [-.31, .2]	r = .01, p = .94, [-.25, .26]	r = .08, p = .53, [-.18, .34]	r = -.1, p = .44, [-.36, .18]

BPVS: British Picture Vocabulary Scale, Third Edition, Standardized scores; AQ-Child: Autism-Spectrum Quotient- Child's Version; []= Bootstrapped and bias-corrected 95% confidence intervals around the Pearson's correlation r.

Appendix H- Systematic review of resting state literature on arousal in Autism

This appendix is an article that is currently under review at a journal for publication.

Is autonomic function during resting-state atypical in Autism: A systematic review of evidence.

Iti Arora[a,*], Alessio Bellato[a], Danielle Ropar[b], Chris Hollis[a,c,d], Madeleine J. Groom[a]

[a]Division of Psychiatry and Applied Psychology, School of Medicine, University of Nottingham, Institute of Mental Health, Innovation Park, Triumph Road, Nottingham, NG7 2TU, United Kingdom

[b]School of Psychology, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom

[c]NIHR MindTech Healthcare Technology Co-operative, Institute of Mental Health, University of Nottingham, Nottingham, NG7 2TU, United Kingdom

[d]NIHR Nottingham Biomedical Research Centre, Institute of Mental Health, Innovation Park, Triumph Road, Nottingham, NG7 2TU, United Kingdom

Email Addresses:

Iti Arora: iti.arora.3@gmail.com

Alessio Bellato: alessio.bellato@hotmail.it

Danielle Ropar: danielle.ropar@nottingham.ac.uk

Chris Hollis: chris.hollis@nottingham.ac.uk

Madeleine Groom: maddie.groom@nottingham.ac.uk

Corresponding Author: Iti Arora (iti.arora.3@gmail.com)

Abstract

Arora, I., Bellato, A., Ropar, D., Hollis, C., Groom, M. Is autonomic function during resting-state atypical in Autism: A systematic review of evidence. NEUROSCIE BIOBEHAV REV X XXX-XXX, 2020.

Theories of differences in resting-state arousal in autistic individuals are influential. Differences in arousal during resting-state would impact engagement and adaptation to the environment, having a cascading effect on development of attentional and social skills. In this review, we evaluate the evidence for differences in autonomic arousal (measured using indices of heart rate, pupillometry or electrodermal activity) during resting-state in autistic individuals; and importantly, whether certain contextual or methodological factors impact reports of such differences. We conducted a systematic review of the literature and of 1207 titles initially identified, 60 papers met our inclusion criteria. Of the 51 studies that investigated group differences between neurotypical and autistic participants, 60.8% of the studies found evidence of group differences. While findings of hyperarousal were more common, particularly using indices of parasympathetic function, findings of hypoarousal and autonomic dysregulation were also consistently present. Importantly, experimental context played a role in revealing such differences. The evidence is discussed with regard to important methodological factors and implications for future research are described.

Keywords: Autism Spectrum Disorder, Autonomic Arousal, Resting State, Heart Rate Variability, Electrodermal Activity, Pupillometry

1. Introduction

Autism Spectrum Disorder (referred to as Autism henceforth) is a heterogeneous neurodevelopmental condition with prevalence estimated at 1% in the UK (Laurie and Border, 2020). Autism is well-characterized at the behavioural level by a variety of symptoms, including difficulties with social interaction and communication alongside repetitive and restricted behaviours (RRBs), from an early age (American Psychiatric Association, 2013).

An influential theory in the field of autism proposed that autistic individuals have atypical profiles of physiological arousal during resting-state (i.e., states of rest or relaxation). First put forward by Hutt et al. (1964), this theory suggested that autistic individuals may be in a "chronically high state of arousal" (Hutt et al, 1964, p.908); which may lead to sensory over-responsivity and prevent habituation to environmental stimuli. According to this theory, social avoidance and repetitive behaviours in autism may be a coping mechanism to regulate arousal. Indeed, if autistic individuals are in a chronic state of hyperarousal at rest, they might be hyper-reactive to different sensory stimuli in the environment and might feel overwhelmed. Avoiding rich sources of sensory stimulation, such as social situations, and engaging in repetitive behaviours to reduce the amount of sensory stimulation received, might therefore help to down-regulate arousal (Kinsbourne, 2011; McCormick et al., 2014). Theoretically then, these two core areas of differences (social avoidance and RRBs) in autistic individuals could be explained by a profile of resting hyperarousal.

On the other hand, it has also been proposed that states of hypoarousal at rest might underlie core features of autism (DesLauriers and Carlson, 1969). According to this theory, reduced responsiveness to social environments might be explained by chronic hypoarousal, while RRBs might serve the purpose of stimulating an under-aroused system (Lovaas et al., 1987). It is important to note that these two theories are not mutually exclusive; there might be subgroups of autistic individuals with profiles of resting-state hyper- or hypo-arousal; and the same individuals may present with one or the other profile in different contexts. However, both hyper- and hypo- aroused states at rest are likely to impact engagement with the environment and responsivity to cognitive tasks.

If present, differences in resting-state arousal may develop earlier than the first symptoms of autism typically appear. Evaluating the utility of theories of differences in resting-state profiles of arousal in

autism thus has important implications for early detection, diagnostic practices and intervention routes in autism. Early differences in profiles of resting-state arousal may impact subsequent acquisition of adaptive, socialization and cognitive skills and may contribute to the heterogeneity in the autistic phenotype (Charman et al., 2005). Thus, proper examination of the evidence for these theories has importance towards understanding developmental pathways of autism and parsing the heterogeneity of the autistic spectrum.

This is the motivation behind the present review, which aims to evaluate the evidence for differences in profiles of resting-state arousal in autism. In experimental contexts, resting-state refers to an absence of sensory stimulation or the demands of a cognitive task. In studies that use cognitive tasks, evoked responses that are time-locked to stimuli or responses tend to be the focus, with any other spontaneous activity considered irrelevant and a source of noise. On the other hand, in resting-state studies of arousal, it is the spontaneous activity of the central or peripheral nervous system that is the focus. Even in studies that are specifically focussed on task-related measures, a baseline measure is typically taken of the index in question, to look at differences from baseline when task-evoked activity occurs. This is because it can be difficult to interpret task-related differences in any function, without first investigating differences at rest (Wang et al., 2013).

If the theories of atypicalities in resting-state arousal in autistic individuals are true, there should be differences between autistic and neurotypical controls in autonomic arousal during resting-state, which would influence how autistic individuals then respond to stimulation or task demands. In this review, we chose to focus on autonomic arousal because indices of autonomic arousal have been most commonly used to study profiles of arousal in autism. Further, autonomic indices of arousal are relatively easy and inexpensive to measure, and thus have high utility with regard to implementation in clinical practice. Before presenting the methods and results of the review, we describe the role of the autonomic nervous system in cognition and how this may be altered in autism.

1.1 *What is Autonomic Arousal?*

Arousal refers to one's state of alertness and vigilance towards internal and external stimuli. Arousal can be theoretically divided into tonic arousal, which refers to diurnal fluctuations in alertness and

energy towards the external world, and phasic arousal, which refers to fluctuations in arousal that are spontaneous or in response to events or stimuli in the environment (Orekhova and Stroganova, 2014). Tonic and phasic arousal are interdependent, for instance, optimal phasic responsivity occurs at certain levels of tonic arousal (Aston-Jones and Cohen, 2005). An optimal state of arousal is crucial to regulate dynamic and flexible adaptation to different contexts and is governed by interactions between the central and peripheral nervous systems. The autonomic nervous system (ANS) refers to the branch of the peripheral nervous system (PNS) that regulates involuntary functions of internal organs (such as breathing, heartbeats and digestion) to support the ongoing adaptation of the body to the demands of the environment. The ANS is typically divided into the sympathetic and parasympathetic nervous systems (SNS and PNS, respectively), although, recently, the enteric nervous system has been considered as another division of the ANS (Wood, 2008). Due to lack of articles directly measuring activity of the enteric system in autism, this will not be considered any further in this article. For those interested, Rao and Gershon (2016) and Yarandi et al. (2016) discuss evidence in autism in relation to enteric system function.

The SNS regulates what is traditionally called the 'flight or fight' response and it is crucial for responding to environmental stressors appropriately, by preparing the body for action in response to a threat. It does so by broadly upregulating the cardiovascular and endocrine systems with associated responses such as increases in heart rate and pupil dilations (Porges, 1992). In contrast, the PNS serves the complementary 'rest and digest' function. During times of rest, the PNS promotes a "calm, physiological state" (Klusek et al., 2015, p.3) by slowing down the heart and promoting bodily functions such as digestion and urination. At times of stress, reduced activity of the PNS allows increased activation of the SNS by releasing its brake and enabling physiological excitation (Porges, 1992). While the SNS and PNS serve complementary functions, which may be antagonistic in nature, they work in coordination to maintain homeostasis and regulate responsivity to the environment (Berntson et al., 1991).

The ANS is regulated by and provides input to the CNS. Specifically, the ANS sends signals to brainstem regions that directly influence systems involved in regulating consciousness and release of neurotransmitters (Thayer and Brosschot, 2005). The locus coeruleus in the brainstem, which is the

primary source of norepinephrine (NE) in the cortex (Aston-Jones and Cohen, 2005; Loughlin et al., 1986), receives autonomic signals through the nucleus tractus solitaris (NTS) and in turn has reciprocal connections with higher level regions in the prefrontal cortex, hypothalamus, insula and amygdala (Van Bockstaele and Aston-Jones, 1995, as reviewed by Sara and Bouret, 2012; Critchley and Garfinkel, 2018). Arousal regulation thus occurs through concurrent and coordinated involvement of ANS, the brainstem and cortical systems. Further, indices of activity in the peripheral ANS such as pupil dilation partly reflect arousal and responsivity in the central nervous system, and vice-versa (Murphy et al., 2014; Murphy et al., 2011).

The most common indices of peripheral ANS function are heart rate (HR) and heart rate variability (HRV), electrodermal activity (EDA) and pupil size (Wass et al., 2015). HR is a measure of the average number of beats of the heart per minute. HRV is an important index of adaptive autonomic function to the environment. HR is regulated by both SNS and PNS, with activation of the SNS being related to accelerations in HR and PNS activation being associated with HR decelerations. EDA reflects activity in the sweat glands that are regulated by the SNS. Finally, both SNS and PNS are involved in constriction and dilation of the pupil, but pupil size also correlates with activity in the LC and thus has been found to be a valid peripheral index of ANS function (Wass et al., 2015).

Differences in peripheral indices of ANS function, including heart rate, EDA and pupil size, are closely linked with differences in sensory responsivity (Schoen et al., 2009), cognition (Gilzenrat et al., 2010; Howells et al., 2012), socialization (Porges, 2011), and emotion processing (Cuve et al., 2018); all of which are domains of functioning that are affected in autism (Kushki et al., 2014). Analysing these peripheral indices of ANS could thus prove useful to investigate mechanisms underlying stress and psychopathology in autism.

1.2. Autism and Autonomic Arousal

Specific evidence for differences in peripheral indices of autonomic arousal in autism is mixed. Autistic individuals present with a high prevalence of sleep disorders, suggesting differences in regulation of diurnal cycles (Tudor et al., 2012). There is also evidence to suggest that autistic people may struggle to respond effectively to stressful social contexts by upregulating their autonomic response as

neurotypical individuals do (Edmiston et al., 2016). Further, autistic individuals may demonstrate atypical attention and behavioural responses to sensory stimuli in their environment, which might be indicative of difficulties maintaining a stable level of alertness and vigilance, and in regulating phasic responsivity to the environment (McCormick et al., 2014). Importantly, studies have reported significant differences between autistic and neurotypical groups in phasic autonomic activity when measured at baseline (prior to starting a cognitive task) which persist during the task. Task-based atypicalities in autonomic activity in autistic individuals might therefore be partly driven by differences in arousal during resting-state (Hubert et al., 2009; Mathersul et al., 2013b).

In light of recent evidence, recent theoretical models support a hyperarousal model of autism. These cite reduced parasympathetic activation as a mechanism driving atypical arousal in autism. Porges' Polyvagal Theory (Porges, 2003) cites an important role of the vagus nerve in social engagement, stating that cortical brain regions exert influence on the ANS through the myelinated vagus, via the brainstem, which supports social interaction with others. They propose that differences in this social engagement system in autism are paralleled by reduced vagal influence over the heart via the vagus nerve. Similarly, the neurovisceral integration theory (Thayer and Lane, 2000) draws links between parasympathetic activity and emotion dysregulation and anxiety, both of which are highly prevalent in autism (McVey, 2019). Specifically, this theory suggests that reduced HRV, reflecting reduced activation of PNS, is associated with hypervigilance to the environment, and reduced flexibility in adapting to the environment, leading to deficits in emotion regulation and increased anxiety (Friedman, 2007). Importantly, the neurovisceral integration theory implicates cortical structures (such as prefrontal cortex, anterior cingulate cortex, amygdala and insula) in regulating autonomic responsivity. Structural, functional and connectivity differences in these cortical structures are also implicated in the neurobiology of autism (Kushki et al., 2014).

There is additional evidence for differences in cortical arousal from resting-state EEG studies which have reported differences in power in high and low frequency oscillations, particularly in the left hemisphere, indicative of differences in arousal between autistic and control participants in the CNS (Wang et al., 2013). It is possible then, that findings of ANS differences in autistic individuals are related to differences in CNS function (Gu et al., 2015). In summary, theoretical models have implicated

atypical interactions between central and peripheral nervous system function in autism and this has been linked to autistic symptoms such as sensory over-responsivity, hypervigilance, anxiety, and reduced socialization skills.

A number of recent reviews have attempted to bring together the vast body of research in autonomic function in autism. However, these have tended to focus on specific aspects of functioning in autism; such as physiological responsivity to sensory and socio-emotional stimuli (Lydon et al., 2016), emotion recognition (Cuve et al., 2018); or on specific indices of autonomic function such as cardiac function (Benevides and Lane, 2015) and cortisol (Taylor and Corbett, 2014). Evidence for differences in autonomic arousal at rest across autonomic measures has not been reviewed systematically and thoroughly.

This is the motivation behind the present review, which aims to systematically evaluate the evidence for differences in profiles of arousal during resting-state in autism. A careful evaluation of this evidence might shed light on whether there are such differences, but more importantly, on factors that may underlie such differences. Specifically, there might be certain contexts or specific measures that are more likely to reveal differences in autonomic arousal during resting-state in autistic individuals. This is the lens we will adopt in this review.

We will focus on any studies that have directly measured an index of peripheral autonomic arousal (such as heart rate, EDA or pupil size) at rest or baseline (i.e., before a task). We believe that this will not only shed light on the utility of resting-state theories of dysregulated autonomic arousal in autism; but more importantly, results from this review may guide understanding of where such differences lie and which methodological or sample characteristics might be important to understand heterogeneity in the findings.

Resting-state is typically measured in two ways: either participants are asked to relax, sit or lie down quietly or they are asked to passively look at something (a dot on a wall, a calm video that is age appropriate). There are pros and cons to measuring resting-state in these different ways. Resting-state could be considered a measure of inward-directed attention, when an individual is not asked to process, evaluate or respond to anything external. Therefore, traditionally, it is measured while participants are in contexts that induce rest such as lying down quietly, with eyes open or closed, not doing anything.

However, such measurements can be quite demanding for children who struggle to sit still for extended periods of time. Thus, passive attention resting-states, where individuals are given something to look at such as an age-appropriate video are often used in these cases, particularly with younger children (Bazelmans et al., 2019). Further, resting-state measurements where individuals are asked to sit quietly with eyes open or closed might introduce a different type of noise to the data, since different participants might think of different things and there might be factors between clinical groups that impact such data systematically. Passive attention resting-state measurements (which provide participants something to look at) might control for this noise while not necessarily asking participants to perform a task. In our review, we included studies using both types of measurement and investigated whether these contextual factors influence the pattern of findings in any way.

1.3. Purpose of this review

We applied a systematic approach to gathering and evaluating evidence on differences in autonomic arousal during resting-state in autistic individuals. In this review, we focus on describing the findings and evaluating their implications for the field. Specifically, we reviewed studies that compare autistic and neurotypical groups on ANS measures of cardiac function (i.e. heart rate variability), electrodermal activity, and pupil size, both at rest and during pre-task baseline periods. We did not include evidence from studies measuring CNS arousal or cortisol/neurotransmitters, because indices of arousal at CNS are debated, and some of this evidence has been reviewed (Berman et al., 2015; Kleberg, 2015; Wang et al., 2013).

The present review aims to answer the following questions:

1. What is the evidence for atypical ANS activity during resting-state in autistic individuals as compared with neurotypical controls?
2. Does it take the form of hypo- or hyper-arousal?
3. Are there any patterns in the findings that may indicate that particular indices of autonomic measurement or particular contexts of measurement are more reliable in revealing differences between autistic and neurotypical groups?

2. Methods

We searched PsycInfo, MEDLINE and EMBASE databases from 1975 to 17th May 2019. We used keywords in the fields of autism or autism spectrum disorder, arousal and arousal regulation, and autonomic nervous system (see Figure 1 for a PRISMA flowchart of the articles screened, adapted from Moher et al. (2009)). We supplemented these keywords with words that refer to the key measures typically used to assess ANS function, including 'electrodermal activity/galvanic skin response', 'pupil dilation', 'heart rate' and 'heart rate variability' (see Supplementary Materials for a full list of inclusion/exclusion criteria). We decided not to conduct a meta-analysis since there was huge variability in study methods and measures used. We obtained full-text articles for all those that passed the initial screening (as summarized in Figure 1), and these were reviewed against inclusion/exclusion criteria, by two reviewers. Thereafter, we extracted data on key features for each article included in the review. The reviewers involved in the screening process discussed any articles that were unclear before reaching a decision on their inclusion or exclusion. Finally, the papers were analysed based on key factors relevant to the analysis, such as presence/absence of significant group differences, evidence of hyperarousal or hypoarousal in the patient group compared to the control group and other factors related to the methodology of the study.

[Insert Figure 1 here]

[Insert Table 1 here]

3. Results

3.1. Studies included

After full-text review, a total of 60 studies were included in this review (see Fig 1). One of these studies was a conference publication from a peer-reviewed journal (Tiinanen et al, 2011). A summary of the ANS measures used in these studies (including their acronyms and abbreviations, and their interpretation with regard to ANS function) can be found in Table 1. Of the 60 studies, 51 studies made 130 comparisons on 53 samples of autistic and neurotypical groups on various autonomic measures at rest/baseline (i.e. a defined period of inactivity immediately prior to a cognitive task). 17 studies measured linear associations between autonomic function during resting-state/baseline and clinical

symptoms and/or behavioural functions associated with autism. 41 studies reported data from cardiac measures, either as the sole measure (n = 35) or in combination with other measures (n = 6). 19 studies reported data from EDA, either as the sole measure (n = 13) or in combination with others (n = 6). 7 studies reported data from pupil measures, either as the sole measure (n = 5) or in combination with others (n = 2). A description of all the studies included in the review (with key methodological factors and main findings summarized) can be found in Table 2.

[Insert Table 2 here]

3.2. Spread of group differences:

We categorized each study that compared neurotypical and autistic participants on an ANS measure based on whether or not they reported a significant group difference on at least one ANS measure. Some studies reported findings for different indices of the same ANS domain, such as multiple indices of heart-rate variability from cardiac data (for example, time- domain and spectral-domain measures of HRV), or multiple indices from different ANS domains, e.g., EDA and HRV measures. Studies have been categorized as finding a significant group difference if they found a significant difference between the neurotypical and autistic groups on at least one measure. Of the 51 studies on 53 samples, 20 studies (39.2%) found null effects, while 31 studies (60.8%) reported significant group differences (see Table 3). Two studies (Keith et al., 2019b; Kushki et al., 2013) reported marginally significant effects (p-values of the effect being 0.1 and 0.06 respectively) on their group comparison and have been included in the significant group differences category.

Of the 31 studies (33 samples) that found group differences, 21 studies (67.8%) found evidence of hyperarousal, five studies (16.1%) found evidence of hypoarousal and the remaining five studies (16.1%) found other effects indicative either of overall autonomic dysregulation or differences in adaptation to the experimental context (Table 3). Here, autonomic dysregulation refers to findings that could not be categorized as hyperarousal or hypoarousal, e.g., evidence of both hyperarousal and hypoarousal on different measures, or evidence of higher or lower variability in the autonomic index. Differences of reduced adaptation to the experimental context refer to studies wherein multiple measurements were taken during resting-state and change between time-points was measured; there were differences reported between groups in change in autonomic arousal over time.

Many studies compared autistic and neurotypical participants on several ANS measures. In order to represent this information, we analysed each group comparison made on a resting-state ANS measure across studies. When each group comparison was individually accounted for, it emerged that only 51 group comparisons were significant, out of the 130 comparisons in 53 samples (39.23%); with the remainder (79 comparisons; 60.77%) reporting no significant differences on indices of autonomic arousal between people with and without autism (See Table 3). It is possible that certain autonomic measures were more likely to reveal autonomic differences between groups, or other factors played a role in this. We will evaluate the role of various factors on the nature of results in Sections 3.3- 3.5.

[Insert Table 3-4 here]

3.3. Contextual factors

It is likely that the context of measurement influences states of arousal and thus, the likelihood of finding true effects. The studies included in this review (see Table 2) used a variety of measurement contexts, from sitting quietly with eyes closed to watching a calming video passively. We investigated whether these contextual factors had an impact on reports of group differences. In Table 4, we describe pertinent contextual factors we analysed, including duration of autonomic function measurement, what participants were asked to do during measurement, and whether activities (e.g cognitive tasks) were scheduled to take place after resting-state measurement. For studies that used ANS measures of different types (i.e. cardiac, electrodermal or pupil), we evaluated the effects of these factors on each

type of measure separately. This led to 58 comparisons across 51 studies. These results are further described in Sections 3.3.1- 3.3.4 below.

3.3.1. Length of ANS Measurement Period

We categorized studies based on the length of time over which the ANS activity measure was calculated: a) very short (less than or up to 2 minutes), b) short (3-5 minutes) or c) long (more than 5 minutes) (see Table 5). Due to missing information on length of ANS measurement in four studies, we could make 54 out of 58 comparisons for this factor. When the measurement periods were very short (n = 18/54), the number of studies that found group differences (n = 8) was similar to the number of studies that did not (n = 10). On the other hand, in periods of measurement of 3-5 minutes (n = 27/54), the number of significant effects (n = 18) were double the number of null effects (n = 9). In longer periods of measurement (5-10 minutes) (n = 9/54), the number of significant group differences (n = 8) were much higher than the null findings (n = 1). It is possible that periods of measurement shorter than 2 minutes are not reliable at revealing differences in states of autonomic arousal in autism. It should be noted though that the majority of the studies fell in the 'short' category, with most studies reporting measurements between 3-5 minutes (See Table 5).

[Insert Table 5 here]

We analysed whether the type of differences found (hyperarousal or hypoarousal) was impacted by the length of measurement. As can be seen from Table 5, among the studies that found group differences, findings of hyperarousal were more likely regardless of the length of measurement. It should be noted though that across all studies, a small proportion of studies tended to find hypoarousal or other forms of autonomic atypicalities.

3.3.2. Experimental context during measurement

We also considered whether the experimental context could have affected findings, e.g., whether participants were asked to do something during the resting-state/baseline measurement. We divided the studies such that a study either asked participants not to do anything (No Activity Resting State, e.g.,

sit or lie down quietly and relax), or participants were asked to passively attend to something (Passive Attention Resting State, e.g., watching a video or looking at a screen). Due to missing information in eight studies (which compared groups on 10 ANS measures), we could make 48 of 58 comparisons. As can be seen in Table 6, in the passive attention condition, the frequency of finding significant group differences was fairly even (n = 13/23 studies found significant effects). However, this was markedly higher when a no activity resting-state measurement (without anything external to attend to) was used (n = 18/25 studies found significant effects). Interestingly, when looking at whether type of finding (i.e. hyper- or hypo- arousal) was impacted by context during measurement, it appears that studies using passive attention measurement were more likely to report hyperarousal in autistic participants (Table 6). In fact, 84.6% of the studies with passive attention activity during resting-state, which reported significant group differences, found evidence of hyperarousal, while 15.4% found evidence of hypoarousal. On the other hand, among the studies where no activity was carried out by participants during resting-state measurement, 61.1% found hyperarousal, 22.2% found hypoarousal and 16.7% found evidence of autonomic dysregulation but not specifically hyper- or hypo-arousal.

3.3.3. Experimental context after measurement:

Finally, we categorised studies according to whether they included an active cognitive task immediately after the resting-state period on the basis that when participants expect a task to follow, this might impact their ANS activity during the pre-task resting-state period. Therefore, we divided studies into whether they were followed by any tasks or not. Most studies (n = 47/58) included a task after resting-state. As can be seen in Table 7, when the resting-state measurement was followed by a task, the number of studies reporting a group difference (24/47) was similar to the number of studies reporting no group differences. In comparison, most studies that did not have a task following the resting-state period, reported a significant group difference (n = 10/11). A caveat to this analysis is that studies may not have reported that another task followed the resting state measurement.

[Insert Table 6-7 here]

We examined whether the direction of the effect (hypo- or hyper-arousal) was impacted by the expectation of a task to follow or not. As shown in Table 7, there was not a clear pattern. Of the studies that found group differences, findings of hyperarousal were more likely whether a task followed or did not follow the resting-state measurement. A small proportion of studies found evidence of hypoarousal or autonomic dysregulation as well.

We highlight the role of experimental context here since autonomic arousal should vary with contextual demands and differences found in studies may therefore be state-dependent rather than a stable difference attributable to autism. Often authors do not clearly describe this context or give sufficient credit to the possible role of experimental circumstances. Mathersul et al. (2013a, 2013b) reported contrasting findings from the same sample in two different studies. In one study (Mathersul et al, 2013b), SCL was recorded while participants spent two minutes with their eyes closed and found no significant overall group differences between adults with and without autism. Interestingly, in another paper with the same sample of adults with and without autism (Mathersul et al, 2013a), the authors measured SCL for the duration of 500ms before stimulus onset in a social judgement task. In this study they reported hypoarousal in autistic adults compared to neurotypical adults. It is unclear why the two studies show differences in findings in the same group of participants, and any effect of changes in experimental context were not reported by the authors. It is likely that both length of measurement and change in experimental context (from a no-activity resting-state to a pre-task baseline) influenced the measurement and arousal state in controls and autistic individuals differently. This highlights the importance of considering contextual factors in studies of autonomic arousal.

3.3.4. Summary of Contextual Factors

Overall, longer periods of autonomic measurement (3 minutes or longer) were more likely to yield significant group effects. Further, contexts of pure resting-state measurements (where no activity was reportedly given to the participants during or after the resting-state measurement) appeared to be more likely to discriminate autistic from neurotypical groups. Regardless of these contextual factors, findings of hyperarousal appeared to be more likely when group differences were found. However, a small proportion of studies across contexts yielded findings of hypoarousal or autonomic dysregulation that

should not be disregarded. Interestingly, resting-state measurements where some sort of stimulation (typically age-appropriate neutral videos) was provided to the participants seemed to be more likely to yield findings of hyperarousal than not, suggesting that in presence of stimulation, autistic participants might find it difficult to regulate their arousal.

3.4. Type of Autonomic Measure Used

We analysed whether specific ANS measures were more likely to capture significant differences between autistic and neurotypical groups. As can be seen in Table 8, studies using cardiac measures tended to find group differences more often than not (n = 23/34) as compared to pupil studies (n = 2/5) and studies using skin conductance (n = 9/19) which were as likely to find group differences as not. It should be noted though that many more studies in this review used cardiac measures, which seem to be the most often used to investigate autonomic arousal in autism.

We next consider the direction of group differences (hypo- or hyper-arousal) based on the measure used among the studies that found significant group differences. As can be seen from Table 8, cardiac and pupil measures tended to find hyperarousal while the skin conductance measures were more likely to find hypoarousal. These measures all capture different things at different levels of autonomic function and the difference in findings might be informative.

[Insert Table 8 here]

3.4.1. Pupil Studies

Very few studies included in this review used Pupillometry to compare autistic and neurotypical groups on autonomic arousal (n = 5), of which three found null effects and two found evidence of hyperarousal (See Table 9). All used an average pupil diameter size measure as their measure of autonomic arousal. Overall, evidence from pupillometry was inconclusive, with some evidence for hyperarousal in pre-school children and in adults, and no significant differences between autistic and neurotypical populations captured during childhood and adolescence. Notably, studies that used pupillometry in childhood and adolescence tended to include wide varying age ranges in their studies, which might impact sensitivity of this measure to differences between groups. It is noteworthy that due to the nature

of measurement, pupillometry studies always involve directed looking at a screen. This means that in the context of resting-state, these studies are reflective of arousal during an outward-directed attention paradigm in the sense that participants were always asked to fixate on a central point on the screen.

[Insert Table 9 here]

3.4.2. Cardiac indices

Heart Rate and RSA were the most commonly used indices to measure cardiac autonomic function in autism. Both these indices were not highly reliable at picking up differences in autonomic function, with 14 out of 23 studies using HR finding group differences (See Table 10) and six out of 11 using RSA finding group differences (See Table 11). However, when they found group differences, they were both more likely to find evidence of hyperarousal (n = 13/14 studies using HR and n = 6/6 studies using RSA) than hypoarousal.

Similarly, 10 studies used spectral measures of heart rate variability (See Table 12). Of these, six studies found evidence of group differences on a spectral measure, all in the direction of hyperarousal. Only seven studies used time-domain measures of heart rate variability (See Table 13). Of these, four studies found group differences, either in the direction of hyperarousal (50%) or evidence of some form of autonomic dysregulation (50%).

The pattern of results from RSA and spectral measures is indicative of reduced parasympathetic activation in autism, given that RSA is a validated measure of vagal tone and the spectral measures that found differences tended to be in the direction of reduced HF-HRV or increased LF-HRV. Schaaf et al. (2015) were the only ones in this review that measured cardiac Pre-Ejection Period at baseline, which is a validated measure of sympathetic arousal using cardiac indices. They did not find any differences on this measure between autistic and neurotypical groups.

[Insert Tables 10-14 here]

A few studies found evidence from spectral or time-domain measures of overall autonomic dysregulation, as indexed by higher overall variance in HRV in autistic than neurotypical participants (Billeci et al., 2018; Bricout et al., 2018; Zahn et al., 1987). One study found evidence for reduced autonomic adaptation between eyes-open and eyes-closed resting-state in autistic participants; reporting that while neurotypical participants demonstrated increased parasympathetic activation (as measured

by RSA) during eyes closed as compared to eyes open conditions, the autistic participants did not exhibit this adaptation to changing context (Mathewson et al., 2011). Saghir et al. (2017) measured differences in multi-scale entropy which quantifies the complexity of the heartbeat time series and reported no group differences. According to the authors, this measure represents the ability of the organism to adapt to different environments. Therefore, it might be a useful way of quantifying readiness of the ANS to adapt in autistic individuals in future studies.

A few studies used different indices of cardiac autonomic function other than the commonly used spectral or time-domain measures (See Table 14). Ming et al. (2005) measured indices of cardiac vagal tone using a device that has been validated to be an index of brainstem function in real-time. They reported that Cardiac Vagal Tone (measured as pulse interval variability) was significantly lower in autistic children. This finding was then replicated in an independent sample by the authors (Ming et al., 2016).

Toichi and Kamio (2003) used measures of cardiac vagal index (CVI) and cardiac sympathetic index (CSI), which are calculated from the time-series of consecutive heartbeats. This is a non-linear method of quantifying variance in HRV. They found no differences in either measure in adolescents with or without autism. While there was no overall group difference, they categorized their participants based on responsivity to a subsequent task and discovered that a subgroup of autistic participants who did not show activation of parasympathetic system to the subsequent task had significantly reduced CVI at rest as compared to controls. This might indicate that a subgroup of those with autism have reduced parasympathetic activation and they might show different functional abilities.

[Insert Table 15 here]

3.4.3. Skin Conductance Indices

Two types of skin conductance measures were used (See Table 15). 16 studies compared groups on SCL, of which only six found group differences. Of these, five studies (83%) found evidence of hypoarousal while just one study (16%) found evidence of hyperarousal. Six studies used spontaneous fluctuations in skin conductance (NS-SCRs). Of these, three studies found no group differences while three found evidence of either hyperarousal in the form of higher variability in NS-SCRs (n = 2), or hypo-arousal, i.e., lower variability in NS-SCRs (n = 1).

Zahn et al. (1987) measured skin conductance (SCL and NSSCRs) at baseline and found that, compared to neurotypical adults, autistic adults showed slower reduction in SCL over time during the resting state. They interpreted this to mean slower adaptation to the environment in autistic adults during the baseline period. This is similar to a finding of higher variability in NS-SCRs during resting state in neurotypical than autistic participants (Neuhaus et al., 2015) and appears to index less readiness to respond to or adapt to changes in the experimental context. In neurotypical participants, a positive relationship was found between the number and amplitude of EDRs during baseline and social skills, indicating that those with higher social skills had more frequent and increased spontaneous electro-dermal responsivity at baseline, while this relationship was not present in the autistic group. It is possible that the integration of functioning of the ANS and higher-level brain systems that are associated with social skills, does not develop in the same manner in autistic individuals.

Mathersul et al. (2013b) measured SCL while participants spent 2 minutes with their eyes closed and found no significant overall group differences between adults with and without autism. However, they found more variability in the autistic group's SCL compared to the control group. Using cluster analysis, they found subgroups within the autistic sample with high and low SCL. While the high SCL subgroup did not differ statistically on SCL from controls, the low SCL subgroup was statistically significantly different from both controls and the high SCL autistic subgroup, demonstrating hypoarousal. Further, the authors reported differences in social abilities between the two subgroups. While all autistic adults showed low perspective taking skills, only the hypo-aroused subgroup showed poorer emotion recognition, a tendency to judge faces more negatively and reduced affective empathy.

3.4.4. Studies using multiple autonomic indices

Few studies measured autonomic arousal at rest using multiple indices. Bujnakova et al. (2016) reported shorter RR intervals and reduced HF-HRV in the autistic children as compared to neurotypical children but no differences in LF-HRV; suggesting that the autistic participants demonstrated a hyperaroused profile, possibly driven by reduced parasympathetic activation. Importantly, they concurrently measured skin conductance and found reduced skin conductance in autistic than neurotypical participants, suggesting that autistic participants showed reduced sympathetic activity as well.

Similarly, Neuhaus et al. (2014; 2015) measured RSA and NSSCRs at baseline before a reward task, as children with and without autism sat quietly for 5 minutes. They found reduced RSA (suggesting parasympathetic hyperarousal), but also reduced variability in number of NSSCRs over time during the rest period in autistic children, compared to typically developing controls (suggesting sympathetic hypoarousal). These two studies highlight the importance of measuring ANS using multiple indices together. Both studies demonstrated evidence of hyperarousal using cardiac indices (which are impacted by both sympathetic and parasympathetic differences) and hypoarousal using electrodermal indices (which specifically measures SNS). Together, they suggest a profile of dysregulation in autonomic function in autistic individuals wherein possibly flexible adaptation to the context is impaired.

3.4.5. Summary of evidence based on Type of Autonomic Measures Used

In summary, cardiac indices were the most used measures of autonomic arousal among the studies included in this review. Studies using these measures were more likely to identify group differences between those with and without autism than studies using EDA or pupillometry. Importantly, the pattern of findings was impacted by the specific indices used. Cardiac indices more frequently detected autonomic hyperarousal, specifically when using measures such as RSA or HF-HRV. Pupil measures, also detected hyperarousal more often. On the other hand, indices of electrodermal activity were the most likely to find evidence of hypoarousal. Bringing these findings together, it appears that there is evidence for co-occurring underactivation of both the parasympathetic system (from cardiac indices) and sympathetic system (from SCL) which might be why a few studies also found evidence of reduced adaptation of arousal to changes in context. Importantly, some studies found evidence of subgroups with different profiles of autonomic arousal in those with autism such that only a subgroup of autistic participants showed hyper- or hypo- arousal. Thus, it is possible that contradictory findings from cardiac and electrodermal indices reflect subgroups with opposing profiles, although given the findings of Bujnakova et al. (2016), Neuhaus et al. (2014; 2015), it appears possible that these two profiles co-exist among the same individuals.

3.5. Impact of other factors on study findings

Next, we will consider factors such as sample size, differences in age, IQ, exposure to medication, co-occurring conditions in Sections 3.5.1- 3.5.6. Data on IQ, exposure to medication and co-occuring conditions is described for each study in Supplementary materials. In order to analyse these factors, we collapsed across measures and analysed data for each of the 51 studies included in the review that compared groups on an ANS measure.

3.5.1 Sample Size

We considered whether studies with larger sample sizes were more likely to find significant effects, which might suggest that a number of studies have simply been unable to capture true effects due to reduced power. We categorized studies (based on number of clinical participants) as having either small sample sizes (clinical $n < 20$), medium sample sizes (clinical $20 < n < 50$) or large sample sizes (clinical $n > 50$). This did not change the pattern of findings in any way (See Table 16). Studies with large sample sizes were as likely to find null effects as significant effects, similarly to studies with small or medium sample sizes.

[Insert Table 16 here]

3.5.2. Age

Most studies (n = 45/51, 88.2%) controlled for age in some form, either by ensuring age-matched groups, or statistically controlling for age in their analyses. When studies were excluded for not doing so, pattern of results did not change. Studies reported significant group differences slightly more frequently after age was controlled for (n = 28/45, 62.2%) as compared to when it was not controlled for (n = 17/45, 37.8%). There was still a higher likelihood of finding hyperarousal, but findings of hypoarousal and autonomic dysregulation were present as well.

We analysed whether autonomic differences were more likely to emerge in particular age ranges or not. Across different age groups, there were no such patterns. At all age groups, some studies showed group differences with pre-school children (Anderson et al., 2013; Billeci et al., 2018), children and adolescents (Bal et al., 2010; Bricout et al., 2018) and adults (Eilam-Stock et al., 2014; Kuiper et al., 2019) while other studies did not find group differences with pre-school children (McCormick et al.,

2014; Nuske et al., 2014), children and adolescents (Schaaf et al., 2015; Tessier et al., 2018), and adults (Bolte et al., 2008; Dijkhuis et al., 2019). Similarly, the findings of hyperarousal came equally from studies of children and adolescents (Bal et al., 2010; Matsushima et al., 2016) and adults (Mathewson et al., 2011; Top et al., 2018) and findings of hypoarousal were also equally likely from studies of children and adolescents (Bujnakova et al., 2017; Pace and Bricout, 2015) and adults (Eilam-Stock et al., 2014; Mathersul et al., 2013a). It should be noted though that age ranges tend to be quite large, and autonomic function itself undergoes developmental changes fairly quickly particularly during childhood.

One study that aimed to test age effects specifically (Tessier et al., 2018) examined spectral HRV in children (6 to 13 years) and adults (16 to 27 years) before and after sleep at rest. Interestingly, they reported a group effect in adults but not in children such that only autistic adults presented with reduced HF-HRV (and hence reduced parasympathetic activation) as compared to neurotypical adults.

Some studies examined relationships between age and arousal. The findings may be useful because they provide information about typical ANS function at different ages, and can therefore help pinpoint at which points in development, autistic individuals show atypical ANS function. A number of studies reported no significant relationships between age and arousal variables in pre-school aged children (Nuske et al., 2014); in children and adolescents (Chang et al., 2012; Hu et al., 2018); in adolescents and adults (Dijkhuis et al., 2019; Thapa et al., 2019). However, these studies tended to include participants from a limited age range thus potentially reducing the power to find developmental or maturational effects.

Studies that included a broader age range of participants reported evidence of changes in autonomic indices with age. For instance, DiCriscio and Troiani (2017) who included a broad age range of participants from 5 to 16 years of age reported a negative relationship between age and baseline pupil size such that older children had smaller baseline pupil sizes. Similarly, studies found evidence of reducing HR with age in samples of children and adolescents (Daluwatte et al., 2013; Kushki et al., 2014; Porges et al., 2013). Interestingly, this finding did not apply to all measures of cardiac autonomic function. For instance, Porges et al. (2013) did not find an association between age and RSA in children and adolescents. Cai et al. (2019) who included adults over a large age range, did not find any

association between age and various indices of HRV (HF, SDNN and RMSSD). These relationships between age and autonomic function were not reported to vary based on clinical group, it therefore appears that those with autism might show a similar maturation of autonomic function as those without autism, at least from childhood onwards.

Only one study evaluated the effect of age on autonomic function in younger children. Patriquin et al. (2014) measured RSA at multiple time points from 5 to 48 months of age in a group of 106 typically-developing children. Using developmental trajectory modelling, they found evidence of two subgroups in their sample with a 'typical' and an 'atypical' trajectory of RSA development. In the 'typical' group, RSA gradually increased from 5 to 48 months of age. On the other hand, the 'atypical' group showed an increase in RSA from 5 to 24 months and thereafter a plateau in RSA development until 48 months of age. This 'atypical' group also showed difficulties with social responsiveness at 48 months of age. Studies that evaluate trajectory of development of autonomic function such as this might be more able to pick up on subtle differences in autonomic regulation in autism.

Overall, while it appears that during childhood and adolescence those with autism show similar maturation in autonomic function, there is preliminary evidence of atypical maturation of these functions during early childhood, which might affect later development of lower- and higher-level functions.

3.5.3. IQ

We categorized studies included in the review according to how IQ was treated in their study. Of the 51 studies, 22 studies either did not report IQ characteristics at all, or reported an exclusion criterion (such as IQ<70) and then did not report group IQ characteristics subsequently, or reported that their autistic and neurotypical groups were significantly different on IQ but then did not subsequently examine whether this related with differences in ANS measures and did not control for IQ in the analysis. These studies were categorized as 'Not Reliable' with regard to control for any influences of IQ, since any effects of differences in IQ between groups on ANS function cannot be examined within these studies. The remaining 29 studies either reported no group differences on IQ or statistically controlled for IQ in their analyses when groups were different or examined how IQ related with ANS

measures and thus, with regard to IQ, they were categorised as ‘Reliable’ because in these studies, we can identify if findings are influenced by IQ. When studies categorized as ‘Not reliable’ were removed from the analysis, this did not affect frequency of group differences. Of the 29 ‘Reliable’ studies, 17 (58.6%) found group differences on ANS measures while 12 (41.4%) did not; thus within these higher quality studies, proportion of studies that reported significant group differences was similar to the all the studies included in the review. Of the studies that did find group differences, 14 found evidence of hyperarousal, two found evidence of hypoarousal and one study found evidence of some form of autonomic dysregulation.

Only a few studies evaluated effects of IQ. Typically, studies included only participants above a certain level of intellectual ability (IQ>75 or 80). In many studies, participants with and without autism did not differ from each other on IQ. While this controls for variance in IQ and thus provides potentially autism specific effects, autism is a spectrum with a wide range of intellectual ability. By not including those who have co-occurring intellectual disability, any effects that intellectual ability may bring in interaction with autism cannot be discovered.

One cross-sectional study (Porges et al., 2013) which included individuals from 6 to 21 years found a trend towards a relationship between IQ and RSA at baseline such that higher IQ was associated with higher parasympathetic activation, within the autistic group. This study indicates a potentially protective role of IQ in autistic children. Kootz et al. (1982) also divided their sample of autistic participants into two groups, based on whether they were able to learn how to do an active cognitive task. Participants who did not meet criterion on this active cognitive task also were more severely impaired with regard to development and had lower mental age. In this study, HR measured during resting-state in three separate sessions. The higher and lower functioning groups were not different from each other on HR, but the lower functioning group showed a significant decrease in resting HR over the course of the three sessions, which might reflect habituation to the context. Another cross-sectional study (Daluwatte et al., 2013) divided their large sample of children and adolescents into those with high or low IQ. They found that children with autism and higher-IQ showed a profile of hyper-arousal (as measured by heart rate) compared to typically developing children, and they did not differ from the lower-IQ autistic group. The implications of these latter two studies are less clear, given that they are reliant on null

effects between groups of autistic children with higher and lower IQ. These studies do highlight though, the importance of looking at the role IQ might play in autonomic function in autistic individuals.

3.5.4. Presence of co-occurring symptoms

34 of 51 studies did not report on presence or absence of co-occurring conditions in their samples of those with autism. In nine (out of 51) studies, participants with co-occurring conditions were excluded. Typically, this meant that participants with a cardiac or respiratory disease which might affect autonomic response and/or participants with co-morbid mental or psychiatric conditions (undefined) were excluded. Seven out of these nine studies found group differences in autonomic function. In five (out of 51) studies, participants' co-occurring symptoms were reported but there was not enough power to control for this factor in analysis. Typically, these studies reported that some of their participants had co-occurring ADHD, anxiety disorders or externalizing disorders. Only three (out of 51) studies both reported and investigated the influence of co-occurring conditions on autonomic function.

Hollocks et al. (2014) divided their autistic sample into two, those with and without clinically significant symptoms of anxiety disorder. They reported that the autistic group without anxiety demonstrated significantly higher heart rate at baseline (before the start of a psychosocial stress task) as compared to the autistic group with anxiety and controls; and the difference between the autistic group with anxiety and controls reached only borderline significance. Thapa et al. (2019) found effects of comorbidities on LF-HRV but the direction of this effect was not specified. Bujnakova et al. (2017) divided their sample of autistic participants into those that had comorbidities (ADHD, anxiety disorders, disruptive disorders) and were treated with medication (different participants were on different medications for ADHD, depression, epilepsy, bipolar disorder etc.) and those who did not have any comorbidities and did not take any medications. The results are reported below in Section 3.5.5 since the study focused on effect of medication. Overall, within these three studies, different types of co-occurring symptoms were investigated and therefore, it is difficult to draw any conclusions on how these might impact autonomic function in autism.

Nine studies tested linear relationships between co-occurring symptoms and heart rate variability. Of these, five investigated the relationship between HRV and anxiety based on the suggestion that

hyperarousal in autism is linked to presence of anxiety in autistic individuals (Cuve et al., 2018). One study reported that higher heart rate was associated with higher symptoms of anxiety (Keith et al., 2019a); importantly, this relationship was significant only when adolescents self-reported their symptoms of anxiety, but not with parental report. This is important to consider in a population where autistic individuals' emotional experiences can sometimes be hard for parents to observe.

On the other hand, four studies did not find any links between symptoms of anxiety and HRV (Cai et al., 2019; Edmiston et al., 2016; Klusek et al., 2013; Mathewson et al., 2011). Edmiston et al. (2016) reported that reduced RSA was associated with higher symptoms of depression in their autistic group; and similarly, Neuhaus et al. (2014) found a relationship between higher baseline RSA and lower internalizing symptoms.

Only two studies included in this review examined the relationship between sensory processing and arousal. Matsushima et al. (2016) reported that reduced vagal activity, which differentiated children with and without autism, was associated with higher visual and auditory hyperreactivity (as measured by a brief parent-report scale) within those with autism. On the other hand, Daluwatte et al. (2015) reported that resting pupil diameter was not associated with sensory processing scores in autistic and neurotypical participants.

Overall, results were quite variable with regard to whether co-occurring symptoms are associated with autonomic function or not. Most studies used different measures of co-occurring symptoms in relation to different measures of autonomic function. There is preliminary evidence to suggest that autonomic arousal might be linked with internalizing symptoms in autistic individuals. However, this evidence is not yet robust.

3.5.5. Exposure to Medication

Individuals with autism often take medications to manage symptoms of co-occurring conditions, such as medications for depression and anxiety, ADHD, tics, sleep disturbances, challenging behaviours and epilepsy. Exposure to such medications might impact autonomic function. For instance, standard medications for ADHD (such as methylphenidate) often have side-effects on autonomic function, such as increase in heart rate and blood pressure (Bellato et al., 2020). In contrast, noradrenergic agnostic

medications (including guanfacine and clonidine) to treat ADHD and/or tics can produce bradycardia and hypotension. Given the high co-occurrence of ADHD in autism, it is important to understand whether presence of any effects to do with such medications are controlled for in the literature.

Many studies in this review did not report (n = 16/51) possible exposure to medication. Some studies excluded participants if exposed to medication (13/51) or asked them to withdraw medication during the study (7/51). These latter studies were more likely than not to report group differences (14 such studies found group differences while six did not). There was heterogeneity in their findings such that findings of hyperarousal were more likely, but evidence of hypoarousal or autonomic dysregulation or differences in adaptation were also found. Thus, control of exposure to medication did not impact the heterogeneity of the results but did appear to make it more likely to find group differences.

Eight of 51 studies reported medication use in their sample but did not have enough power to investigate whether this influenced their findings. Only seven studies examined impact of exposure to medication on autonomic function findings. Of these, one study (Dijkhuis et al, 2019) reported that baseline HR and HRV were not associated with medication use; one study reported that controlling for medication use did not influence group differences on autonomic measures (Saghir et al, 2017); and one study controlled for medication use by using this as a factorial covariate in their models but did not report whether it influenced results (Van Hecke et al, 2009).

Bujnakova et al. (2017) reported that exposure to medication (ADHD medications, antidepressants and epilepsy medications) had an ameliorating effect on SCL in autistic participants, such that only the non-treated group of autistic participants showed hypoarousal, while the treated group showed similar arousal to neurotypical participants. Notably, the majority of the participants in this study in the treated group had comorbid ADHD, which is a population known to have a hypoarousal profile (Bellato et al., 2020), which might have driven these effects.

In contrast, three studies (using measures of HR or HRV) reported that autistic individuals who were exposed to medications demonstrated profiles of hyperarousal, and those who were untreated showed arousal levels similar to neurotypical participants (Cai et al., 2019; Daluwatte et al., 2013; Mathewson et al., 2011). Daluwatte et al. (2013) also found similar effects in a comparison group with other neurodevelopmental conditions, such that exposure to medication was linked with hyperarousal. While

this might suggest that findings of hyperarousal might be driven by exposure to medications, it is important to point out that medication use is often associated with higher symptom severity of autism. For instance, Cai et al. (2019) found that use of medication was linked with lower HRV and more severe autistic symptoms. However, use of medication did not predict significant variance in HRV after autism symptom severity and emotion regulation strategies were accounted for. Finally, Thapa et al. (2019) found that medication as a factor only appeared to be linked with LF-HRV, but not with HR, HF-HRV or other measures. They found reduced LF-HRV in the medicated autism group (majority of the sample was using antidepressants or antipsychotics, but overall, their autistic sample had reduced HF-HRV. This would imply that while the autistic sample in their study overall demonstrated a profile of reduced parasympathetic activity (and hence hyperarousal) as compared to neurotypical participants, within the autistic group, participants who were medicated showed a profile also of reduced sympathetic arousal as compared to autistic participants who were not medicated. Thapa et al. (2019) did not compare their medicated and unmedicated autistic participants separately with neurotypical participants. Given that these findings of medication are on a different measure (LF-HRV) than the overall group differences (HF-HRV), it is difficult to interpret them. However, in this sample, when they re-categorized people based on presence of comorbidities, a factor that highly overlapped with exposure to medication, LF-HRV was implicated in this result as well (although the direction of the effect was not clearly described). It is thus difficult to tease apart whether exposure to medication impacts profiles of arousal or whether this might reflect presence of other co-occurring conditions, particularly since medication use and comorbidities are related to one another. Thus, exposure to medication may in itself, be an indicator of a subgroup of individuals with autism who present with more severe social-emotional challenges, which might be accompanied by differences in autonomic function.

3.5.6. Summary of other factors

Overall, we did not find any evidence that sample size or age were associated with the pattern of group differences across studies. While there was evidence of maturation of autonomic arousal indices with age, this did not appear to be different for the autistic groups from childhood onwards. There is preliminary evidence for different trajectories of autonomic arousal maturation in toddlerhood which

may have cascading effects on autonomic function later. Similarly, there is unclear evidence for any variance in autonomic function as influenced by intellectual ability, mainly due to the lack of studies explicitly investigating this. It is also hard to draw any conclusions with regard to whether co-occurring symptoms or exposure to medications influences autonomic arousal in autistic individuals. This is primarily due to under-reporting and lack of control of these factors in the literature. However, there is some evidence to suggest that there might be autonomic arousal differences in autistic individuals related to the presence of co-occurring symptoms of other conditions (such as ADHD, anxiety or internalizing symptoms) wherein autonomic function is known to also be affected. Further, exposure to medications for such conditions does seem to impact autonomic arousal profiles in autistic individuals, and this is important to control for in future studies.

3.6. Symptom associations

17 studies investigated associations between measures of autonomic function at rest and measures of either symptoms of autism or other behavioural measures relevant to autism.

3.6.1 Autonomic function and Autism symptom severity

There is some evidence that reduced parasympathetic activation (and thus, hyperarousal) is associated with higher autism symptom severity, although this is not robust. Eight studies examined the relationship between HF-HRV or RSA and autism symptom severity (measured using either parent-report scales such as the Social Responsiveness Scale (SRS) or Autism Spectrum Quotient (AQ) or through direct-observation based assessments such as the Autism Diagnostic Observation Schedule (ADOS)). Of these, six studies found significant negative associations between measures of heart rate variability and autism symptom severity; across autistic and neurotypical participants (Cai et al., 2019; Van Hecke et al., 2009); only in the autistic sample (Edmiston et al., 2016; Hu et al., 2018; Matsushima et al., 2016); or only in the neurotypical sample (Klusek et al., 2013). These studies suggest that higher symptom severity of autism is associated with reduced parasympathetic activation, and thus, profiles of hyperarousal. Further, Edmiston et al. (2016) found relationships between higher RSA and reduced symptom severity as measured by SRS, but not with the Social Communication Questionnaire (SCQ).

Interestingly, two studies evaluated relationships between autonomic indices and specific items on measures of autism that tap into specific symptoms. Matsushima et al. (2016) found a relationship between reduced power in HF-HRV and higher symptoms of RRBs, but not overall symptoms of autism, as measured by the SRS. Similarly, Billeci et al. (2018) reported an association between increased heart rate variability with poor initiation of join attention (a specific item on the ADOS).

Two studies using the same sample did not find significant associations between cardiac function and autism symptom severity using SRS (Patriquin et al., 2013a; 2013b) in young children 4 to 7 years old. These were the only studies that measured dimensional relationships in such young children, all the other studies measured these in children 6 years of age and above.

Two studies measured the association between baseline pupil size and traits or symptoms of autism. Anderson et al. (2013) found that higher tonic pupil sizes were correlated with higher scores on the ADOS in two separate samples of participants. In contrast, DiCriscio and Troiani (2017) did not find a significant relationship between baseline pupil size traits of autism as measured by the SRS. No studies looked at dimensional relationships between skin conductance measures and autism symptomatology.

Overall, there was variance both in measures used for autism symptom severity and the measure of parasympathetic function, which might be the reason for the variation in findings. The same measures of symptom severity sometimes were related to autonomic function and at other times not, suggesting that possibly, these measures are not sensitive enough to the specific aspects of function that autonomic function impacts. It might be that differences in autonomic function are associated with differences in specific skills within autistic symptoms such as social interaction or restricted, repetitive behaviours. Further, many symptom measures (other than ADOS) were questionnaire based (self or parent report) which may be less reliable than assessing symptoms directly using behavioural tasks.

3.6.2. Autonomic function and social-emotional skills

Six studies measured associations between autonomic arousal and various social skills.

Of these, two examined associations between arousal and language and communication skills and reported consistent results such that higher cardiac arousal was associated with worse language and communication skills (Klusek et al., 2013; Patriquin et al., 2013a). Klusek et al. (2013) tested whether

IBI and RSA could serve as predictors of pragmatic language skills, but their regression models proved non-significant once receptive/expressive vocabulary were accounted for.

Five studies reported consistent findings that reduced RSA was linked to worse social-emotional skills (Bal et al., 2010; Cai et al., 2019; Neuhaus et al., 2014; Patriquin et al., 2013b; Van Hecke et al., 2009). This is in line with Porges' polyvagal theory which links vagal activity with development of socialization skills. Interestingly, Van Hecke et al. (2009) only found these relationships to be true across neurotypical and autistic groups; within each group, these relationships became non-significant possibly due to reduced variance. Bal et al. (2010) reported that children with higher amplitude RSA at baseline recognized emotions faster. Cai et al. (2019) examined emotion regulation strategies in adults with and without autism and found that those with higher resting HRV demonstrated use of better emotion regulation strategies across samples of autistic and neurotypical participants. Together these studies suggest that higher parasympathetic activation is linked with better social-emotional skills across autistic and neurotypical individuals.

Finally, two studies (Neuhaus et al., 2014; 2015) measured RSA and NSSCRs at baseline before a reward task in children with and without autism as they sat quietly for 5 minutes. They found reduced RSA (suggesting hyperarousal) in autistic than neurotypical individuals and higher variability in number of NSSCRs (suggesting hypoarousal) in the baseline period over time in neurotypical than in autistic participants. Thus, their sample of autistic participants demonstrated hyperarousal on one measure and hypoarousal on the other, suggesting profiles of both parasympathetic and sympathetic underactivation. The authors reported that higher frequency and amplitude of NSSCRs (and therefore, more variability in SNS function) was associated with better social skills (as measured by the Social Skills Improvement System, tapping into higher level skills such as cooperation, empathy, self-control) in the neurotypical group; and with more problem behaviours (measured by the same scale, comprising of internalizing, externalizing and hyperactivity behaviours) in the autistic group (Neuhaus et al., 2015). This was not interpreted by the authors since this was not the focus of the article but suggests that autonomic function is not integrated with higher order functions in the same way in autistic and neurotypical participants. Further, higher baseline RSA was associated with better social functioning (measured by Social Skills Improvement System and VABS), fewer social problems (measured by

CBCL), and with internalizing subscales of CBCL (but not the externalizing subscales). The authors then used a regression model to examine whether social skills, internalizing and externalizing symptoms predicted variance in RSA and found independent and significant effects of all 3 in predicting variance in RSA; notably, higher externalizing symptoms were associated with higher RSA. Therefore, while higher RSA was associated with better social skills and lower internalizing symptoms, it was associated in this study with higher externalizing symptoms. The findings from skin conductance and RSA were reported in separate articles and thus, the authors did not integrate the findings from the two measures together.

Overall, again, heterogeneity in the measured constructs, the choice of scale or instrument, and the autonomic measure used, makes it difficult to draw out any consistent patterns. Despite this, there is some evidence that reduced parasympathetic function might be related to worse social-emotional skills. Further, there is preliminary evidence that parasympathetic and sympathetic activity are differentially associated with internalizing and externalizing behaviours, within autistic and neurotypical participants.

4. Discussion

This review aimed to systematically evaluate the evidence for differences in profiles of arousal during resting-state in autism. Of the 51 studies that investigated group differences between those with and without autism, 61% of the studies found evidence of group differences. However, when counting each group comparison from each study (yielding 130 comparisons), findings of null effects were more prevalent with 61% of the group comparisons yielding null effects. Further, within significant findings, while evidence of hyperarousal was more common, findings of hypoarousal were also consistently present in a small proportion of studies. Thus, overarching theories that suggest either hyper- or hypo-arousal as a dominant state in autistic individuals (DesLauriers and Carlson, 1969; Hutt et al., 1964) are not consistently supported by evidence in this review. Rather, the profile seems more mixed than this and may vary between settings and individuals. This is in line with findings from other reviews of ANS in autism, which have also typically tended to conclude that evidence for autonomic dysfunction in autism is at best variable and inconsistent, with between-group findings of hyperarousal, hypoarousal or null effects (Cuve et al., 2018; Lydon et al., 2016). We also highlighted methodological

inconsistencies, such as use of different measures, poor control of extraneous factors such as co-occurring symptoms, IQ and exposure to medications impacting ANS functions, use of small sample sizes and hence reduced power to find true effects; all of which might have contributed to some of the heterogeneity in the findings.

An important finding of our review is that the experimental setting might have influenced findings. Reports of group differences in arousal were in fact more common in studies where resting-state was measured without any stimulation given to participants, as compared to studies where participants were asked to passively attend to some sort of stimulation. Not providing specific stimulation is likely to facilitate focus on internal states as compared to passive attention measurements where attention is focused on something external such as a silent movie or a fixation cross. Possibly, not being given a specific task to do is more demanding for autistic individuals, since it lacks the structure of a specific task or activity (Brodzeller et al., 2017). Importantly, it is possible that asking autistic participants to sit quietly and still or lie down with their eyes closed (or without the expectation of a task) influences their autonomic state (or they adapt to this differently) as compared to when participants' attention is directed to something fixed and external. This finding indicates that tasks that require inward-directed attention, or a lack of external focus, might be particularly important in identifying sources of difference in autism. In line with this, there is some evidence for differences in functional and structural organization of the Default Mode Network in autistic individuals (Padmanabhan et al., 2017) which is an interconnected network of brain structures involved in self-referential processing, and which becomes more active during states of inward-directed attention (Buckner et al., 2008). Methodologically, it is also important to note here that pure resting-state studies more often reported that participants were given some time to adapt to the laboratory context before autonomic measurement began. This might have influenced the findings as autistic participants are known to struggle with new environments (Lau et al., 2019). Similarly, studies that reportedly focused on solely resting-state measurement, as compared to those in which the resting-state measurement was followed by a task (cognitive or physical), were more likely to report group differences. If a task immediately follows a resting state measurement, this is likely to induce preparatory states in participants, or anxiety, which would vary depending upon the nature of the task that follows, thus introducing noise which might vary systematically between groups.

Interestingly, with regard to the direction of significant findings, studies where participants were asked to passively attend to something external were more likely to report findings of hyperarousal (when they found group differences) than studies where participants were asked not to do anything and simply relax. Possibly, autistic participants might find it harder to down-regulate arousal in the presence of stimulation, which supports evidence of hyper-responsivity to sensory stimulation in autism (Green et al., 2015).

Across the studies that found significant differences between groups, findings of hyperarousal in the autistic group were the most frequent, particularly from indices of cardiac function and pupillometry. Using indices of RSA (which measures vagal tone) and spectral measures of HRV, there is some evidence in support of theories of reduced parasympathetic activation in autistic individuals. Some studies also reported associations between reduced parasympathetic function and worse autism symptom severity (although this varied depending upon the arousal measure and the autism symptom severity scale used). However, given the high number of null findings using cardiac measures, it appears unlikely that resting-state cardiac indices of autonomic arousal could serve as an autism-specific index for diagnostic or treatment monitoring purposes. Indeed, it should be noted that reduced parasympathetic activation appears to be a trans-diagnostic factor that relates with socialization and communication skills in individuals in many other conditions such as anxiety disorders, and externalizing disorders such as oppositional-defiant disorder, both of which are noted as co-occurring with autism (Simonoff et al., 2008). In line with this, we found some evidence for reduced parasympathetic activation being associated with worse social-emotional skills, internalizing and externalizing symptoms (Neuhaus et al., 2014). These findings support suggestions of reduced vagal tone playing a role in atypicalities in socialization and emotional regulation (Porges, 2003; Thayer and Lane, 2000). Therefore, it appears that profiles of reduced parasympathetic function in autism might index a trans-diagnostic risk that relates with severity of impairment in specific domains of socialization and emotional regulation (and possibly, also index co-occuring symptoms of other conditions such as internalizing and externalizing disorders), rather than relating with autistic symptoms as a whole.

As compared to cardiac indices, studies using electrodermal activity provided more evidence for presence of hypoarousal in autistic individuals. EDA is under the control of the sympathetic branch of

the ANS (Wass et al., 2015). It is difficult to interpret such contradictory findings of hyperarousal (driven by parasympathetic system) and hypoarousal (driven by the sympathetic system), particularly since most studies used only one of the two measures. Studies in our review which used multiple indices together were more informative and provided evidence of co-existence of hyper- and hypoarousal within the same individuals (Bujnakova et al., 2016; Neuhaus et al., 2014; 2015). This provides evidence of overall autonomic dysregulation or generally reduced responsivity of the ANS to the environment in autism. Indeed, a few studies provided specific evidence for reduced adaptation to the context in autistic groups (Mathewson et al., 2011; Neuhaus et al., 2015; Zahn et al., 1987) which is in line with findings of reduced responsivity to socially stressful contexts in autism (Edmiston et al., 2016). Only one study in our review combined measurement of ANS function with measurement of CNS function. Eilam-Stock et al. (2014) reported hypoarousal using EDA in the autistic group and NSSCRs in the autistic participants were less strongly correlated to activation in frontal brain regions (as measured by fMRI) that are involved in regulating peripheral autonomic function. Importantly, they also reported that in those with autism, reduced NSSCRs were correlated with more activation in sensory regions, suggesting that possibly during the task, their attention was more outwardly directed than internally directed during the measurement. It might therefore be that people with autism struggled to 'switch off' (inside a loud scanner), so that those without autism were more able to enter a 'resting mode' in this potentially stressful context. These studies highlight the importance of both experimental context but also of using multiple indices of ANS and CNS in order to understand where differences specific to autism lie.

Very few studies using pupillometry met our inclusion criteria for this review. While only half the studies using pupillometry found group differences, all the ones that found group differences found evidence of hyperarousal. Pupil dilation/constriction reflects a balance between sympathetic and parasympathetic influences and is mediated by the brainstem regions of LC-NE. It is possible that findings of hyperarousal using pupillometry are indicative of atypicalities in brainstem function or top-down regulation of brainstem which influences both parasympathetic activation and pupil constriction/dilation (Bast et al., 2018). This is partly corroborated by the studies (Ming et al., 2005; 2016) who found reduced vagal tone using a measure which is correlated with brainstem function. It is

interesting to note that studies using pupillometry also found linear associations between tonic arousal (as indexed by pupil diameter) and autism symptom severity (Anderson et al., 2013). Other pupillometry parameters have been reported to have high specificity for autism, such as the pupillary light reflex (PLR) (Daluwatte et al., 2015; Dinalankara et al., 2017; Wagner et al., 2016), which has been found to be predictively associated with a later diagnosis of autism in 10 month old infants at elevated risk of autism (Nystrom et al., 2018). PLR indexes an automatic process of sensory responsivity, which is a core symptom of autism (American Psychiatric Association, 2013). Further research is needed using pupillometry to index states of rest and responsivity to stimuli in autistic individuals.

Finally, a suggestion has been made that resting-state physiology might not be homogeneous in autism and that there might be subgroups of autonomic responders linked with resting state physiology of hyper- or hypo-arousal (Hirstein et al., 2001; Schoen et al., 2008). Our review found some support for this suggestion (Bujnakova et al., 2017; Mathersul et al., 2013b; Toichi and Kamio, 2003; van Engeland, 1984). These studies divided their group of participants based on autonomic response on a subsequent task (for example higher or lower responsivity to sensory stimuli) and found that when divided in this way, a subgroup of hypo- or hyperaroused participants emerged. It is possible that a number of null findings are due to averaging over different profiles of arousal between subjects in a group and it would be important to consider sub-groups in the future. However, it is important to note that these subgroups emerged when their responsivity to sensory stimulation was investigated. Therefore, just a measurement of resting state, without evaluating adaptation to different contexts, may be less effective in finding subgroups if they exist. Importantly, in future studies, it will be important to investigate whether these subgroups relate with differential profiles of co-occurring symptoms of ADHD, anxiety etc.

We also considered whether factors such as age, exposure to medication, length of autonomic measurement, co-occurring symptoms and intellectual ability influenced findings. Studies that analysed autonomic function from at least 3 minutes of data or more tended to more frequently report significant differences between groups. Studies that used shorter measurements might not be able to reliably establish autonomic function profiles, although this likely depends on the measure used. Exposure to medication and co-occurring symptoms of other conditions appear to be important confounding factors.

However, it is difficult to tease apart how these interact with autonomic function in autism since medication is linked both with higher symptom severity and particularly with presence of co-occurring difficulties. There was some evidence that IQ might be somehow associated with measures of autonomic arousal. For example, one study reported that higher IQ was associated with higher parasympathetic activation, suggesting the possibility that IQ acts as a protective factor and facilitates responsivity to the environment in those with autism (Porges et al., 2013). Future studies should explore how presence of co-occurring conditions and individual differences in IQ are related with autonomic function in autism. We were unable to look at any differences in ANS profiles based on gender since most studies included either only male participants or predominantly male participants.

We did not find any evidence for atypical maturation of ANS indices from childhood onwards in autism. However, there is preliminary evidence for atypical maturation of ANS indices from infancy to early childhood, specifically as measured by RSA (Patriquin et al., 2014) in those with autism. This is corroborated by a recent study by Sheinkopf et al. (2019) who reported reduced maturation of RSA and hence atypical development of vagal tone in early childhood in those with autism as compared to those without autism. Notably, in this study, there were no group differences between those with and those without autism at any time point from 1 to 6 years. However, the trajectory of change in RSA was atypical in those with autism. Possibly, early differences in development of ANS in interaction with the environment might lead to later differences in autonomic arousal and responsivity to the environment. This requires further investigation.

In summary, evidence included in this review did not consistently support theories of hyper- or hypo-arousal as a dominant state during rest in autistic individuals. Experimental context of measurement and index of autonomic arousal used impacted the nature of findings. There was some evidence for profiles of both parasympathetic and sympathetic underactivation, as well as possibly, presence of subgroups of autistic individuals with different autonomic profiles. There was an indication that autistic individuals might show differences in autonomic responsivity and adaptation to changing environmental contexts.

Recommendations for future research:

- It appears that experimental context plays an important role: those with autism might struggle to effectively regulate arousal to adapt to different contexts. More research is needed to understand whether differences in responsivity to different contexts are present in all individuals with autism or in a subgroup, and whether this is related to difficulties in maintaining an optimal state of physiological arousal. Importantly, systematic manipulation of the measurement context, manipulating inward and outward direction of attention is crucial in understanding where differences emerge.
- Future studies in the area should use multiple indices of ANS and CNS simultaneously in order to identify at which level the differences lie and what they are due to. Measurement of resting-state arousal can still be informative towards understanding mechanisms in the development of autism.
- Further investigation is also required in in infancy and toddlerhood, particularly longitudinal research. This might help us evaluate whether there are early differences in maturation of ANS indices which have cascading effects on development of socialization skills later.
- We found some evidence that social symptom severity in autism is related to increased pupil size and reduced parasympathetic activation. These findings merit further investigation, specifically with regard to vagal tone, brainstem function and the activity and integrity of the LC-NE in autism.
- An emerging area of research that is promising is the role of remote measurement technologies, such as sensing wearables and smartphones that would move measurement out of the lab into the real-world and into real-time contexts. These technologies can help evaluate the impact of environmental stimuli such as noise, crowds, different types of natural social interactions, that appear core to the autism symptomology. Evaluating the role and impact of arousal on attention and information processing in such real-world contexts is of further utility since atypical arousal regulation may impair attentional processing in a context-dependent manner, which is difficult to capture in controlled lab settings.

Acknowledgements

This work was supported by a Doctoral Studentship awarded by the Baily Thomas Charitable Fund (to Iti Arora), the National Institute for Health Research Nottingham Biomedical Research Centre Mental Health & Technology Theme [grant number BRC-1215-20003] and the University of Nottingham.

1

References

American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. https://doi.org/10.1176/appi.books.9780890425596.

Anderson, C.J., Colombo, J., Unruh, K.E., 2013. Pupil and salivary indicators of autonomic dysfunction in autism spectrum disorder. Developmental Psychobiology 55, 465-482. https://doi.org/10.1002/dev.21051

Aston-Jones, G., Cohen, J.D., 2005. AN INTEGRATIVE THEORY OF LOCUS COERULEUS-NOREPINEPHRINE FUNCTION: Adaptive Gain and Optimal Performance. Annual Review of Neuroscience 28, 403-450. https://doi.org/10.1146/annurev.neuro.28.061604.135709

Bal, E., Harden, E., Lamb, D., Hecke, A.V., Denver, J.W., Porges, S.W., 2010. Emotion recognition in children with autism spectrum disorders: relations to eye gaze and autonomic state. J Autism Dev Disord 40. https://doi.org/10.1007/s10803-009-0884-3

Bast, N., Poustka, L., Freitag, C.M., 2018. The locus coeruleus-norepinephrine system as pacemaker of attention - a developmental mechanism of derailed attentional function in autism spectrum disorder. European Journal of Neuroscience 47, 115-125. https://doi.org/10.1111/ejn.13795

Bazelmans, T., Jones, E.J.H., Ghods, S., Corrigan, S., Toth, K., Charman, T., Webb, S.J., 2019. Heart rate mean and variability as a biomarker for phenotypic variation in preschoolers with autism spectrum disorder. Autism Research 12, 39-52. https://doi.org/10.1002/aur.1982

Bellato, A., Arora, I., Hollis, C., Groom, M.J., 2020. Is autonomic nervous system function atypical in attention deficit hyperactivity disorder (ADHD)? A systematic review of the evidence. Neurosci Biobehav Rev 108, 182-206. https://doi.org/10.1016/j.neubiorev.2019.11.001

Benevides, T.W., Lane, S.J., 2015. A review of cardiac autonomic measures: considerations for examination of physiological response in children with autism spectrum disorder. Journal of autism and developmental disorders 45, 560-575. https://doi.org/10.1007/s10803-013-1971-z

Berman, J.I., Liu, S., Bloy, L., Blaskey, L., Roberts, T.P.L., Edgar, J.C., 2015. Alpha-to-Gamma Phase-Amplitude Coupling Methods and Application to Autism Spectrum Disorder. Brain Connectivity 5, 80-90. https://doi.org/10.1089/brain.2014.0242

Berntson, G.G., Cacioppo, J.T., Quigley, K.S., 1991. Autonomic determinism: The modes of autonomic control, the doctrine of autonomic space, and the laws of autonomic constraint. Psychological Review 98, 459-487. https://doi.org/10.1037/0033-295X.98.4.459

Billeci, L., Tonacci, A., Narzisi, A., Manigrasso, Z., Varanini, M., Fulceri, F., Lattarulo, C., Calderoni, S., Muratori, F., 2018. Heart rate variability during a joint attention task in toddlers with autism spectrum disorders. Frontiers in Physiology 9, 467. https://doi.org/10.3389/fphys.2018.00467

Bishop-Fitzpatrick, L., Minshew, N.J., Mazefsky, C.A., Eack, S.M., 2017. Perception of life as stressful, not biological response to stress, is associated with greater social disability in adults with autism spectrum disorder. Journal of autism and developmental disorders 47, 1-16. https://doi.org/10.1007/s10803-016-2910-6

Bizzell, E., Ross, J., Rosenthal, C., Dumont, R., Schaaf, R., 2019. Sensory Features as a Marker of Autism Spectrum Disorders. Journal of Autism and Developmental Disorders. https://doi.org/10.1007/s10803-019-03948-8

Bolte, S., Feineis-Matthews, S., Poustka, F., 2008. Brief report: Emotional processing in high-functioning autism - Physiological reactivity and affective report. Journal of Autism and Developmental Disorders 38, 776-781. https://doi.org/10.1007/s10803-007-0443-8

Bricout, V.A., Pace, M., Dumortier, L., Favre-Juvin, A., Guinot, M., 2018. Autonomic Responses to Head-Up Tilt Test in Children with Autism Spectrum Disorders. Journal of abnormal child psychology 46, 1121-1128. https://doi.org/10.1007/s10802-017-0339-9

Brodzeller, K.L., Ottley, J.R., Jung, J., Coogle, C.G., 2017. Interventions and Adaptations for Children with Autism Spectrum Disorder in Inclusive Early Childhood Settings. Early Childhood Education Journal 46, 277-286. https://doi.org/10.1007/s10643-017-0859-5

Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network: anatomy, function, and relevance to disease. Ann N Y Acad Sci 1124, 1-38. https://doi.org/10.1196/annals.1440.011

Bujnakova, I., Ondrejka, I., Mestanik, M., Fleskova, D., Sekaninova, N., Farsky, I., Tonhajzerova, I., 2017. Potential effect of pharmacotherapy on sympathetic arousal in autism. Acta Medica Martiniana 17, 16-23. https://doi.org/10.1515/acm-2017-0013

Bujnakova, I., Ondrejka, I., Mestanik, M., Visnovcova, Z., Mestanikova, A., Hrtanek, I., Fleskova, D., Calkovska, A., Tonhajzerova, I., 2016. Autism spectrum disorder is associated with autonomic underarousal. Physiological research 65, S673-S682. https://doi.org/10.33549/physiolres.933528

Cai, R.Y., Richdale, A.L., Dissanayake, C., Uljarevic, M., 2019. Resting heart rate variability, emotion regulation, psychological wellbeing and autism symptomatology in adults with and without autism. International Journal of Psychophysiology 137, 54-62. https://doi.org/10.1016/j.ijpsycho.2018.12.010

Chang, M.C., Parham, L.D., Blanche, E.I., Schell, A., Chou, C.P., Dawson, M., Clark, F., 2012. Autonomic and behavioral responses of children with autism to auditory stimuli. American Journal of Occupational Therapy 66, 567-576. https://doi.org/10.5014/ajot.2012.004242

Charman, T., Taylor, E., Drew, A., Cockerill, H., Brown, J.A., Baird, G., 2005. Outcome at 7 years of children diagnosed with autism at age 2: Predictive validity of assessments conducted at 2 and 3 years of age and pattern of symptom change over time. Journal of Child Psychology and Psychiatry 46, 500-513. https://doi.org/10.1111/j.1469-7610.2004.00377.x

Corbett, B.A., Muscatello, R.A., Baldinger, C., 2019. Comparing stress and arousal systems in response to different social contexts in children with ASD. Biological Psychology 140, 119-130. https://doi.org/10.1016/j.biopsycho.2018.12.010

Critchley, H.D., Garfinkel, S.N., 2018. The influence of physiological signals on cognition. Current Opinion in Behavioral Sciences 19, 13-18. https://doi.org/10.1016/j.cobeha.2017.08.014

Cuve, H.C., Gao, Y., Fuse, A., 2018. Is it avoidance or hypoarousal? A systematic review of emotion recognition, eye-tracking, and psychophysiological studies in young adults with autism spectrum conditions. Research in Autism Spectrum Disorders 55, 1-13. https://doi.org/10.1016/j.rasd.2018.07.002

Daluwatte, C., Miles, J.H., Christ, S.E., 2013. Atypical pupillary light reflex and heart rate variability in children with autism spectrum disorder. J Autism Dev Disord 43. https://doi.org/10.1007/s10803-012-1741-3

Daluwatte, C., Miles, J.H., Sun, J., Yao, G., 2015. Association between pupillary light reflex and sensory behaviors in children with autism spectrum disorders. Research in Developmental Disabilities 37, 209-215. https://doi.org/10.1016/j.ridd.2014.11.019

DesLauriers, A.M., Carlson, C.F., 1969. Your child is asleep: Early infantile autism: Etiology, treatment, and parental influences.

DiCriscio, A.S., Troiani, V., 2017. Pupil adaptation corresponds to quantitative measures of autism traits in children. Scientific reports 7, 6476. https://doi.org/10.1038/s41598-017-06829-1

Dijkhuis, R.R., Ziermans, T., van Rijn, S., Staal, W., Swaab, H., 2019. Emotional Arousal During Social Stress in Young Adults With Autism: Insights From Heart Rate, Heart Rate Variability and Self-Report. Journal of Autism and Developmental Disorders. https://doi.org/10.1007/s10803-019-04000-5

Dinalankara, D.M.R., Miles, J.H., Nicole Takahashi, T., Yao, G., 2017. Atypical pupillary light reflex in 2-6-year-old children with autism spectrum disorders. Autism Research 10, 829-838. https://doi.org/10.1002/aur.1745

Edmiston, E.K., Jones, R.M., Corbett, B.A., 2016. Physiological Response to Social Evaluative Threat in Adolescents with Autism Spectrum Disorder. Journal of Autism and Developmental Disorders 46, 2992-3005. https://doi.org/10.1007/s10803-016-2842-1

Eilam-Stock, T., Xu, P., Cao, M., Gu, X., Dam, N.T., Anagnostou, E., 2014. Abnormal autonomic and associated brain activities during rest in autism spectrum disorder. Brain 137. https://doi.org/10.1093/brain/awt294

Faja, S., Murias, M., Beauchaine, T.P., Dawson, G., 2013. Reward-based decision making and electrodermal responding by young children with autism spectrum disorders during a gambling task. Autism Research 6, 494-505. https://doi.org/10.1002/aur.1307

Friedman, B.H., 2007. An autonomic flexibility-neurovisceral integration model of anxiety and cardiac vagal tone. Biol Psychol 74, 185-199. https://doi.org/10.1016/j.biopsycho.2005.08.009

Gilzenrat, M.S., Nieuwenhuis, S., Jepma, M., Cohen, J.D., 2010. Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. Cognitive, Affective and Behavioral Neuroscience 10, 252-269. https://doi.org/10.3758/CABN.10.2.252

Green, S.A., Hernandez, L., Tottenham, N., Krasileva, K., Bookheimer, S.Y., Dapretto, M., 2015. Neurobiology of Sensory Overresponsivity in Youth With Autism Spectrum Disorders. JAMA Psychiatry 72, 778-786. https://doi:10.1001/jamapsychiatry.2015.0737

Gu, X., Eilam-Stock, T., Zhou, T., Anagnostou, E., Kolevzon, A., Soorya, L., Hof, P.R., Friston, K.J., Fan, J., 2015. Autonomic and brain responses associated with empathy deficits in autism spectrum disorder. Human Brain Mapping 36, 3323-3338. https://doi.org/10.1002/hbm.22840

Hirstein, W., Iversen, P., Ramachandran, V.S., 2001. Autonomic responses of autistic children to people and objects. Proceedings of the Royal Society B: Biological Sciences 268, 1883-1888. https://doi.org/10.1098/rspb.2001.1724

Hollocks, M.H., Howlin, P., Papadopoulos, A.S., Khondoker, M., Simonoff, E., 2014. Differences in HPA-axis and heart rate responsiveness to psychosocial stress in children with autism spectrum disorders with and without co-morbid anxiety. Psychoneuroendocrinology 46. https://doi.org/10.1016/j.psyneuen.2014.04.004

Howells, F.M., Stein, D.J., Russell, V.A., 2012. Synergistic tonic and phasic activity of the locus coeruleus norepinephrine (LC-NE) arousal system is required for optimal attentional performance. Metab Brain Dis 27, 267-274. https://doi.org/10.1007/s11011-012-9287-9

Hu, X., Han, Z.R., Wang, H., Hu, Y., Wang, Q., Feng, S., Yi, L., 2018. The relation of parental emotion regulation to child autism spectrum disorder core symptoms: The moderating role of child cardiac vagal activity. Frontiers in Psychology 9. https://doi.org/10.3389/fpsyg.2018.02480

Hubert, B.E., Wicker, B., Monfardini, E., Deruelle, C., 2009. Electrodermal reactivity to emotion processing in adults with autistic spectrum disorders. Autism 13, 9-19. https://doi.org/10.1177%2F1362361308091649

Hutt, C., Hutt, S.J., Lee, D., Ounsted, C., 1964. AROUSAL AND CHILDHOOD AUTISM. Nature 204, 908-909. https://doi.org/10.1038/204908a0

Joseph, R.M., Ehrman, K., McNally, R., Keehn, B., 2008. Affective response to eye contact and face recognition ability in children with ASD. Journal of the International Neuropsychological Society 14, 947-955. https://doi.org/10.1017/S1355617708081344

Keith, J.M., Jamieson, J.P., Bennetto, L., 2019a. The Importance of Adolescent Self-Report in Autism Spectrum Disorder: Integration of Questionnaire and Autonomic Measures. Journal of abnormal child psychology 47, 741-754. https://doi.org/10.1007/s10802-018-0455-1

Keith, J.M., Jamieson, J.P., Bennetto, L., 2019b. The Influence of Noise on Autonomic Arousal and Cognitive Performance in Adolescents with Autism Spectrum Disorder. Journal of Autism and Developmental Disorders 49, 113-126. https://doi.org/10.1007/s10803-018-3685-8

Kinsbourne, M., 2011. Repetitive movements and arousal. The neuropsychology of autism, 367-394.

Kleberg, J.L., 2015. Resting state arousal and functional connectivity in autism spectrum disorder. Journal of Neurophysiology 113, 3035-3037. https://doi.org/10.1152/jn.00292.2014

Klusek, J., Martin, G.E., Losh, M., 2013. Physiological arousal in autism and fragile X syndrome: group comparisons and links with pragmatic language. American journal on intellectual and developmental disabilities 118, 475-495. https://doi.org/10.1352/1944.7558-118.6.475

Klusek, J., Roberts, J.E., Losh, M., 2015. Cardiac autonomic regulation in autism and Fragile X syndrome: a review. Psychological bulletin 141, 141-175. https://doi/10.1037/a0038237

Kootz, J.P., Marinelli, B., Cohen, D.J., 1982. Modulation of response to environmental stimulation in autistic children. Journal of autism and developmental disorders 12, 185-193. https://doi.org/10.1007/BF01531308

Kuiper, M.W.M., Verhoeven, E.W.M., Geurts, H.M., 2019. Stop Making Noise! Auditory Sensitivity in Adults with an Autism Spectrum Disorder Diagnosis: Physiological Habituation and Subjective Detection Thresholds. Journal of Autism and Developmental Disorders 49, 2116-2128. https://doi.org/10.1007/s10803-019-03890-9

Kushki, A., Brian, J., Dupuis, A., Anagnostou, E., 2014. Functional autonomic nervous system profile in children with autism spectrum disorder. Molecular Autism 5, 39. https://doi.org/10.1186/2040-2392-5-39

Kushki, A., Drumm, E., Mobarak, M.P., Tanel, N., Dupuis, A., Chau, T., 2013. Investigating the autonomic nervous system response to anxiety in children with autism spectrum disorders. PLoS One 8. https://dx.doi.org/10.1371%2Fjournal.pone.0059730

Lau, B.Y., Leong, R., Uljarevic, M., Lerh, J.W., Rodgers, J., Hollocks, M.J., South, M., McConachie, H., Ozsivadjian, A., Van Hecke, A., 2019. Anxiety in young people with autism spectrum disorder: Common and autism-related anxiety experiences and their associations with individual characteristics. Autism, 1362361319886246. https://doi.org/10.1177%2F1362361319886246

Laurie, M., Border, P., 2020. Autism in: Technology, U.P.O.o.S.a. (Ed.), https://post.parliament.uk/research-briefings/post-pn-0612/#fullreporthttps://post.parliament.uk/research-briefings/post-pn-0612/#fullreport

Loughlin, S., Foote, S., Grzanna, R., 1986. Efferent projections of nucleus locus coeruleus: morphologic subpopulations have different efferent targets. Neuroscience 18, 307-319. https://doi.org/10.1016/0306-4522(86)90156-9

Lovaas, I., Newsom, C., Hickman, C., 1987. Self-stimulatory behavior and perceptual reinforcement. Journal of applied behavior analysis 20, 45-68. https://doi.org/10.1901/jaba.1987.20-45

Lydon, S., Healy, O., Reed, P., Mulhern, T., Hughes, B.M., Goodwin, M.S., 2016. A systematic review of physiological reactivity to stimuli in autism. Developmental neurorehabilitation 19, 335-355. https://doi.org/10.3109/17518423.2014.971975

Mathersul, D., McDonald, S., Rushby, J.A., 2013a. Automatic facial responses to briefly presented emotional stimuli in autism spectrum disorder. Biological Psychology 94, 397-407. https://doi.org/10.1016/j.biopsycho.2013.08.004

Mathersul, D., McDonald, S., Rushby, J.A., 2013b. Autonomic arousal explains social cognitive abilities in high-functioning adults with autism spectrum disorder. International Journal of Psychophysiology 89, 475-482. https://doi.org/10.1016/j.ijpsycho.2013.04.014

Mathewson, K.J., Drmic, I.E., Jetha, M.K., Bryson, S.E., Goldberg, J.O., Hall, G.B., Santesso, D.L., Segalowitz, S.J., Schmidt, L.A., 2011. Behavioral and cardiac responses to emotional stroop in adults

with autism spectrum disorders: Influence of medication. Autism Research 4, 98-108. https://doi.org/10.1002/aur.176

Matsushima, K., Matsubayashi, J., Toichi, M., Funabiki, Y., Awaya, T., Kato, T., 2016. Unusual sensory features are related to resting-state cardiac vagus nerve activity in autism spectrum disorders. Research in Autism Spectrum Disorders 25, 37-46. https://doi.org/10.1016/j.rasd.2015.12.006

McCormick, C., Hessl, D., Macari, S.L., Ozonoff, S., Green, C., Rogers, S.J., 2014. Electrodermal and behavioral responses of children with autism spectrum disorders to sensory and repetitive stimuli. Autism Res 7, 468-480. https://doi.org/10.1002/aur.1382

McVey, A.J., 2019. The neurobiological presentation of anxiety in autism spectrum disorder: A systematic review. Autism Research 12, 346-369. https://doi.org/10.1002/aur.2063

Ming, X., Julu, P.O., Brimacombe, M., Connor, S., Daniels, M.L., 2005. Reduced cardiac parasympathetic activity in children with autism. Brain Dev 27. https://doi.org/10.1016/j.braindev.2005.01.003

Ming, X., Patel, R., Kang, V., Chokroverty, S., Julu, P.O., 2016. Respiratory and autonomic dysfunction in children with autism spectrum disorders. Brain and Development 38, 225-232. https://doi.org/10.1016/j.braindev.2015.07.003

Moher, D., Liberati, A., Tetzlaff, J., Altman, D., 2009. Group, P., & others.(2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6, e1000097. https://doi.org/10.1371/journal.pmed.1000097

Murphy, P.R., O'Connell, R.G., O'Sullivan, M., Robertson, I.H., Balsters, J.H., 2014. Pupil diameter covaries with BOLD activity in human locus coeruleus. Human Brain Mapping 35, 4140-4154. https://doi.org/10.1002/hbm.22466

Murphy, P.R., Robertson, I.H., Balsters, J.H., O'Connell, R.G., 2011. Pupillometry and P3 index the locus coeruleus-noradrenergic arousal function in humans. Psychophysiology 48, 1532-1543. https://doi.org/10.1111/j.1469-8986.2011.01226.x

Neuhaus, E., Bernier, R., Beauchaine, T.P., 2014. Brief report: Social skills, internalizing and externalizing symptoms, and respiratory sinus arrhythmia in autism. Journal of Autism and Developmental Disorders 44, 730-737. https://doi.org/10.1007/s10803-013-1923-7

Neuhaus, E., Bernier, R.A., Beauchaine, T.P., 2015. Electrodermal Response to Reward and Non-Reward Among Children With Autism. Autism Research 8, 357-370. https://doi.org/10.1002/aur.1451

Nuske, H.J., Vivanti, G., Dissanayake, C., 2014. Brief report: Evidence for normative resting-state physiology in autism. Journal of Autism and Developmental Disorders 44, 2057-2063. https://doi.org/10.1007/s10803-014-2068-z

Nystrom, P., Gliga, T., Jobs, E.N., Gredeback, G., Charman, T., Johnson, M.H., Bolte, S., Falck-Ytter, T., 2018. Enhanced pupillary light reflex in infancy is associated with autism diagnosis in toddlerhood. Nature Communications 9, 1678. https://doi.org/10.1038/s41467-018-03985-4

Orekhova, E.V., Stroganova, T.A., 2014. Arousal and attention re-orienting in autism spectrum disorders: Evidence from auditory event-related potentials. Frontiers in Human Neuroscience 8, 34. https://doi.org/10.3389/fnhum.2014.00034

Pace, M., Bricout, V.-A., 2015. Low heart rate response of children with autism spectrum disorders in comparison to controls during physical exercise. Physiology & Behavior 141, 63-68. https://doi.org/10.1016/j.physbeh.2015.01.011

Padmanabhan, A., Lynch, C.J., Schaer, M., Menon, V., 2017. The default mode network in autism. Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2, 476-486. https://doi.org/10.1016/j.bpsc.2017.04.004

Patriquin, M.A., Lorenzi, J., Scarpa, A., 2013a. Relationship between respiratory sinus arrhythmia, heart period, and caregiver-reported language and cognitive delays in children with autism spectrum disorders. Applied Psychophysiology Biofeedback 38, 203-207. https://doi.org/10.1007/s10484-013-9225-6

Patriquin, M.A., Lorenzi, J., Scarpa, A., Bell, M.A., 2014. Developmental trajectories of respiratory sinus arrhythmia: Associations with social responsiveness. Developmental Psychobiology 56, 317-326. https://doi.org/10.1002/dev.21100

Patriquin, M.A., Scarpa, A., Friedman, B.H., Porges, S.W., 2013b. Respiratory sinus arrhythmia: A marker for positive social functioning and receptive language skills in children with autism spectrum disorders. Developmental Psychobiology 55, 101-112. https://doi.org/10.1002/dev.21002

Porges, S.W., 1992. Vagal tone: a physiologic marker of stress vulnerability. Pediatrics 90, 498-504.

Porges, S.W., 2003. The Polyvagal Theory: Phylogenetic contributions to social behavior. Physiology and Behavior 79, 503-513. https://doi.org/10.1016/S0031-9384(03)00156-2

Porges, S.W., 2011. The Polyvagal Theory: Neurophysiological Foundations Of Emotions, Attachment, Communication, and Self-Regulation (Norton Series On Interpersonal Neurobiology). Company, New York.

Porges, S.W., Macellaio, M., Stanfill, S.D., McCue, K., Lewis, G.F., Harden, E.R., 2013. Respiratory sinus arrhythmia and auditory processing in autism: modifiable deficits of an integrated social engagement system? Int J Psychophysiol 88. https://doi.org/10.1016/j.ijpsycho.2012.11.009

Rao, M., Gershon, M.D., 2016. The bowel and beyond: The enteric nervous system in neurological disorders. Nature Reviews Gastroenterology and Hepatology 13, 517-528. https://doi.org/10.1038/nrgastro.2016.107

Riby, D.M., Whittle, L., 2012. Physiological reactivity to faces via live and video-mediated communication in typical and atypical development. J Clin Exp Neuropsychol 34. https://doi.org/10.1080/13803395.2011.645019

Saghir, H., Dupuis, A., Chau, T., Kushki, A., 2017. Atypical autonomic nervous system complexity accompanies social cognition task performance in ASD. Research in Autism Spectrum Disorders 39, 54-62. https://doi.org/10.1016/j.rasd.2017.04.004

Sara, S.J., Bouret, S., 2012. Orienting and reorienting: the locus coeruleus mediates cognition through arousal. Neuron 76, 130-141. https://doi.org/10.1016/j.neuron.2012.09.011

Schaaf, R.C., Benevides, T.W., Leiby, B.E., Sendecki, J.A., 2015. Autonomic dysregulation during sensory stimulation in children with autism spectrum disorder. Journal of autism and developmental disorders 45, 461-472. https://doi.org/10.1007/s10803-013-1924-6

Schoen, S.A., Miller, L.J., Brett-Green, B., Hepburn, S.L., 2008. Psychophysiology of children with autism spectrum disorder. Research in Autism Spectrum Disorders 2, 417-429. https://doi.org/10.1016/j.rasd.2007.09.002

Schoen, S.A., Miller, L.J., Brett-Green, B.A., Nielsen, D.M., 2009. Physiological and behavioral differences in sensory processing: A comparison of children with Autism Spectrum Disorder and Sensory

Modulation Disorder. Frontiers in Integrative Neuroscience 3. https://doi.org/10.3389/neuro.07.029.2009

Sheinkopf, S.J., Levine, T.P., McCormick, C.E.B., Puggioni, G., Conradt, E., Lagasse, L.L., Lester, B.M., 2019. Developmental trajectories of autonomic functioning in autism from birth to early childhood. Biological Psychology 142, 13-18. https://doi.org/10.1016/j.biopsycho.2019.01.003

Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., Baird, G., 2008. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry 47, 921-929. https://doi.org/10.1097/CHI.0b013e318179964f

South, M., Larson, M.J., White, S.E., Dana, J., Crowley, M.J., 2011. Better fear conditioning is associated with reduced symptom severity in autism spectrum disorders. Autism Research 4, 412-421. https://doi.org/10.1002/aur.221

Taylor, J.L., Corbett, B.A., 2014. A review of rhythm and responsiveness of cortisol in individuals with autism spectrum disorders. Psychoneuroendocrinology 49, 207-228. https://doi.org/10.1016/j.psyneuen.2014.07.015

Tessier, M.P., Pennestri, M.H., Godbout, R., 2018. Heart rate variability of typically developing and autistic children and adults before, during and after sleep. International Journal of Psychophysiology 134, 15-21. https://doi.org/10.1016/j.ijpsycho.2018.10.004

Thapa, R., Alvares, G.A., Zaidi, T.A., Thomas, E.E., Hickie, I.B., Park, S.H., Guastella, A.J., 2019. Reduced heart rate variability in adults with autism spectrum disorder. Autism research : official journal of the International Society for Autism Research. https://doi.org/10.1002/aur.2104

Thayer, J.F., Brosschot, J.F., 2005. Psychosomatics and psychopathology: looking up and down from the brain. Psychoneuroendocrinology 30, 1050-1058. https://doi.org/10.1016/j.psyneuen.2005.04.014

Thayer, J.F., Lane, R.D., 2000. A model of neurovisceral integration in emotion regulation and dysregulation. Journal of affective disorders 61, 201-216. https://doi.org/10.1016/S0165-0327(00)00338-4

Tiinanen, S., Maatta, A., Silfverhuth, M., Suominen, K., Jansson-Verkasalo, E., Seppanen, T., 2011. HRV and EEG based indicators of stress in children with Asperger syndrome in audio-visual stimulus test. Conference proceedings : ... Annual International Conference of the IEEE Engineering in Medicine

and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference 2011, 2021-2024. https://doi.org/10.1109/IEMBS.2011.6090371

Toichi, M., Kamio, Y., 2003. Paradoxical autonomic response to mental tasks in autism. Journal of Autism and Developmental Disorders 33, 417-426. https://doi.org/10.1023/A:1025062812374

Top, D.N., Luke, S.G., Stephenson, K.G., South, M., 2018. Psychophysiological arousal and auditory sensitivity in a cross-clinical sample of autistic and non-autistic anxious adults. Frontiers in Psychiatry 9, 783. https://doi.org/10.3389/fpsyt.2018.00783

Tudor, M.E., Hoffman, C.D., Sweeney, D.P., 2012. Children with autism: sleep problems and symptom severity. Focus on Autism and Other Developmental Disabilities 27, 254-262. https://doi.org/10.1177%2F1088357612457989

Van Bockstaele, E., Aston-Jones, G., 1995. Integration in the ventral medulla and coordination of sympathetic, pain and arousal functions. Clinical and Experimental Hypertension 17, 153-165. https://doi.org/10.3109/10641969509087062

van Engeland, H., 1984. The electrodermal orienting response to auditive stimuli in autistic children, normal children, mentally retarded children, and child psychiatric patients. Journal of autism and developmental disorders 14, 261-279. https://doi.org/10.1007/BF02409578

van Engeland, H., Roelofs, J.W., Verbaten, M.N., Slangen, J.L., 1991. Abnormal electrodermal reactivity to novel visual stimuli in autistic children. Psychiatry research 38, 27-38. https://doi.org/10.1016/0165-1781(91)90050-Y

Van Hecke, A.V., Lebow, J., Bal, E., Lamb, D., Harden, E., Kramer, A., Denver, J., Bazhenova, O., Porges, S.W., 2009. Electroencephalogram and heart rate regulation to familiar and unfamiliar people in children with autism spectrum disorders. Child Development 80, 1118-1133. https://doi.org/10.1111/j.1467-8624.2009.01320.x

Wagner, J.B., Luyster, R.J., Tager-Flusberg, H., Nelson, C.A., 2016. Greater Pupil Size in Response to Emotional Faces as an Early Marker of Social-Communicative Difficulties in Infants at High Risk for Autism. Infancy 21, 560-581. https://doi.org/10.1111/infa.12128

Wang, J., Barstein, J., Ethridge, L.E., Mosconi, M.W., Takarae, Y., Sweeney, J.A., 2013. Resting state EEG abnormalities in autism spectrum disorders. Journal of neurodevelopmental disorders 5, 24. https://doi.org/10.1186/1866-1955-5-24

Wass, S.V., de Barbaro, K., Clackson, K., 2015. Tonic and phasic co-variation of peripheral arousal indices in infants. Biological Psychology 111, 26-39. https://doi.org/10.1016/j.biopsycho.2015.08.006

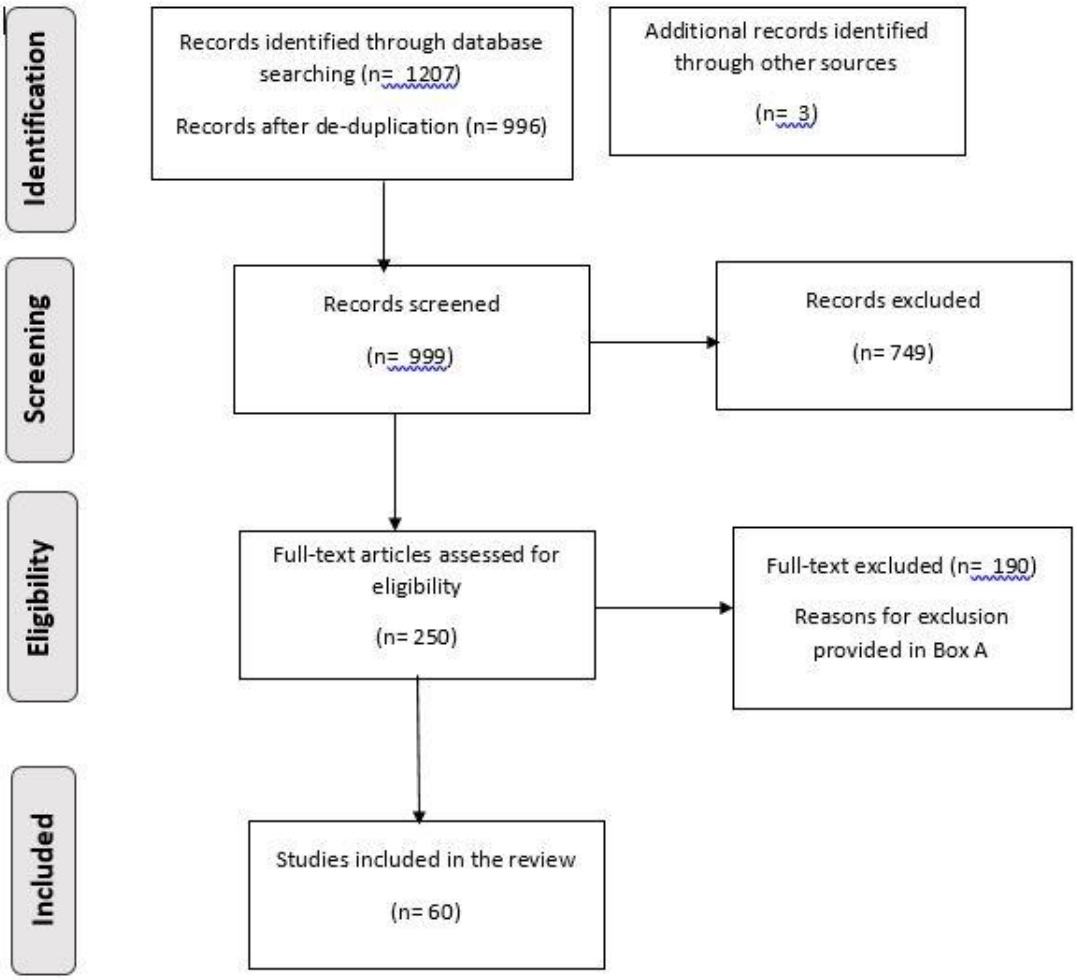
Wood, J.D., 2008. Enteric nervous system: reflexes, pattern generators and motility. Current opinion in gastroenterology 24, 149-158. https://doi:10.1097/MOG.0b013e3282f56125

Yarandi, S.S., Peterson, D.A., Treisman, G.J., Moran, T.H., Pasricha, P.J., 2016. Modulatory effects of gut microbiota on the central nervous system: How gut could play a role in neuropsychiatric health and diseases. Journal of Neurogastroenterology and Motility 22, 201-212. https://dx.doi.org/10.5056%2Fjnm15146

Zahn, T.P., Rumsey, J.M., Van Kammen, D.P., 1987. Autonomic nervous system activity in autistic, schizophrenic, and normal men: effects of stimulus significance. Journal of abnormal psychology 96, 135-144. https://doi.org/10.1037//0021-843x.96.2.135

Zantinge, G., van Rijn, S., Stockmann, L., Swaab, H., 2017. Psychophysiological responses to emotions of others in young children with autism spectrum disorders: Correlates of social functioning. Autism Research 10, 1499-1509. https://doi.org/10.1002/aur.1794

Zantinge, G., van Rijn, S., Stockmann, L., Swaab, H., 2019. Concordance between physiological arousal and emotion expression during fear in young children with autism spectrum disorders. Autism 23, 629-638. https://doi.org/10.1177%2F1362361318766439



Box A: Reasons for exclusion upon full-text review

- Article not in English (4)
- Notice of retraction or correction (1)
- Same data as reported in another paper for baseline autonomic arousal (3)
- Too little information provided in the study (1)
- Article uses definition of ASC that is not consistent with the modern diagnostic criteria of ASC (2)
- Conference abstract (36)
- Does not use a measure of autonomic function focused on in this review (5)
- Not an empirical study, including an editorial, a commentary, a letter or a review (10)
- Focus on a topic other than autonomic function (4)
- Effect of an intervention on ANS (4)
- No control group or only a psychiatric group or no case control comparison tested and relationship between autonomic measures and symptoms not tested either (27)
- No pre-task measure- measurement only during task or no rest or passive baseline measure (75)
- No comparisons at baseline reported (10)
- Baseline measured is an active baseline (8)

Fig. 1. PRISMA flowchart describing the numbers of studies identified, screened, excluded, and included in the systematic review process.

Table 1. Description of measures which were used in the studies included in the review, including their relation with functioning of the autonomic nervous system and the methodology usually used to collect and extract these measures.

DOMAIN	MEASURE	ACRONYM	METHODOLOGY & SIGNIFICANCE	PARAMETERS	ANS INDICATOR	NUMBER OF REVIEWED STUDIES USING THE MEASURE
ELECTRO-DERMAL ACTIVITY	Skin Conductance Level	SCL	SCL measures slow changes in electrical conductivity in the skin over time. It is measured by applying constant electrical voltage between two electrodes, typically placed on the palms of the hand. SCL is a measure of the electrical activity flowing between the electrodes. It is influenced by activity of the eccrine sweat glands, which is under SNS influence.	Mean SCL, Change in SCL over time (measured as a slope)	Higher SCL: increased sympathetic arousal	16 studies
	Non-Specific Skin Conductance Response	NS-SCR	NS-SCRs refer to phasic changes (difference from baseline) in the electrical conductivity of the skin that occur in absence of an identifiable external event/stimulus. They are measured using the same methodology as SCL.	Number/Rate of NS-SCRs Mean Amplitude of NS-SCRs	Higher NS-SCRs: increased phasic arousal/responsivity, not specific to any identifiable external event/stimulus	6 studies
PUPILLOMETRY	Pupil diameter		Typically measured using eye-tracking tools, for example, using image-based eye-trackers that use infra-red illumination. Highly sensitive to changes in luminance, pupil size is influenced by both SNS and PNS.	Mean pupil diameter	Higher mean pupil diameter: increased tonic arousal	7 studies
HEART RATE	Heart rate	HR	Refers to the number of heart beats per minute, it is measured using an electrocardiogram, which measures the electrical activity of the heart.	Mean HR	Higher HR: hyper-arousal	23 studies
	Inter-beat interval, Heart Period	IBI, HP	The time interval between successive R-R waves (i.e. consecutive heart beats)	Mean IBI, Mean HP	Higher IBI, HP: hypo-arousal	6 studies
HEART RATE VARIABILITY (HRV)	Standard deviation of	SDNN	Average variability (indexed through standard deviation) of durations of inter-beat intervals over a period of time, SDNN is calculated after	SDNN	Higher SDNN: increased HRV: higher	4 studies

DOMAIN	MEASURE	ACRONYM	METHODOLOGY & SIGNIFICANCE	PARAMETERS	ANS INDICATOR	NUMBER OF REVIEWED STUDIES USING THE MEASURE
	normal-to-normal intervals		abnormal or ectopic beats have been removed from the data and therefore, it is specific to normal inter-beat intervals. In short-term resting recordings, parasympathetic influences are the main source of variation in HRV.		parasympathetic function: hypo-arousal	
	Co-efficient of Variation	CV	Co-efficient of variation of the IBIs, calculated by dividing SDNN by the mean IBI: since HR is mathematically associated with HRV, this normalizes SDNN with respect to HR	CV	Higher CV: increased HRV: higher parasympathetic function: hypo-arousal	1 study
	Root Mean Square of Successive Differences	RMSSD	A measure of beat-to-beat variance in HR, measured by averaging the squared values of successive IBIs and then calculating a square root of the resulting value. It reflects vagally-mediated changes in HR.	RMSSD	Higher RMSSD: higher HRV: increased PNS function: hypo-arousal	6 studies
	Percentage of Normal-to-normal intervals >10 ms/50ms	pNN10, pNN50	Calculated as the percentage of adjacent NN intervals (from all NN intervals) that differ from each other by more than 10 or 50 ms respectively. It is correlated to PNS activity.	pNN10, pNN50	Higher pNN10/ pNN50: higher HRV: higher PNS function: hypo-arousal	2 studies
	Pre-ejection period	PEP	PEP indexes the time-interval between the the beginning of electrical stimulation of the ventricles to the opening of the aortic valve to pump blood. It is a validated index of SNS influences on the heart.	PEP length	Higher PEP length: reduced SNS function: hypo-arousal	1 study
	Respiratory sinus arrhythmia	RSA	Represents the variability in IBIs in the high-frequency range of respiration; RSA indexes changes in HR associated with respiration. Changes in RSA are mediated via the vagus nerve and thus, is considered a valid index of PNS.	RSA	Increased RSA: increased PNS functioning: hypo-arousal	14 studies
	Low frequency	LF	A frequency domain measure of HRV, LF measures spectral power between 0.04-0.15 Hz on the fast fourier transform (FFT) spectrum of HRV. In resting conditions, LF reflects baroreflex activity.	Absolute LF power Relative LF power in normalized units	Increased LF: increased baroreflex effect: increased HRV	5 studies

DOMAIN	MEASURE	ACRONYM	METHODOLOGY & SIGNIFICANCE	PARAMETERS	ANS INDICATOR	NUMBER OF REVIEWED STUDIES USING THE MEASURE
				Peak LF frequency Power spectrum density of LF frequency range		
	High frequency	HF	A frequency domain measure of HRV , it measures activity in the 0.15-0.40Hz range on the fast fourier transform spectrum of HRV. It is linked with respiratory influences on HR and is an index of parasympathetic influences on HR.	Absolute HF power Relative HF power in normalized units Peak HF frequency Power spectrum density of HF frequency range	Increased HF: increased PNS functioning: hypo-arousal	12 studies
	Low/high frequency	LF/HF	The ratio between spectral power in the low and high frequency range (see above for specific ranges in Hz). Traditionally, it has been used to index the balance between SNS and PNS activity. However, this is challenged in the literature.	LF/HF ratio	Traditional interpretations (currently under debate): Increased LF/HF ratio: sympathetic dominance Reduced LF/HF ratio: parasympathetic dominance	7 studies
	Multi-Scale Entropy	MSE	An index of the regularity and complexity of the IBI time series at multiple timescales.	MSE	Higher MSE: higher complexity in heartbeat time series: better readiness to adapt to the environment	1 study
	Cardiac Sympathetic Index	CSI	This is a geometric analysis of a non-linear plot of RRIs (wherein each RRI is plotted against its consecutive RRI). CSI is calculated as the longitudinal component of the plot divided by the transverse component of the plot. CSI has been linked to sympathetic function.	CSI	Higher CSI: higher sympathetic function: hyperarousal	1 study

DOMAIN	MEASURE	ACRONYM	METHODOLOGY & SIGNIFICANCE	PARAMETERS	ANS INDICATOR	NUMBER OF REVIEWED STUDIES USING THE MEASURE
	Cardiac Vagal Index	CVI	This is a geometric analysis, similar to CSI but calculated as a multiplication of the longitudinal and transverse components of the plot. It has been linked to parasympathetic function.	CVI	Higher CVI: higher parasympathetic function: hypoarousal	1 study
	Cardiac Vagal Tone	CVT	It refers to pulse-synchronized phase shifts in consecutive cardiac cycles. It is calculated after phase demodulation to filter out sympathetic influences, and therefore is suggested to be specific to vagal tone.	CVT	Higher CVT: higher parasympathetic function: hypoarousal	2 studies

Table 2. Studies included in the review: key methodological characteristics and main findings are described

First Author, Year	Age Groups[a]	Patient n (ASD[b])	Control n	ANS measure(s)	Paradigm	Length of measurement	Data duration	Main Finding
Anderson, 2013	Pre-school	Sample 1: 12 Sample 2: 18	Sample 1: 11 NT[c], 9 DS[d] Sample 2: 19 NT	Pupil	Looking at a blank grey slide	3 min	1 min	Sample 1: ASD>NT, DS (Hyper-arousal) Sample 2: ASD>NT (Hyper-arousal) Pupil size positively correlated with autism

								symptom severity in both samples
Bal, 2010	Children and Adolescents	17	36	Cardiac	Sitting quietly	2 min	2 min	ASD>NT on HR, ASD<NT on RSA (Hyper-arousal) Higher RSA related with better emotion recognition in ASD sample.
Billeci, 2018	Pre-school	20	20	Cardiac	Sitting quietly	5 min	5 min	ASD>NT on LF power, SDNN and CV (increased HRV, autonomic dysregulation) Increased CV associated with poor initiation of joint attention in ASD sample.
Bishop-Fitzpatrick, 2017	Adults	40	25	Cardiac	Sitting quietly	10 min	5 min	ASD>NT on HR (Hyper-arousal)
Bizzell, 2019	Children	12	12	Cardiac	Sitting quietly	3 min	3 min	No group differences
Bolte, 2008	Adults	10	10	Cardiac	Not described	Not reported	Not reported	No group differences
Bricout, 2018	Children	20	19	Cardiac	Rest in supine position	10 min	10 min	ASD>NT on LF power and total spectral power (increased HRV, autonomic dysregulation)
Bujnakova, 2017	Children and Adolescents	23	14	EDA	Lying down quietly	5 min	5 min	ASD<NT (Hypo-arousal)
Bujnakova, 2016	Children and Adolescents	15	15	Cardiac, EDA	Lying down quietly	5 min	5 min	EDA: ASD<NT (Hypo-arousal) Cardiac: ASD>NT on HR, ASD<NT on IBI, HF-HRV (Hyper-arousal)
Cai, 2019	Adults	24	20	Cardiac	Rest in supine position with eyes closed	10 min	5 min	Higher resting HRV associated with use of better emotion regulation strategies across ASD and NT participants
Chang, 2012	Children	25	25	EDA	Sitting quietly	3 min	3 min	ASD>NT (Hyper-arousal)

Corbett, 2019	Children	31	25	Cardiac	Not described	5 min	5 min	No group differences
Daluwatte, 2013	Children and Adolescents	152	107 NT, 36 NDD[e]	Pupil, Cardiac	Looking at a screen	5 min	5 min (for cardiac) Unclear (for pupil)	Cardiac: ASD>NT on HR (Hyper-arousal) Pupil: No group differences
Daluwatte, 2015	Children and Adolescents	152	107	Pupil	Looking at a screen	5 min	Unclear	Correlation between pupil diameter and sensory processing scores not significant in NT and ASD groups
DiCriscio, 2017	Children and Adolescents	42 children of which 12 had a diagnosis of autism		Pupil	Looking at a grey screen	10 seconds	10 seconds	Correlation between pupil diameter and autistic traits was not significant
Dijkhuis, 2019	Adults	51	28	Cardiac	Looking at a silent video	5 min	1 min (HR) 5 min (RMSSD)	No group differences
Edmiston, 2016	Adolescents	21	13	Cardiac	Sitting quietly	5 min	5 min: Analysed in 1 min segments	ASD<NT on RSA ASD>NT on variability in RSA (Hyper-arousal) Higher RSA associated with reduced autism symptom severity and with less internalizing symptoms
Eilam-Stock, 2014	Adults	17	15	EDA	Looking at a crosshair during an fMRI scan	6 min	6 min	ASD<NT (Hypo-arousal)
Faja, 2013	Children	21	21	EDA	Looking at a picture	120 sec	120 sec	No group differences
Hollocks, 2014	Children and Adolescents	20 ASD, 32 ASD+Anxiety	23	Cardiac	Watching cartoons	20 min	15 min	ASD>NT, ASD+Anxiety on HR (Hyper-arousal)
Hu, 2018	Children	29	N/A	Cardiac	Sitting quietly	2 min	2 min (analysed as 4 30 sec epochs)	Lower resting HF-HRV related to higher autistic traits. Higher self-reported parents' emotion regulation difficulties associated with higher parent-reported

								autistic traits in children only for children with relatively lower HF-HRV
Joseph, 2008	Children and Adolescents	20	20	EDA	Not described	2 min	2 min	No group differences
Keith, 2019[a]	Adolescents	25	21	Cardiac, EDA	Sitting quietly	5 min	5 min (analysed as average per minute)	EDA: No group differences Cardiac: ASD>NT (marginal significance) (Hyper-arousal)
Keith, 2019[b]	Adolescents	26	22	Cardiac	Sitting quietly	5 min	5 min	Higher mean HR associated with higher adolescent self-reported anxiety
Klusek, 2013	Children and Adolescents	40	28	Cardiac	Watching a movie	10 min	5.5 min	No group differences Reduced RSA associated with higher autism symptom severity in NT group.
Kootz, 1982	Children, Adolescents and Adults	16 (divided into high and low mental age)	N/A	Cardiac	Sitting quietly	15 min	Unclear	No group differences between higher and lower functioning ASD groups on mean HR
Kuiper, 2019	Adults	33	31	Cardiac, EDA	Sitting quietly	10 min	5 min	EDA: No group differences Cardiac: ASD>NT on HR (Hyper-arousal)
Kushki, 2014	Children and Adolescents	40	34	Cardiac	Watching a movie	15 min	3 min	ASD>NT on HR (Hyper-arousal)
Kushki, 2013	Children and Adolescents	12	17	Cardiac, EDA	Watching a movie	30 min	Middle 10 min	EDA: ASD>NT (Hyper-arousal) Cardiac: ASD>NT on HR (Marginally significant) (Hyper-arousal)
Mathersul, 2013[a]	Adults	30	31	EDA	Unclear, presumably looking at a screen	500 ms	500 ms	ASD<NT (Hypo-arousal)
Mathersul, 2013[b]	Adults	28	31	EDA	Sit quietly with eyes closed	2 min	2 min	No group differences, presence of a hypoaroused sub-group

Mathewson, 2011	Adults	15	16	Cardiac	Resting with eyes open and eyes closed	6 min	6 min (analysed as minute by minute average)	ASD>NT on HP, ASD<NT on RSA (Hyper-arousal) HP not correlated with symptoms of anxiety.
Matsushima, 2016	Children	37	32	Cardiac	Watching a timer on an IPAD	2 min	2 min	ASD<NT on HF-HRV (Hyper-arousal) Reduced HF-HRV associated with higher symptoms of RRBs and higher visual and auditory hyper-reactivity.
McCormick, 2014	Pre-school	54	33	EDA	Watching a video	2 min	2 min	No group differences
Ming, 2005	Children	28	17	Cardiac	Sitting on an inclined chair with music or videos if required	25 min	10 min	ASD>NT on HR, ASD<NT on CVT (Hyper-arousal)
Ming, 2016	Children	19	18	Cardiac	Sitting on an inclined chair with music or videos if required	25 min	10 min	ASD>NT on HR, ASD<NT on CVT (Hyper-arousal)
Neuhaus, 2014	Children and Adolescents	18	18	Cardiac	Sitting quietly	5 min	Last 2 min (analysed as 4 30 sec epochs)	ASD<NT on RSA (Hyper-arousal) Higher RSA associated with better social functioning and fewer social problems.
Neuhaus, 2015	Children	18	18	EDA	Sitting quietly	5 min	Last 2 min analysed as 4 30 second epochs	NT group showed higher variability in NS-SCRs during the resting-state than ASD (autonomic dysregulation) Higher variability in NS-SCRs associated with better social skills in NT group

								and with more problem behaviours in ASD group.
Nuske, 2014	Pre-school	25	21	Pupil	Looking at a grey slide	13 sec	7 sec	No group differences
Pace, 2015	Children	10	10	Cardiac	Rest- not described	5 min	5 min	ASD<NT on HR (Hypo-arousal)
Patriquin, 2013[a]	Pre-school and Children	23	N/A	Cardiac	Watching a video	3 min	3 min	Reduced RSA associated with more parent-reported language and cognitive delays
Patriquin, 2013[b]	Pre-school and Children	23	N/A	Cardiac	Watching a video	3 min	3 min	Higher RSA associated with better social behaviour and receptive language abilities
Patriquin, 2014	Pre-school	106 NT		Cardiac	Watching a video	2 min	2 min	Atypical development of RSA (between 5-48 months) associated with more social responsiveness difficulties at 48 months of age
Porges, 2013	Children, Adolescents and Adults	78	68	Cardiac	Not described	2 min	2 min	ASD<NT on HP and RSA (Hyper-arousal)
Riby, 2012	Adolescents	12	12	EDA	Relax in a silent room	5 min	5 min	No group differences
Saghir, 2017	Children and Adolescents	45	34	Cardiac	Watching a movie	5 min	5 min	No group differences
Schaaf, 2015	Children	59	29	Cardiac	Sitting quietly	3 min	3 min	No group differences
Schoen, 2009	Children and Adolescents	38	33 NT, 31 SMD[f]	EDA	Sitting quietly	3 min	3 min	ASD<NT, SMD (Hypo-arousal)
South, 2011	Children and Adolescents	30	30	EDA	Not described	Not reported	Not reported	No group differences
Tessier, 2018	Sample 1: Children and Adolescents Sample 2: Adults	Sample 1: 13 Sample 2: 16	Sample 1: 13 Sample 2: 17	Cardiac	15 minutes before and after sleep- no other description	5 min	5 min	Sample 1: No group differences Sample 2: ASD<NT on normalized HF power (Hyper-arousal)
Thapa, 2019	Adolescents and Adults	55	55	Cardiac	Sitting quietly	5 min	5 min	ASD>NT on HR, ASD<NT on HF-HRV, RMSSD (Hyper-arousal)

Tiinanen, 2011[h]	Children	20	21	Cardiac	Sitting quietly	40 sec	40 sec	No group differences
Toichi, 2003	Adolescents and Adults	20	20	Cardiac	Looking at a blank white wall	3 min	50 sec	No group differences on CSI or CVI (presence of a subgroup with reduced CVI and thus, hyper-arousal)
Top, 2018	Adults	31	36 NT, 28 NT+Anxiety[g]	Pupil	Looking at a fixation cross	3-4 min	20 seconds	ASD>NT, NT-Anx (Hyper-arousal)
Van Engeland, 1984	Children	35	45	EDA	Not described	5 min	5 min	No group differences
Van Engeland, 1991	Children	20	20	Pupil, EDA	Not described	Unclear	1 min (for EDA) Unclear (for pupil)	Pupil: No group differences EDA: No group differences
Van Hecke, 2009	Children	19	14	Cardiac	Looking at a blank screen	3 min	3 min	ASD<NT on RSA (Hyper-arousal) Higher RSA associated with lower autism symptom severity
Zahn, 1987	Adults	13	20	Cardiac, EDA	Not described	5 min	EDA: 5 min (analysed as average per minute) Cardiac: 5 min (analysed as average per 10 sec epochs)	EDA: Slope of SCL declined more rapidly during resting state in NT than ASD (reduced adaptation to context in ASD) Cardiac: No group differences on HR, ASD>NT on Maxima's MSSD (higher HRV, autonomic dysregulation)
Zantinge, 2017	Pre-school	28	45	Cardiac	Watching a video	3 min	1 min	No group differences
Zantinge, 2019	Pre-school	21	45	Cardiac	Watching a video	3 min	1 min	No group differences

[a]Age groups: Pre-school children: <= 6 years, Children: 6-12 years, Adolescents: 12-18 years, Adults: >18 years. [b]ASD: Autism Spectrum Disorder, [c]NT= Neurotypical, [d]DS= Down's Syndrome, [e]NDD: neurodevelopmental disorders other than ASD; [f]SMD: Sensory Modulation Disorder; [g]NT-Anx: neurotypical individuals presenting with symptoms of anxiety. [h]One article is a conference publication from a peer-reviewed journal (Tiinanen et al, 2011).

Table 3: Spread of Group Differences in Studies included in the review

	No group differences	Group differences			
		Overall	Hyper-arousal	Hypo-arousal	Other
Number of Studies	20/51 (39.2%)	31/51 (60.8%)	21/31 (67.8%)	5/31 (16.1%)	5/31 (16.1%)
Number of Group Comparisons	79/130 (60.77%)	51/130 (39.23%)			

Each study included in the review that compared neurotypical and autistic participants on an ANS measure is categorized based on whether or not they reported a significant group difference on at least one ANS measure. Studies that found group differences have been categorized based on whether they found evidence of hyperarousal, hypoarousal or other evidence of other autonomic arousal differences (such as evidence of both hyperarousal or hypoarousal on difference autonomic indices, increased variability on an autonomic index or differences in change in autonomic indices over time during resting state measurement). Since many studies reported on multiple measures of autonomic function, an additional categorization is presented of each group comparison carried out on an autonomic index and the proportion of group comparisons that observed a significant group difference between autistic and neurotypical participants.

Table 4: Description of experimental contextual factors in studies included in the review that compared groups of autistic and neurotypical participants

First Author	Measure	Duration of measurement	Resting-State Paradigm	Experimental context during measurement	Followed by a task	Significant Group Differences present	Hyper/Hypo/Other/N/A
Bujnakova, 2016	Cardiac	Short	Lie down quietly	No activity	No	Yes	Hyper
Neuhaus, 2014	Cardiac	Short	Sitting quietly	No activity	No	Yes	Hyper
Tessier, 2018	Cardiac	Short	15 min before and after sleep- no other description	No activity	No	Yes	Hyper
Thapa, 2019	Cardiac	Short	Sitting quietly	No activity	No	Yes	Hyper
Bal, 2010	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Edmiston, 2016	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Keith, 2019	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Kuiper, 2019	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Mathewson, 2011	Cardiac	Short	Resting- eyes open, eyes closed	No activity	Yes	Yes	Hyper
Bishop-Fitzpatrick, 2017	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Hyper
Chang, 2012	Skin Conductance	Short	No stimulation- inside a pretend spaceship	No activity	Yes	Yes	Hyper
Pace, 2015	Cardiac	Short	Rest- not described	No activity	Yes	Yes	Hypo
Bujnakova, 2017	Skin Conductance	Short	Lie down quietly	No activity	No	Yes	Hypo
Bujnakova, 2016	Skin Conductance	Short	Lie down quietly	No activity	No	Yes	Hypo
Schoen, 2009	Skin Conductance	Short	Sitting quietly	No activity	Yes	Yes	Hypo
Billeci, 2018	Cardiac	Short	Sitting quietly	No activity	Yes	Yes	Overall autonomic dysregulation
Bricout, 2018	Cardiac	Short	Rest in supine position	No activity	Yes	Yes	Increased heart rate variability
Neuhaus, 2015	Skin Conductance	Short	Sitting quietly	No activity	Yes	Yes	Differences in adaptation
Tiinanen, 2011	Cardiac	Very short	Sitting quietly	No activity	Yes	No	N/A
Tessier, 2018	Cardiac	Short	15 min before and after sleep- no other description	No activity	No	No	N/A

Bizell, 2019	Cardiac	Short	Sitting quietly	No activity	Yes	No	N/A
Schaaf, 2015	Cardiac	Short	Sitting quietly	No activity	Yes	No	N/A
Keith, 2019	Skin Conductance	Short	Sitting quietly	No activity	Yes	No	N/A
Kuiper, 2019	Skin Conductance	Short	Sitting quietly	No activity	Yes	No	N/A
Mathersul, 2013[b]	Skin Conductance	Short	Sitting quietly with eyes closed	No activity	Yes	No	N/A
Riby, 2012	Skin Conductance	Short	Relax in a silent room	No activity	Yes	No	N/A
Daluwatte, 2013	Cardiac	Short	Unclear- looking at a screen	Passive Attention	Yes	Yes	Hyper
Matsushima, 2016	Cardiac	Short	Watching a timer on an IPAD	Passive Attention	Yes	Yes	Hyper
Hollocks, 2014	Cardiac	Long	Watching cartoons	Passive Attention	Yes	Yes	Hyper
Kushki, 2014	Cardiac	Long	Watching an animated movie	Passive Attention	Yes	Yes	Hyper
Van Hecke, 2009	Cardiac	Short	Looking at a blank screen	Passive Attention	Yes	Yes	Hyper
Ming, 2005	Cardiac	Long	Rest on a chair inclined to 30 degrees with music or videos if required- subject dependent	Passive Attention	No	Yes	Hyper
Ming, 2016	Cardiac	Long	Rest on a chair inclined to 30 degrees with music or videos if required- subject dependent	Passive Attention	No	Yes	Hyper
Kushki, 2013	Skin Conductance	Long	Watching movie	Passive Attention	Yes	Yes	Hyper
Top, 2018	Pupil	Very short	Looking at a fixation cross	Passive Attention	Yes	Yes	Hyper
Anderson, 2013	Pupil	Short	Look at a blank grey slide	Passive Attention	Yes	Yes	Hyper
Anderson, 2013	Pupil	Short	Look at a blank grey slide	Passive Attention	Yes	Yes	Hyper
Mathersul, 2013[a]	Skin Conductance	Very short	Unclear- presumably looking at a screen	Passive Attention	Yes	Yes	Hypo
Eilam-Stock, 2014	Skin Conductance	Short	Looking at a crosshair inside fMRI	Passive Attention	No	Yes	Hypo
Dijkhuis, 2019	Cardiac	Short	Looking at a silent nature video	Passive Attention	Yes	No	N/A
Klusek, 2013	Cardiac	Short	Watching a movie	Passive Attention	Yes	No	N/A
Saghir, 2017	Cardiac	Short	Watching a movie	Passive Attention	Yes	No	N/A
Toichi, 2003	Cardiac	Short	Sit quietly looking at a blank white wall	Passive Attention	Yes	No	N/A

Zantinge, 2017	Cardiac	Short	3 min fish video	Passive Attention	Yes	No	N/A
Zantinge, 2019	Cardiac	Short	3 min fish video	Passive Attention	Yes	No	N/A
Kushki, 2013	Cardiac	Long	Watching movie	Passive Attention	Yes	No	N/A
McCormick, 2014	Skin Conductance	Short	Watching a video	Passive Attention	Yes	No	N/A
Faja, 2013	Skin Conductance	Very short	Sitting quietly, looking at a picture	Passive Attention	Yes	No	N/A
Nuske, 2014	Pupil	Very short	Looking at grey slides	Passive Attention	No	No	N/A
Daluwatte, 2013	Pupil	Short	Unclear- presumably looking at a screen	Passive Attention	Yes	No	N/A
Porges, 2013	Cardiac	Short	Baseline	Unclear	Yes	Yes	Hyper
Zahn, 1987	Cardiac	Short	5 min rest period- not described	Unclear	Yes	Yes	Increased heart rate variability
Zahn, 1987	Skin Conductance	Short	5 min rest period- not described	Unclear	Yes	Yes	Differences in adaptation
Corbett, 2019	Cardiac	Short	No description	Unclear	Yes	No	N/A
Bolte, 2008	Cardiac	Unclear	Not described	Unclear	Yes	No	N/A
Joseph, 2008	Skin Conductance	Very Short	Unclear- before visual stimulation	Unclear	Yes	No	N/A
van Engeland, 1984	Skin Conductance	Unclear	Not described	Unclear	Yes	No	N/A
van Engeland, 1991	Skin Conductance	Unclear	Not described	Unclear	Yes	No	N/A
South, 2011	Skin Conductance	Unclear	Not described, likely looking at a screen, possibly performing a preference task as they acclimate to the lab of which picture they prefer	Unclear	Yes	No	N/A
van Engeland, 1991	Pupil	Unclear	Not described	Unclear	Yes	No	N/A

Duration of measurement refers to the length of resting state measurement based on which the autonomic index in the study has been calculated. It is categorized as followed: Very short (less than two minutes), Short (3-5 minutes) and Long (more than 5 minutes). For studies that used multiple types of indices of autonomic function (pupil, cardiac and EDA), each type of index is represented separately. Experimental context during measurement refers to characterization of studies based on whether the experimental context during the resting state measurement involved a No Activity resting state (i.e., participants were asked not to do anything) or a Passive Attention Resting State (i.e. participants were asked to passively attend to something external).

Table 5*: Spread of group differences and nature of differences based on length of autonomic measurement*

Length of autonomic data	No Group Differences	Group Differences

		Overall	Hyper-arousal	Hypo-arousal	Other
Very Short	10/18 (55.56%)	8/18 (44.44%)	6/8 (75%)	1/8 (12.5%)	1/8 (12.5%)
Short	9/27 (33.33%)	18/27 (66.67%)	11/18 (61.1%)	4/18 (22.2%)	3/18 (16.7%)
Long	1/9 (11.11%)	8/9 (88.89%)	6/8 (75%)	1/8 (12.5%)	1/8 (12.5%)

Each study that compared autistic and neurotypical groups on an ANS index is categorized based on the length of data that the autonomic index is based on and proportion of significant group differences is presented. For studies that used ANS measures of different types (i.e. cardiac, electrodermal or pupil), each index is represented separately. Length of autonomic data has been categorized as follows: Very Short (upto 2 minutes), Short (3-5 minutes), Long (more than 5 minutes). For studies that found group differences, the proportion of studies that found evidence of hyperarousal, hypoarousal or other indications of differences in autonomic arousal (increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

Table 6: Spread of group differences depending upon experimental context during measurement of autonomic function

Experimental Context	No group differences	Group differences			
		Overall	Hyper-arousal	Hypo-arousal	Other
No Activity	7/25 (28%)	18/25 (72%)	11/18 (61.1%)	4/18 (22.2%)	3/18 (16.7%)
Passive Attention	10/23 (43.48%)	13/23 (56.52%)	11/13 (84.6%)	2/13 (15.4%)	0/13 (0%)

Each study is categorized based on whether the experimental context during the resting state measurement involved a No Activity resting state (i.e., participants were asked not to do anything) or a Passive Attention Resting State (i.e. participants were asked to passively attend to something). Proportion of significant group differences is presented. For studies that found evidence of group differences, proportion of studies that found evidence of hyperarousal, hypoarousal or other differences in autonomic function (e.g., increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

Table 7: Spread of group differences based on whether a task followed the resting measurement or not

Resting State followed by a Task	No group differences	Group differences			
		Overall	Hyper-arousal	Hypo-arousal	Other
No Task	1/11 (9.1%)	10/11 (90.9%)	7/10 (70%)	3/10 (30%)	0/10 (0%)
Task	23/47 (48.9%)	24/47 (51.1%)	16/24 (66.7%)	3/24 (12.5%)	5/24 (20.8%)

Each study is categorized based on whether the resting state measurement was followed by a task or not. Proportion of significant group differences is presented. For studies that found evidence of group differences, proportion of studies that found evidence of hyperarousal, hypoarousal or other differences in autonomic function (e.g., increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

Table 8: Spread of group differences based on the measure of autonomic function used

Autonomic Measure	No group differences	Group differences			
		Overall	Hyper-arousal	Hypo-arousal	Other
Cardiac	11/34 (32.4%)	23/34 (67.6%)	19/23 (82.6%)	1/23 (4.4%)	3/23 (13%)
EDA	10/19 (52.6%)	9/19 (47.4%)	2/9 (22.2%)	5/9 (55.6%)	2/9 (22.2%)
Pupil	3/5 (60%)	2/5 (40%)	2/2 (100%)	0/3 (0%)	0/3 (0%)

Each study that compared autistic and neurotypical groups on an ANS index is categorized based on the type of autonomic index used (cardiac, EDA or pupil) and proportion of significant group differences is presented. For studies that used ANS measures of different types (i.e. cardiac, electrodermal or pupil), each index is represented separately. For studies that found group differences, the proportion of studies that found evidence of hyperarousal, hypoarousal or other indications of differences in autonomic arousal (increased variability in the autonomic index, differences between groups in how the autonomic index changes over time during the resting state measurement) is presented.

Table 9
Summary of results from studies comparing autistic and neurotypical groups on pupil size.

First Author	Age Range	Patient n	Control n	Arousal measure	Hyper/Hypo/None
Anderson, 2013	Pre-school children	Sample 1: 12 Sample 2: 18	Sample 1: 11 NT, 9 DS Sample 2: 19	Pupil size	Hyper
Top, 2018	Adults	31	28, 36	Pupil size	Hyper
Nuske, 2014	Pre-school children	25	21	Pupil size	None
Daluwatte, 2013	Children and Adolescents	152	107 NT, 36 NDD	Pupil size	None
van Engeland, 1991	Children and Adolescents	20	20	Pupil Size	None
					Count: 2 : 0 : 3

Table 10: Summary of results from studies comparing autistic and neurotypical groups on Heart Rate.

First Author	Age Range	Patient n	Control n	Arousal measure	Hyper/Hypo/None
Ming, 2016	Children	19	18	HR	Hyper
Ming, 2005	Children	28	17	HR	Hyper
Bal, 2010	Children and Adolescents	17	36	HR	Hyper
Daluwatte, 2013	Children and Adolescents	152	107 TD, 36 NDD	HR	Hyper
Bujnakova, 2016	Children and Adolescents	15	15	HR	Hyper
Hollocks, 2014	Children and Adolescents	52	23	HR	Hyper
Kushki, 2014	Children and Adolescents	40	34	HR	Hyper
Keith, 2019	Adolescents	25	21	HR	Hyper
Porges, 2013	Children, adolescents and young adults	78	68	HR	Hyper
Kuiper, 2019	Adults	33	31	HR	Hyper
Mathewson, 2011	Adults	15	16	HR	Hyper
Thapa, 2019	Adults	55	55	HR	Hyper
Bishop-Fitzpatrick, 2017	Adults	40	25	HP	Hyper
Pace, 2015	Children	10	10	HR	Hypo
Zantinge, 2017	Pre-school children	28	45	HR	None
Zantinge, 2019	Pre-school children	21	45	HR	None
Billeci, 2018	Pre-school children	20	20	HR	None
Tiinanen, 2011	Children	20	21	HR	None
Klusek, 2013	Children and Adolescents	40	28	HR	None
Kushki, 2013	Children and Adolescents	12	17	HR	None
Bolte, 2008	Adults	10	10	HR	None
Dijkhuis, 2019	Adults	51	28	HR	None
Zahn, 1987	Adults	13	19	HR	None
					Count: 13:1:9

Table 11: Summary of results from studies comparing autistic and neurotypical groups on Respiratory Sinus Arrhythmia.

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/Hypo/None
Van Hecke, 2009	Children	19	14	RSA	Hyper
Neuhaus, 2014	Children and Adolescents	18	18	RSA	Hyper
Bal, 2010	Children and Adolescents	17 (1 F)	36 (13 F)	RSA	Hyper
Edmiston, 2016	Adolescents	21	13	RSA	Hyper
Porges, 2013	Children, adolescents and young adults	78	68	RSA	Hyper
Mathewson, 2011	Adults	15	16	RSA	Hyper
Corbett, 2019	Children	31	25	RSA	None
Klusek, 2013	Children and Adolescents	40	28	RSA	None
Schaaf, 2015	Children	59	29	RSA	None
Kushki, 2014	Children and Adolescents	40	34	RSA	None
Kuiper, 2019	Adults	33	31	RSA	None
					Count: 6:0:5

Table 12: Summary of results from studies comparing autistic and neurotypical groups on Spectral measures of HRV

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/HypoNone
Billeci, 2018	Pre-school children	20	20	LF, HF, LF/HF ratio	Higher LF (hyper), no other differences
Matsushima, 2016	Children	37	32	HF-HRV	Reduced HF-HRV (Hyper)
Bricout, 2018	Children	20	19	LF, HF, LF/HF ratio, Total power	Higher power in LF and higher total power (Hyper)
Bujnakova, 2016	Children and Adolescents	15	15	Power and peak frequency in LF and HF bands	Reduced power in HF (Hyper)
Tessier, 2018	Children and Adults	16 adults, 13 children	17 adults, 13 children	LF, HF, LF/HF ratio	Lower HF (n.u.) in adult ASD as compared to adult NT (Hyper)
Thapa, 2019	Adolescents and Adults	55	55	LF, HF	Reduced HF-HRV (Hyper), no other differences
Tiinanen, 2011	Children	20	21	LF, HF, LF/HF ratio	None
Bizell, 2019	Children	12	12	HF-HRV	None
Daluwatte, 2013	Children and Adolescents	152	107 TD, 36 NDD	Normalized HF, LF/HF ratio	None
Hollocks, 2014	Children and Adolescents	52	23	HF, LF/HF ratio	None
					Count: 6:0:4

Table 13: Summary of results from studies comparing autistic and neurotypical groups on time-domain measures of HRV

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/Hypo/Other[a]/None
Bujnakova, 2016	Children and Adolescents	15	15	RR Intervals	Shorter RR intervals (Hyper)
Thapa, 2019	Adolescents and Adults	55	55	RMSSD, SDNN	Lower RMSSD (Hyper)
Billeci, 2018	Pre-school children	20	20	SDNN, CV, pNN10	Increased SDNN and CV (Other)
Zahn, 1987	Adults	13	19	HR Maxima's MSSD	Maxima's MSSD higher in ASD (Other)
Bricout, 2018	Children	20	19	RMSSD, pNN50	None
Daluwatte, 2013	Children and Adolescents	152	107 TD, 36 NDD	SDNN, RMSSD	None
Dijkhuis, 2019	Adults	51	28	RMSSD	None
					Count: 2:0:2:3

[a]Other refers to findings of differences in autonomic function that cannot be categorized as evidence of hyper or hypo-arousal, for example, evidence of differences between groups of change in autonomic function over time during resting state measurement or evidence of differences in variability in the autonomic index

Table 14: Summary of results from studies comparing autistic and neurotypical groups on other cardiac measures

First Author	Age Range	Patient n	Control n	Arousal Measure	Hyper/Hypo/None
Ming, 2016	Children	19	18	CVT, CSB	Reduced CVT and CSB in ASD (Hyper)
Ming, 2005	Children	28	17	CVT, CSB	Reduced CVT and CSB in ASD (Hyper)
Schaaf, 2015	Children	59	29	PEP	No differences
Saghir, 2017	Children and Adolescents	45	34	Multi-Scale Entropy	No differences
Toichi and Kamio, 2003	Adolescents and Adults	20	20	CVI, CSI	No overall group differences- a subgroup of ASD with reduced CVI compared to NT
					Count: 2:0:3

Table 15. Summary of results from studies comparing autistic and neurotypical groups on electrodermal activity

First Author	Age Range	Patient n	Control n	Arousal measure	Hyper/Hypo/Other[a]/No differences
Chang, 2012	Children	25	25	SCL	Hyper
Kushki, 2013	Children and Adolescents	12	17	SCL and NS-SCR	Hyper
Bujnakova, 2017	Children and Adolescents	23	14	SCL	Hypo
Bujnakova, 2016	Children and Adolescents	15	15	SCL	Hypo
Schoen, 2009	Children and Adolescents	38	33, 31	SCL	Hypo
Eilam-Stock, 2014	Adults	17	15	SCL and NSSCRs	Hypo
Mathersul, 2013[a]	Adults	30	31	SCL	Hypo
Neuhaus, 2015	Children	18	18	Amplitude and frequency of NS-SCR	Other- Differences in Adaptation
Zahn, 1987	Adults	13	20	SCL, NSSCRs	Other- Differences in Adaptation
McCormick, 2014	Pre-school children	54	33	SCL	None
van Engeland, 1984	Children	35	45	NSSCRs	None
Faja, 2013	Children	21	21	NS-SCR	None
Joseph, 2008	Children and Adolescents	20	20	SCL	None
van Engeland, 1991	Children and Adolescents	20	20	SCL	None
South, 2011	Children and Adolescents	30	30	SCL	None
Keith, 2019	Adolescents	25	21	SCL	None
Riby, 2012	Adolescents	12	12	SCL	None
Mathersul, 2013[b]	Adults	28	31	SCL	None overall, presence of hypoaroused sub-group
Kuiper, 2019	Adults	33	31	SCL	None
					Count: 2:5:2:10

[a]Other refers to findings of differences in autonomic function that cannot be categorized as evidence of hyper or hypo-arousal, for example, evidence of differences between groups of change in autonomic function over time during resting state measurement (i.e., differences in adaptation of autonomic arousal during resting state) or evidence of differences in variability in the autonomic index

Table 16: Spread of group differences based on sample size

Sample Size	No group differences	Group differences
Small	7/22 (31.8%)	15/22 (68.2%)
Medium	10/23 (43.5%)	13/23 (56.5%)
Large	3/6 (50%)	3/6 (50%)

Each study that compared autistic and neurotypical groups on an ANS index is categorized based on the sample size of the autistic sample included in the study and proportion of significant group differences is presented. Sample sizes are characterized as followed: Small (N≤20), Medium (N=21-50) and Large (N>50).

Supplementary Materials for Arousal Review Article

SM1. Inclusion/Exclusion criteria

We identified articles that compared ANS activity at rest between a group of individuals with Autism and a group of typical individuals at any age. We also included studies that investigated autonomic activity in a group of typical individuals if they investigated autistic traits in their samples. We also included studies that may not have included group comparisons but looked at continuous relationships between autonomic activity at rest and symptom severity of ASD or function in different domains relevant to ASD.

We defined resting state in this study as a defined period of time wherein no task was given to the participants: this included activities such as sitting quietly, lying down with eyes open or closed, looking at a video silently (see Table x for a full list of all measurement contexts). We included studies which measured resting state as a baseline before a task if they included the data that was reported pre-task. We did not include baseline indices when the pre-task baseline was active- for example in some studies that focused on emotional arousal, the pre-task baseline was an active emotionally neutral cognitive task, not a passive resting state.

SM2. Table describing demographic characteristics of each study

First Author, Year	IQ characteristics of Study	IQ Categorization[a]	Comorbidities in ASD participants	Medication Use in ASD participants
Anderson, 2013	Sample 1: IQ statistically matched with DS Sample 2: IQ statistically matched with NT	Reliable	Sample 1: Comorbidities not reported Sample 2: ASD participants free of comorbid impairments	Sample 1: Participants medication free during experiment Sample 2: Participants medication free during experiment
Bal, 2010	IQ>75, No group differences on IQ	Reliable	Not reported	Reported, not analyzed, some participants taking psychoactive drugs at the time of experiment
Billeci, 2018	IQ statistically controlled in analysis	Reliable	Not reported	Excluded for use of psychotropic medication.
Bishop-Fitzpatrick, 2017	No group differences on IQ	Reliable	Not reported	Not reported
Bizzell, 2019	IQ>70, group differences not described	Not reliable	Not reported	Excluded for use of SSRI medications
Bolte, 2008	No group differences on IQ	Reliable	Not reported	Not reported
Bricout, 2018	IQ>70, group differences not described	Not reliable	Excluded for presence of comorbid psychiatric condition	Excluded for medication use
Bujnakova, 2017	IQ>80, group differences not described	Not reliable	Reported and their influence on autonomic measures analyzed	Reported and their influence on autonomic measures analyzed
Bujnakova, 2016	IQ>80, group differences not described	Not reliable	Reported, not analyzed	Medication use reported and participants medication free during experiment
Cai, 2019	IQ>80, no group differences on IQ	Reliable	Reported, not analyzed	Reported and their influence on autonomic measures analyzed
Chang, 2012	IQ not reported	Not reliable	Not reported	Excluded for medication use
Corbett, 2019	IQ>70, group differences on IQ significant, relationship of IQ with ANS measures examined	Reliable	Not reported	Not reported
Daluwatte, 2013	IQ reported and its influence analysed	Reliable	Not reported	Reported and their influence on autonomic measures analyzed
Daluwatte, 2015	IQ not described (sample same as Daluwatte, 2013)	Not reliable	Not reported	Reported and their influence on autonomic measures analyzed

DiCriscio, 2017	IQ measured and its association with DV evaluated	Reliable	Reported, not analyzed	Not reported
Dijkhuis, 2019	IQ>80; significant group differences on IQ but IQ not significantly correlated with autonomic measures and therefore not controlled in analysis	Reliable	Not reported	Reported and their influence on autonomic measures analyzed
Edmiston, 2016	Reported, no significant group differences on IQ	Reliable	Not reported	Reported and participants were medication free during experiment
Eilam-Stock, 2014	No significant group differences on IQ	Reliable	Excluded for comorbid conditions except obsessive compulsive disorder	Excluded if using any psychoactive drugs in the last 5 weeks before experiment
Faja, 2013	No significant group differences on IQ	Reliable	Not reported	Not reported
Hollocks, 2014	Significant group differences in IQ, statistically controlled in analysis	Reliable	Reported, effect of presence of anxiety disorder analysed	Excluded if using medications associated with anxiety or depression, but other medication use not reported
Hu, 2018	No control group presented. Influence of clinical group's IQ controlled for in analysis	Reliable	Not reported	Not reported
Joseph, 2008	No significant group differences on IQ	Reliable	Not reported	Not reported
Keith, 2019[a]	No significant group differences on IQ	Reliable	Not reported	Not reported
Keith, 2019[b]	No significant group differences on IQ	Reliable	Reported, not analyzed	Reported, not analyzed, some participants taking psychotropic drugs at the time of experiment
Klusek, 2013	ASD and NT groups not significantly different on IQ	Reliable	Not reported	Reported, not analyzed, some participants taking psychoactive drugs at the time of experiment
Kootz, 1982	No NT group present. Effect of IQ analyzed	Reliable	Not reported	Not reported
Kuiper, 2019	IQ>70, no significant group differences on IQ	Reliable	Not reported	Excluded if using beta-blocker medications, other medication use reported
Kushki, 2014	Significant group differences on IQ, relationship of IQ to autonomic measures examined	Reliable	Reported, not analyzed	Reported, not analyzed, some participants taking psychoactive drugs at the time of experiment

Kushki, 2013	Significant group differences on IQ, relationship of IQ to autonomic measures examined	Reliable	Excluded if history of psychiatric disorder	Excluded if using medications that influence ANS
Mathersul, 2013[a]	No significant group differences on IQ	Reliable	Excluded if history of psychiatric or developmental disorders (other than ASD)	Not reported
Mathersul, 2013[b]	No significant group differences on IQ	Reliable	Excluded if history of psychiatric or developmental disorders (other than ASD)	Not reported
Mathewson, 2011	No significant group differences on IQ	Reliable	Excluded if history of psychiatric disorder	Reported and their influence on autonomic measures analyzed
Matsushima, 2016	ASD and NT groups significantly different on IQ, IQ not controlled for in the analysis	Not reliable	Reported, not analyzed	Reported, not analyzed
McCormick, 2014	ASD and NT groups significantly different on IQ, IQ not controlled for in the analysis	Not reliable	Not reported	Not reported
Ming, 2005	Not reported	Not reliable	Not reported	Excluded if using medications that influence the ANS such as clonidine, resperidone, amphetamines and other psychostimulants. Some participants were on other medications at the time of experiment.
Ming, 2016	Not reported	Not reliable	Not reported	Excluded if taking medications known to affect ANS. Some participants were on other medications at the time of experiment.
Neuhaus, 2014	Groups not significantly different on full scale IQ, but they were significantly different on verbal IQ. Correlations between autonomic measure and full scale IQ (but not verbal IQ) reported	Not reliable	Not reported	Not reported
Neuhaus, 2015	Groups not significantly different on full scale IQ, but	Not reliable	Not reported	Participants required to be free of stimulant medications for 36

	they were significantly different on verbal IQ. Relationship of IQ with autonomic measures not reported			hours before experiment
Nuske, 2014	NT and ASD significantly different on IQ, relationship of autonomic measure and IQ examined and reported	Reliable	Not reported	Participants not taking medication at the time of experiment
Pace, 2015	IQ>70, no other information provided	Not reliable	Excluded for comorbid psychiatric condition	Excluded if taking any psychoactive medications
Patriquin, 2013[a]	Same sample as Patriquin et al, 2013[b]	Reliable	Not reported	Not reported
Patriquin, 2013[b]	Receptive language used to index cognitive function, its relationship with ANS measures reported. No control group present in this study	Reliable	Not reported	Not reported
Patriquin, 2014	Not reported	Not reliable	Not reported	Not reported
Porges, 2013	IQ measured and its relationship with ANS measures analyzed	Reliable	Not reported	Excluded if taking medications that influence ANS
Riby, 2012	Not reported	Not reliable	Not reported	Not reported
Saghir, 2017	IQ>50, ASD and NT groups significantly different on IQ, IQ was controlled in statistical analysis	Reliable	Not reported	Proportion of participants on and off medications (unspecified) during experiment reported. Effect of being on medication on group differences examined and reported
Schaaf, 2015	IQ>75, ASD and NT groups significantly different on IQ, this was not controlled for in analysis	Not reliable	Participants screened for presence of psychiatric conditions and number of participants who screened positive for different psychiatric conditions has been provided	Participants not taking medications that might influence ANS such as benzodiazepines or SSRIs
Schoen, 2009	IQ>70, measured only for ASD group (and not in NT group) to check if inclusion criterion was met	Not reliable	Not reported	Not reported
South, 2011	No significant group differences between ASD and NT participants on IQ	Reliable	Not reported	Not reported
Tessier, 2018	IQ>80, ASD and NT participants significantly different	Not reliable	Excluded for comorbid conditions	Excluded if taking medications

	on IQ, this was not controlled for in analysis			
Thapa, 2019	IQ>70, no other information provided	Not reliable	Reported and their influence on autonomic measures analyzed	Reported and their influence on autonomic measures analyzed
Tiinanen, 2011	IQ in 'normal range', no other information provided	Not reliable	Not reported	Not reported
Toichi, 2003	IQ>60, IQ for each group reported but any group differences, if present, not reported	Not reliable	Participants free of any comorbid psychiatric conditions	Participants free of medications
Top, 2018	No group differences on IQ between ASD and NT participants	Reliable	Not reported	Not reported
Van Engeland, 1984	Wide variation in IQ between ASD and NT groups, IQ not controlled in analysis	Not reliable	Not reported	No participants used psychotropic drugs
Van Engeland, 1991	IQ in "normal" range, IQ controlled for in analysis	Reliable	Not reported	No participants used psychotropic drugs
Van Hecke, 2009	No significant group differences on IQ, IQ used as a covariate in analysis	Reliable	Not reported	Reported and their influence on autonomic measures analyzed
Zahn, 1987	IQ described for autistic participants but not for NT participants, IQ not controlled for in analysis	Not reliable	Not reported	If on medications, participants discontinued use of medication for a month prior to experiment
Zantinge, 2017	Significant group differences between autistic and NT participants, IQ controlled for in analysis	Reliable	Not reported	Not reported
Zantinge, 2019	Significant group differences between autistic and NT participants, relationship between IQ and ANS measures examined and reported	Reliable	Not reported	Not reported

[a]IQ Categorization: Studies categorized as Reliable if they reported IQ characteristics and differences between groups and either controlled for differences in analysis or evaluated the relationship of IQ with ANS measures of interest. Studies categorized as Not Reliable if they did not report on IQ, or reported significant group differences but did not control for this in analysis.