Do the cognitive and neural mechanisms underlying inattention differ between very preterm and term-born children?

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Abstract

Background: Compared with their term-born peers, school aged children born very preterm (≤32 weeks gestation) are at increased risk of inattention. It remains unclear whether the cognitive and neural mechanisms underlying inattention are the same in both very preterm and term-born children.

Aims: The aim of this study was to determine whether the cognitive and neural mechanisms underlying inattention differ between term-born and very preterm children. Chapter 3 explored cognition, while Chapters 4 & 5 explored neural processing in terms of event-related potentials (ERPs) and frequency analysis of functional connectivity respectively, to identify mechanisms underlying inattention.

Method: A sample of 65 children born very preterm (≤32 weeks gestation) aged 8-11 years was recruited. A comparison group of 48 term-born peers (≥37 weeks gestation) matched for inattention symptoms using the parent-rated Strengths and Weaknesses of ADHD and Normal behaviour (SWAN) questionnaire was selected for comparison. All children were asked to complete neurocognitive tests to assess basic cognitive processes, executive function and sustained attention. Electroencephalography (EEG) was recorded from a sub-sample of children (very preterm *n*=43; term-born *n*=40) while they completed a sustained attention task. The contingent negative variation ERP component and theta and alpha frequency changes following the cue stimulus were derived from the EEG as neural indices of response preparation. Similarly, following the presentation of cued and uncued target stimuli, the P1, P2, and P3 ERP components were derived from the EEG as neural indices of stimulus detection, stimulus categorisation, and evaluation of task-relevance respectively.

Results: In both groups, more severe parent-rated inattention on the SWAN was predicted by poorer verbal and visuo-spatial short term memory, visuo-spatial working memory, and greater response time variability, and by smaller amplitude of the P2 ERP to uncued targets at the neural level. In children born very preterm only,

Abstract

slower motor processing speed, and smaller theta increases at the neural level, predicted more severe parent-rated inattention. Similarly, in term-born children only, shorter P2 ERP latencies to all targets predicted more severe parent-rated inattention.

Conclusions: In sum, the cognitive and neural mechanisms underlying inattention in term-born and very preterm children were partially overlapping, but some mechanisms were unique to only one group. These results present candidate mechanisms that may be useful for the identification of children at risk for inattention, and as potential targets for intervention.

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Table of Contents

List of Tables

CHAPTER 2: METHODS

CHAPTER 3: COGNITIVE PREDICTORS OF INATTENTION

CHAPTER 4: ERP PREDICTORS OF INATTENTION

CHAPTER 5: FUNCTIONAL CONNECTIVITY AND INATTENTION

List of Figures

CHAPTER 2: METHODS

CHAPTER 3: COGNITIVE PREDICTORS OF INATTENTION

CHAPTER 4: ERP PREDICTORS OF INATTENTION

CHAPTER 5: FUNCTIONAL CONNECTIVITY AND INATTENTION

Chapter 1: General Introduction

In England and Wales, around 12,000 babies per year are born at less than 32 weeks gestation (National Statistics, 2014). These children are categorised as 'very preterm', where categorisation is conducted according to gestational age at birth, with children born at less than 28 weeks referred to as 'extremely preterm', and those born at 32-36 weeks as 'late and moderately preterm'. While medical advances have resulted in improved survival rates for very preterm children over the last 30 years, this early birth can affect brain development, and as a result, can have long-term impacts on cognition, behaviour and academic achievement (Johnson, 2007). Studies with birth-weight defined samples, where very low birth weight (VLBW) is defined as <1500g, and extremely low birth weight (ELBW) as <1000g, have reported similar neurobehavioural outcomes (e.g. Rickards, Kelly, Doyle, & Callanan, 2001).

Preterm birth and/or low birth weight have been identified as risk factors in the development of psychiatric disorders, and in particular, attention-deficit/hyperactivity disorder (ADHD; Bhutta et al., 2002; Aarnoudse-Moens, Smidts, Oosterlaan, Duivenvoorden, & Weisglas-Kuperus, 2009), autism spectrum disorders (ASD; Gardener, Spiegelman, & Buka, 2011) and anxiety disorders (Burnett et al., 2011). Of these disorders, the risk of ADHD is most common, with prevalence estimates ranging between 9-11% in the very preterm population, representing a 2-3 times increased risk compared with term-born children (Johnson & Marlow, 2011; Treyvaud et al., 2013). This is of concern due to the negative long-term outcomes across a wide range of domains observed in individuals with ADHD (Shaw et al., 2012). Poorer social skills, poorer academic performance and low self-esteem are observed in children and adolescents with ADHD (Harpin, 2005). By adulthood other difficulties are reported even in individuals who no longer meet diagnostic criteria, including poorer occupational and economic outcomes and higher divorce rates (Klein et al., 2012). Not only does of ADHD affect multiple aspects of an individuals' life throughout childhood and into adulthood, but more concerning is that negative impacts are still present even in those who receive treatment for ADHD (Shaw et al., 2012). Moreover, there is evidence to suggest higher levels of ADHD symptoms even in children born very preterm who do not reach clinical thresholds for diagnosis (Johnson & Marlow, 2011), and such children may also suffer from consequences associated with ADHD. As yet it is unclear whether the mechanisms underlying ADHD symptoms are the same in preterm and term-born children. Improving our understanding of the mechanisms underlying ADHD in preterm and term-born children is a useful first step towards identifying children at risk and finding ways to reduce poor long-term outcomes.

In this chapter I will provide a general introduction to what is known about the presentation and aetiology of ADHD in both general and preterm populations, and the arising implications and research questions (Section 1.1). In Section 1.2 I then present the aims of this thesis and introduce the methods I used to achieve these aims. Section 1.3 briefly introduces the literature surrounding the analyses presented in each experimental chapter, which will be addressed in more depth in the relevant chapters. Finally, Section 1.4 provides an overview of the structure of this thesis.

1.1 ADHD following preterm birth

1.1.1 Presentation and aetiology of ADHD in the general population

ADHD is a neurodevelopmental disorder characterised by developmentally inappropriate levels of inattention and hyperactivity/impulsivity. Prevalence estimates of ADHD vary between 3-20% (Gaddow et al., 2000; Gomez, Harvey, Quick, Scharer, & Harris, 1999), with a world-wide pooled estimate of 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Even assuming the more conservative prevalence estimates are accurate, ADHD is a disorder affecting the equivalent of a child in every classroom, indicating its widespread nature. Diagnosis can fall into three presentation types (categorised as subtypes in the DSM-IV; APA, 1994); the combined (ADHD/C) presentation, whereby a child displays both inattentive and hyperactive-impulsive symptoms, or the predominantly inattentive (ADHD/I), or predominantly hyperactive-impulsive (ADHD/HI) presentations, where children display primarily inattentive or hyperactive-impulsive symptoms respectively. A meta-analysis recently indicated that ADHD/I is the most common subtype, but due to a bias in clinic referrals ADHD/C is more commonly diagnosed (Willcutt, 2012).

In the general population, ADHD is understood to be a neurodevelopmental disorder of primarily genetic origin. The evidence for the role of genetics is strong, with heritability estimates pooled from twin studies reaching 76% (Faraone et al., 2005). Candidate genes have been identified, particularly those with a role in regulating neurotransmitters such as dopamine and serotonin (Faraone et al., 2005). Heritability is not only observed for both ADHD/C and ADHD/I diagnoses, but also for inattentive and hyperactive/impulsive behaviours more generally (Willcutt et al., 2012). In addition, environmental factors, particularly socio-economic status (SES) and family dysfunction, have been shown to predict ADHD (Scahill et al., 1999).

There has been a long-running debate as to whether the different presentations of ADHD can be considered distinct disorders (Milich, Balentine, & Lynam, 2001) and this is reflected in the ever-changing nomenclature for ADHD. The third edition of the diagnostics and statistical manual of mental health disorders (DSM-III; APA, 1980) first introduced criteria for the predominantly inattentive presentation of ADHD, referring to Attention Deficit Disorder with or without hyperactivity. It was in the DSM-IV (APA, 1994) that the subtypes were named the combined (ADHD/C), predominantly inattentive (ADHD/I) and predominantly hyperactive-impulsive (ADHD/HI) subtypes, but research has shown that the DSM-III subtypes of attention deficit disorder with or without hyperactivity correspond closely to the DSM-IV subtypes of ADHD/I and ADHD/C (Morgan, Hynd, Riccio, & Hall, 1996). Meanwhile, the most recent edition of the DSM (DSM-V; APA, 2013) refers to combined, inattentive and hyperactive-impulsive *presentations* rather than subtypes. This reflects the fact that the pattern of symptoms displayed by an individual may change across their lifetime, and thus the presentation that they show may differ at different time points, but their diagnosis of ADHD would remain stable.

One important issue to consider is that diagnosis of the combined subtype/presentation of ADHD requires demonstration of a minimum of 6 symptoms from both inattentive and hyperactive-impulsive categories, thus these children must demonstrate at least 12 symptoms. In contrast, other subtypes may be diagnosed with a minimum of 6 symptoms from one subscale only. Ultimately this means that many of the children with ADHD/C display a greater number of symptoms in general compared to those with ADHD/I or ADHD/HI. Not only this, but children with a diagnosis of ADHD/I may display 5 symptoms from the hyperactive-impulsive category, along with 6 symptoms from the inattentive category, but they would remain sub-threshold for an ADHD/C diagnosis. Such issues with diagnosis make research into differences between subtypes/presentations difficult because the result is groups of children with ADHD/I diagnoses that are heterogeneous in the levels of hyperactive-impulsive symptoms displayed, and because diagnoses for an individual can change between ADHD/C and ADHD/I across childhood, it is difficult to know whether a group of children with ADHD/I diagnoses truly represents an ADHD/I population, or merely a less severe ADHD/C population.

A review emerging prior to the publication of DSM-V suggested that while there is strong evidence for a distinction between inattentive and hyperactive-impulsive symptoms, there is little evidence to support the validity of ADHD/HI beyond the age of 7, and only weak evidence to support the distinction between ADHD/C and ADHD/I in terms of aetiology, cognition, academic performance and treatment response (Willcutt et al., 2012). Moreover Willcutt et al. reported that longitudinal studies demonstrated that a large proportion of children met criteria for a different subtype at follow-up assessments compared to their original diagnosis. This long-term instability casts doubt on the distinction between subtypes as separate and stable disorders with differing aetiology, however differences in the impairments associated with the inattentive versus hyperactive-impulsive symptom domains indicate the clinical relevance of this discrimination.

1.1.2 **Presentation and aetiology of ADHD in children born preterm**

At the group level, children born very preterm tend to display increased levels of inattention, while remaining below clinical cut-offs for hyperactivity/impulsivity, consistent with the ADHD/I form of the disorder (Johnson et al., 2010; Szatmari, Saigal, Rosenbaum, & Campbell, 1993). These findings are observed both in diagnostic studies that use DSM-V-based criteria, and in descriptive studies that use questionnaires that split inattentive and hyperactive-impulsive domains (Johnson and Marlow, 2011). Contrary to epidemiological patterns usually observed in ADHD diagnosis, although there is an excess of ADHD in the very preterm population, there is no concomitant excess of additional behavioural difficulties such as conduct disorder in the same population and diagnoses in very preterm children do not show the same 3:1 (boys: girls) gender bias (Johnson et al., 2010; Szatmari et al., 1993). Once again, this is more similar to patterns seen for the ADHD/I subtype, which is less frequently comorbid with oppositional or conduct problems (Willcutt et al., 2012), and is more frequently seen in females (Willcutt, 2012). Even in studies where symptoms in very preterm groups fail to reach clinical significance and 'abnormal' cut-offs, it should be noted that studies continue to find higher mean symptom scores for ADHD in very preterm children compared to term-born peers (Johnson & Marlow, 2011). This suggests that in many cases children with sub-clinical levels of symptoms may be overlooked because they do not satisfy diagnostic criteria, yet may still have higher levels of ADHD behaviours that negatively impact their social, emotional and academic development (Brogan et al., 2014). The potential implication of this is that without formal diagnosis, families and teachers of these children may not receive guidance that could facilitate better developmental support.

Evidence concerning the origin of ADHD in preterm populations is not consistent with the patterns observed in children with ADHD in the general population. A study of mothers who had given birth to term, as well as preterm children, indicated that genetic factors could not explain the relationship between preterm birth and ADHD (Lindström, Lindblad, & Hjern, 2011). Similarly, unlike in ADHD populations, studies have failed to find a relationship between psychiatric symptoms and SES in preterm children (Loe, Lee, Luna, & Feldman, 2011). Moreover, it has been observed that there is a 'gestational gradient', whereby the risk of psychiatric disorders increases as gestational age at birth decreases (Aarnoudse-Moens, Weisglas-Kuperus, Goudoever,

& Oosterlaan, 2009; Johnson, 2007) which reinforces the idea that the increased ADHD prevalence is linked to preterm birth and/or perinatal medical factors rather than to genetics or later environmental factors during development. We also know that ADHD diagnosis is more stable in very preterm children from childhood to adulthood than in term-born controls (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2015a). These patterns have led researchers to propose that very preterm children may show a more 'pure' and biologically determined form of ADHD (Wolke, 1998).

Current research implicates aberrant neural development following very pretem birth in the later development of ADHD, with various imaging studies revealing structural and functional abnormalities in very preterm children relating to cognitive and behavioural impairment. The combination of developmental disturbance to typical maturational processes and destructive processes in the developing brain of children born very preterm is likely to impact the neuropsychological systems responsible for attentional processing. Major changes occur in the developing foetal brain during the last trimester of pregnancy, the period that is disrupted for children born very preterm. The cortex develops its folds, increasing the surface area dramatically (Kappellou et al., 2006), and overall cortical volume increases at a linear rate (Huppi et al, 1998). The third trimester is also the period in which the prefrontal cortex (important for executive control) and temporal lobe (important for memory and learning) develop the most (Orasanu et al., 2016).

Disruptions during this critical period due to early emergence from the intrauterine environment are likely to alter the typical maturational processes (Blackburn, 1998). In a preterm baby, immaturity of the central nervous systems and other physiological systems can make the transition to the extra uterine environment at birth more challenging, and although efforts are made to reproduce the conditions of the uterine environment, time on neonatal intensive care units exposes preterm babies to different environmental stimulations, often including medical intervention (Aucott et al., 2002).

Along with the disruptions to typical neural development, very preterm children have increased vulnerability to brain injury from complications. Babies born between 23-32 weeks gestation are susceptible to periventricular leukomalacia (PVL), resulting from necrosis of white matter cells, particularly of the glial cells that support neurons, caused by decreased blood flow (thus oxygen). PVL can be particularly damaging as this period of vulnerability coincides with critical neural organisation processes involving white matter cells such as the progression of the development of oligodendrocyte lineage, essential for myelination (Back et al. 2001).

The aberrant white matter development resulting from combined developmental and brain injury processes alters the connectivity of the neural networks, and some authors have gone so far as to hypothesise that preterm birth represents a disease of connectivity (Lubsen et al., 2011). Given that attentional processing involves large-scale interregional networks (Fan et al., 2005), interregional connectivity is essential. A recent review reported evidence of altered structural connectivity and atypical development of white matter tracts, even in preterm children who do not appear to show any major brain injury or impairment (Ment, Hirtz, & Hüppi, 2009). Such abnormalities appear to be long-term, with a longitudinal study showing 55% of adolescents born very preterm had abnormalities that could still be identified by neuroradiologists blind to birth status, most commonly enlarged ventricles and thinning or atrophy of the corpus callosum (Stewart et al., 1999). Moreover, associations between atypical white matter development and inattention have been observed in adolescents born very preterm (Skranes et al., 2007).

1.1.3 Neurocognitive models of (in)attention

Dominant theoretical neurocognitive models of attention (and consequently *in*attention) consider attention to be a multi-dimensional construct comprising different components that are separable but interrelated (e.g. Posner and Petersen, 1990; Treisman, 1998). Each component performs different functions in the attentional system in order to enable the allocation of resources to appropriate sensory and cognitive information processing systems. An early but influential model developed by Posner and Petersen (1990), referred to three attentional components;

(i) orienting attention, (ii) maintaining attention, and (iii) top-down control of attention. These components allow individuals to selectively allocate resources to relevant stimuli, to sustain a level of mental arousal and alertness to maintain engagement with a task, and to flexibly switch the focus of resources to different types of processing. The exact number of components has been debated within the literature, with prominent factor analyses proposing four-factor models that identified a fourth memory/encoding factor (Robertson, Ward, Ridgeway and Nimmo-Smith, 1996; Mirksy, Anthony, Duncan, Ahearn and Kellam, 1991). However, these four-factor models continue to highlight the three components proposed in Posner and Petersen (1990) of orienting/selective attention, maintaining/sustained attention and executive/top-down/switching attention. Indeed, whether factors that appear to reflect memory should be retained in a model of attention is questionable. Thus it is generally accepted that there are at least these three components despite slight differences in nomenclature, and moreover, fMRI BOLD activation during the Attentional Network Test (ANT; designed to require orienting, sustaining and switching) has supported the presence of these three attentional networks as separable neural networks (e.g. Fan et al., 2005). A more recent update for the original model reviews 20 years of cognitive neuroscience research that supports this framework (Petersen and Posner, 2012).

Historically, neuropsychological models of attention have arisen from studies in adult populations, and only more recently have they been considered in relation to development from infancy. While some research groups have found support for the adult models in child samples (e.g. Mirksy et al., 1991; Manly et al., 2001), more recent studies in younger samples have identified only two factors (Beckenridge et al., 2013; Steele et al., 2012). According to Steele et al. (2012), the factors apparent in children younger than 6 years represented a single sustained-selective attention component, along with an executive component. Meanwhile, the two factors observed in children younger than 4.5 years in Beckenridge et al. (2013) were less easily defined and interpreted, with a large amount of cross-loading across the factors, but children between 4.5 and 6 years demonstrated a three-factor structure more similar to the selective, sustained and executive components seen in adults. A study specifically reviewing the development of selective, sustained and executive attention across childhood using the ANT, found that both the orienting/selective attention component and the alerting/sustained attention component showed stability between ages 6-10 years (Rueda et al., 2004). Interestingly, the executive component showed a clear improvement at 6-7 years, before stabilising. More research needs to be conducted in order to understand at which point the attentional system develops from two components to three, but evidence supports the idea that the three-factor model of selective, sustained and executive attention develops by middle-childhood, the age group of interest for this thesis. The analyses in Chapter 3 focus on cognitive processes related to executive attentional control while analyses of a cued-continuous performance task in Chapters 4 and 5 investigate processes relevant to sustained attention (behavioural measures, cue-locked ERP and frequency measures) and selective attention (ERP differences between cued and uncued targets).

The advancement in neuroscience techniques has allowed for a greater understanding of the neural networks that underpin these attentional systems, and these are reviewed in full in Petersen and Posner (2012). The alerting/sustained attention system is thought to be modulated by noradrenaline (Petersen and Posner, 2012), although different authors have highlighted different brain areas. While one study implicated a right-lateralised fronto-parieto-thalamic network (Sturm and Willmes, 2001), another suggested left lateralised fronto-parietal network. It has been proposed that this discrepancy may relate to laterality differences is tonic and phasic alerting (Petersen and Posner, 2012). The orienting/selective attention system is thought to consist of a right-lateralised network that is modulated by the cholinergic system, involving two sub-processes (Petersen and Posner, 2012). Corbetta and Shulman (2002) demonstrated that initial orienting was associated with a dorsal system that included the frontal eye fields and the interparietal sulcus, while reorienting was associated with a more ventral system involving the temporoparietal junction and the ventral frontal cortex. The executive control network has been linked to the anterior cingulate and the lateral prefrontal cortex, and is thought to be modulated by dopamine (Petersen and Posner, 2012).

Interestingly, in younger children it appears that the functions carried out by the executive control network in adults are instead provided by the orienting system, and when a child reaches 3-4 years of age, the executive attention network increasingly takes over these functions, becoming more dominant in controlling attention as the child develops (Posner et al., 2012). This is concurrent with the behavioural evidence supporting a two-factor model of attention in younger children described above. On the basis of converging evidence from behavioural, genetic and imaging studies, Posner et al. (2012) proposed that this shift is driven by changes in connectivity; the connectivity of the executive attention network depending on the maturation of large projection cells found in the cingulate and insula, which may occur later in development, driven by both genetics and environmental influences. Making a similar argument, Rothbart et al. (2011) reconcile seemingly contrasting findings that task-performance becomes associated with smaller regions of activation as children develop (Durston and Casey, 2006), but that resting connectivity networks become more global (Fair et al., 2009), by hypothesising that as more focal activity requires fewer neurons, global connections become stronger to link the regions.

In atypical development of attention, such as that observed in ADHD, recruitment of atypical neural networks has been observed in 8-12 year old boys relative to typically developing peers in all three components of attention (Konrad et al., 2006). Specifically, during alerting children with ADHD showed less right-sided activation in the anterior cingulate, during reorienting more fronto-striatal-insular activation was observed, and there was less fronto-striatal activation during executive control. This supports the idea that altered connectivity within neural networks may be a key driver of ADHD, and lends further support to the idea that aberrant in connectivity in children born very preterm is likely to be a major driver of the increased risk of inattention.

1.1.4 Implications and questions

Evidence of a gestational age related gradient in outcomes suggests that the cause of ADHD in children born preterm may be the prematurity per se (Aarnoudse-Moens et al., 2009; Johnson, 2007) while in term-born children it is thought to result from a gene-environment interaction (Faraone et al., 2005). However, it remains unclear whether the cognitive and neural mechanisms that underlie the behavioural symptoms of ADHD in preterm and term-born children are similar or different. Different initial causal factors may lead to similar developmental trajectories with equivalent cognitive and neural mechanisms that result in similar phenotypic presentation. Alternatively, different causal factors may lead to separable trajectories that affect different mechanisms but still lead to similar phenotypic presentations. This is an important question with significant clinical implications, particularly given that such mechanisms can be used as intervention targets, in diagnosis assessments, or to assess the success of interventions.

Children born very preterm are at greater risk for increased inattention rather than hyperactivity/impulsivity in terms of both symptoms and disorders (Brogan et al., 2014; Johnson et al., 2010). Moreover converging evidence has shown that increases in inattention rather than hyperactivity/impulsivity are more strongly associated with adverse neuropsychological and academic outcomes in term-born children (Willcutt et al., 2012) and children born very preterm (e.g. Jaekel et al., 2012). As inattention appears to be the core deficit in very preterm children with ADHD, a comparison of the mechanisms underlying inattention specifically is likely to be of the greatest value. It is thought that increasing the understanding of the mechanisms underlying inattention in term-born and preterm groups is likely to provide a basis for the identification of risk factors for inattention, prediction of future outcomes, and the formation and evaluation of targeted interventions, although such research is beyond the scope of this thesis.

If inattention in very preterm children is qualitatively different to that in term-born populations, different underpinning mechanisms are likely to emerge, raising questions about the generalisability of ADHD findings to inattention in children born very preterm. Alternatively, if inattention is qualitatively the same, with the same underlying mechanisms in both groups, the predominantly inattentive clinical presentation of ADHD in very preterm children could provide researchers with a potentially more ‘pure’ group in which to assess relationships between cognitive and neural processing and inattention, without conflating the results with those processes which are related to hyperactivity/impulsivity. Similarly, it may provide a new avenue of research into the validity of the predominantly inattentive subtype as a distinct disorder.

1.2 Aim of the thesis

The overarching aim of this thesis was to determine whether cognitive and neural mechanisms underlying inattention differ between term-born and very preterm children. Inattentive behaviour in both preterm and ADHD populations has been attributed to neurobiological changes, whether resulting from altered neural development following preterm birth, or from the combination of genetic and environmental risk factors. The same neurobiological changes in the brain that ultimately manifest in inattentive behaviour are thought to operate via mechanisms that can be measured at the cognitive and electrophysiological level. As such, measures of cognitive performance and electrophysiological activity were chosen for the present study to provide a comprehensive characterisation of the mechanisms by which structural and functional alterations within the brain can result in inattentive behaviour.

To date, most researchers have examined inattention in children born very preterm using a case-control approach, whereby a group of very preterm children with high levels of inattention is compared to a group of typically developing term-born children, who, as they are typically developing, tend to have low levels of inattention. While this provides an essential first step towards understanding the deficits present in very preterm children, it does not compare like with like, preventing us from understanding whether the causal pathways underpinning inattention are alike in both groups. In order to understand whether there are differences in the mechanisms underpinning inattention in very preterm children compared to term-born children, I considered it important to investigate candidate mechanisms in groups of children with similar levels of symptoms, who differ only in terms of gestation. In contrast to previous studies that have selected participants using clinical diagnosis or using recommended clinical cut-offs for ADHD risk/diagnosis (e.g. Potgieter, Vervisch, & Lagae, 2003; van der Meere, Börger, Potgieter, Pirila, & De Cock, 2009), here participants in both term-born and very preterm groups demonstrated a range of levels of inattention. By using a dimensional approach, which has been recommended for groups with heterogeneous outcomes (Gabrieli, Ghosh, & Whitfield-Gabrieli, 2015), I hoped to identify how individual differences in cognitive and neural processing can explain variance in inattentive behaviour and to compare the cognitive and neural functions that were found to underlie inattention in very preterm and term-born children aged 8-11 years.

Section 1.3 below introduces the areas of cognition and electrophysiology evaluated in the experimental chapters of the thesis, and Section 1.4 provides an outline of the thesis and explains how the aim of the thesis will be addressed.

1.3 What we know so far

1.3.1 Cognitive mechanisms

Chapter 3 of this thesis focuses on increasing our understanding of the cognitive mechanisms underlying inattention in term-born and very preterm children. Executive function is an umbrella term that refers to a set of interrelated higher-order cognitive skills which are important for the completion of goal-directed action. These include inhibitory control (successfully withholding inappropriate responses or ignoring sensory distractions), working memory (successful retention of information in the presence of concurrent processing) and task switching (successful shifting of attention between competing tasks). Difficulty in these areas can result in some of the behaviours associated with ADHD, such as interrupting (failure of inhibitory control) and losing place in activities (failure of working memory). Indeed, executive function is an area of cognition that has been strongly implicated in ADHD (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and is also impaired in children born very preterm (Aarnoudse-Moens et al., 2009; Mulder, Pitchford, Hagger, & Marlow, 2009). Moreover, evidence has begun to directly link impaired executive function to inattention in children born preterm (Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, & Oosterlaan, 2013; de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012; Mulder, Pitchford, & Marlow, 2011b; Scott et al., 2012) and in individuals with ADHD (Chhabildas, Pennington, & Willcutt, 2001; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Rogers, Hwang, Toplak, Weiss, & Tannock, 2011) .

To date, most studies of inattention in preterm children compare preterm children to typically developing term-born peers who tend to have average levels of attention. By not including a term-born comparison group who display both severe inattention and above average attention, studies may have failed to accurately capture associations between cognition and inattention that are present in the term group. This is one aspect I intended to address in my own analyses by selecting a term-born comparison group matched to a preterm group on levels of inattention. In addition, given that poor basic cognitive functioning has also been identified in both preterm and ADHD samples, studies investigating the role of executive functioning should also account for the influence of variation in basic cognitive processing. In particular, slow processing speed has been implicated in ADHD/I (Diamond, 2005) and inattention in children born very preterm (Mulder, Pitchford, & Marlow, 2011b), and poor short term memory (Shum, Neulinger, Ocallaghan, & Mohay, 2008) and visuo-spatial processing (Simms et al., 2015; Foulder-Hughes & Cooke, 2003; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999) are also associated with very preterm birth. Poor basic processing could be at the root of the executive impairment, or directly linked to inattention. This is an important issue to address in order to determine the most appropriate targets for intervention. Therefore, the study reported in Chapter 3 of this thesis included measures of basic cognitive functioning in addition to measures of executive function.

1.3.2 Event-related potentials

There is a plethora of research utilising event-related potentials (ERPs) to advance our understanding of the neural underpinnings of atypical processing associated with ADHD (see Johnstone, Barry, & Clarke, 2013 for a recent review). ERPs present an opportunity to assess neural activity elicited in response to stimuli with millisecond temporal resolution in order to provide an insight into how the brain functions. Given that ADHD is a neurodevelopmental disorder, assessing the neural characteristics of sensory and cognitive processes provides an additional meter by which we can understand impairments and how best to address them. Atypical characteristics in ERP components thought to represent orienting to cues, stimulus discrimination and evaluation of stimulus relevance have been identified in individuals with ADHD (Johnstone et al., 2013). It is also proposed that ERPs have clinical utility in ADHD diagnosis and treatment, and they have been used as endophenotypes to aid the assessment of heritability of the disorder (e.g. Albrecht et al., 2008) and to assess the success of treatment (e.g. Sunohara et al., 1999). Studies using ERPs to evaluate inattention in preterm children are scarce however, with only one published study to date (Potgieter, Vervisch, & Lagae, 2003). As such, this technique has not been fully exploited and provides an opportunity to explore the mechanisms underlying inattention in children born preterm.

Chapter 4 of this thesis discusses the relevant literature published in the area to date, and reports the results of an investigation of attentional processing during a sustained attention task using ERPs. In this study I aimed to identify neural correlates of inattention and compare these in term-born and very preterm children. I also assessed whether ERP measures improved upon the explanatory power in predicting inattention over cognitive measures alone. Moreover, in accordance with emerging evidence that slow processing speed may predict poor behavioural and academic outcomes in preterm children (Mulder, Pitchford, & Marlow, 2010; Mulder et al., 2011a; Rose, Feldman, & Jankowski, 2011), I separated the different stages of neural processing (stimulus detection, stimulus categorisation, stimulus evaluation and preparation of the motor response) to examine whether inattention was predicted by the speed of processing at any particular stage.

1.3.3 **Connectivity**

Recent work has begun to implicate impaired connectivity in ADHD, moving away from a focus on distinct functions or brain regions (Konrad & Eickhoff, 2010). Similarly, aberrant connectivity is frequently cited as a potential mechanism for poor neurocognitive (Nosarti et al., 2006; Woodward, Clark, Bora, & Inder, 2012), neurobehavioural (Fischi-Gómez et al., 2015; Skranes et al., 2012), and academic (Mulder, Pitchford, & Marlow, 2010; Rose et al., 2011) outcomes in preterm children. Electrophysiological measures of oscillatory activity during tasks presents an option for investigating functional connectivity that is low-cost and more readily available compared to fMRI. While these techniques have been exploited to study the role of connectivity in individuals with ADHD (e.g. Mazaheri et al., 2010, 2014; McLoughlin, Palmer, Rijsdijk, & Makeig, 2014; Murias, Swanson, & Srinivasan, 2007), there is a dearth of research into oscillatory connectivity in relation to inattention in children born very preterm.

Chapter 5 of this thesis discusses the relevant literature published in the area to date, and aims to compare how fronto-occipital connectivity is related to inattention in term-born and very preterm children by investigating oscillatory electrophysiological activity. I used a method of measuring fronto-occipital connectivity thought to reflect top-down attentional control that has been shown to differentiate children with ADHD from their typically developing peers (Mazaheri et al., 2010a, 2014a).

1.4 Thesis outline

Chapter 2 of the thesis presents the study design and sample characteristics. This is followed by three experimental chapters, each of which present a literature review, further description of relevant methods, and analyses that aimed to address different aspects of the overarching thesis aim. Measurement and analysis of both cognitive and neural correlates of inattention were included in an effort to produce converging evidence that would provide a coherent picture of the mechanisms underlying inattention in term-born and preterm children. In particular, it was hoped that the selection of a sample of term-born children who demonstrated varying levels of inattentive symptoms ranging from severe to above average attention would fully capture the presence of any underlying mechanisms, allowing for direct comparison with those observed in children born very preterm.

In Chapter 3 I compare the cognitive mechanisms underlying inattention in term-born and very preterm children. This study incorporates measures of executive function as well as more basic cognitive functioning, to further elucidate and compare the mechanisms that explain variance in inattention in term-born and very preterm children, and to determine whether inattention results from global or selective executive function deficits. Chapter 4 compares the neural mechanisms underlying inattention using ERP methodology. I assessed stimulus processing during a sustained attention task, targeting ERP components that are known to show attentional modulation. It was hoped that this analysis would help us to understand more about the possible role of processing speed by separating the neural processing responsible for a behavioural response into its constituent parts. Chapter 5 investigates electrophysiological oscillations and fronto-occipital connectivity thought to be associated with top-down attentional control. The particular focus of this analysis was to compare how long-range connectivity that is important during attention underpins inattention in term-born and very preterm children. While Chapter 3 analyses build on an expanding body of literature into cognitive correlates of inattention in children born very preterm, analyses in Chapter 4 and 5 are among the first using electrophysiology in this way in this population. Finally, chapter 6 provides a general discussion of the findings and their implications.

Chapter 2: Methods

2.1 Ethical Approval

Ethical approval for this study was granted by Coventry and Warwickshire NHS Research Ethics Committee (ref: 13/WM/0203), and permission to use the Nottingham University Hospitals NHS Trust as a participant identification centre was granted by Nottingham University Hospitals NHS Trust Research and Innovation department (ref: 13CP004).

2.2 Participants

2.2.1 **Recruitment**

Two groups of children aged 8-11 years (the age at which ADHD symptoms are most prominent) were recruited for this study. The first group comprised 65 children born very preterm (VP; ≤32 weeks gestation) and the second group comprised 48 children born at term (37-42 weeks gestation). For a timeline of study recruitment and testing see Appendix 1.

2.2.1.1 Preterm Sample

All babies born ≤32 weeks gestation from 1st January 2003 to 31st March 2006 and admitted for neonatal intensive care in Nottingham University Hospitals (NUH) NHS Trust were identified in January 2013 from hospital records. A total of 407 births were identified, all of whom were traced to determine their current status and contact details. Of those traced, one child was deceased leaving a total of 406 eligible births. A further 8 children had moved away from the study area (> 1 hour travel from the study centre). The parents of 296 (72.9%) eligible children were contacted in batches of 50 to invite their child to participate in the study, of which 94 (23.2% of total eligible births) were recruited. The parents of the remaining 102 children were never contacted because it was not feasible to test any more children within the time constraints of the study. Of the 94 children recruited, 8 parents withdrew consent prior to the study assessment, and testing could not be scheduled for a further 21, resulting in a total of 65 children who were tested (16% of total eligible births; see Figure 2.1). Exclusion criteria for the VP children were, (i) any neurological or sensory impairment precluding participation in testing and (ii) non-fluency in English of the parent or child. Exclusion criteria were included in the recruitment information and no recruited children were excluded.

Analyses were conducted to compare the recruited sample with the rest of the eligible cohort to determine the representativeness of the sample. In order to provide a measure of socio-economic status (SES), the Index of Multiple Deprivation (IMD) ranking was identified for the mother's residential address provided at hospital admission. This is based on postcode and produces a census-based ranking of deprivation reflecting a range of indices economic, social and housing deprivation (McLennan et al., 2011). Rankings were aggregated into tertiles to categorise the residence as a low (ranks 0-10827), middle (ranks 10828 to 21654) or high (ranks 21655 to 32482) SES household.

The very preterm sample tested did not differ from the remaining eligible children with respect to gestational age, birth weight, or sex, however they were of significantly higher SES at the time of hospital admission (see *Table 2.1*). This is likely to reflect a common sampling bias within psychological research, whereby volunteers are more often of higher SES. This will be considered when interpreting the results and in relation to the representativeness of the findings from this study to the very preterm population as a whole.

Table 2.1: Characteristics of the very preterm children tested vs. those that were not tested.

	Tested (*n*=65)	Untested Total Eligible Births (*n*=406)	*p*
Birth factors			
Birth weight (kg)			
Mean (*SD*)	1.48 (0.42)	1.45 (0.43)	.586
Range	.66-2.45	.48-3.24	
Gestation (weeks)			
Mean (*SD*)	29.92 (1.92)	29.88 (2.18)	.890
Range	26-32	23-32	

Female sex, *n*(%)	29 (44.6%)	154 (45.4%)	.805
Demographics			
SES, *n*(%)			
Low SES	19 (29.7%)	175 (51.2%)	.006*
Middle SES	21 (32.8%)	86 (25.1%)	
High SES	24 (37.5%)	81 (23.7%)	

Note: Continuous variables were compared using independent samples t-tests, rank variables were compared using Pearson's chi-square. **p*<0.05.

2.2.1.2 Term Sample

Recruitment of term-born children was conducted in two stages (see *Figure 2.1*) in order to produce a sample with varying levels of inattention. The study was advertised via emails to parents of appropriately aged children in the University of Nottingham School of Psychology families database (families who have previously expressed an interest in participating in research studies), letters to parents sent via local schools, a press release, and flyers and posters distributed in the local community.

In stage one, parents of 124 term-born children aged 8-11 years completed a survey which included demographic information and the Strengths and Weaknesses of ADHD and Normal Behaviour (SWAN) parent rating scale (Swanson et al., 2006), the results of which provide an index of inattentive behaviour and ADHD symptoms (described in full below in Section 2.2.4.1). For each completed survey, ratings of inattentive behaviour were calculated from the inattentive subscale of the SWAN. On the basis of these scores, children with levels of inattentive behaviour from all sectors of the distribution, varying from far above average to far below average, were selected and invited to take part. A total of 96 children were selected and invited for stage two (see *Figure 2.1*). Of these 5 withdrew and for a further 43 children there was either no response to invitations to participate or it was not possible to schedule a test session. Parents of 28 children were not contacted on the basis that their children's SWAN scores were already well represented within the test sample. Consequently, 48 term-born children completed the PATCH Study test battery in an identical procedure to that given to very preterm children (see Study

Procedure below). Exclusion criteria for the term-born children were (i) any neurological or sensory impairment precluding participation in study tests, (ii) non-fluency in English of parent or child, and (iii) gestation of less than 37 weeks or greater than 42 weeks. No children met the exclusion criteria at stage one.

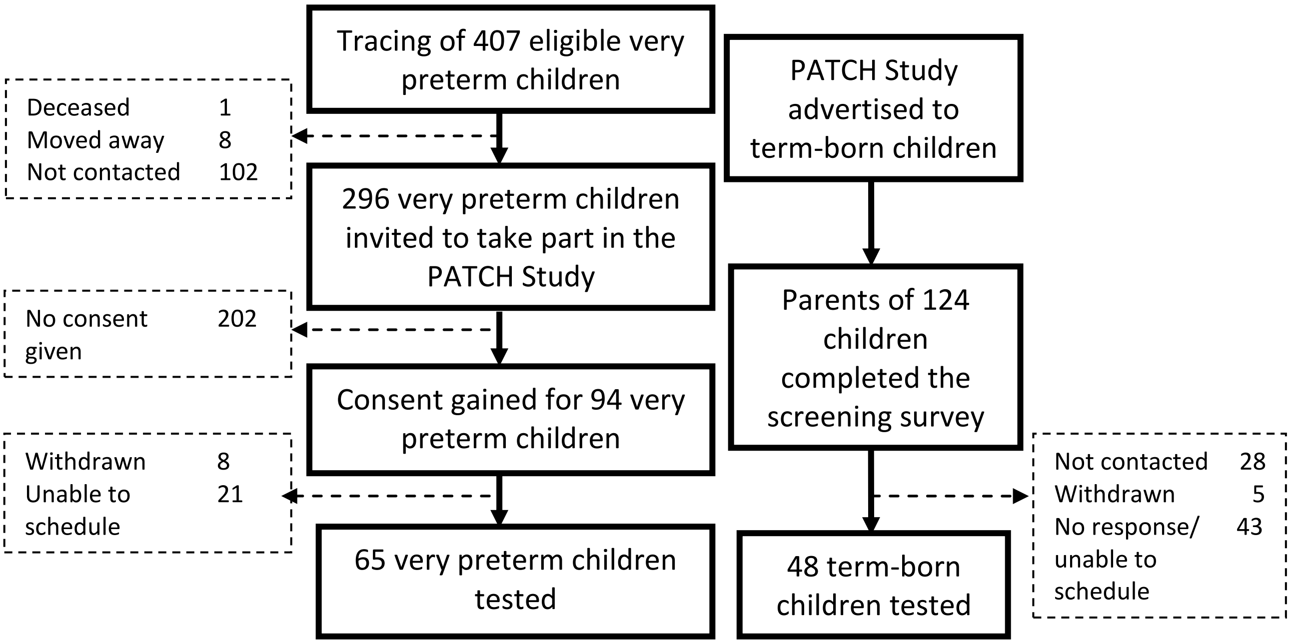

Figure 2.1: Flow chart showing the recruitment procedure for very preterm and term-born groups

2.2.2 Sample Characteristics

Table 2.2 shows the demographic information, participant characteristics and scores on clinical symptom questionnaires for the term-born and very preterm children tested in the PATCH Study.

2.2.3 Measures

2.2.3.1 Index of Multiple Deprivation

Categorisation of high, middle or low SES families was conducted using the same postcode-based method used for comparing tested and untested very preterm children described above, however in this case it was based upon the IMD ranking for each child's primary residence at the time of participation in the study.

2.2.3.2 Wechsler Abbreviated Scale for Intelligence

An age standardised estimate of full scale IQ was calculated from the Wechsler Abbreviated Scale for Intelligence (WASI; Wechsler, 1999). The vocabulary and matrices reasoning subtests were administered and scored as per the test manual. Taken together, raw scores were converted into age standardised estimates of the two-subtest full scale IQ (FSIQ-2). A FSIQ-2 score was not obtained for one term-born child who failed to complete both subtests.

2.2.3.3 Strengths and Weaknesses of ADHD-symptoms and Normal-behaviour (SWAN)

The SWAN rating scale (Swanson et al., 2006) is a parent-report measure of a child's ADHD symptoms. It has been considered more appropriate for use in community populations (Swanson et al., 2006) as it allows measurement of variation in above average attention in addition to below average attention (more severe *in*attention; Arnett et al., 2013). It comprises 30 items, of which 9 assess inattentive symptoms, 9 hyperactive-impulsive symptoms, 9 conduct/oppositional behaviour symptoms and 3 sluggish cognitive tempo. For each item, parents rated their child on a 7-point scale ranging from -3 ('far above average'), through 0 ('average'), to +3 ('far below average'). Negative scores represent fewer than average ADHD symptoms, scores close to zero represent average behaviour, and positive scores represent more severe ADHD symptoms.

The raw score from the inattentive subscale was used as the primary outcome measure in this study as well as for screening term-born children for recruitment. It was calculated as the sum of the raw score from each item of the inattentive subscale, giving a possible range of -27 to +27. Higher scores represent higher levels of inattention. Due to the computerised nature of scale completion, there were no missing items for any participant as the algorithm would not allow the parent to proceed if any items were not complete.

2.2.3.4 Conner's 3 Parent Rating Scale (Conner's 3-P)

Children were assessed for the level of DSM-IV ADHD symptoms for both the combined and the predominantly inattentive subtypes using the Conner's 3-P (Conners, 2008), as well as for the severity of inattentive, and of hyperactive-impulsive symptoms displayed. The correlation between inattentive and hyperactive-impulsive symptoms in each group was also assessed. The Conner's 3-Parent (Conners, 2008) was completed by parents to provide a more comprehensive clinical measure of ADHD symptoms for sample characterisation. It comprises 110 items designed to measure the frequency of symptoms of ADHD and the most common co-morbid problems, with subscales assessing inattention, hyperactivity, executive functioning, learning problems, peer relations, aggression and conduct disorder. It includes subscales based upon DSM diagnostic criteria for the predominantly inattentive subtype of ADHD (ADHD/I) and the combined subtype of ADHD (ADHD/C). These were used in this analysis to provide both a categorical and dimensional outcome to characterise (i) the number of children considered to show 'at risk' levels of symptoms in each group, and (ii) the relative symptom severity in each group. For each item, parents rated their child on a 4-point scale ranging from 0 ('never or almost never') through to 4 ('all the time'). Higher scores represent symptoms of a greater frequency and/or intensity.

Raw scores for the DSM ADHD/I and DSM ADHD/C subscales were converted into their relevant age- and sex- standardised *T*-scores, ranging from 40 or below (no risk), to 90 or above (very high risk). Children with *T*-scores above the suggested clinical cut off of 65 were classified as showing 'at risk' levels of symptoms. A total of 19 items (0.001% of all Conners data) were missing across the full sample. These values were replaced with the subscale mean for each individual.

2.2.3.5 Social Communication Questionnaire (SCQ)

As children born very preterm are also at increased risk for developing Autism Spectrum Disorders (ASD; Gardener, Spiegelman, & Buka, 2011) participants were screened for ASD symptoms using the SCQ Lifetime version (Rutter, Bailey, & Lord, 2003).This was used to provide a measure of the child's autism spectrum symptoms. It consists of 40 yes/no items designed to measure symptoms in the domains of reciprocal social interaction, communication and repetitive/restricted behaviours and interests, which was designed as a screening companion to the Autism Diagnostic Interview (Rutter et al., 2003). Raw scores for the lifetime SCQ were calculated by summing the items that were scored as per the scoring guidelines. Children with scores above the suggested clinical cut off of 15 were considered to show 'at risk' levels of symptoms. Parents of 3 very preterm and 2 term-born children failed to complete one side of the questionnaire, thus their data were excluded from this comparison.

2.2.3.6 Multidimensional Anxiety Scale for Children (MASC 2-P)

As children born very preterm are also at increased risk for developing anxiety disorders (Burnett et al., 2011), participants were screened for anxiety symptoms using the MASC-2P (March et al., 1999) to provide a comprehensive norm-referenced parent-report measure of the child's anxiety symptoms. This consists of 50 items designed to measure symptoms of separation anxiety/phobias, generalised anxiety disorder, social anxiety, obsessions and compulsions, physical anxiety symptoms and harm avoidance. For each item, parents rated their child on a 4-point scale ranging from 0 ('never true of my child') through to 4 ('always true of my child'). Higher scores represent symptoms of a greater frequency and/or intensity. Raw scores for the total anxiety subscale were converted into their relevant age- and sex- standardised *T*-scores. Children with *T*-scores above the suggested clinical cut off of 60 were considered to show 'at risk' levels of symptoms. The total anxiety subscale was used in this analysis to characterise (i) the relative anxiety symptom severity in each group, and (ii) the number of children considered to show 'at risk' levels of anxiety symptoms in each group. Parents of 1 very preterm child failed to complete one whole side of the questionnaire, thus their data were excluded from this comparison.

For the Conner's 3-P, MASC 2-P and SCQ, data for all items were double entered and errors verified to ensure accuracy of the final dataset. Summed scores were computed using a computerised algorithm written in MATLAB.

2.2.4 **Group Comparisons**

Very preterm and term-born children did not differ significantly on sex, ethnicity, and socio-economic status (SES) as derived from the IMD. However the term-born group was significantly younger than the very preterm group (Cohen's *d*=0.83), thus it was considered appropriate to control for age in subsequent analyses. As expected, the very preterm group had significantly lower IQ (mean difference=10 points). This is in line with a meta-analysis of previous research, showing that very preterm children often demonstrate IQ within the average range (100 ±1SD) but significantly lower than term-born controls (Bhutta et al., 2002). It was not deemed appropriate to adjust for IQ in statistical analyses because the measurements used in the IQ tests are likely to require some of the same cognitive skills measured in the study, and thus such an adjustment would remove variance of interest (Taylor, 2006). Further, it has been shown that the cognitive deficits seen in preterm samples are better characterised as selective processing deficits rather than as a domain general intellectual deficit (Johnson, 2007), and as such, investigation of separate domains was considered to be more informative. Other authors have also asserted that adjustment for IQ is inappropriate in studies of cognition within the field of neurodevelopmental disorders, specifically in ADHD populations (Dennis et al., 2009).

Table 2.2: Characteristics of term-born and very preterm children.

	Very Preterm (n=65[a])	Term (n=48[a])	*p*
Participant characteristics			
Age (years)			
Mean (*SD*)	10.1 (0.9)	9.6 (1.0)	.006*
Range	8.4-11.5	8.0-11.7	
Gestation (weeks)			
Mean (*SD*)	29.9 (1.9)	40.0 (1.08)	

Range	26-32	37-42	
FSIQ-2[b]			
Mean (*SD*)	101.1 (13.9)	111.1 (9.9)	<.001*
Range	67-131	83-127	
Demographics, *n*(%)			
Female sex	29 (44.6%)	22 (45.8%)	.898 *n.s.*
Race			
White	47 (82.3%)	42 (87.5%)	.855 *n.s.*
Mixed	7 (12.3%)	4 (8.3%)	
Asian	1 (1.8%)	1 (2.1%)	
Black	1 (1.8%)	1 (2.1%)	
Chinese	0 (0%)	0 (0%)	
Other	1 (1.8%)	0 (0%)	
SES			
Low SES	12 (18.5%)	13 (27.1%)	.074 *n.s.*
Middle SES	25 (38.5%)	9 (18.8%)	
High SES	28 (43.1%)	26 (54.2%)	
Conner's 3 ADHD symptom scores			
Conner's 3 *T*-scores, mean *(SD)*			
DSM ADHD/I	62.11 (15.48)	57.79 (13.51)	.136 *n.s.*
DSM ADHD/C	61.63 (14.42)	58.48 (14.08)	.399 *n.s.*
Inattention	60.71 (15.64)	57.13 (12.29)	.215 *n.s.*
Hyperactivity/ Impulsivity	62.15 (16.24)	59.06 (14.47)	.297 *n.s.*
IA-HI correlation, *r*	.78	.83	.233 *n.s.*
Conner's 3 scores above clinical cut offs, *n*(%)			
DSM ADHD/I	22 (34.4%)	12 (25.0%)	.286 *n.s.*
DSM ADHD/C	21 (32.3%)	13 (27.1%)	.549 *n.s.*
Inattention	22 (33.8%)	10 (20.8%)	.129 *n.s.*
Hyperactivity/ Impulsivity	22 (33.8%)	15 (31.3%)	.771 *n.s.*
SWAN inattention scores			
Mean (*SD*)	-.068 (10.89)	-4.67 (12.22)	.080 *n.s.*
Range	-26 to 26	-27 to 20	
MASC anxiety disorder total symptom scores [c]			
T-scores, mean*(SD)*	55.87 (13.59)	52.42 (10.50)	.147 *n.s.*
T-scores above clinical cut offs, *n*(%)	17 (27.0%)	9 (18.8%)	.310 *n.s.*
SCQ autism spectrum symptom scores [d]			
Lifetime symptom scores, mean*(SD)*	6.66 (7.67)	5.53 (5.88)	.327 *n.s.*

Scores above clinical cut offs, *n*(%)	11 (17.7%)	3 (6.5%)	.086 *n.s.*

Note: Continuous variables were compared using independent samples t-tests, rank variables were compared using Pearson's chi-square, correlations were compared using Fischer's r-to-z. SD=standard deviation, FSIQ-2= two-subtest full scale intelligence quotient. IA-HI correlation = correlation between inattentive (IA) and hyperactive-impulsive (HI) symptoms as measured using the Conner's 3 subscale *T*-scores. * $p<0.05$, *n.s.*= not significant. [a] accurate unless otherwise indicated. [b] very preterm(*n*) = 65, term(*n*)= 47 due to missing data. [c] very preterm(*n*) = 64, term(*n*)= 48 due to missing data. [d] very preterm(*n*) = 62, term(*n*)=46 due to missing data.

In the very preterm group, SWAN scores ranged from 'far above average' attention to 'far below average' attention, or severely *in*attentive (-26 to 26), with a group mean around the 'average' level of attention (-.068). Similarly, in the term-born group, SWAN scores ranged from 'far above average' attention to 'below average' attention, or very *in*attentive (-27 to 20), with a group mean just above 'average' (-4.67). This demonstrates that a term-born sample with a wide range of inattention scores was successfully recruited, although the most severe-rated child in the preterm group was rated with more severe inattention than in the term group. By design, the very preterm and term-born groups did not differ significantly on SWAN parent-rated inattention scores.

The success in matching preterm and term-born children on ADHD symptoms is further supported by the data indicating that they were also matched on the intensity/frequency of symptoms on the DSM ADHD/I subscale and the DSM ADHD/C subscale of the Conner's 3 parent rating scale (Conners, 2008), and in the proportion of children who scored as 'at risk' on these subscales (see Table 2.2). Further, they did not differ on the intensity/frequency of inattentive or hyperactive-impulsive symptoms more generally, and both groups showed high correlations between inattentive and hyperactive-impulsive symptoms. Overall, a high proportion of both samples scored as 'at risk' on these subscales (very preterm: 32-34%; term-born: 27-25%) far above the estimated prevalence of ADHD in the general population of 5% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). However, mean levels of inattentive and hyperactive-impulsive symptoms were below the clinical cut-off of (*T* <65 for all subscales) indicating that the average level of inattention and hyperactivity within both groups was not elevated above typical ranges.

Groups did not differ significantly in symptom severity or in the proportion of children scoring above clinical cut offs for Autism Spectrum Disorder or Anxiety Disorders (see Table 2.2). As with the ADHD scores, although the proportion of children scoring as ‘at risk’ of ASD on the SCQ were larger than the 4-5% rate observed in general population studies of children of a similar age (Chandler et al., 2007), particularly in the children born very preterm (term-born = 6.5%; very preterm = 17.7%), the mean levels of ASD symptoms were well below the clinical cut-off of scores >15 indicating that the average level of ASD symptoms within both groups was not elevated above typical ranges.

Prevalence estimates of anxiety disorders during middle childhood are extremely variable ranging between 2.5%-41.2% (Cartwright-Hatton, McNicol, & Doubleday, 2006), however the authors of a study of a British population reported a prevalence of 3-4% in children aged 8-11 years (Ford, Goodman, & Meltzer, 2003). As such the proportion of children scoring above clinical cut-offs in the two groups could be said to higher than would be expected in the general population (term-born = 18.8%; very preterm = 27.0%), indicating that a substantial number of children in this sample were rated as at risk of anxiety disorders. Once again, the mean levels of anxiety symptoms within each group were below the clinical cut-offs (*T*<60) indicating that the average levels of anxiety symptoms on the group level were not elevated above typical ranges.

2.2.5 **EEG sample**

Some children could not tolerate the EEG procedure and as such, EEG data was not collected from all children in the PATCH Study. The analyses in Chapters 4 & 5 include EEG data from 40 term-born children and 43 very preterm children.

Participant characteristics, demographics and clinical symptoms were compared for children with and without EEG data. Those who completed the EEG testing were of significantly higher IQ (completed EEG, M=107.18, SD = 12.71; did not complete EEG, M = 100.68, SD = 13.58; *t*(112) = -2.39, *p*=0.019) and were born at a significantly later gestation (completed EEG, M=34.91 weeks, SD = 5.28; did not complete EEG, M =

32.52 weeks, SD = 4.84; *t*(55.36) = -2.27, *p*=0.027). This is likely to reflect reduced tolerance for EEG procedures in children with neuropsychological difficulties and an increased risk of a broad range of difficulties in children with lower IQ and children born at earlier gestations, and will be considered in the interpretation of the results. Children who completed EEG testing did not differ from those who did not complete EEG testing on any other measured variable including SWAN inattention.

The characteristics of the reduced sample are reported in *Table 2.3* below. As in the total sample, in the reduced sample children born very preterm were significantly older than those born at term (mean difference = 0.56 years) and of a significantly lower IQ (mean difference = 9.84 points). Accordingly results were adjusted for age in the following analyses. In line with other analyses in this thesis, adjustments for IQ were not considered appropriate. In the reduced sample, it was also observed that children born very preterm were scored as significantly more anxious on parent-rated anxiety symptoms, but there was no significant difference in the number of very preterm children scoring above the 'at risk' cut off for anxiety disorder. Group differences in IQ and anxiety were considered during the interpretation of results. Groups did not differ significantly on any other variable.

Table 2.3: Characteristics of tested children in term and very preterm groups who completed EEG testing.

	Very Preterm (*n*=43)[a]	Term (*n*=40)[a]	*p*
Participant characteristics			
Age (years)			
Mean (*SD*)	10.14 (0.82)	9.58 (1.08)	.010**
Range	8.41-11.41	8.00-11.66	
Gestation (weeks)			
Mean (*SD*)	30.02 (1.96)	40.04 (1.14)	
Range	26-32	37-42	
FSIQ-2[b]			
Mean (*SD*)	102.44 (13.87)	112.28 (9.01)	<.001***
Range	67-131	89-127	
Demographics, n(%)			
Female sex	22 (51.2%)	19 (47.2%)	.659 *n.s.*
Race			.450 *n.s.*

White	34 (79.1%)	35 (87.5%)	
Mixed	6 (14.1%)	4 (10.0%)	
Asian	2 (4.7%)	0	
Black	1 (2.3%)	1 (2.5%)	
Chinese	0	0	
Other	0	0	
SES			
Low SES	7 (16.3%)	11 (26.8%)	.165 *n.s.*
Middle SES	16 (37.2%)	8(19.5%)	
High SES	20 (46.5%)	21 (53.7%)	
Conner's 3 ADHD symptom scores			
Conner's 3 *T*-scores, mean (*SD*)			
DSM ADHD/I	61.42 (14.98)	56.32 (11.73)	.087 *n.s.*
DSM ADHD/C	61.91 (16.48)	57.46 (12.59)	.182 *n.s.*
Inattention	59.40 (14.87)	56.10 (12.91)	.282 *n.s.*
Hyperactivity/ Impulsivity	61.88 (16.41)	57.95 (13.87)	.240 *n.s.*
IA-HI correlation, r	.733	.788	.865 *n.s.*
Conner's 3 *T*-scores above clinical cut offs, n(%)			
DSM ADHD/I	14 (32.6%)	8 (19.5%)	.174 *n.s.*
DSM ADHD/C	14 (32.6%)	10 (24.4%)	.407 *n.s.*
Inattention	14 (32.6%)	7 (17.1%)	.101 *n.s.*
Hyperactivity/ Impulsivity	15 (34.9%)	12 (29.3%)	.582 *n.s.*
SWAN inattention scores			
Mean (*SD*)	-1.15 (10.06)	-3.56 (12.88)	.345 *n.s.*
Range	-26 to 21	-27 to 20	
MASC anxiety disorder total symptom scores [c]			
T-scores, mean(*SD*)	57.45 (12.83)	52.15 (10.11)	.043*
T-scores above clinical cut offs, n(%)	13 (31.0%)	7 (17.9%)	.175 *n.s.*
SCQ autism spectrum symptom scores [d]			
Lifetime symptom scores, mean(*SD*)	6.05 (6.89)	5.21 (5.37)	.550 *n.s.*
Scores above clinical cut offs, n(%)	6 (14.6%)	2 (5.3%)	.168 *n.s.*

Note: Continuous variables were compared using independent samples t-tests, rank variables were compared using Pearson's chi-square, correlations were compared using Fischer's r-to-z. VP= very preterm; SD=standard deviation, FSIQ-2= two-subtest full scale intelligence quotient. IA-HI correlation = correlation between inattentive (IA) and hyperactive-impulsive (HI) symptoms as measured using the Conner's 3 subscale *T*-scores. * *p*<0.05, *n.s.*= not significant. SWAN = Strengths and Weaknesses of ADHD and Normal behaviour. MASC = Multidimensional Anxiety Scale for Children. SCQ = Social Communication Questionnaire. [a] accurate unless otherwise indicated. [b] very preterm(*n*) = 43, term(*n*)= 39 due to missing data; [c] very preterm(*n*) = 42, term(*n*)= 39 due to missing data; [d] very preterm(*n*) = 41, term(*n*)= 38 due to missing data.

2.3 Study Procedure

Each child attended the laboratory in the School of Psychology at the University of Nottingham with a parent or guardian to complete the test battery, which included the questionnaire measures of behaviour (completed by parents), in addition to a battery of standardised, experimental, and electrophysiological tests completed by the child. All children were tested by the same experimenter. The total time of the testing session, including breaks and equipment set-up was three hours, with up to two hours of testing. Full descriptions of each test are given in the relevant chapters.

Due to the length of the testing session and the number of tests included it was not considered sensible to fully randomise test order between subjects. Instead, test order was fixed across two blocks of behavioural tests and one block of electrophysiological testing. Within blocks the tests were ordered in such a way as to minimise order and practice effects and maintain engagement throughout. This was achieved by varying the response and presentation style and separating similar tests (See Table 2.4 for details of test order). By aggregating the behavioural tests into two blocks, and counterbalancing the order of completion across participants (approximately half of the participants completed Block A before Block B, with the other half completing Block B before Block A), some protection was provided against order effects. Block C constituted the EEG testing session, therefore it was completed last for all children. The set-up time acted to extend the break given to children.

Upon arrival, each child was introduced to the experimenter who described how the session would proceed and emphasised that they could withdraw at any point. Parents were asked to complete questionnaires while the child completed the study tests. The child first completed the behavioural tests in Blocks A and B, with the experimenter talking the child through each test as appropriate. Brief breaks were given if requested. Following this, participants were given a break of approximately 15 minutes where they were offered a drink and snack. The experimenter then described the EEG set-up and ensured that the parent and child were happy to continue. The EEG set-up took approximately 45 minutes during which an age-appropriate film was played to entertain the child. The child then completed Block C. The EEG equipment was subsequently removed and the experimenter washed the EEG gel from the child's hair. Reimbursement of travel expenses was provided to the parent and the child was given a cinema voucher to thank them for taking part.

Table 2.4: Table demonstrating the study procedure with test timings and counterbalancing.

Block A	25 minutes		Chapter
Verbal short term memory	5 minutes	Counterbalanced with block B	3
Visuo-spatial processing	5 minutes		3
Motor processing speed	5 minutes		3
Switching and interference control	5 minutes		3
Verbal working memory	5 minutes		3
Block B	35 minutes		
Visuo-spatial short term memory	10 minutes	Counterbalanced with block A	3
Verbal IQ	10 minutes		2
Non-verbal IQ	10 minutes		2
Visuo-spatial working memory	5 minutes		3
Break with option for drink and snack	15 minutes	Breaks	
EEG set-up with a film for the child	45 minutes		
Block C	20 minutes		
CPT-AX	20 minutes		4 & 5

Note: Thesis chapters where each test is analysed are listed in the right-most column.

Chapter 3: Cognitive Predictors of Inattention

3.1 Background

As outlined in the general introduction, while ADHD in the general population is by and large recognised as the result of a gene-environment interaction (Faraone et al., 2005), it is thought that the increased risk for inattention in very preterm children arises as a result of aberrant neurodevelopment following birth at very preterm gestations (Lindström, Lindblad, & Hjern, 2011). With potentially differing causes, the mechanisms underlying inattentive symptoms in children born very preterm may be different from those in term-born children with ADHD. The goal of much clinical research is to understand the nature and causes of disorders for effective diagnosis and treatment. In neurobehavioural disorders such as ADHD, the study of cognitive skills underlying symptoms can be useful for providing measurable indices of brain function to inform intervention efforts. For example, measuring the speed at which an individual is able to detect a target gives us an index of how quickly their visual system operates, while asking an individual to categorise sounds gives an index of the accuracy of their auditory system. Such concepts can be extended to more complex cognitive processes, thus supplying researchers with a way to measure mechanisms which may lie on the causal pathway between the ultimate cause and the development of behavioural symptoms. This analysis therefore aimed to explore a range of cognitive processes in term-born and very preterm children to determine whether the potential mechanisms underlying inattentive symptoms are the same, distinct, or partially overlapping.

3.1.1 **Cognition and inattention in children born preterm: What we know so far**

3.1.1.1 Executive function

Executive function is an area of cognition that has been strongly implicated in ADHD (e.g. Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005) and is also impaired in children born very preterm (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012). Executive function is an umbrella term used for a collection of interrelated neurocognitive processes including inhibitory control, working memory and task switching. These higher-order processes are essential for top-down control of lower-level processing to allow for the efficient completion of goal-directed actions.

Loe, Feldman, and Huffman (2014) focussed specifically on the mediating effect of executive function on the relationship between preterm birth and parent-rated behavioural difficulties. They incorporated both parent-rated and performance-based measures of executive function. Behavioural difficulties were rated by parents using the Child Behaviour Checklist (CBCL; Achenbach & Edelbrock, 1981), which combines scores across problems in different areas including inattention, but also difficulties in social and emotional domains. Consequently, although this study did not provide conclusions about predictors of inattention specifically, their analysis did show that parent-rated measures of executive function (although not performance-based measures) mediated the relationship between preterm birth and behavioural difficulties in children aged 3-5 years. This finding reinforces the importance of the role of executive function in preterm children’s behavioural difficulties, but raises questions as to why performance-based measures were not found to mediate behavioural, social and emotional outcomes. Evidence suggests that children born very preterm display selective deficits (Johnson, 2007), thus by combining the scores of the performance measures of executive function to create a single variable and using the CBCL, the study design may have masked varation in outcomes and reduced the ability to detect specific relationships between executive functioning and different domains of behavioural problems. It is interesting to note that significant relationships were found between the two parent-report measures, both of which are vulnerable to subjectivity, and no relationships were demonstrated between the performance-based measures of executive function and behavioural problems. Although this study targeted executive function, its methodology did not target associations between specific executive functions and specific behavioural difficulties. In the following review of the relevant literature, I summarise the findings concerning the role of particular executive functions that have been most consistently investigated in relation to inattention in one or both populations (preterm and/or ADHD); specifically working memory, inhibitory control and task switching.

Working memory

When looking to studies that have investigated the role of specific executive functions in inattention in very preterm children, there is particular support for the role of working memory. Working memory refers to the ability to hold information in memory while simultaneously conducting additional processing, whether that processing requires manipulation of the memoranda itself, or maintenance of the memoranda with concurrent processing of other information. According to the Baddeley and Hitch working memory model (Baddeley & Hitch, 1974), and supported by studies such as Alloway, Gathercole, and Pickering (2006), working memory can be separated into verbal and visuo-spatial domains.

In an early study predominantly focussed on the assessment of general intellectual deficit in children born extremely preterm (24-28 weeks gestation), Nadeau, Boivin, Tessier, Lefebvre, and Robaey (2001) found that a specific sequential memory factor taken from a factor analysis of subscales from the McCarthy Scales (McCarthy, 1972) measured at 5 years of age explained 16% of the variance in teacher-rated inattention two years later. While this study measured neuromotor and general cognitive development rather than executive functions per se, the measure of sequential memory was interpreted as an index of working memory. These findings were taken as initial evidence that working memory may play an important role in inattention in preterm samples, and have prompted further investigation in this area.

Mulder, Pitchford, and Marlow (2011b) found that teacher-rated inattention in 9-10 year old children born very preterm (<31 weeks gestation) could be explained by a combination of slower processing speed and poorer verbal working memory. Similarly, de Kieviet, van Elburg, Lafeber, and Oosterlaan (2012) found that poor working memory was a predictor of inattention in 7-8 year old children born very preterm (<32 weeks gestation). Further they demonstrated that it was visuo-spatial working memory specifically, and not verbal working memory that accounted for group differences in inattention. Aarnoudse-Moens, Weisglas-Kuperus, Duivenvoorden, van Goudoever, and Oosterlaan (2013) compared relationships between executive function and inattention in 4-12 year old children born very preterm (<31 weeks gestation) against those in term-born controls. Although in preschool-aged children working memory did not predict parent- or teacher-rated inattention in term or very preterm children, at primary school age, visuo-spatial working memory predicted parent- and teacher-rated inattention in both term and very preterm groups. Verbal working memory did not predict inattention in any group. Taken in combination with the finding that verbal working memory was only identified as a predictor for teacher- and not parent-rated inattention in Mulder et al. (2011b), this evidence suggests that working memory is a factor that may be particularly relevant to classroom settings, and that may become more apparent with age as children more often encounter situations where working memory is required. Furthermore, there appears to be a distinction between verbal and visuo-spatial working memory, with visuo-spatial working memory being more heavily implicated as a mechanism underlying inattention in very preterm children.

Cognitive control

In contrast, evidence surrounding the role of inhibitory control is less consistent. Inhibitory control refers to the ability to resist making an inappropriate, and often prepotent, response. Scott et al. (2012) showed that for 5-6 year old children born extremely preterm (<28 weeks gestation), risk of ADHD/I diagnosis was significantly increased in those who showed deficits in measures of inhibitory control. Similarly, Aarnoudse-Moens et al. (2013) found that for preschool children born very preterm, inhibitory control was the only cognitive measure that predicted parent-rated inattention, and at primary school age inhibitory control predicted teacher-rated inattention along with visuo-spatial working memory and IQ. More recently, it was shown that inhibitory control measured at 20 months corrected age predicted attention at age 8 years, was poorer for those born preterm, and partially mediated the association between preterm birth and poor attention (Jaekel, Eryigit-

Madzwamuse, & Wolke, 2015). However, Mulder et al. (2011b) found that inhibitory control did not predict either parent or teacher ratings of inattention in a group of 9-10 year old children born very preterm. Likewise, Shum, Neulinger, Ocallaghan, and Mohay (2008) found no evidence of an association between interference control and parent or teacher ratings of inattention in a group of 7-9 year olds born very preterm. Interference control is considered to be a sub-domain of inhibitory control (Friedman & Miyake, 2004) and the terms are used interchangeably by some researchers. Interference control refers to the ability to suppress conflicting information that may interfere with an individual's ability to make the task-appropriate response. The discrepancy between studies with relation to the role of inhibitory control could simply reflect the inconsistency with which impairments in this area are observed in preterm samples. The children sampled by Scott et al. (2012) were extremely preterm, compared to the very preterm children sampled in Mulder et al. (2011b), and this gestational difference could have accounted for the absence of a relationship in the very preterm children. Alternatively, the discrepancy may be related to the age of the sample at testing. Evidence has suggested that as children born preterm grow older, impairments in inhibitory control may reduce (Aarnoudse-Moens, Duivenvoorden, Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012).

Meanwhile, evidence exploring whether inattention in very preterm children is related to task switching, another element of cognitive control, is limited to one published study. Task switching, also referred to as set shifting, refers to the ability to respond based upon one rule, and to flexibly switch to respond based upon another rule. Scott et al. (2012) found that like inhibitory control, risk of an ADHD/I diagnosis in 5-6 year olds born extremely preterm was significantly increased in those who showed deficits in measures of task switching.

3.1.1.2 Basic cognitive processing

It is important to consider that most executive function tasks are not pure measures of the target function as they incorporate various lower-level processing skills. To advance our understanding of the relationship between executive functioning and inattention in children born very preterm, it is important to also account for the influence of variation in lower level processing. Some basic cognitive processes have themselves been implicated in inattention in very preterm children, with the strongest evidence implicating processing speed, discussed below. While processing speed is of particular relevance to the measurement of executive functions using tasks involving speeded responses, such as computerised measures of inhibitory control and task switching, working memory is likely to also rely on other basic cognitive processes. Specifically, poor short term memory will likely impact working memory in general, and poor visuo-spatial processing will likely impact visuo-spatial working memory. Visuo-spatial processing may also be involved in performing tasks measuring other executive functions. For example, Aarnoudse-Moens et al. (2012) noted that Trailmaking, a common measure of task switching, has a relatively large visuo-spatial component. If lower level cognitive processes are also linked to inattentive behaviour, or account for associations between executive functions and inattention, they may present more appropriate targets for intervention. The following sections review literature relating to role of basic cognitive processes in inattention.

Processing speed

Processing speed refers to how quickly an individual is able to process information, and has been shown to be slower in preterm samples (Aarnoudse-Moens et al., 2012; Foulder-Hughes & Cooke, 2003; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Mulder et al., 2011). It has also been linked to executive function performance in preterm samples (Rose et al., 2011). Moreover Mulder et al. (2011b) found that parent-rated inattention in very preterm children could be explained by slower processing speed, and that in combination with poorer visuo-spatial working memory, slower processing speed also explained teacher-rated inattention in 9-10 year old children born very preterm. Interestingly, although the control sample of 22 children in Mulder et al. (2011b) was too small for detailed analysis, initial correlations suggested that the association between processing speed and inattention was restricted to the children born very preterm. The authors proposed a cascade of effects whereby very preterm birth results in atypical development of white matter in the brain, the integrity of which has been linked to slow processing speed (Soria-Pastor et al., 2008). Individual variations in processing speed have in turn been linked to differences in executive function (Kail & Salthouse, 1994), which may then lead to differences in inattention. However, with such a small sample size of term-born children, Mulder et al.'s speculation that the effects of processing speed are restricted to very preterm children as a result of atypical white matter growth requires further investigation particularly as no studies have confirmed the reliability of this finding as yet. In particular, the association between slow processing speed and increased inattention in very preterm children is not consistently found. Aarnoudse-Moens et al. (2013) found that processing speed was unrelated to parent- and teacher-rated inattention in children born very preterm aged 4-12. Such contrasting results may result from differences in measurement techniques. All behavioural measures of processing speed consist of multiple 'processing' stages, from the detection and sensory processing of a stimulus, to evaluating it and responding. While Mulder et al. (2011b) incorporated both motor and verbal measures, Aarnoudse-Moens et al. (2013) used a computer-based response time measure incorporated into their inhibitory control task. De Kieviet et al. (2012) may provide another solution to the contrary findings. They implemented an ex-Gaussian analysis of their response time measure, which allowed the separation of the typical processing speed (mu) and variability (sigma) from atypical lapses in attention (tau) when investigating predictors of inattention in 7-8 year old children born very preterm. This closer examination suggested that it was increased tau, thought to represent a greater frequency of lapses in attention, rather than slow processing speed per se, that was linked to higher levels of inattention, and that in combination with poorer visuo-spatial working memory, increased tau completely mediated the relationship between preterm birth and increased levels of inattention. As such, it remains unclear whether basic processing speed impacts on inattention directly, or mediates the association between inattention and executive function. It is also possible that deficits in this area are specific to inattention in preterm samples, but such findings have yet to be established.

Other basic processing

Short term memory, the ability to immediately recall items, has been identified as being impaired in children born very preterm (Briscoe, Gathercole, & Marlow, 1998; Bull, Espy, & Wiebe, 2008; Shum et al., 2008). Moreover, visuo-spatial short term memory has been shown to predict parent-rated inattention (Shum et al., 2008). In spite of this finding, it is often absent from studies investigating cognitive mechanisms of preterm inattention, including those investigating working memory. Similarly, basic visuo-spatial processing, the ability to accurately process visuo-spatial information, has also been shown to be impaired in children born very preterm (Foulder-Hughes & Cooke, 2003; Luciana et al., 1999; Simms et al., 2015), and there is evidence that poor visuo-spatial processing impacts on preterm children’s mathematics difficulties (Simms et al., 2015). To date, studies have failed to investigate whether poor visuo-spatial processing may affect inattentive behaviour, and whether it may account for the relationship between poor visuo-spatial memory (working and short-term) or executive function and inattention.

3.1.1.3 Conclusions

Taken together, these studies highlight the role of executive function and, to a lesser extent, processing speed and short term memory, in the aetiology of inattention in children born very preterm. Visuo-spatial working memory has been specifically implicated in multiple studies. Support for the role of inhibitory control is mixed and appears to be age-dependent, while evidence for the contribution of task switching is limited. These studies provide us with some understanding of possible mechanisms that may be important in explaining inattention in preterm children.

However, limitations in existing studies restrict our understanding of the mechanisms underlying inattention in very preterm children, and how these may compare to those underlying inattention in term-born children. As discussed above, many studies fail to include measures of basic cognitive processes that may be confounding results. The methodology of some studies discussed did not target associations between specific executive functions and specific behavioural difficulties (Loe et al., 2014). Other studies used relatively restricted measures of inattention such as the Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997) which incorporates only a few items measuring inattention (Mulder et al., 2011b). Even those that use more extensive ADHD rating scales (e.g. DuPaul ADHD rating scale; DuPaul, Power, Anastopoulos, and Reid (1998) as used in Shum et al. (2008)) used scales designed to measure only variation in inattentive behaviour, ignoring variation in the positive end of the behavioural spectrum. Furthermore, it remains unclear how alike these mechanisms are to those present in term-born children with attention difficulties, due to the exclusive use of term-born control groups who exhibit lower levels of inattention than the preterm children. Many studies did not compare the relationships observed in preterm children with those in term-born children. In studies that did, such as Aarnoudse-Moens et al. (2012), smaller variation in inattention ratings in the term-born control sample may have limited the comparison of relationships between inattention and cognition in the two samples. The failure to directly compare term-born and preterm samples with similar ranges of inattention remains the biggest barrier to understanding similarities between the underlying mechanisms in the two populations.

3.1.2 Findings from studies in ADHD

To some extent we are able to refer to the ADHD literature to compare the above findings to the mechanisms identified in ADHD samples. While an exhaustive review of cognition in ADHD is beyond the scope and focus of this thesis, below I briefly summarise studies that have investigated inattention in relation to the key aspects of cognition outlined above, including studies of the ADHD-inattentive sub-type, dimensional inattention and comparisons of ADHD in term and very preterm children.

In particular, Diamond (2005) has proposed that the predominantly inattentive subtype of ADHD, most consistent with the preterm ADHD phenotype, is driven by a combination of slow processing speed and poor working memory. Indeed, poor working memory has been shown to relate to teacher-rated inattention even in community samples (Gathercole et al., 2008) and studies have shown that, in typically developing children, processing speed mediates the relationship between working memory and classroom behaviour, including teacher-rated inattention (Jarrold, Mackett, & Hall, 2014). Furthermore, evidence has implicated poor inhibitory control as a mechanism underlying inattention, despite its traditional association with hyperactivity/impulsivity (Chhabildas et al., 2001). Thus, on the surface, it appears that similar cognitive skills are implicated in the development of inattention in children with ADHD/I and in children born very preterm. However, without a direct comparison, differences in samples and tasks make it difficult to draw conclusions about whether the causes of inattention differ between children born very preterm and at term.

Only one study to date has compared groups of preterm and term-born children matched on ADHD status. Van der Meere, Börger, Potgieter, Pirila, and De Cock (2009) compared the performance of very low birth weight preterm children (<1500g and <34 weeks gestation) and normal birth weight (>2500g and >37 weeks gestation) term-born children, with and without diagnosed ADHD, specifically looking at the effect of presentation rate on the go/no-go inhibitory control task. They found that both ADHD groups showed poorer inhibitory control and slower reaction times for slow presentation rates, but there were no differences between ADHD groups with and without very low birth weight. Similarly there were no differences between non-ADHD groups with and without very low birth weight. Their findings suggested that for both very low birth weight and normal birth weight children who are diagnosed with ADHD, deficits can be seen in inhibitory control and state regulation, but that it was ADHD diagnosis, rather than birth weight, that differentiated children. However, the findings of this study remain limited. Aside from small sample sizes (only 12 children in the very low birth weight ADHD group), a particular concern of the sampling is that the very low birth weight children with ADHD were diagnosed with either the combined or the hyperactive-impulsive subtypes. Considering the evidence suggesting that children who develop ADHD as a result of preterm birth more often show profiles consistent with the predominantly inattentive subtype, it may be that the sample studied were not representative of the 'preterm ADHD' phenotype, and the study focus here was on ADHD, rather than the primary deficit of inattention. A further sampling concern is that the sample studied were selected on the basis of birth weight, and as such included children born at 34 weeks gestation, although the mean gestational age was comparable to other samples of very preterm children at 29 weeks. However it is recommended that samples defined by gestational age are used to examine the effects of maturity of birth (Johnson, Wolke, & Marlow, 2008) as low birth weight samples may include children with more mature neural development who are of low birth weight for reasons other than prematurity per se (e.g. constitutionally small, foetal growth restriction). Finally, with the focus restricted to inhibitory control, and the analysis restricted to performance differences, the study can tell us little about how different cognitive processes relate to symptom severity. A dimensional approach is more viable in groups with lots of heterogeneity such as preterm samples, allowing for the examination of relationships between cognitive proficiency and behaviour.

3.1.3 **The current analysis**

Analysis of a more comprehensive number of cognitive processes, both at the executive level, but also at a more basic level, is needed to elucidate how different factors contribute to inattention in preterm children. To address this, in the current study I included measures of basic cognitive processing in addition to those measuring executive function. In addition, a sample of term-born children matched to the preterm sample on levels and range of inattention scores was recruited in order to directly compare relationships between cognition and inattention.

The aims of the current analysis were to identify and compare the cognitive mechanisms underlying inattention in very preterm and term-born children. In doing so, I hoped to answer the questions of (i) whether the cognitive mechanisms underlying inattentive behaviour are the same in children born very preterm and those born at term, and (ii) whether inattention is the result of global executive deficits, or is linked to specific areas of weakness. The cognitive measures selected for investigation are described below.

Firstly, a measure of processing speed was chosen in order to investigate its role in inattention. In particular, building on the evidence from Mulder et al. (2011b), I aimed to investigate in greater detail whether the relationship between processing speed and inattention may be restricted to children born very preterm. I used a measure that prevented the need for excessive cognitive effort that may be confounded by ability in other areas (such as verbal processing speed measures) and that reduced the likely impact of attentional lapses shown by de Kieviet et al. (2012) to be a common confound in response time-derived measures of processing speed.

While evidence for the role of working memory in inattention has been strong, few studies have compared the relative contribution of verbal and visuo-spatial working memory. De Kieviet et al. (2012) included tests of verbal and visuo-spatial working memory but the tests were designed in different labs. Consequently, the cognitive load elicited by the verbal and visuo-spatial paradigms may not have been equally matched, potentially introducing confounds. This led me to design similar verbal and visuo-spatial counterparts using dual-task paradigms with identical domain neutral concurrent processing tasks, in order to look more closely at this distinction. Further, no other studies have measured the role of short-term memory in the absence of cognitive load, thus, measures of verbal and visuo-spatial short term memory were also used to elucidate more clearly whether observed working memory-inattention relationships are indeed driven by poorer memory at the executive level (working memory) or explained by more basic memory deficits (short term memory). Basic visuo-spatial processing has also been shown to be impaired in children born very preterm (Foulder-Hughes & Cooke, 2003; Luciana et al., 1999; Simms et al., 2015). Accordingly a basic measure of visuo-spatial processing with no memory component was selected to verify whether poorer visuo-spatial processing might account for stronger relationships between visuo-spatial working memory and inattention than verbal working memory, particularly in preterm children.

Task switching has received little scrutiny in inattention in very preterm children studies, but where it has been examined, it has been related to the risk of a diagnosis of the inattentive subtype of ADHD in preterm children (Scott et al., 2012). Evidence investigating the role of task switching in inattention has thus far been restricted to 5-6 year old children in studies of preterm children, so this study aimed to identify its role in inattention in 8-11 year old children, an age where inattentive symptoms tend to emerge more prominently.

Finally, a measure of interference control was selected. Interference control is considered to be a sub-domain of inhibitory control (Friedman & Miyake, 2004), and although some studies suggest it is impaired in preterm samples (de Kieviet et al., 2014; Ford et al., 2011) it has only been investigated in relation to inattention in one study (Shum et al., 2008). Findings regarding the relevance of inhibitory control to inattentive behaviour have been mixed, with some finding significant relationships (Aarnoudse-Moens et al., 2012; Scott et al., 2012; van der Meere et al., 2009) and others not (Mulder et al., 2011b). However, as inhibition and interference control have been strongly implicated in the aetiology of ADHD in general population populations (Chhabildas et al., 2001; Lijffijt, Kenemans, Verbaten, & van Engeland, 2005) it was considered an important mechanism to include in order to explore mechanisms underlying inattention in term-born and very preterm children.

3.1.4 **Aims and hypotheses**

The primary aim of this analysis was to determine whether the cognitive mechanisms underlying inattention were different in very preterm and term-born children. A secondary aim was to establish whether inattention is the result of global cognitive impairment, global executive impairment or specific areas of weakness.

In line with the findings from Mulder et al. (2011b), it was hypothesised that processing speed would predict parent-rated inattention only in children born very preterm. It was predicted that working memory would predict parent-rated inattention in both groups, in line with evidence in term-born (Gathercole et al., 2008), and very preterm children (Aarnoudse-Moens et al., 2013; de Kieviet et al., 2012; Mulder et al., 2011b; Nadeau et al., 2001). Moreover, it was predicted that visuo-spatial working memory would explain more variance than verbal working memory, consistent with de Kieviet et al. (2012). It was predicted that task switching and interference control would be associated with parent-rated inattention, corresponding with the findings of Scott et al. (2012). However, due to inconsistency with which such impairments are reported in the literature, and the apparent age-dependency of inhibitory impairment, it was not clear whether these mechanisms would explain significant unique variance in parent-rated inattention. Finally, aside from processing speed, it was hypothesised that although short term memory and visuo-spatial processing are likely to relate to parent-rated inattention, variation in performance on executive function tasks would explain parent-rated inattention beyond that explained by lower level processing (visuo-spatial processing, short-term visuo-spatial memory, short-term verbal memory).

To summarise, it was predicted that:

- Processing speed would predict parent-rated inattention in the very preterm group, but not the term-born group
- Visuo-spatial working memory would predict parent-rated inattention in both groups and would explain more variance than verbal working memory
- Task switching and interference control would relate to parent-rated inattention in both groups, but may explain significant unique variance
- Variation in executive functioning would explain variance in parent-rated inattention beyond that explained by basic cognitive processing

Between-groups differences in performance on the cognitive tasks were not a main focus of the study and it was unclear what to expect with the inclusion of a term-born comparison group who were matched to the very preterm group in their level of parent-rated inattention. Children born very preterm are known to have impairments in a variety of domains, and poorer cognitive performance than term-born comparison groups is usually predicted. However, as the domains tested in this analysis were chosen for their possible relation to inattention, and the term sample included children with similar levels of inattention to those displayed by preterm children, it was deemed possible that inattention in the term sample may result in similar performance to children born very preterm across the range of measures tested here. A tentative hypothesis was that there would be no between-group differences in performance on the cognitive tasks, although it should be acknowledged that poorer performance in children born very preterm would not have been considered surprising.

3.2 Method

3.2.1 **Participants**

A full description of all children tested is presented in Chapter 2 (see Table 2.2, page 21, for group comparisons in participant characteristics). In brief, the study sample comprised 48 term-born children and 65 children born very preterm aged 8-11 years. Children born very preterm were of significantly higher age than the term-born children (term-born mean(*SD*) = 9.6 (1.0); very preterm mean(*SD*) = 10.1 (0.9); *p*=0.006).

3.2.2 **Procedure & Measures**

3.2.2.1 Procedure

Children completed a test battery of tasks measuring basic cognitive processing and executive function, while their parent or guardian completed questionnaire measures of clinical symptoms. A full description of the procedure is presented in Chapter 2. Measures relevant to the analysis presented here are described in full below and are summarised in *Table 3.1*.

Table 3.1: Summary of measures and tasks by domain.

Domain	Acronym	Measure or Task	Score
Clinical Symptoms			
Inattentive behaviour	SWAN	Strengths and Weaknesses of ADHD and Normal (SWAN) behaviour parent rating scale	Raw score from inattentive subscale
Basic Cognitive Processing			
Motor processing speed	MPS	Finger-tapping subtest from the NEPSY-II	Composite of time (s) for 20 repetitions on each hand
Visuo-spatial processing	VS-P	Arrows subtest from the NEPSY-II	Total raw score
Verbal short term memory	V-STM	Immediate word recall	Total number of items recalled in the correct serial position
Visuo-spatial short term memory	VS-STM	Immediate pathway recall	
Executive Function			
Verbal working memory	V-WM	Word recall with concurrent face processing task in retention interval	Total number of items recalled in the correct serial position
Visuo-spatial working memory	VS-WM	Pathway recall with concurrent face processing task in retention interval	
Global task-switching	GS	SwIFT; Switching Inhibition and Flexibility test (an adapted dimension-change shape sorting task which measures switching and interference control)	Global switch costs
Local task-switching	LS		Local switch costs
Interference control	IC		Congruency costs

Note: ADHD = Attention-Deficit/Hyperactivity Disorder. NEPSY-II = Developmental Neuropsychology Test 2nd Edition. WASI = Wechsler Abbreviated Scale for Intelligence. SwIFT = Switching Inhibition and Flexibility test.

3.2.2.2 Measures of clinical symptoms

Parent-rated inattention

Parent ratings from the inattentive subscale of the SWAN were used as an index of inattentive behaviour. The score was calculated as the sum of the raw score from each item of the inattentive subscale, giving a possible range of -27 to +27. Higher scores represent higher levels of inattention. Due to the computerised nature of scale completion, there were no missing items for any participant as the algorithm would not allow the parent to proceed if any items were not complete.

3.2.2.3 Measures of basic cognitive processing

Motor processing speed

Children completed the finger tapping subtest from the Developmental Neuropsychology Test (NEPSY-II; Korkman, Kirk, & Kemp, 2007) as a measure of motor processing speed. This consisted of tapping the forefinger and thumb together as quickly as possible for 20 repetitions on both the dominant and non-dominant hand. This was followed by tapping the thumb to each finger in sequence for five sequences as quickly as possible, again with both the dominant and non-dominant hand. A composite of raw scores for the repetitions trials was used in the analyses. It was calculated by summing the time taken (in seconds) for 20 repetitions on the dominant and non-dominant hand, and dividing the total by two. Higher scores represent slower processing speed. Two term-born and six very preterm children did not complete this task due to insufficient time caused by delays in the testing session.

Visuo-spatial processing

Children completed the arrows subtest from the NEPSY-II (Korkman et al., 2007) as a measure of visuo-spatial processing. On each trial the child was presented with a target surrounded by arrows on a page, and was required to indicate which arrows were pointing straight to the centre of the target. They were not allowed to trace the line with their fingers. The subtest was administered and scored as per the test manual.

The total raw score was used in analyses, with a maximum score of 38 arrows correctly identified, where higher scores represent better visuo-spatial processing. One term-born and five very preterm children did not complete this task due to insufficient time caused by delays in the testing session.

Verbal short term memory

Children completed a simple computer-based immediate verbal recall task programmed using PsychoPy (Peirce, 2009). They were seated at a comfortable distance from a computer screen and asked to wear a set of headphones. Volume was set to a level that was comfortable for the child. Written instructions appeared on the screen and were read out by the experimenter.

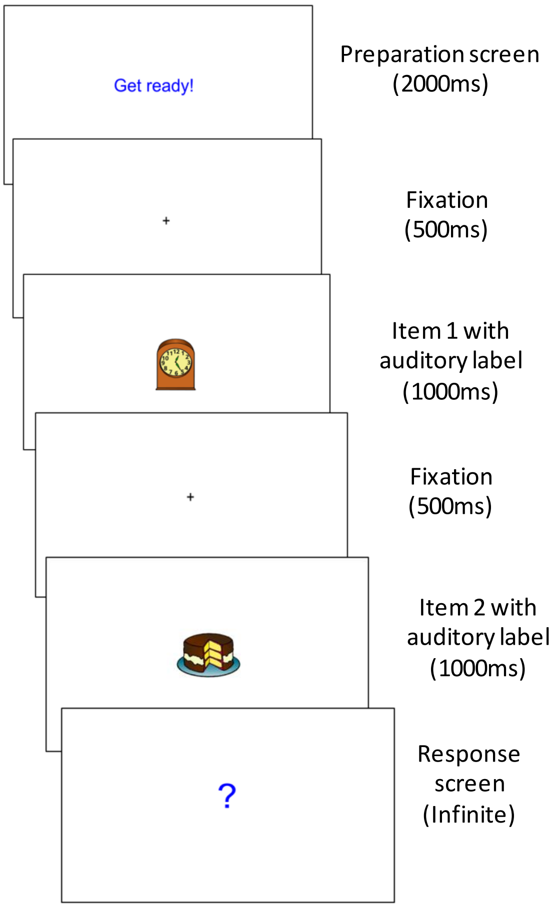

Figure 3.1: Schematic showing an example two-span trial of the verbal short term memory task

Each child was required to listen to a list of words as the corresponding picture was shown on the computer screen and when cued, to try to recall the words out loud in same order that they heard them. They were explicitly told that if they realised they had forgotten a word, they could say the word ‘something’ in the place of that word so that other words were recalled in the correct position. Single-syllable words with the corresponding coloured pictures (Rossion and Pourtois, 2004) were chosen from the original Snodgrass and Vanderwart (1980) stimulus set. Pictures were chosen to present alongside the auditory representation of the item as opposed to the written word, in order to encourage a concrete representation of each item while accounting for possible differences in reading ability. All children were given the same lists of words in the same order, which was pseudo-randomised to avoid word repetitions within trials.

For each trial, a fixation cross was presented for 500ms, then the first item was presented aurally (spoken in a female voice) through the headphones, with the corresponding picture appearing on the screen for 1000ms. The 500ms fixation and 1000ms presentation of memoranda was repeated to the end of the word list for that trial. At the end of the word list, a blue question mark was presented in the centre of the screen as a recall cue for an infinite period of time, until the experimenter moved the task on. The experimenter recorded the position of each word correctly recalled on a record sheet. The experimenter then pressed the ‘spacebar’ key on the keyboard for correct trials, or the ‘x’ key for incorrect trials. Between each trial, a screen saying ‘get ready’ was presented for 2000ms. Children were not given feedback on accuracy. An example trial is shown in *Figure 3.1*.

The task started with only two words per span, and was programmed to allow up to eight items per span to avoid ceiling effects, increasing in one-item increments. For each child, three trials were given per span length. In order to proceed to the next span level, two of the three trials in that span level had to be recalled correctly. Only exact matches were considered correct. A trial was considered correct only when all words were recalled in the correct serial position. Between each span increment, a screen was presented for 2000ms to say that there would be an extra word to remember. The total number of items recalled in the correct serial position was calculated to provide a score of verbal short term memory. Three very preterm children did not complete this task due to insufficient time caused by delays in the testing session.

Visuo-spatial short term memory

Children completed a simple computer-based visuo-spatial immediate recall task programmed using PsychoPy (Peirce, 2009). They were seated a comfortable distance from the computer screen. Written instructions were presented on the screen and were read out by the experimenter, asking children to help a pirate to find his treasure. A four-by-four grid of black squares on a white background was presented. For each trial, after a delay of 500ms, gold coins appeared one-by-one for

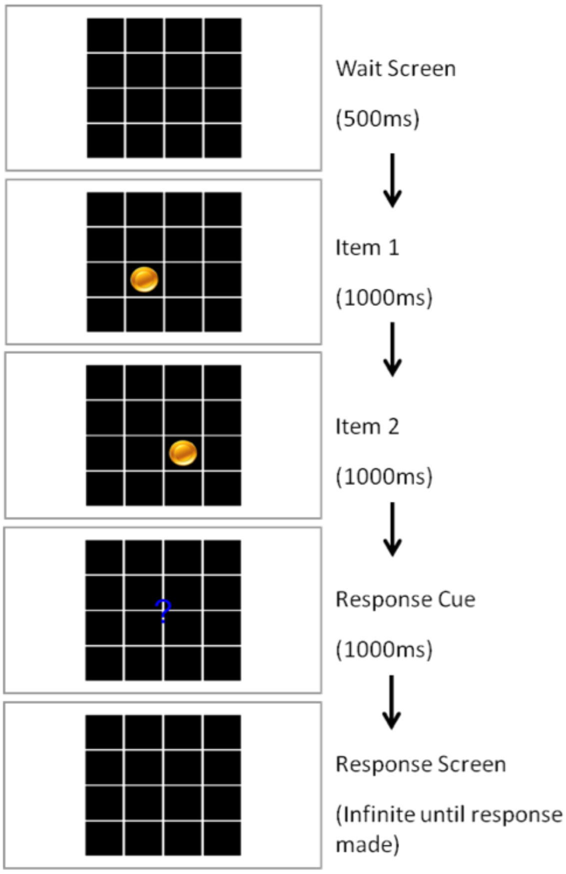

Figure 3.2: Schematic showing an example two-span trial of the visuo-spatial short term memory task.

1000ms each in different positions across the grid.

Following this, a blue question mark was presented for 1000ms in the centre of the grid to cue the child to recall the positions of the coins (see *Figure 3.2*). They were asked to click on the squares (using the mouse) where the coins appeared, and to try to do it in the same order that they saw the coins appear. The software recorded the locations of mouse-clicks and, when the child had clicked in the corresponding number of locations on the grid, the task proceeded to the next trial. Between each trial, a screen was presented for 2000ms telling the child to ‘get ready’. Trials were only considered correct if all locations were recalled in the correct serial position.

As with the verbal memory tasks, three trials were given per span length. In order to proceed to the next span level, two of the three trials in that span level had to be recalled correctly. The experiment started with only two locations per span, and was programmed to allow up to eight locations per span to avoid ceiling effects. Between each span increment increase a screen was presented for 2000ms to state that there would be an extra coin to remember.

No locations were repeated within a single trial. Sequences were chosen that aimed to minimise factors aside from item number that have been shown to affect trial difficulty such as the number of internal crossings (Busch, Farrell, Lisdahl-Medina, & Krikorian, 2005; Orsini, Pasquadibisceglie, Picone, & Tortora, 2001) and distance between locations (Orsini, Simonetta, & Marmorato, 2004). The total number of items recalled in the correct serial position was calculated to provide a score of visuo-spatial short term memory. Two term-born children did not complete this task due to insufficient time caused by delays in the testing session.

3.2.2.4 Measures of executive function

Verbal working memory

The task used to measure verbal working memory was identical to the verbal short term memory task described above (see Section 3.2.2.3), with the exception of a 5000ms retention interval between the list presentation and recall, during which children completed a concurrent processing task. Different word lists from the short term task were used to prevent practice effects but stimuli were selected in the same way. Instructions were adjusted to explain the nature of the new aspect of the task and to give examples of the concurrent processing task. Once again instructions were both presented on screen and orally by the experimenter.

In order to ensure comparable concurrent processing during both the verbal working memory task described here, and the visuo-spatial working memory task described below, the same concurrent processing task was used. A relatively domain neutral task was selected as it has been shown that recall can be negatively impacted when the concurrent processing task taps into the same domain being measured in the memory task (Shah & Miyake, 1996). The concurrent processing task chosen involved

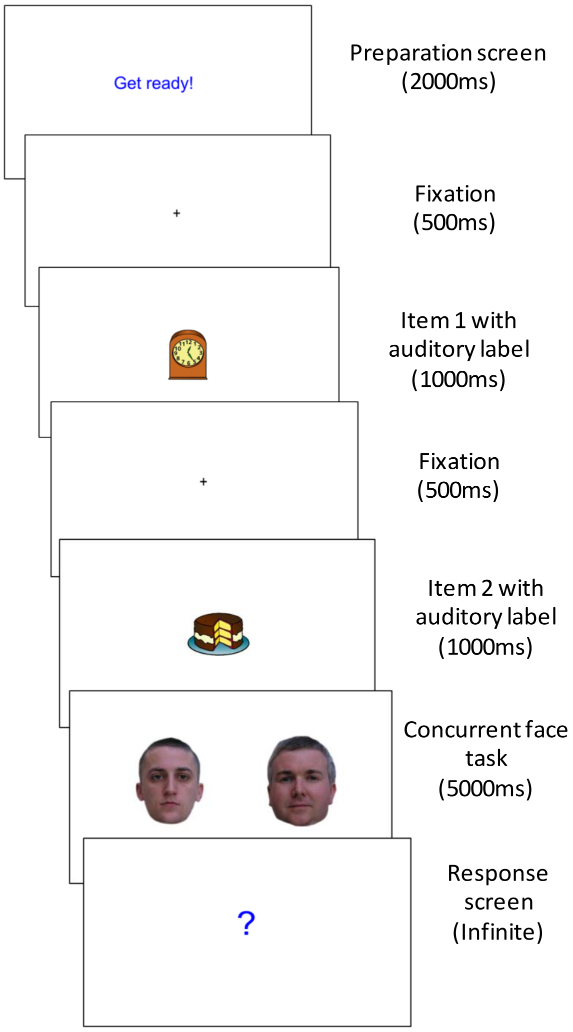

Figure 3.3: Schematic showing an example two-span trial of the verbal working memory task

a simple ‘same or different’ judgement of two photographs of faces presented on the screen, taken from the Glasgow Face Matching Test (Burton, White, & McNeill, 2010) and presented in a random order. Previous research shows that this task is not verbal, nor does it correlate with visual short term memory (*r*=0.050; Burton et al., 2010)

The child was asked to judge whether the faces presented were two pictures of the same person, or pictures of two different people, and to give their response out loud to the experimenter by saying ‘same’ or ‘different’. The experimenter then pressed the ‘1’ key on the keyboard for ‘same’ and the ‘2’ key for ‘different’. If the child completed a judgement before the 5000ms retention interval was complete, they were presented with a second set of faces, and so on, to ensure that despite individual differences in processing speed, all children were required to process the task for the full 5000ms. The experimenter ensured that children did not use the interval simply to rehearse the memoranda. Following this, a blue question mark appeared in the centre of the screen to cue word recall, as in the verbal short term memory task described above.

Scoring was conducted as for the short term memory task above, with the same span levels and the same criteria for proceeding to the next span. The procedure of the recall task was not contingent on successful face judgements. An example trial can be seen in *Figure 3.3*. The total number of items recalled in the correct serial position was calculated to provide a score of verbal working memory with higher scores indicating better working memory. One term-born child and three very preterm children did not complete this task due to insufficient time caused by delays in the testing session.

Visuo-spatial working memory

The visuo-spatial working memory task was identical to the visuo-spatial short term memory task described above (see Section 3.2.2.3), with the exception of a 5000ms retention interval during which children completed a concurrent processing task. The concurrent processing task used was identical to the domain-neutral face-processing task used in the verbal working memory task, where children were asked to judge whether two photographs of faces were two photographs of the same person, or photographs of two different people. On each trial, following the presentation of the coin locations, the concurrent processing task was presented for 5000ms, before the response grid appeared on screen with the blue question mark to cue location recall.

Written and oral instructions were adjusted and examples of the amended procedure were given. Scoring was conducted as for the short term memory task above with the same span levels and the same criteria for proceeding to the next span. The total number of items recalled in the correct serial position was calculated to provide a score of visuo-spatial working memory with higher scores indicating better working memory. Two term-born children and one very preterm child did not complete this task due to insufficient time caused by delays in the testing session.

Switching and interference control

Children completed a modified version of the SwIFT (Switching, Inhibition and Flexibility task; FitzGibbon, Cragg, & Carroll, 2014), a simple computerised shape and colour matching task programmed using PsychoPy (Peirce, 2009). The child was seated a comfortable distance from the screen wearing a set of headphones. The volume in the headphones was set to a comfortable level for the child. Written instructions were presented on the screen and read out by the experimenter. Throughout the task, prompt and response stimuli consisted of two different shapes (specifically designed so that they did not have verbal labels, henceforth described as shape A and shape B) and two different colours (also specifically chosen as faded colours that were difficult to verbally label; red-ish and blue-ish, henceforth referred to as red and blue for ease of description), so that four possible stimuli could be used (A-red A-blue, B-red, B-blue). On each trial, the outline of a black box was presented at the top centre of the screen for 1000ms. The prompt stimulus was then presented within the box, together with an auditory cue (a female voice saying ‘colour’ or ‘shape’). After a delay of 500ms, two response stimuli were then presented below, one on the right and one on the left of the screen. If children heard the word ‘colour’ they were required to choose the response stimulus that matched the prompt on the basis of colour. If they heard ‘shape’, they were required to choose the response stimulus that matched the prompt on the basis of the shape. All stimuli remained on the screen until the child responded. To choose the response stimulus on the left side of the screen, children pressed the ‘z’ key on the keyboard, or for the response stimulus on the right side of the screen, the ‘m’ key. Star-shaped stickers were placed on the keys as reminders, and children were told to ‘keep their fingers on the stars’, so that they could respond as quickly as possible. An example of a full trial is shown in Figure 3.4.

The task was designed so that there were six different trial types resulting from two levels of congruency (congruent and incongruent) and three levels of switching (pure, switch mixed, and non-switch mixed). To begin with, each child completed two blocks of 12 pure trials. In each of these ‘pure’ blocks, children were required to match on the same dimension throughout the duration of the block, producing one block of 12 trials where children matched the response stimuli to the prompt only on the basis of colour, and a separate block of 12 trials where they matched only on the basis of shape. The order of these blocks was counterbalanced across participants.

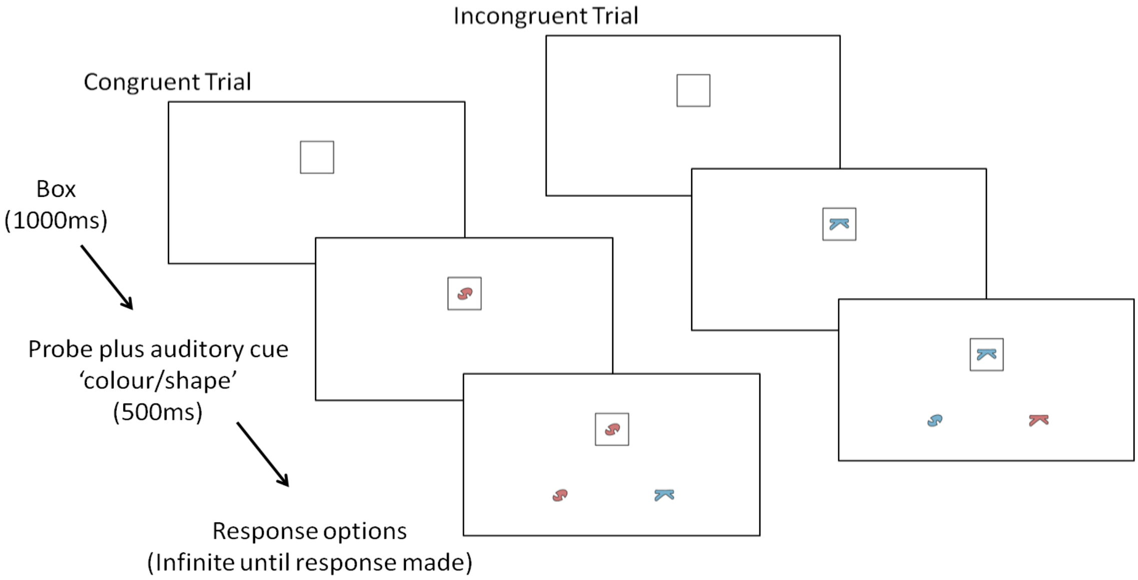

Figure 3.4: Schematic for examples of congruent (left) and incongruent (right) trials on the SwIFT.

Prior to these blocks, children completed two practice trials with visual feedback. If the child gave incorrect responses on practice trials, more practice trials were given until the child responded correctly on two consecutive trials.

Following the two ‘pure’ blocks, children completed three ‘mixed’ blocks of 24 trials, where half of the trials required them to match on colour, and the other half required them to match on shape. Trials were organised so that after the first trial in each block, subsequent trials could be labelled as either ‘switch trials’, whereby the dimension used for matching was different to the one on the previous trial (e.g. trial two: ‘shape’, trial three: ‘colour’), or ‘non-switch trials’, whereby the same dimension was used for matching as in the previous trial (e.g. trial two: ‘shape’, trial three: ‘shape’). So in total there were 24 pure trials, 34 non-switch mixed trials and 35 switch mixed trials. This allowed us to measure both global task switching, by comparing response time on mixed blocks to pure blocks, and local task switching, by comparing performance on switch trials to non-switch trials within the mixed blocks. A further 3 trials, one at the beginning of each of the 3 the mixed blocks, could not be considered to be either ‘switch’ or ‘non-switch’ as there was no preceding trial and were excluded from the analysis.

Half of all trials in each block were labelled as ‘congruent trials’. For congruent trials the correct response stimulus matched the prompt stimulus on both colour and shape dimensions, while the incorrect response stimulus did not match on either dimension (for an example of a congruent trial see Figure 3.4, left). On congruent trials the prompt matches the response stimulus on the left on both the colour and shape dimension, but does not match the response stimulus on the right on either dimension, thus regardless of the instruction, the response stimulus on the left would be the correct response option). The other half of trials were ‘incongruent trials’. For incongruent trials, the correct response stimulus only matched the prompt stimulus on the dimension the child had been instructed to match on, and the incorrect response stimulus matched the prompt stimulus on the irrelevant dimension, creating conflict (for an example of an incongruent trial see Figure 3.4, right. On incongruent trials for example, the prompt might match the response stimulus on the left on colour, and the response stimulus on the right on shape, thus if the instruction was ‘shape’ the correct response option would be the stimulus on the right, but the stimulus on the left matches on colour, creating interference). This allowed us to measure interference control, by comparing response time on incongruent trials to congruent trials across all blocks (both pure and mixed).

Two measures of task switching were computed for analyses; local and global switch costs. Local switch costs were calculated by subtracting the median response time on correct non-switch trials within the mixed blocks, from that on correct switch trials within the mixed blocks. Global switch costs were calculated by subtracting the median response time on correct trials in the pure blocks, from that on correct trials in the mixed blocks. Higher cost scores represent slower switching.

A measure of interference control was also derived from the SwIFT task by calculating congruency costs. These were calculated by subtracting median response time on correct congruent trials from that on correct incongruent trials across the whole task. Higher cost scores represent poorer interference control. Five term-born and four very preterm children did not complete this task due to insufficient time caused by delays in the testing session.

3.3 Analysis

3.3.1 Assessment of group differences in task performance

As groups were matched for inattention, group differences in cognitive performance were not the main focus and were not necessarily expected, however they were considered important to assess to provide context. To test the hypothesis that the groups would not differ on cognitive task performance, a multivariate analysis of covariance was conducted on all of the cognitive measures with group as a between subjects factor and age as a covariate to account for the older age of the very preterm children. Any significant multivariate effects were followed up with relevant univariate analyses of variance and post-hoc tests.

3.3.2 Assessment of mechanisms underlying inattention

To test hypotheses that motor processing speed, working memory measures, task switching and interference control would be associated with parent-rated inattention, partial correlations were conducted. The effect of age was controlled in order to account for the discrepancy in age between the groups. These correlations were conducted initially collapsed across both groups to maximise the power to detect associations that were consistent across groups, and then repeated split by group to identify any associations restricted to one group, and to test the hypothesis that processing speed would only be associated with parent-rated inattention in preterm children. Where significant correlations were identified in split-group analyses, Fischer's *r* to *z* was applied to assess the statistical significance of any between-group difference in the size of the correlations.

Finally, to test the hypotheses that variation in executive functioning would explain variance in parent-rated inattention beyond that explained by basic cognitive processing, a hierarchical regression was conducted. Variables entered into the models were those that were statistically significantly correlated to parent-rated inattention ($p < 0.05$) in one or both groups in partial correlation analyses. All predictor variables were grand-mean centred in order to prevent potential problems of multicollinearity and model interpretation that can result from the introduction of interaction terms, as advised in Jaccard, Wan and Turrisi (1990). Group was entered into the first step, along with age, to account for the effect of age on performance throughout. In the second step, the low-level cognitive measures of motor processing speed, verbal short-term memory and visuo-spatial short-term memory were entered. In the third step, the executive function measures of visuo-spatial and verbal working memory and interference control were added. On the basis of the theoretical assumption that low-level processes contribute to executive functions (e.g. short-term memory contributes to working memory), low-level processes were entered at an earlier stage of the model so that any observed contributions of executive function measures would be measured after controlling for differences in more basic cognition. In the final step when executive function measures were added, a data-driven forward-entry selection technique was used so that only those variables that added significant variance above and beyond that accounted for in the preceding steps were entered. This approach has been used previously (Aarnoudse-Moens et al., 2013) to better separate out effects amongst variables that are related to one another. In the final step, the group interaction terms for all cognitive measures were added to investigate any between-group differences in predictors of parent-rated inattention. Similarly, a data-driven forward-entry selection technique was used in this step so that only group-interactions that accounted for significant unique variance were entered into the final model.

3.3.3 **Treatment of data**

Little's test indicated that missing data were missing completely at random ($\chi^2(109)=99.965$, $p=0.720$), and the reasons for non-completion throughout the study were due to insufficient time for completion due to delays in the testing session, rather than for systematic reasons that may have confounded the results. As such, missing data points were replaced using the expectation maximisation procedure implemented in SPSS. Data were examined for multivariate outliers using Mahalanobis Distances and calculating χ^2 values for all participants. No multivariate outliers were detected in either group (for all participants $p>0.05$), thus analyses reported below include all data points. Assumptions for each statistical analysis were checked, and where appropriate, corrections of violations were applied and are reported. As always with a large number of comparisons, the risk of type one errors is increased. As the correlations were to guide variable selection for the regression analysis, it was decided that the application of Bonferroni corrected alpha levels for the correlations was too conservative. Elsewhere, where appropriate, Bonferroni corrected alpha levels were applied and are reported. The risk for type one errors was considered when interpreting results.

3.4 Results

3.4.1 **Between-group performance differences**

Group differences in performance on cognitive tests and parent-rated inattention scores were examined using a MANCOVA with group (term-born or very preterm) as the between subjects factor and age entered as a covariate. Using Pillai's Trace, multivariate tests showed that there was a significant main effect of group when controlling for age ($V=0.249$, $F(10,101)=3.344$, $p=0.001$) and a significant main effect of age ($V=0.268$, $F(10,101)=3.701$, $p<0.001$). The univariate tests reported in *Table 3.2* therefore refer to the model corrected for age.

Levene's test indicated equality of error variances ($p>0.05$) for all variables except global switch costs ($F(1,103)=4.951$, $p=0.028$). MANCOVA is robust to violations of homogeneity of error variance where the variance ratio is <3. The variance ratio for global switch costs was 2.76, meeting this criterion, therefore univariate tests are reported below. Further, violations of this assumption increase risk of a Type 1 error, and as can be seen below, this did not occur given that group effects relating to global switch costs are non-significant.

Table 3.2: Age adjusted marginal means and standard errors (SE) for performance measures of term-born and very preterm children.

Measure	VP		Term		Between-group differences		
	Mean	SE	Mean	SE	F	p	η_p^2
Parent-rated inattention	- .51	1.41	-4.58	1.66	1.99	.141	.035
Visuo-spatial processing	27.47	.47	28.47	.55	3.13	.048*	.054
Motor processing speed	6.51	.13	7.19	.15	5.89	.004***	.097
Verbal short term memory	37.58	1.26	42.17	1.48	4.93	.009**	.078
Verbal working memory	21.18	1.25	26.72	1.47	4.40	.014*	.072
Visuo-spatial short term memory	34.32	1.47	40.86	1.72	11.38	<.001***	.171

Visuo-spatial working memory	16.17	1.21	18.58	1.47	2.83	.063§	.049
Local switching	92.39	22.14	67.42	25.95	1.02	.365	.018
Global switching	231.01	18.32	244.84	21.47	0.19	.827	.003
Interference control	201.52	13.49	160.27	15.80	2.52	.085	.044

Note: $^{§}p<0.07$, * $p<0.05$, **$p<0.01$, ***$p<0.001$ and still significant using Bonferroni corrected alpha of $p<0.005$. VP= very preterm, η_p^2= partial eta squared.

As shown in *Table 3.2* the term-born and very preterm children did not differ on parent-rated inattention and the variability in scores was similar between groups as expected given the selection procedure. The term-born children performed significantly better on tests of verbal short-term memory, verbal working memory, and visuo-spatial short-term memory. Only the difference in visuo-spatial short-term memory remained significant after applying a Bonferroni corrected alpha of $p<0.005$. Contrary to expectations, the very preterm children demonstrated significantly faster motor processing speed. This indicates that despite being matched on inattention, children born very preterm continued to exhibit some cognitive deficits relative to term-born peers in verbal and visuo-spatial short term memory and visuo-spatial working memory (although with small effect sizes), and that motor processing speed was not impaired in the preterm group relative to the term-born controls.

3.4.2 **Relationships with inattention**

The pattern of association between parent-rated inattention and cognitive processes was investigated using partial correlations controlling for age, both across groups and split by group, shown in *Table 3.3* and 3.4. Full correlation matrices are reported in Appendix 2.

Across groups it was found that poorer verbal and visuo-spatial short term memory and poorer verbal and visuo-spatial working memory were associated with greater parent-rated inattention. In addition, interference control in terms of increased slowing on incongruent trials was associated with greater parent-rated inattention.

Visuo-spatial processing, motor processing speed, and measures of task switching were not related to parent-rated inattention when assessed across both groups combined.

Split group correlations showed poorer verbal short term memory was correlated significantly with greater parent-rated inattention in both groups, and the Fischer's comparison revealed that this relationship did not differ significantly between the two groups (*z*=0.28, *p*=0.391).

Table 3.3: Partial correlations between parent-rated inattention and cognitive task-performance.

	Inattention vs. Task Performance		
	Collapsed Across Groups	Very Preterm	Term
Visuo-spatial processing	-.130	-.108	-.097
Motor processing speed	.160	.462***	-.003
Visuo-spatial short term memory	-.332***	-.225	-.366*
Visuo-spatial working memory	-.400***	-.478***	-.272
Verbal short term memory	-.370***	-.321**	-.369*
Verbal working memory	-.256**	-.227	-.208
Local switching	.148	.145	.140
Global switching	.091	.120	.070
Interference control	.186*	.242*	.041

Note: All correlations have been controlled for the effect of age. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

In the term-born group, poorer visuo-spatial short term memory was correlated significantly with greater parent-rated inattention, and although the correlation did not reach significance in the very preterm children, Fischer's comparison revealed again that the strength of the relationship did not differ significantly between the two groups (*z*=0.83, *p*=0.203). In the very preterm group, poorer visuo-spatial working memory was correlated significantly with parent-rated inattention, and although in the term-born children the correlation did not reach significance, Fischer's comparison revealed again that the relationship did not differ significantly between the two groups (*z*=-1.17, *p*=0.121). When the correlations were carried out separately in each group, the relationships for verbal working memory no longer met the criterion for significance in either group. As shown in Table 3.3, the correlations that do not reach significance in one or other group are always in the same direction and of a similar magnitude in both groups, so this is likely to result from a loss of power in the split group correlations rather than indicating different processes in the two groups.

As shown in Table 3.3, the split-group correlations also revealed that only in children born very preterm did slower processing speed relate to more severe parent-rated inattention, a difference which was confirmed by the Fischer's comparison (*z*=2.52, *p*=0.005). Similarly, the split-group correlations revealed that the relationship observed between poorer interference control and more severe parent-rated inattention was only present in children born very preterm. Although here the Fischer's comparison was not significant (*z*=1.13, *p*=0.129), the correlation coefficient of *r*=0.04 indicated that this association was absent in the term-born group. In contrast, there were no significant associations between parent-rated inattention and either global or local measures of task switching.

Next, in order to assess the independent contribution of these variables for explaining the variance in parent-rated inattention, any variable that showed a significant correlation with parent-rated inattention in either term-born or very preterm children was entered into a hierarchical multiple regression, with parent-rated inattention as the outcome variable. Group and age were entered into the first step, measures of low-level cognitive processing (motor processing speed and short-term memory) were entered in the second step, measures of executive functioning in the third step (visuo-spatial working memory, verbal working memory and interference control), and group interaction terms into the final step (group*motor processing speed, group*visuo-spatial short term memory, group* verbal short term memory, group*visuo-spatial working memory, group*verbal working memory and group*interference control. Results are reported in *Table 3.4*.

Age and group membership alone did not explain significant variance in parent-rated inattention (Model 1; *F*(2,110)=1.994, *p*=0.141).

With the addition of low level cognitive predictors in Model 2, the model explained 22.9% of the variance (Model 2; *F*(5,107)=6.350, *p*<0.001), with both visuo-spatial and verbal short term memory, but not motor processing speed, explaining significant unique variance.

Table 3.4: Regression model for cognitive predictors of parent-rated inattention

	Inattention			
	Model 1 R^2=.035 -	Model 2 R^2=.229*** ΔR^2= .194***	Model 3 R^2=.272*** ΔR^2 =.043*	Model 4 R^2=.304*** ΔR^2 =.031*
Predictor	*β*	*β*	*β*	*β*
Group	.180	.111	.092	.107
Age	.021	.173	.194*	.138
Motor processing speed		.171	.119	.160
Visuo-spatial STM		-.232*	-.175	-.192*
Verbal STM		-.290**	-.233*	-.204*
Visuo-spatial WM			-.239*	-.221*
Verbal WM			-	-
Interference control			-	-
Group*motor processing speed				.190*
Group*visuo-spatial STM				-
Group*verbal STM				-
Group*visuo-spatial WM				-
Group*verbal WM				-
Group*interference control				-

Note: *p<0.05; ** p<0.01;*** p<0.001. - = did not meet criteria for forward entry model selection.

Of the executive function predictors, only visuo-spatial working memory contributed enough unique variance to be entered into Model 3. The model was significantly improved (ΔR^2 =.043*) and explained 27.3% of the variance in parent-rated inattention (Model 3; $F(6,106)=6.608$, $p<0.001$). Age, verbal short term memory and visuo-spatial working memory now each explained unique variance.

In the final step, with the introduction of interaction terms only the group*processing speed interaction contributed enough unique variance to be entered into Model 4. This model significantly improved upon Model 3 (ΔR^2 =.031*), and it explained 30.4% of the variance in parent-rated inattention (Model 4; $F(7,105)=6.538$, $p<0.001$). In this model, verbal and visuo-spatial short term memory, visuo-spatial working memory, and the interaction between group and motor processing speed all explained unique variance, reflecting the pattern of correlations reported above (see Figure 3.5).

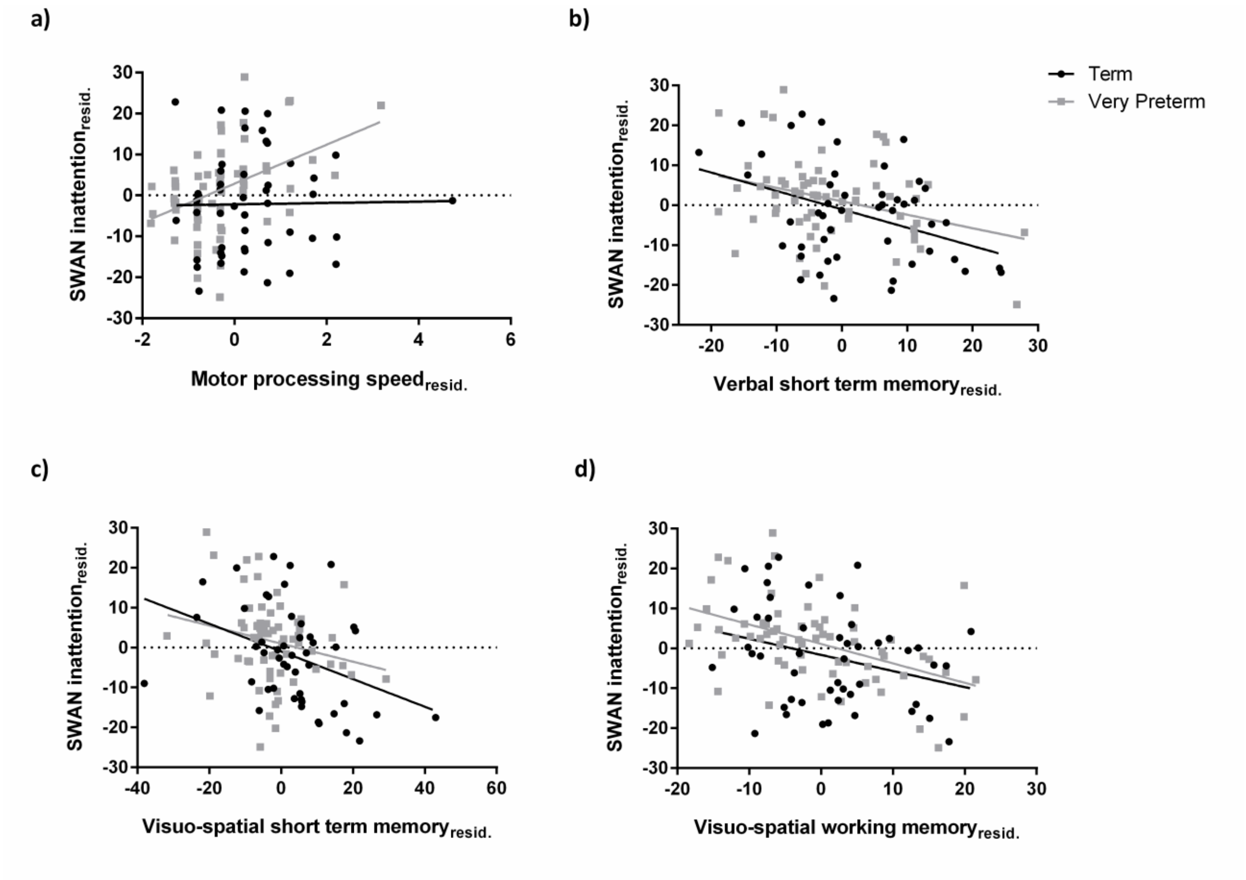

Figure 3.5: Scatter plots showing the association between parent-rated inattention and (a) motor processing speed, (b) verbal short term memory, (c) visuo-spatial short term memory and (d) visuo-spatial working memory while controlling for age at assessment. Values plotted are unstandardised residuals from regressing each variable against age. The dotted line represents 'average' attention, while positive

scores indicate more severe ratings of inattention and negative scores indicate above average ratings of attention.

3.4.2.1 Secondary analysis

Post-hoc analyses were performed to determine whether the group difference in processing speed and the significant group*motor processing speed interaction predicting inattention, as described above, were driven by children with better than average attention or by those with poorer than average inattention. The sample was divided into better and poorer attenders by assigning all those with a SWAN score of zero or below as ‘better attenders’ and all those children with a SWAN score of one or above as ‘poorer attenders’, where a score of ‘0’ reflects average attention.

Group effects

To further understand the finding that children born very preterm had faster processing speed than those born at term, I conducted a two-by-two ANCOVA with processing speed as the dependent variable and with attention (better or poorer) as one between subjects factor, and group (preterm or term) as another between-subjects factor, controlling for age. This analysis confirmed that children born very preterm were faster than children born at term (main effect Group: *F*(1,108) = 10.224, *p*=0.002, mean difference = 0.656s), and showed that better attenders had faster motor processing speed than poorer attenders (main effect Attention: (*F*(1,108) = 4.966, *p*=0.028, mean difference = 0.433s). There was also a marginally significant interaction between Attention and Group (*F*(1,108) = 3.130, *p*=0.080). Although this did not quite reach significance, it is highly relevant to the hypothesis that processing speed would predict inattention in the very preterm group, but not the term-born group. For this reason, further post-hoc t-tests were conducted but must be interpreted with caution given that the initial interaction does not quite reach significance.

Post-hoc t-tests confirmed that differences in motor processing speed between higher and lower attenders were only evident in preterm children (mean difference = 0.783s, *p*=0.002), and not in term-born children (mean difference = 0.083s, *p*=0.787). Further, the comparison of term-born versus pre-term children on processing speed was significant only in the 'better attenders' group (very preterm mean (*SD*) = 7.145(*0.171*); term-born mean (*SD*) = 6.139(*0.167*); mean difference = 1.006s, *p*<0.001), with no effect evident in the 'poorer attenders' group (very preterm mean (*SD*) = 7.228(*0.258*); term-born mean (*SD*) = 6.922(*0.82*); mean difference = 0.306s, *p*=0.347). This suggests that the group difference was driven by better than average attenders.

Processing speed and inattention

The significant group*motor processing speed interaction predicting inattention reflects the presence of the association between inattention and motor processing speed only in the children born very preterm. Although it is clear from the above analysis that the group difference in motor processing speed was driven by better than average attenders, it remains unclear whether the association with inattention in the preterm children is also driven by better attenders (implicating it as a protective factor against inattention), or by poorer attenders (implicating it as a risk factor for inattention).

Split group correlations were conducted. Preterm children who were poorer attenders were significantly older than preterm children who were better attenders (10.33 years and 9.89 years respectively; *t*(63)=2.088, *p*=0.041), thus age effects were controlled. For children born very preterm, in poorer attenders slower processing speed was significantly correlated with more severe parent rated inattention (*r*(28)=0.522, *p*=0.003), but there was no correlation in better attenders (*r*(31)=0.005, *p*=0.977), a difference which was confirmed by the Fischer's comparison (*z*=2.09, *p*=0.019).This suggests that the association between inattention and processing speed in preterm children was driven by poorer attenders.

These post-hoc analyses suggest that the group difference in processing speed between term-born controls and very preterm children was driven by better attenders in the preterm group (i.e. those with low scores on the SWAN, see Figure 3.6a) while the association between processing speed and parent-rated inattention in children born very preterm was driven by poorer attenders only.

3.5 Discussion

The analyses reported in this chapter aimed to determine whether cognitive mechanisms underlying inattention were different in term-born and very preterm children. It aimed to expand on previous research by comparing very preterm children to a sample of term-born children who showed similar variance in parent rated inattention. It also aimed to account for the effects of variation in lower level cognitive processes when examining the influence of executive functioning. Overall, it was found that children born very preterm displayed poorer memory and visuo-spatial processing, but better processing speed than children born at term. In both groups more severe parent-rated inattention was predicted by poorer short term memory (verbal and visuo-spatial) and poorer visuo-spatial working memory, and in children born very preterm, it was also predicted by slower processing speed. These findings are discussed in more detail below.

3.5.1 **Mechanisms underlying inattention**

The selection of a term-born sample with similar levels of inattention is an advantage when comparing mechanisms that underlie inattention between preterm and term-born children. Unlike previous studies, interpretations of any differences emerging between the associations observed in the two groups are not restricted by insufficient variation in inattention ratings in the term-born comparison group. Overall, it was observed that in both very preterm and term-born children, inattentive behaviour was associated with specific areas of weakness rather than with cognitive performance difficulties across the board. These findings are discussed in greater detail below.

As hypothesised, visuo-spatial working memory was associated with inattention in both term-born and very preterm children. This builds on previous findings that working memory is a key factor underlying inattention in preterm (Aarnoudse-Moens et al., 2012; Mulder et al., 2011b; Nadeau et al., 2001) and term-born children (Gathercole et al., 2008). The findings here specify the role of visuo-spatial working memory over and above verbal working memory. This fits with findings that have been relatively well established in ADHD samples (Martinussen, Hayden, Hogg-

Johnson, & Tannock, 2005), as well as typically developing children (Gathercole et al., 2008), and preterm samples (de Kieviet et al., 2012). These findings go beyond existing research by providing evidence to show that while short term memory explains some of the variance in parent-rated inattention, even when accounting for this and for other aspects of lower level cognitive processing, visuo-spatial working memory predicts additional unique variance in inattention. Interestingly, verbal working memory did not explain sufficient variance beyond that explained by basic cognitive processing. By directly comparing term-born and very preterm samples with similar levels of inattention, it is possible to conclude that poor memory across multiple domains is common to inattention in both groups.

My results were consistent with the hypothesis that motor processing speed would predict inattention in the very preterm group, but not the term-born group, echoing the findings of Mulder et al. (2011b). Moreover, with the use of a larger term-born sample matched to the preterm group on inattention, this study confirmed that this association was restricted to the very preterm children only, a finding that emerged in the Mulder study but could not be confirmed due to the small sample size and the fact that their levels of attention were higher than that of the preterm children. Although overall processing speed was better in the children born very preterm than in the children born at term who displayed similar levels of inattention (which will be discussed below), post hoc correlations splitting the preterm children into better and poorer attenders demonstrated that the association between inattention and processing speed in this group was driven by children with poorer than average parent-rated inattention. This suggests that slower motor processing speed is a risk factor for inattention in children born very preterm. While the findings here are consistent with some prior research (Mulder et al., 2011b), other studies have failed to find an association between processing speed and behavioural difficulties, (Aarnoudse-Moens et al., 2012; de Kieviet et al., 2012). These contrary findings are likely to be due to differences in the task used to measure processing speed and differences in the outcome measures. Processing speed is a difficult concept to define, with most measures comprising the combination of a variety of different mental ‘processes’ (e.g. detection of stimulus, evaluation of stimulus, initiation of motor response), any of which may be impaired. Aarnoudse-Moens et al. (2012) and de Kieviet et al. (2012) used computerised response time tasks to assess processing speed, measures that are averaged over a variety of trials and susceptible to interference from lapses in attention. In contrast, Mulder et al. (2011b) used a motor processing speed task in which the child was required to circle targets as quickly as possible, and a verbal processing speed task in which they were required to read out a list of ones and twos as quickly as possible. In an attempt to reduce the number of processes required and the confounding effect of attentional lapses, I used a short (~8 seconds) finger tapping task which did not require detection of a stimulus in order for the response to be made, no require any ability to read. However, the contrary nature of findings in this area highlight the need for more sensitive measures of processing speed to be used across different samples in order to further elucidate the role of processing speed. Measures such as event-related potentials, which allow measurement of different parts of processing at the neural level with millisecond temporal resolution may be beneficial.

It could be argued that the regression analysis presented in this analysis supports suggestions that processing speed is at the source of a cascade of cognitive impairment that impacts on behaviour (Mulder, Pitchford, & Marlow, 2011a). However, this would suggest that it is also at the root of executive function difficulties (Mulder, Pitchford, & Marlow, 2011a; Rose et al., 2011). Memory factors explained additional unique variance beyond the variance explained by processing speed alone however. This suggests that memory has an impact on inattention independent of that associated with processing speed. Moreover, evidence that visuo-spatial working memory explained significant unique variance supported the hypothesis that variation in specific executive functions would explain variance in inattention beyond that explained by basic cognitive processing.

No other cognitive measures explained significant unique variance in inattention in either group, and this reflects the uncertainty in my hypotheses about whether variance in task switching and interference control would explain unique variance. The fact that other measures didn’t predict significant unique variance in inattention is particularly interesting given that split group correlations revealed an association between poorer interference control and more severe parent-rated inattention in the very preterm children only. The only prior study of the association between interference control and inattention in preterm children did not find an association (Shum et al., 2008), and findings concerning inhibitory control are mixed, with some studies suggesting it plays an important role (Aarnoudse-Moens et al., 2012; Scott et al., 2012), while others find it to be unrelated (Mulder et al., 2011b). It is interesting and unanticipated that this association was restricted to very preterm children as it was hypothesised that the same effects would be observed in both groups. However, as the association observed was relatively small and interference control did not explain unique variance in inattention, it does not appear to be a key mechanism in the aetiology of inattention in children born preterm. These findings add further complexity to the question of how inhibitory control processes relate to inattention in children born very preterm, as well as term-born children, and suggest that a more detailed investigation of inhibitory processes and interference control in children born very preterm is warranted. Meanwhile, contrary to hypotheses, task switching was unrelated to inattention in both groups, suggesting it is not a core deficit in inattention.

It is important to note that the amount of variance in inattention explained by these cognitive predictors remains modest at 33.2%, suggesting that these cognitive processes are not the only factors involved in the aetiology of inattention in this sample of term-born and pre-term children. Given that some associations present across groups no longer met significance when groups were split, presumably due to a loss of power, this study may have benefitted from larger sample sizes to be confident that all effects were successfully detected and appropriately represented. Unfortunately, as is often the case, pragmatics took priority and further testing was not possible within the timescale of the PhD project.

3.5.2 Patterns of strengths and weaknesses in cognitive performance in very preterm children

Performance differences between term-born and very preterm children were not specifically hypothesised in this study due to the selection of a term-born comparison group that was matched to the preterm sample on levels of inattention, and the testing of cognitive domains that were thought a priori to be associated with inattention. In spite of this, it was acknowledged that due to the wide range of cognitive impairment linked to very preterm birth, it was possible that we might see poorer performance in the very preterm group in some areas. The results of this study indicated that despite considerable overlap in performance scores of the two groups, memory is a particular area of weakness in children born very preterm, consistent with evidence showing that short term memory is impaired in preterm samples (Briscoe et al., 1998; Bull et al., 2008; Shum et al., 2008), along with the larger body of evidence documenting difficulty with working memory (including Böhm et al., 2010; Clark & Woodward, 2010; Curtis, Lindeke, Georgieff, & Nelson, 2002; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Luu, Ment, Allan, Schneider, & Vohr, 2011; Ni et al., 2011; Rose & Feldman, 1996; Saavalainen et al., 2007; Vicari, Caravale, Carlesimo, Casadei, & Allemand, 2004). The same is true for visuo-spatial processing, which has been repeatedly shown to be impaired in preterm populations (Foulder-Hughes & Cooke, 2003; Luciana et al., 1999; Simms et al., 2015). The absence of group differences in task switching and interference control in the present study were also in line with the results of a meta-analysis which concluded that findings relating to impaired inhibitory control and task switching in preterm samples are inconsistent (Mulder et al., 2009). It is important to remember that selection of a term-born sample with similar levels of inattention to the preterm sample makes interpretation of between-group performance differences more complex. Nonetheless, it is likely that the presence of between-group differences in the areas of memory and visuo-spatial processing, but absence in areas of task switching and interference control is likely to reflect the pattern of relative cognitive strengths and weaknesses across domains in preterm children when matched to term-born children on inattention. This could therefore identify neural processes that are impaired by preterm birth irrespective of whether a child also has high inattentiveness.

The most surprising finding was that children born very preterm had faster processing speed overall than term-born children, even statistically accounting for the older age of the very preterm children. In light of prior reports of slower processing speed in preterm samples (Aarnoudse-Moens et al., 2012; Luciana et al., 1999b; Mulder et al., 2011; Rose et al., 2011), differences in this direction were entirely unexpected. It does not appear to be a finding driven by the selection of a term sample including inattentive children, as the difference in processing speed is predominantly evident in children with better than average ratings of attention. One reason could be that in preterm children, neuroplastic compensatory changes might occur to increase the speed of processing as a protective factor to reduce the impact of other impairments. Such changes may be unnecessary or less likely to occur in term-born populations with more typically developing neuroanatomy and a narrower range of impairments. Although it is not fully clear why this finding emerged, it does indicate that outcomes in children born very preterm are heterogeneous, with some children born very preterm outperforming term-born peers of similar levels of above average attention in this area. Further research is needed to understand more fully the potential role of increased processing speed as a compensatory factor in children born pre-term.

3.5.3 **Conclusion**

The results reported in this chapter extend the findings of previous studies by comparing associations between cognition and inattention within term and preterm children who have similar ranges of severity of inattentive symptoms, rather than using the traditional case-control approach. Aside from the unexpected difference in processing speed, the pattern of group differences in performance between term-born and preterm children corresponds well with existing literature highlighting visuo-spatial processing and memory as areas of particular weakness. It is interesting that impairments are still apparent when the term-born group includes children rated as inattentive, confirming that children born very preterm are at risk of greater cognitive impairment than term-born peers displaying similar levels of inattentive behaviours.

Taken together, the regressions and correlations reported above show strong evidence for the role of short term memory and visuo-spatial working memory as shared mechanisms underlying inattention in both very preterm and term-born children, while motor processing speed appears to be a mechanism relevant to inattention only in very preterm children. In both very preterm and term-born children, inattentive behaviour was associated with specific areas of weakness rather than cognitive difficulties across the board, but the results present emerging evidence to suggest that different pathways may lead to inattention in term born compared to very preterm children. This is in contrast to the conclusion drawn by van der Meere et al. (2009) from their study of children born with very low birth-weight. Moreover, the analyses reported here suggest that although some of the lower-level processes that are required for visuo-spatial working memory (i.e., short term memory) predicted inattention, difficulty at the executive level explained unique variance above and beyond that accounted for by basic cognitive processing.

Chapter 4: ERP Predictors of Inattention

4.1 Background

Neuroimaging allows for non-invasive investigation of the neural mechanisms that operate during cognitive functioning, and can reveal the ways in which atypical brain structure and/or function relates to the atypical behaviour that defines disorders such as Attention-Deficit/Hyperactivity Disorder (ADHD; Gabrieli et al., 2015). Inattention difficulties in preterm children and ADHD populations are attributed to atypical neurobiological development, thus it is important to assess whether the causes of inattention in preterm and term-born children differ at the neural level.

EEG detects the voltage produced by neural activity that is measurable on the scalp, and as such it has millisecond temporal resolution and reflects true neuronal activation, rather than secondary biophysical processes such as blood-oxygen level (as often used in functional MRI). Event-related potentials (ERPs) are derived from continuous electroencephalography (EEG) recordings by time-locking epochs to events of interest such as stimulus onset, and averaging across multiple trials of the same type to reduce interference from noise. Use of the event-related potentials (ERP) technique also allows the separation of a behavioural response into different processing components such as stimulus detection, categorisation, and evaluation as well as response preparation (Luck, Woodman, & Vogel, 2000) which are often compared on the basis of amplitude and latency. The amplitude of an ERP component is thought to represent the amount of neural resources recruited for that stage of processing, while latency measures the speed of each stage of processing. These characteristics can be compared for each neural component that contributes to the behavioural response. In spite of a growing body of magnetic resonance imaging-based (MRI) research showing links between atypical brain function or anatomy and behavioural difficulties in those born very preterm (Ment et al., 2009), to date only a single electroencephalography (EEG) study has been conducted investigating how neural activity relates to ADHD symptoms in children born preterm (Potgieter, Vervisch, & Lagae, 2003).

In light of the importance of processing speed as a mechanism underlying inattention in children born very preterm described in Chapter 3 (see also Mulder, Pitchford, & Marlow, 2011b), investigation of ERPs, with their high temporal resolution, may be particularly useful to measure processing speed at a neural level. Further, use of ERPs may help ameliorate problems associated with task dependency of behavioural measures of processing speed. Such detail has the potential to help elucidate which stages of processing are linked to inattention, and further define the role of processing speed as a mediator of inattention in preterm children. Not only could the finer temporal detail provided by ERP analysis produce a greater understanding of the mechanisms underlying inattention, but ERPs also have the potential to reveal biomarkers that are able to explain individual differences in symptoms beyond those that can be explained or detected using behavioural data alone. In this way, ERPs could have functional benefit for diagnosis and treatment. Moreover, it has been argued that if biomarkers of inattention can be established, particularly those using relatively inexpensive and non-invasive techniques such as ERPs, these may be of use during diagnosis to aid the assessment of symptoms and predict symptom-associated outcomes (Loo, Lenartowicz, & Makeig, 2016).

4.1.1 **ERPs and inattention in preterm children: What we know so far**

As mentioned above, to date only one published study has utilised ERPs in order to assess ADHD behaviour in children born very preterm. Potgieter et al. (2003) recorded ERPs in school-aged children born with very low birth weight (VLBW; <1500g) and at less than 34 weeks gestation in an attempt to identify a neural marker that might explain the increased risk for ADHD in this population. They compared groups of VLBW children with and without an ADHD diagnosis with groups of normal birth weight (NBW; >2500g) children with and without an ADHD diagnosis on a visual oddball task. Children were required to respond to infrequent oddball targets among more frequent presentations of a single non-target stimulus. They found that, compared to children without ADHD, children with ADHD (VLBW and NBW) had slower and more variable response times, and had a lower hit rate (responded on fewer target trials), suggesting poorer attention. They also made more commission errors (responded on non-target trials) suggesting poorer inhibitory control. However, there were no differences between VLBW and NBW children with ADHD, or between VLBW and NBW children without ADHD. These behavioural findings were coupled with larger N2 ERP components (a component that is thought to reflect inhibitory processing) and reduced positivity at around 500ms (a component the authors thought reflected specific attention to the stimulus) to non-targets in the two ADHD groups compared to the non ADHD groups, suggestive of atypical neural processing during inhibitory control. However, again, there were no differences in ERP measures between VLBW and NBW children with ADHD, nor between VLBW and NBW children without ADHD, suggesting that any differences resulted from ADHD status as opposed to LBW. Both ERP findings were related to inhibitory processing of the non-target stimulus as opposed to more general attentional processing of target stimuli, with any other comparisons revealing no group differences in spite of behavioural findings of lower hit rates in ADHD.

It should be noted that this study suffers from small sample sizes with an average of only 10 participants in each group, and the authors deliberately only included children with a diagnosis of ADHD *with hyperactivity* in their ADHD samples. When considering the growing evidence that preterm children often present with high levels of inattentive symptoms but sub-clinical levels of hyperactivity (Johnson & Marlow, 2011), it is possible that the group selected here were not representative of the ‘preterm ADHD’ phenotype. Furthermore, the sample was selected on the basis of birth weight, and included children born up to 34 weeks gestation. It is recommended that in studies of outcomes following prematurity samples are selected using gestational age rather than birth weight (Johnson, Wolke, & Marlow, 2008) as low birth weight can occur in babies of more mature gestation. A between-groups approach like this may also be negatively affected by the heterogeneity often present in samples of children born preterm, rather than taking advantage of that heterogeneity by investigating associations between neural and behavioural outcomes within the population. In particular, as the focus of the experimental design and analysis was inhibitory processing, the study failed to fully investigate behavioural and neural correlates of inattention specifically. Therefore, there is a need for further studies that target the identification and comparison of relationships between attentional processing and inattentive behaviour in term-born and very preterm samples at the behavioural and electrophysiological levels.

4.1.2 **Measuring the neural correlates of inattention**

Continuous Performance Tasks (CPTs; Rosvold, Enger, Mirsky, Sarason, Bransome Jr., & Beck, 1956) have been frequently used to study attention and are known to evoke ERP components that have been linked to neural substrates of attention (Riccio, Reynolds, Lowe, & Moore, 2002). Originally used to investigate brain damage, traditional CPTs are similar to an oddball task and comprise of the presentation of an infrequent target letter to which subjects must respond, among a sequence of distractor letters subjects must ignore. However, the task has since been adapted in order to target different components of attention. For example, the Conners' CPT has frequent targets and infrequent distractors, and thus accuracy depends on good inhibitory control to withhold responses to infrequent distractors. Alternatively, in the cued CPT (CPT-AX) subjects respond to infrequent cue-target sequences among distractor stimuli, requiring maintenance of attention throughout long periods where no response is required in order to correctly respond when the cue-target sequence is presented. As such, this task is better for measuring sustained attention, and the converse; lapses in attention. Alongside the accurate detection of cue-target sequences, presentations of the target stimulus in isolation (without a preceding cue), and of the cue stimulus in isolation (without a subsequent target), require the participant to refer to working memory and evaluate the relevance of the stimulus presented to the task demands. Moreover, electrophysiological components representing preparatory processes can be measured in the period following presentation of the cue stimulus, and those representing stimulus detection, categorisation and evaluation processes can be measured in the period following presentation of target stimuli.

CPTs are known to be sensitive to the behavioural deficits observed in children with ADHD (Huang-Pollock, Karalunas, Tam, & Moore, 2012; Riccio & Reynolds, 2001), and studies have shown that task performance measures are best predicted by inattentive symptoms rather than hyperactive-impulsive symptoms (Chhabildas et al., 2001). Variants of the CPT have also been used to assess attentional processes in children born very preterm, although without concurrent EEG recording. Findings of such studies are inconsistent, with some studies finding impairment in CPT performance in children born very preterm (Elgen, Lundervold, & Sommerfelt, 2004; Katz et al., 1996; Short et al., 2003), and others finding no impairment relative to term-born peers (Bayless & Stevenson, 2007; Grunau, Whitfield, & Fay, 2004; Kulseng et al., 2006). A meta-analysis aggregating the results of 9 studies showed poorer sustained attention (as measured by lower hit rate on CPT tasks) in children born preterm, but provided evidence of an increasing effect size with decreasing gestational age, and a moderate-large effect size only in studies with an average gestational age of <26 weeks (Mulder et al., 2009). This suggests that, like the risk for ADHD, poor performance on this measure of sustained attention in preterm children may show a gestational age related gradient. To date, studies using CPTs to assess sustained attention in children born preterm have aimed to identify impaired performance relative to controls rather than evaluating whether CPT-derived measures predict levels of inattentive behaviour. Furthermore, although the CPT has been identified as a task well-suited for the identification of neural substrates of attention (Riccio et al., 2002) it has yet to be used in conjunction with EEG in a preterm population. As such, this task was considered appropriate for the measurement of behavioural and electrophysiological measures of processes that may underlie inattentive behaviour in both term-born and very preterm children and was selected for use in the current study.

4.1.3 **Event-related potentials**

Various stages of neural processing are known to be modulated by attention, and different electrophysiological components are thought to represent these processing stages. This study focussed on four specific processes; response preparation following the presentation of a cue stimulus, initial detection of a target stimulus, categorisation of a target stimulus and evaluation of the relevance of that target stimulus. Each of the cognitive processes that occur during these stages are thought to be represented by the ERP components CNV, P1, P2 and P3 respectively. Each component and its potential relevance to inattentive behaviour is discussed in full below.

4.1.3.1 Response Preparation

In paradigms where a warning stimulus, or cue, predicts the upcoming presentation of a target stimulus, slow negative waveforms occurring late during the cue-target interval have been considered an index of response preparation. The impact of these preparatory processes cannot be separated from target processing using behavioural measurements, but the ERP technique allows for this separation. Initially described as contingent negative variation (CNV) by Walter, Cooper, Aldridge, McCallum, and Winter (1964), the CNV is the primary response preparation ERP studied using cue paradigms. Further research has identified that, in some cases, two peaks can be identified in the CNV. The earlier peak occurs 0.7-1s after the cue and is referred to as the O-wave, thought to represent orientation to the cue. Meanwhile, the later peak, the E-wave, also precedes the target but latency is dependent on the length of the inter-stimulus interval. This peak is thought to represent expectancy of and preparation for the upcoming target stimulus (Loveless & Sanford, 1974; Rohrbaugh & Gaillard, 1983).

Larger amplitudes of the CNV are associated with faster response times, and directional cues produce larger CNVs compared to non-directional cues in spatial cueing paradigms, suggesting that larger amplitudes represent better orientation/expectation (Wright, Geffen, & Geffen, 1995). In addition, there is evidence that the CNV has a smaller amplitude in younger children, who in turn have slower and more variable response times, and that CNV amplitude increases in amplitude through to adulthood (Jonkman, 2006) further supporting the notion that larger amplitudes are associated with better orientation/expectation.

There is a growing body of research into the CNV in children and adults with ADHD. Findings are relatively consistent, showing that the CNV is reduced in children with ADHD (Banaschewski et al., 2008; Banaschewski et al., 2003; Ortega, López, Carrasco, Anllo-Vento, & Aboitiz, 2013) and that smaller amplitudes correlate with higher levels of symptoms (Ortega et al., 2013). Furthermore, this reduction in the CNV is thought to be a relatively stable marker of ADHD. In one longitudinal study, other ERP markers that differentiated an ADHD group from controls were normalised by adulthood, but the reduced CNV was still present (Doehnert, Brandeis, Schneider, Drechsler, & Steinhausen, 2013). This finding held even in adults who no longer met diagnostic criteria, but who continued to display significantly higher levels of ADHD symptoms than age-matched controls. Not only does the CNV show promise for use as a biomarker for diagnostic purposes, but it has also been demonstrated to be a potential intervention target. Heinrich, Gevensleben, Freisleder, Moll, and Rothenberger (2004) demonstrated that slow cortical potential training resulted in an increased CNV along with decreases in both symptoms and commission errors on a CPT in children with ADHD compared to a comparison group of children on a 'waiting list' for ADHD referral.

Research examining the CNV in the inattentive subtype of ADHD (ADHD-I) or in relation to inattentive behaviour specifically is limited. Kratz et al. (2011) compared three groups of eight to eleven year old children during an attentional network task, one group diagnosed with the combined subtype of ADHD (ADHD-C), another with ADHD-I, and a third group of typically developing age-matched controls. They did not find any group differences on CNV characteristics. Similarly, in a study that separated the CNV into early and late components (akin to the 'O' and 'E' waves), it was found that typically developing controls and different ADHD subtypes displayed no differences in the characteristics of the early CNV (Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009). However for the late wave, the two ADHD subtypes demonstrated topographical differences, suggesting differing underlying mechanisms for preparation for the upcoming stimulus. Though the subtypes differed topographically, both groups demonstrated deficient expectation of, and preparation for, the subsequent stimulus. These results are limited, and the extent of the relationship between CNV characteristics and inattentive symptoms is unclear due to the use of between-group analyses. Furthermore, this component has not been examined in children born very preterm.

4.1.3.2 Early target processing

The P1 is a positive deflection that occurs over the occipital cortex around 100ms after stimulus onset, and is thought to reflect initial sensory processing, and in the case of visual stimuli, visual discrimination (Luck et al., 2000). This is the earliest component following the onset of a specific stimulus that can be modulated by attention, despite being primarily driven by stimulus properties. Specifically it has been shown that it is larger for attended to and/or cued stimuli, although latency often remains the same (Hillyard, Vogel, & Luck, 1998). This has been interpreted as a type of sensory gain control whereby selective attention amplifies the visual signals to facilitate processing.

Evidence concerning the P1 in children and adults with ADHD is inconsistent. Some studies have found that P1 characteristics do not differ between children with ADHD and typically developing age-matched controls (Jonkman et al., 1997; Oades, 1998; Steger, Imhof, Steinhausen, & Brandeis, 2000; Strandburg et al., 1996). The only study that focussed specifically on the inattentive ADHD subtype found that there was no difference between ADHD/I and typically developing age-matched controls (Brown et al., 2005). Conversely, both Kemner et al. (1996) and Shen, Tsai and Duann (2011) found reduced amplitude P1s in children with ADHD compared to typically developing age-matched controls. Furthermore, Perchet, Revol, Fourneret, Mauguière, and Garcia-Larrea (2001) found that unlike controls, children with ADHD showed no increase in the amplitude of P1 for cued compared to uncued stimuli. This evidence would suggest that although sometimes detected, attention allocation during this period of early stimulus discrimination is not one of the key impairments associated with ADHD.

The only study to date that has assessed the P1 in the context of ADHD in a sample of children born preterm (≤34 weeks gestation) and with VLBW found comparable P1 amplitude and latency across ADHD-VLBW, non-ADHD-VLBW, ADHD-NBW, and non-ADHD-NBW groups in an oddball task (Potgieter et al., 2003). Other studies have found a reduced amplitude P1 in 5 year old children born VLBW (Hövel et al., 2014; Mikkola et al., 2010). Given the evidence that processing speed relates to inattention in children born very preterm, both in the results described in Chapter 3 and in prior literature (Mulder et al., 2011b), it was considered important to explore how characteristics of the P1, particularly P1 latency relate to inattentive behaviour in the present samples. It remains unknown whether the associations observed between processing speed and inattentive behaviour in preterm children result from individual differences in the speed of the earliest stages of processing (such as those indexed by the P1), or whether it is differences in the speed of later processing.

The P2 is a positive deflection in the ERP that occurs around 200ms after stimulus onset and is thought to reflect the comparison of perceptual information with internal representations for stimulus categorisation and termination of further sensory processing (Luck & Hillyard, 1994), thereby facilitating the subsequent stages of processing (Hansen & Hillyard, 1988; Oades, 1998). This stimulus categorisation process has also been shown to be modulated by attention, despite being primarily driven by stimulus properties. It has been shown that task-relevant stimuli enhance the P2 (Luck & Hillyard, 1994), however, in comparison to the P1, there is a scarcity of research surrounding the characteristics of the P2 (Crowley & Colrain, 2004).

Some evidence suggests that P2 amplitude is reduced in children with ADHD/I to target (Brown et al., 2005; Johnstone, Barry, & Clarke, 2007) and non-target stimuli (Brown et al., 2005). Similarly, Holcomb et al. (1986) found that for target stimuli, an ADHD/I group showed a smaller age-related amplitude increase than that observed in controls or in an ADHD/C group. This is in line with the suggestion that lower P2 amplitude represents less allocation of attention to a task-relevant stimulus. Conversely, Johnstone et al. (2009) found that both ADHD subtypes had increased P2 for go and no-go stimuli relative to typically developing controls. Findings with latency are also mixed. Both Brown et al. (2005) and Johnstone et al. (2001) observed longer P2 latencies to target and non-target stimuli compared to age-matched controls, in ADHD inattentive and combined subtypes respectively. This fits with the interpretation that shorter latencies are representative of faster processing which is likely to occur in children with better attention. Conversely Sunohara et al. (1999) found evidence of *shorter* P2 latencies to go stimuli on correct trials in unmedicated children with ADHD compared to typically developing age-matched controls. One study showed typical visual P2 processing in 5 year old children born <28 weeks gestation (Lavoie, Robaey, Stauder, Glorieux, & Lefebvre, 1997) compared to healthy term-born peers. However, there is a scarcity of relevant research in this population and the P2 component has not been investigated in children born very preterm in relation to inattention.

The discrepancies noted above in the P2 ADHD literature suggest that findings are likely to be task- and sample- dependent, however most studies support the notion that inattentive children show atypical P2 characteristics. One possible explanation for these differences is that there may be an optimal speed of processing, thus very short P2 latencies suggest attention is allocated too rapidly whereas very long latencies suggest a failure to allocate attention within an optimal time-scale. Similarly, for P2 amplitude, in some task designs it may be the case that attention can be allocated with minimal effort, and so in contrast to tasks where additional allocation of resources indicates better processing, in easier tasks enhanced P2 may be elicited in children who require extra effort to achieve the same performance level.

4.1.3.3 Later processing

The P3 is a positive deflection that occurs around 300ms after stimulus onset and is thought to reflect higher order executive processing. In particular it has been linked to the updating of working memory (Donchin & Coles, 1998) and evidence shows that the P3 is larger for attended-to stimuli than for unattended stimuli (Heinze, Luck, Mangun, & Hillyard, 1990; Polich, 1986). Although there are no changes in latency under many conditions, it has been shown that instructing participants to daydream can result in delayed latencies, suggesting that delayed latencies reflect inattention to the stimulus (Polich, 1986). It is possible that inattentive behaviour and slower and more variable responses in behavioural tasks are both related to atypical processing at this more complex stage of information processing, as indexed by the P3. This seems particularly likely given the importance of working memory as a predictor in inattentive behaviour.

Smaller P3 amplitudes have been detected in children with ADHD compared to typically developing age-matched controls in a variety of studies, both in children with the combined subtype and the predominantly inattentive subtype of ADHD (Johnstone et al., 2001; Brown et al., 2005; Holcomb, Ackerman, & Dykman, 1986; Kratz et al., 2011). Furthermore, Kratz et al. (2011) found that for cue stimuli, both ADHD/I and ADHD/C groups showed a reduced P3 amplitude compared to controls, whereas only the inattentive subtype showed this reduction for target stimuli, suggesting less allocation of attention to cue stimuli is a common feature of ADHD, but that continued poor attention for target stimuli is more of a difficulty for children with ADHD/I. Moreover, Sunohara et al. (1999) showed that unmedicated children with ADHD had longer P3 latencies than controls, but methylphenidate (even low doses) reduced these. Again, evidence concerning the relationships between P3 and inattention in children born very preterm is limited to the one study conducted by Potgieter et al. (2003). They found that the P3 only differed between groups (NBW-without-ADHD, NBW-with-ADHD, VLBW-without-ADHD, VLBW-with-ADHD) on trials where commission errors occurred. In these trials, P3 amplitude was larger in VLBW and NBW children with ADHD than in VLBW and NBW children without ADHD, and as such VLBW was not a defining factor. Other evidence concerning whether P3 characteristics are typical in preterm populations is mixed, with studies finding either reduced P3 (Dupin, Laurent, Stauder, & Saliba, 2000) or no differences in P3 characteristics (Mikkola et al., 2010) when comparing 5 year old children born very preterm with term-born peers. This evidence suggests that the P3, and thus evaluation of the relevance of a stimulus, may be atypical in children with ADHD, and perhaps in children born very preterm as well, but it remains unclear whether there is a particular relationship between P3 characteristics and inattentive symptoms in both populations. More research is needed to understand the role of the P3 with regard to inattentive symptoms, particularly given the importance of working memory to inattention observed in Chapter 3, along with the link between the P3 and working memory.

4.1.4 **The current analysis**

The current analysis aimed firstly to investigate how task-related cognitive performance and neural activity on the CPT-AX related to inattentive symptoms in term-born and very preterm children. It has been claimed that use of sustained attention tasks such as the CPT-AX could have clinical value in the diagnostic assessment of ADHD (Riccio et al., 2002). Behavioural measures representing sustained attention (hit rate), impulsivity (commission errors), processing speed (response time) and lapses in attention (response time variability) were all derived from the CPT-AX. These allowed me to compare task-performance between term-born and very preterm children and to evaluate these processes as behavioural mechanisms underlying inattention. Alongside the behavioural measures, ERPs derived from the continuous EEG recording were analysed. Specifically, cue-locked negativity (response preparation), the P1 (stimulus detection), the P2 (feature detection and stimulus categorisation) and the P3 (stimulus evaluation) were measured. There were some differences observed in the characteristics of the CNV-like component in our data compared to the CNV reported in the wider literature (discussed below in Section 4.5.2.1), and as such in the current study this component will be referred to as cue-locked negativity. A summary of the measured components and their characteristics as shown in our data can be seen in Table 4.1.

Table 4.1: Summary of ERP components examined in this study with descriptions of their characteristics and interpretation.

Component	Trial Type	Latency	Topography	Interpretation
Cue-locked negativity (CNV)	All cue trials	Early: 600-1000ms Late: 1000-1400ms	Centro-parietal	Response preparation
P1	Cued and uncued targets	75-175ms	Occipital	Stimulus detection
P2	Cued and uncued targets	175-250ms	Fronto-central	Feature detection & stimulus categorisation
P3	Cued and uncued targets	250-350ms	Parietal	Evaluation of stimulus task-relevance

4.1.4.1 Aims and hypotheses

The overarching aims of this analysis were to (i) determine whether behavioural and neural predictors of inattention were different in term-born and very preterm children, (ii) to evaluate whether the use of ERPs provides additional predictive value beyond the use of behavioural measures in the assessment of inattention. In addition, as ERP latency is thought to be another index of processing speed, and given the results in Chapter 3 concerning the association between inattention and motor processing speed in children born very preterm I developed a separate aim concerning ERP latency; (iii) specifically to break down ‘processing’ into specific ERP components and to assess the association between processing speed (ERP component *latency*) and inattention in each. In order to achieve these aims, it was important to firstly assess which of the electrophysiological measures showed evidence of task-related attentional modulation (subsequently referred to as ‘task-related attention’), secondly to assess differences between groups in the behavioural and neural measures, and finally to assess and compare the relationships between these measures and inattentive behaviour (subsequently referred to as ‘parent-rated inattention’).

Assessing task-related attentional modulation

Firstly, it was important to assess the electrophysiological measures to evaluate whether they were modulated by task-related attention in the CPT-AX. To evaluate whether the cue-locked negativity was response-related, and thus an index of preparatory processing (and truly akin to the CNV), I investigated whether cue-locked negativity amplitude was associated with task-performance. It was anticipated that the cue-locked negativity may be separable into early and late components representing the ‘O’ (orientation) and ‘E’ (expectation) waves (Loveless & Sanford, 1974; Rohrbaugh & Gaillard, 1983). As such, it was predicted that smaller mean amplitude of the early wave (representing orientation to the cue) would correspond to poorer performance on accuracy measures such as hit rate and commission errors, while smaller mean amplitude of the late wave (representing target expectation and response preparation) would correspond to poorer performance on speed measures such as response time and response time variability.

For target-locked processing, the CPT-AX paradigm allowed for comparison between cued and uncued targets to confirm the presence of task-related attentional modulation and orienting responses. Both cued and uncued targets are visually identical and differ only in task-demands. On cued-target ‘go’ (AX) trials, the presentation of the cue should act to orient attention and facilitate early stimulus processing such as stimulus detection and stimulus categorisation, in comparison to uncued-target ‘no-go’ (X-not-A) trials. Previous studies show that P1 and P2 amplitudes are larger for attended-to than unattended stimuli (Hillyard, Vogel, & Luck, 1998; Luck & Hillyard, 1994) whilst latencies are less frequently affected by attention (Hillyard, Vogel, & Luck, 1998). As such it was anticipated that amplitudes of the P1 and P2 would be larger for cued than uncued targets, but that latencies would not differ between these trial types. For the P3, it was expected that on cued-target ‘go’ (AX) trials, the presentation of the cue would orient attention, and as the

P3 is larger for attended-to stimuli (Heinze et al., 1990; Polich, 1986), it was predicted that larger P3 amplitudes would be observed for cued targets compared to uncued targets. Once again, evidence concerning latency suggests little effect of task demands (Polich, 1986), and as such no differences on P3 latency between cued and uncued targets were predicted.

There was no basis to expect that effects of task-related attentional modulation would differ between groups, particularly as they were matched on inattention, and as such it was predicted that there would be no interactions between group and target type. To summarise these hypotheses, it was predicted for both groups that:

For cues:

- Larger amplitudes of early cue-locked negativity would be associated with better hit rate and fewer commission errors
- Larger amplitudes of late cue-locked negativity would be associated with faster response times and less response time variability

For targets:

- Larger amplitude P1, P2 and P3 would be observed for cued targets in comparison to uncued targets
- No latency differences would be observed between cued and uncued targets.

Assessing group differences in task performance

The aim of this part of the analysis was to establish whether children born very preterm differed from children born at term on any of the behavioural and electrophysiological measures of attention. As groups were matched on parent-rated inattention, and these task-related attention measures are thought to relate to such symptoms, for the most part group differences were not expected, and it was predicted that groups would not differ on ERP amplitudes. However, given the results in Chapter 3, in which children born very preterm showed faster processing speed than term-born controls, it was predicted that they may also have faster response times as measured by the CPT-AX task. As ERP latency is thought to be another index of speed of processing, I developed further hypotheses concerning ERP latency. It was not clear from the behavioural measure of motor processing speed used in Chapter 3 whether the increased processing speed resulted from increased speed at all stages of processing. Accordingly it was predicted that the increased processing speed for preterm children relative to term-born peers would be observed in shorter latencies for electrophysiological indices of stimulus categorisation, detection, and evaluation, the P1, P2, and P3, respectively. As the CNV/cue-locked negativity is a slow waveform that often lacks a well-defined peak, latency measures are rarely appropriate and will not be examined here.

Assessing relationships with parent-rated inattention

The main aim of the study was to identify and compare the behavioural and electrophysiological measures of attention that predicted inattentive behaviour between term and very preterm children. Behavioural evidence from previous literature shows that a lower hit rate (poorer attention), a higher number of commission errors (poorer inhibitory control) and higher response time variability (poorer regulation of attention) on CPT-AX tasks relate to inattention and that impairments in these performance measures are found both in children with ADHD, specifically the inattentive subtype of ADHD (Chhabildas et al., 2001), and in children born very preterm (Mulder et al., 2009). Accordingly, it was predicted that more severe ratings of parent inattention would be related to a lower hit rate (worse attention), a higher number of commission errors (worse inhibitory control) and higher response time variability (worse regulation of attention).

Further predictions were developed on the basis of the significant relationship between processing speed and parent-rated inattention in the children born very preterm observed in Chapter 3. Previous researchers have suggested that associations between processing speed and behaviour in preterm children are due to a slowing of all processing in affected children (Mulder et al., 2011). Consequently, it was predicted that more severe parent-rated inattention would be related to slower response time only in the children born very preterm. Similarly, stemming from the same rationale, it was predicted that more severe parent-rated inattention would be associated with delayed latencies for *all* ERPs on *all* trial types only in children born very preterm.

Another hypothesis was developed on the basis of the findings of Chapter 3, where it was found that both poorer short term memory and working memory were associated with more severe parent-rated inattention in children in both groups. Previous researchers have suggested that the P3 component is representative of working memory (Donchin & Coles, 1998), therefore it was predicted that more severe parent-rated inattention in all children would be associated with smaller P3 amplitudes. This is also consistent with findings of smaller P3 amplitudes in ADHD populations (Johnstone et al., 2001; Brown et al., 2005; Holcomb, Ackerman, & Dykman, 1986; Kratz et al., 2011). It was expected that this effect would be more prominent for cued targets, where reference to working memory is essential to engage in action, compared to uncued targets. As working memory was a predictor of inattention in both groups, no differences between groups in this association were anticipated.

Other hypotheses were established on the basis of the most consistent findings in the prior ADHD literature. It was predicted that smaller amplitude cue-locked negativity (CNV) would relate to more severe parent-rated inattention (Banaschewski et al., 2008; Banaschewski et al., 2003; Ortega, López, Carrasco, Anllo-Vento, & Aboitiz, 2013). Moreover, if separable early and late components were observed, it was predicted that relationships would be particularly apparent for the late component, in line with (Johnstone et al. (2009). As groups were matched on inattention, it was expected that both groups would show the same associations between parent-rated inattention and cue-locked negativity.

In line with the findings of Kemner et al. (1996) and Shen, Tsai and Duann (2011), it was predicted that smaller P1 amplitudes would be associated with parent-rated inattention, and similarly, in line with findings from (Brown et al., 2005; Johnstone et al., 2007), that smaller P2 amplitudes would be associated with parent-rated inattention. Previous studies have indicated that children with ADHD/I show smaller amplitudes to both cued and uncued stimuli (Brown et al., 2005) thought to represent difficulty maintaining attention throughout the task. However, these relationships were expected to be stronger for cued targets than uncued targets, because it was expected that variations in amplitudes to cued targets would also represent individual differences in the orienting of attention. It was hypothesised that groups would show the same associations between parent-rated inattention and P1 and P2 amplitudes.

To summarise the above hypotheses, it was predicted that more severe parent-rated inattention would be associated with:

- A poorer hit rate, greater numbers of commission errors, and greater response varibility in both groups.
- Slower response times only in children born very preterm.
- Smaller amplitude cue-locked negativity, particularly for the late component, in both groups.
- Longer P1, P2 and P3 latency for both cued and uncued targets, only in children born very preterm.
- Smaller P1, P2 and P3 amplitude, particularly to cued targets, in both groups.

Finally, I aimed to establish whether the evaluation of neural differences can explain additional variance in inattention beyond that explained by behavioural measures, given that these behavioural responses are driven by neural activity. It was predicted that the ERP measures would explain variance beyond that explained by behavioural measures because they are able to isolate weaknesses in specific stages of processing that may be compensated for by subsequent processing and thus not measurable in the behavioural response.

4.2 Method

4.2.1 **Participants**

A full description of participants who completed the EEG tasks is given in Chapter 2 (see Section 2.2.5, page 21). In brief, this sample comprised 40 term-born children and 43 children born very preterm aged 8-11 years. As was observed in the full sample, children born very preterm were of significantly higher age (term-born mean(*SD*) = 9.58 (1.08); very preterm mean(*SD*) = 10.14 (0.82); mean difference 0.56 years) and of a significantly lower IQ (term-born mean(*SD*) = 112.28 (9.01); very preterm mean(*SD*) = 102.44 (13.87); mean difference = 9.84 points) than those born at term. Unlike the full sample, children born very preterm also had significantly more severe parent-rated anxiety symptoms than those born at term (term-born mean(*SD*) = 52.15 (10.11); very preterm mean(*SD*) = 57.45 (12.83); mean difference = 5.30).

4.2.2 **Procedure**

Children were asked to complete a CPT-AX programmed using PsychoPy software (Peirce, 2009) while electroencephalography (EEG) measurements were recorded as the last part of the PATCH test battery. Children were seated at a desk in a quiet, unlit room facing a computer screen while wearing the EEG recording cap. An experimenter remained with them in the testing room at all times.

At the start of the task written instructions appeared on the screen to familiarise the children with the stimuli that represented cues and targets. Contrary to the traditional CPT-AX, the stimuli consisted of black abstract shapes (chosen so that they did not have a verbal label) filled with different patterns presented on a grey background (see Figure 4.1). One stimulus was designated as the target stimulus (in CPT-AX nomenclature, this represents the X stimulus) and one stimulus as the cue stimulus (in CPT-AX nomenclature, this represents the A stimulus). The same shapes were designated as cue and target for all children. The instructions were read out by the experimenter who told each child that they were required to respond as quickly as possible when they saw a cue-target sequence. They were informed that the cue shapes and target shapes might also appear in isolation and it was reiterated that it was only when they saw a cue-target sequence in the specified order that they needed to respond.

A continuous stream of stimuli was presented in the centre of the screen. Each stimulus was presented for 250ms separated by an inter-stimulus interval of 1400ms, during which a central fixation cross was displayed (see Figure 4.1). A cue-target 'go' (A-X) trial was defined as a trial-pair where the stimuli designated as the cue and target were presented consecutively. Each time the child saw the target stimulus immediately following the cue stimulus, they were required to respond as quickly as possible pressing the left-most button on a Cedrus RB-730 button box with their right hand. A star-shaped sticker had been placed on this button to remind children where it was. Children were instructed to keep their finger over the response button so that they could respond as quickly as they could. No response was required to other trial types, including those where the cue and target were presented in isolation from one another.

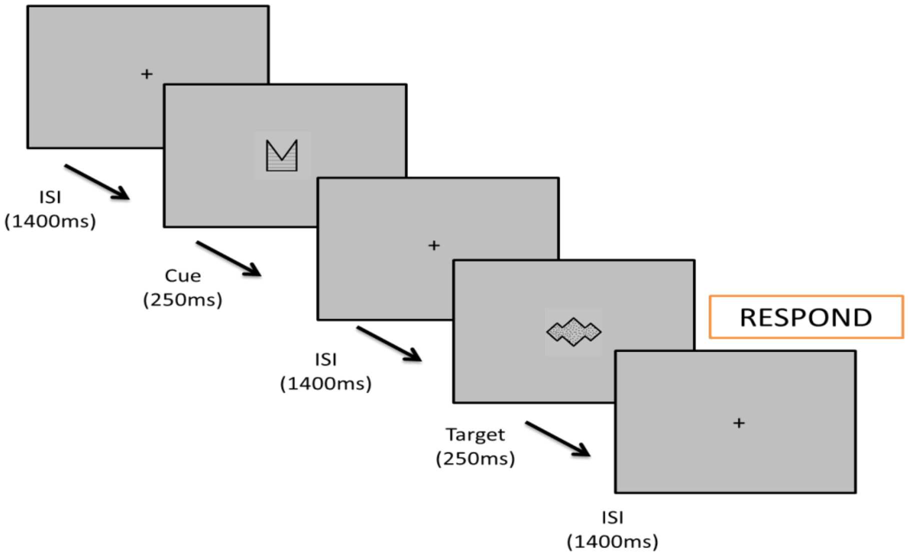

Figure 4.1: Schematic showing a cue-target sequence for the CPT-AX task.

The task consisted of 4 blocks of 100 trials, with the cue stimulus, target stimulus and 11 different distractor stimuli presented. Trials were presented in a pseudo-randomised order, with different orders for each block, but identical orders across participants. 'Go' (A-X) cue-target sequences were presented 10 times within each block, as were cue-without-target 'no-go' trials (A-not-X), and uncued-target 'no-go' (X-not-A) trials. On 'go' trials, participants were required to respond within 1650ms of stimulus onset (prior to the presentation of the subsequent stimulus) to be considered ‘correct’.

4.2.2.1 Behavioural measures

Hit rate. The total number of correct hits (responses made within 200-1650ms from the onset of a cued target) was summed as a measure of accuracy, thought to represent sustained attention. This was reported as a percentage of correct hits out of the maximum score of 40. Higher scores represent more accurate performance, and thus better attention.

Commission errors. The total number of responses made on ‘no-go’ trials (any trial other than a cued target) was summed as a measure of commission errors, thought to represent impulsivity. This was reported as a percentage of erroneous responses out of the 360 ‘no-go’ trials (error rates were too low to permit differentiation between type of ‘no-go’ trial). Higher scores represent less accurate performance and therefore greater impulsivity.

Response time. The median response time on correct hit (A-X) trials was calculated as a measure of response speed. Higher values represent slower response speed.

Response time variability. Finally, the standard deviation of response time on correct hit trials was calculated as a measure of response speed variability. Higher values represent greater variability in response speed.

4.2.2.2 Questionnaire measure

Parent-rated inattention. Parent ratings from the inattentive subscale of the SWAN were used as an index of inattention symptoms, as described in Chapter 3.

4.2.2.3 Electrophysiological Recording

The EEG was recorded at a 1000Hz sampling rate, using a DBPA-1 Sensorium bio-amplifier (Sensorium Inc., Charlotte, VT). Voltage was recorded from 117 active silver/silver-chloride (Ag/AgCl) scalp electrodes using caps customised for our lab (easycap, Munich, Germany) with twisted and fixed electrode cables. We used different caps to account for different head sizes (50cm, 52cm, 54cm, 56cm, 58cm). Electrode positions were based upon the 10/5 system, an extension of the traditional 10/20 system (Oostenveld and Praamstra, 2001), at 117 sites (Fp1, Fpz, Fp2, AFp3, AFp4, AF7, AF3, AF1, AFz, AF2, AF4, AF8, AFF5h, AFF3, AFF1h, AFF2h, AFF4, AFF6h, F7, F5, F3, F1, Fz, F2, F4, F6, F8, FFT7h, FFC5h, FFC1h, FFC2h, FFC4h, FFC6h, FFT8h, FT7, FC5, FC3, FC1, FCz, FC2, FC4, FT8, FTT7h, FCC5h, FCC3h, FCC1h, FCC2h, FCC4h, FCC6h, FTT8h, T7, C5, C3, C1, Cz, C2, C4, C6, T8, TTP7h, CCP5h, CCP3h, CCP1h, CCP2h, CCP4h, CCP6h, TTP8h, TP7, CP5, CP3, CP1, CPz, CP2, CP4, CP6, TP8, TPP7h, CPP5h, CPP3h, CPP1h, CPP2h, CPP4h, CPP6h, TPP8h, P7, P5, P3, P1, Pz, P2, P4, P6, P8, PPO5h, PPO3, PPO1h, PPO2h, PPO4, PPO6h, PO7, PO3, PO1, POz, PO2, PO4, PO8, POO1, POO2, POO4, O1, Oz, O2). An electrode on the left mastoid served as the recording reference and the ground electrode was placed on the chin. Two additional electrodes were placed by the outer canthi of each eye (LHE and RHE) to measure horizontal eye movements, while a further electrode was placed below the left eye (LIO) to measure vertical eye movements. Electrode impedances were maintained below 50kΩ throughout.

4.3 Analysis

4.3.1 EEG Pre-Processing

EEG data were analysed offline using MATLAB (Guide, 1998) with purpose-written scripts which used EEGlab (Delorme & Makeig, 2004), ERPlab (Lopez-Calderon & Luck, 2014) and the Fully Automated Statistical Thresholding for EEG Artefact Rejection (FASTER; Nolan, Whelan, & Reilly, 2010) plug-ins. Data were epoched (-200-1650ms) then average referenced and filtered with a low pass filter below 40Hz and a notch filter at 50Hz and downsampled to 500Hz. Artefact rejection was conducted using FASTER (Nolan et al., 2010). This toolbox detects and corrects for artefacts by assessing the EEG data across four aspects; channels, epochs, independent components, and single-channel single-epochs. At each level, contaminated data is considered to be any data with a z score of ±3 for that metric. In the first step, deviant channels are identified based on; (i) low mean correlations with neighbouring channels, (ii) high channel variance, and (iii) atypical Hurst exponent values. These channels are then interpolated, removing the effect of any bad channels.

In the second step, deviant epochs are identified based on; (i) high amplitude ranges within epochs, (ii) extreme deviation from the mean channel average, and (iii) high variance. These epochs are then removed from the data, removing the effect of epochs contaminated by artefacts such as movement.

In the third step, independent components analysis is conducted and deviant components are identified by; (i) strong correlations with EOG electrodes, (ii) activity observed in only a single electrode, (iii) activity with a flat power spectrum (white noise), (iv) atypical Hurst exponent values, and (v) the median gradient value of the IC timecourse. These are then subtracted from the data, removing the effect of artefacts such as eye blinks, and high amplitude single-electrode pop-off.

Finally, in the fourth step, deviant recordings from specific channels within specific epochs are identified based on; (i) high variance of specific channels within each epoch, (ii) the median gradient to detect high frequency activity, (iii) high amplitude ranges of the channel, (iv) deviation of that channel from the channel average within the epoch. Bad channels within epochs were then interpolated to remove the effects of transient artefacts within epochs.

Following rejection procedures, the average number of trials for cue ERPs was 76.80 (*SD*= 1.40; 96% trials retained), for correct cued target ERPs was 34.96 (*SD*=5.55; 98% trials retained) and for correct uncued target ERPs was 40.00 (*SD*=0.00; 100% trials retained). Average trials per ERP average did not differ between groups for any trial type (*p*>0.1).

4.3.2 **ERP Analysis**

4.3.2.1 Cue-locked ERP Analysis

For each participant, average ERPs time-locked to the onset of the cue stimulus were calculated across all cue trials. Visual inspection of late negativity in the grand average waveforms suggested the largest negativity was observed between 800-

1200ms (see Figure 4.3), however inspection of waveforms for individual participants showed fluctuations throughout the 600-1650ms time window following cue onset, consistent with samples where a large proportion of subjects show high response time variability. This variability across subjects caused us to increase the outer limits of our overall time period.

Two time windows were chosen on the basis of topographical differences over time observed on scalp plots (see Figure 4.9), the first from 600-1000ms and the second from 1000-1400ms. This fits with literature supporting the separation of early and late CNV components (Loveless & Sanford, 1974; Rohrbaugh & Gaillard, 1983).

Electrode CPz was chosen on the basis of inspection of the grand average waveform (see Figure 4.3) and from scalp plots (see Figure 4.2) as it appeared that negativity was maximal at this location. A computerised algorithm (ERPlab) was used to calculate the mean amplitude within the 600-1000ms and 1000-1400ms time windows at electrode CPz.

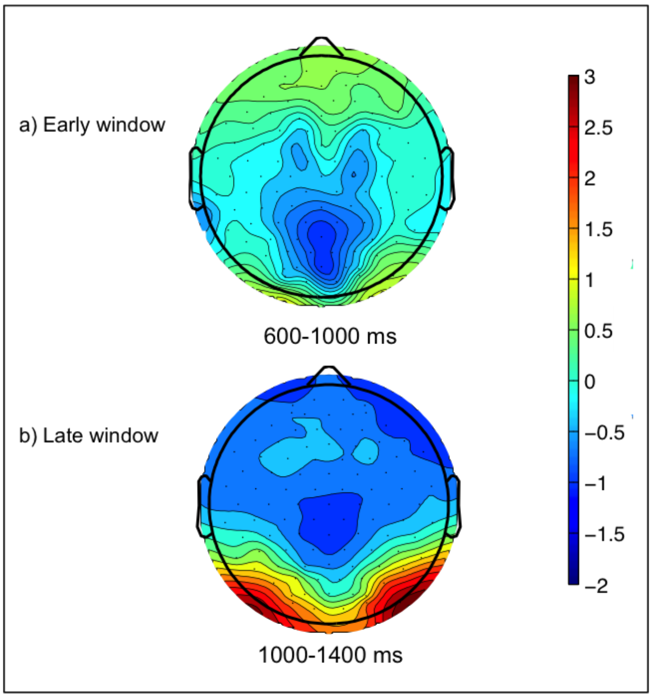

Figure 4.2: Scalp plots showing the topography of the centro-parietal negativity averaged between 600-1000ms (top) and 1000-1400ms (bottom).

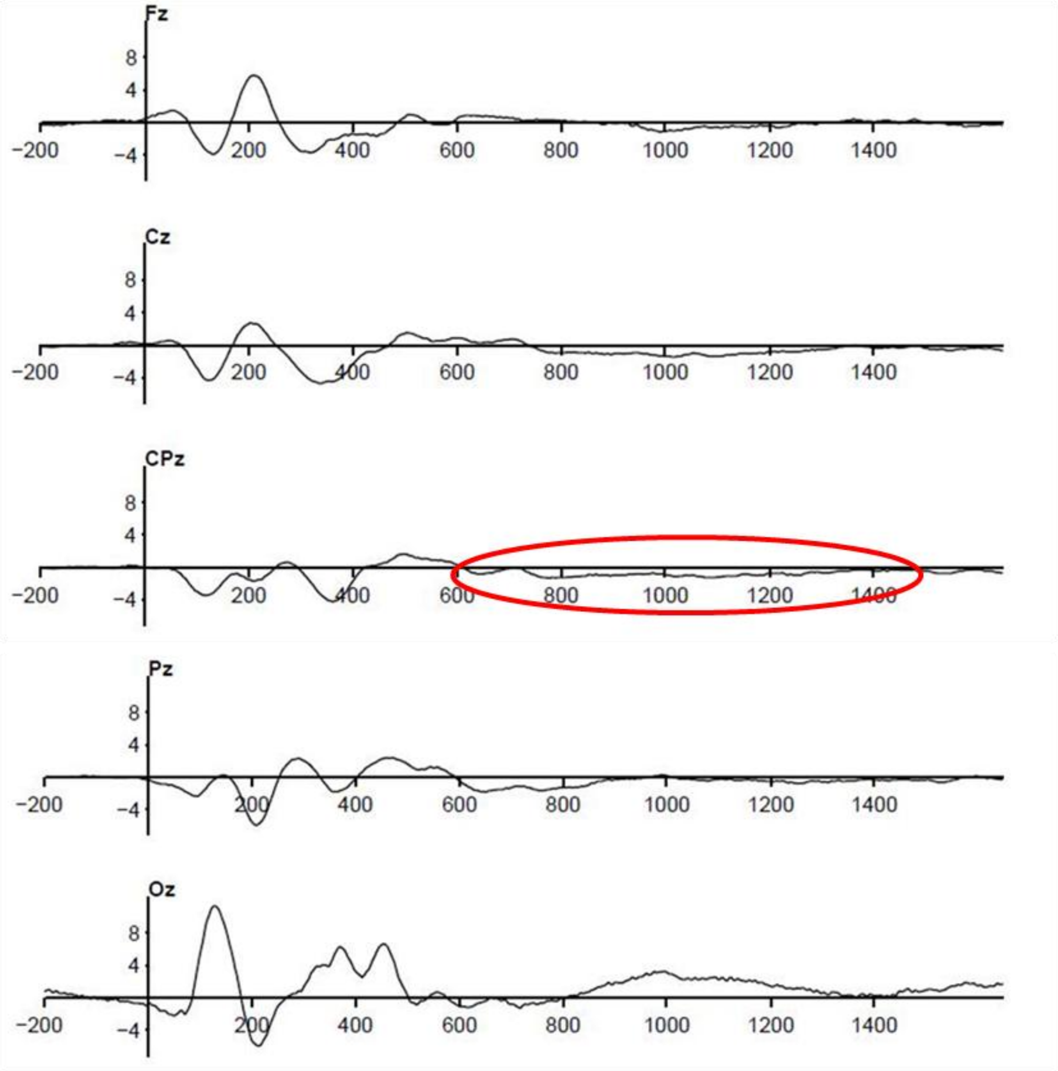

Figure 4.3: Grand averages of the ERP waveforms in response to cue stimuli at midline electrodes Fz, Cz, CPz, Pz and Oz.

4.3.2.2 Target-locked ERP analysis

For each participant, average ERPs time-locked to the onset of the target stimulus were computed separately for correct cued and uncued target trials. Trials where errors of omission and commission were made were too infrequent to be averaged.

Time windows and specific electrode sites of interest were chosen on the basis of a visual inspection of the grand average ERP waveform (Figure 4.4) and scalp plots (Figure 4.5). For the P1, peak amplitude and latency measurements were taken at Oz between 75-175ms post-stimulus onset.

For the P2, inspection of scalp plots revealed different topography for different target types, therefore measures of peak amplitude and latency were taken at both Fz and Cz between 175-250ms post-stimulus onset. For the P3 component, peak amplitude and latency were measured at Pz between 250-350ms post-stimulus onset. A computerised algorithm (ERPlab) was used for initial peak detection. Individual peaks for each participant were then visually inspected and, where necessary, time windows were expanded to allow for accurate peak detection in cases where the latency was up to 50ms earlier or later than the window initially chosen.

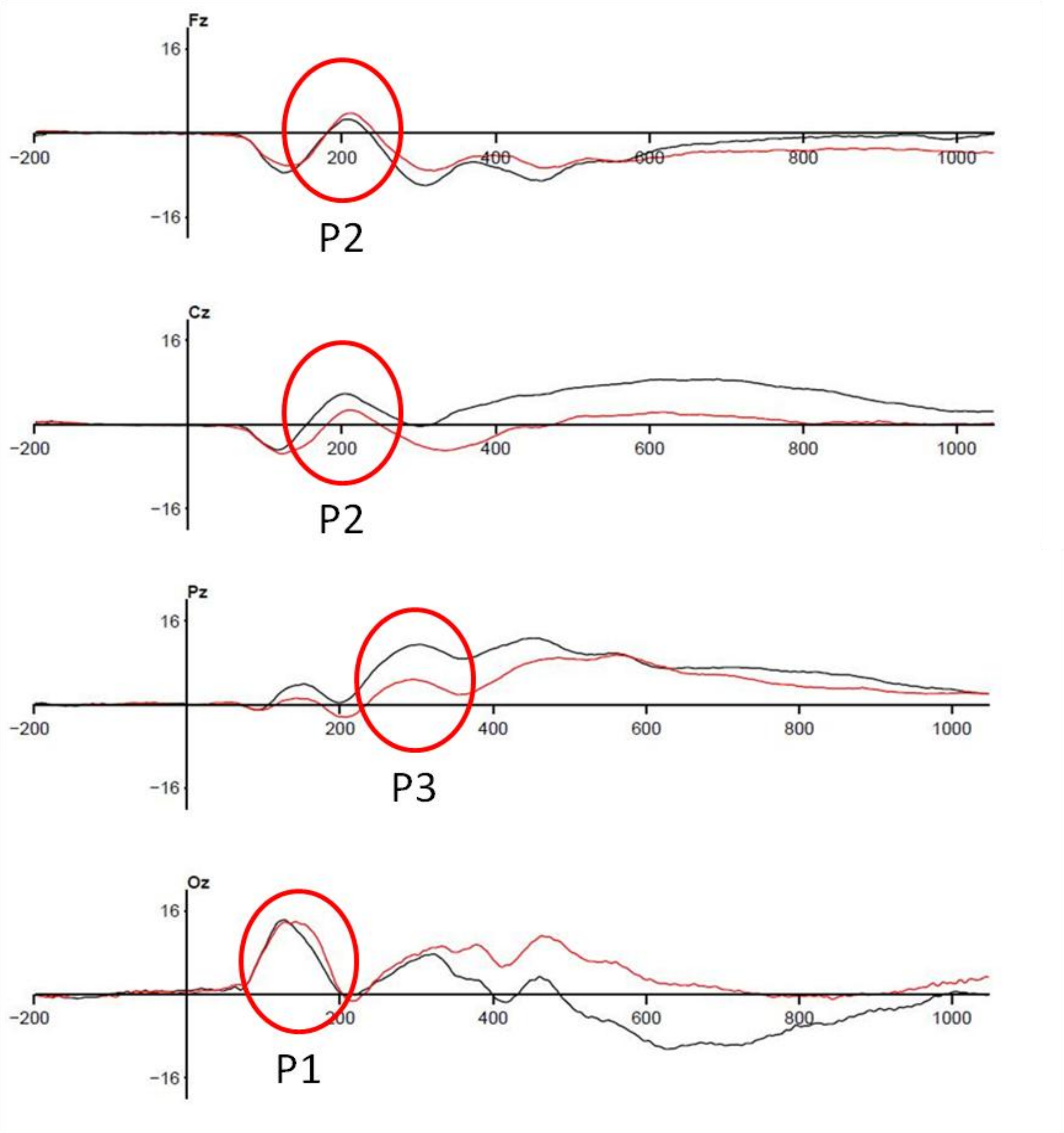

Figure 4.4: Grand averages of the ERP waveforms in response to cued (black) and uncued (red) target stimuli at midline electrodes Fz, Cz, Pz and Oz.

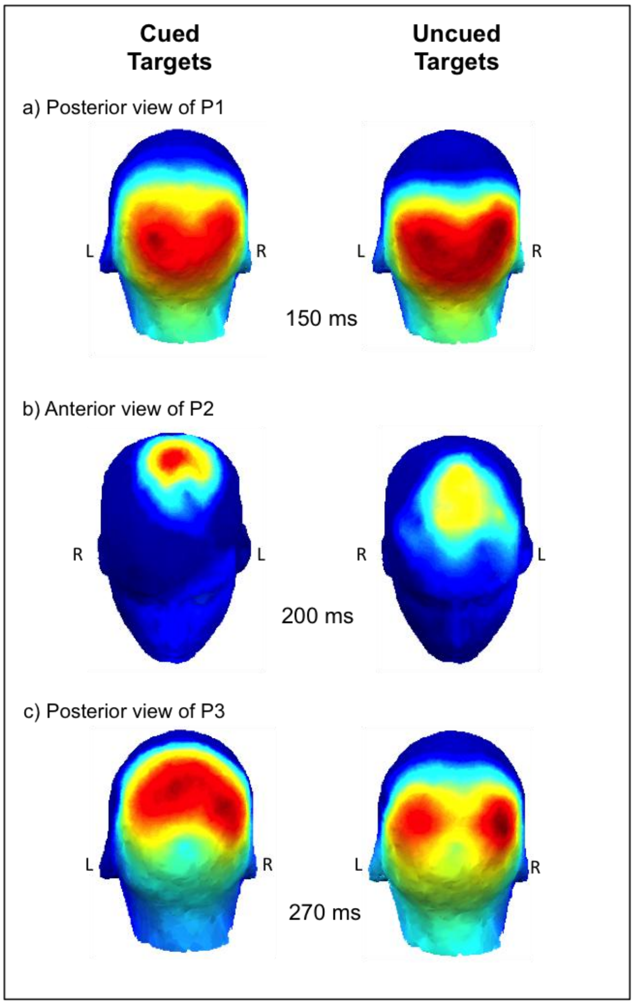

Figure 4.4: Topographical images of the ERP amplitudes reflecting (a) an occipitally maximal P1 component, (b) a fronto-centrally maximal P2 component and (c) a parietally maximal P3 component, for cued and uncued targets.

4.3.3 **Statistical analysis**

As outlined in the hypotheses, there were 2 sections to the analysis of each measure; (1a) for ERP measures; assessment of task-related attentional modulation, and (1b) assessment of between-group performance differences, (2) analysis of relationships between the behavioural and ERP measures and parent-rated inattention. For statistical analysis, behavioural measures and then each ERP component were assessed in sequence.

4.3.3.1 Section 1: Assessment of task-related attentional modulation and group differences

Behavioural task performance

In order to assess whether children born very preterm performed differently on the task to the children born at term, a MANCOVA including all four performance measures was conducted, with group as a between-subjects factor and age entered as a covariate. These measures of task performance are considered measures of attention, thus no separate analysis of task-related attentional modulation was required for this part of the analysis.

Cue-locked ERPs

In order to assess whether these ERP measures were modulated by task-related attention, associations between task-performance measures and cue-locked negativity were investigated. I conducted partial correlations between the mean amplitude of the cue-locked negativity and task-performance measures in order to investigate whether the cue-locked negativity was indeed response-related, while controlling for the effect of age. These were initially conducted collapsed across groups and then repeated split by group in order to identify any differences in the relationships between study groups to test the hypothesis that task-related attentional modulation would be the same in both groups. The strength of the correlation coefficients were compared statistically between groups using Fischer's r-to-z tests.

Group differences in mean amplitude were assessed using a mixed-measures ANCOVA. Mean amplitude of the cue-locked negativity was assessed with a within-subjects factor of time window (early vs. late) and a between-subjects factor of group (term-born vs. very preterm) while controlling for the effect of age.

Target-locked ERPs

For target-locked ERPs, amplitudes and latencies were compared between targets preceded by a cue and those not preceded by a cue for each component (P1, P2 and

P3) in separate mixed-design ANCOVAs in order to assess task-related attentional modulation. These effects were also compared between groups. Target type (cued or uncued; A-X or X-not-A) was entered as a within-subjects factor, group (term or preterm) as a between-subjects factor, and age as a covariate.

Where Mauchley's test of sphericity indicated that the assumption of sphericity was violated, Greenhouse Geisser corrected values are reported instead. It is important to note that in the mixed-measures ANCOVAs where age was included as a covariate, main effects for within-subject measures were independent of the covariate of age as all measures were collected in a single session. As such, pure within-subjects main effects are reported from analyses that exclude the covariate, thus and therefore degrees of freedom may differ for pure within-subjects effects compared to between-groups and interaction effects. This method has been used previously (Annaz, Karmiloff-Smith, Johnson, & Thomas, 2009).

4.3.3.2 Section 2: Assessment of associations with parent-rated inattention

In order to investigate how each of the performance and ERP measures was associated with parent-rated inattention, separate partial correlations were conducted, controlling for age. For amplitude and latency measures of P1, P2 and P3, if the ANCOVA demonstrated there was no difference between cued and uncued targets then the average of cued and uncued targets was calculated and entered into the correlations. For each ERP and performance measure, correlations were conducted initially across the two groups to ensure maximum power when identifying any overall associations, and then separately for each group to identify any associations that differed between groups. Where there were differences in the pattern of correlations across the two groups, Fischer's r-to-z coefficient comparisons were calculated to determine if the correlations were significantly different.

To investigate whether the measurement of ERPs explained variance in parent-rated inattention over and above variance explained using behavioural measures a hierarchical regression was used. Previous correlational analyses acted as a guide to reduce the number of variables entered into the regression models to only those that were significantly related to parent-rated inattention in one or both groups. On the basis of the theoretical assumption that behavioural responses are the result of the neural processes measured by the ERPs, and the aim to assess whether the ERPs explained variance beyond that explained by behavioural measures, behavioural task-performance measures were entered at an earlier step than ERP measures. In the first step, age and group were entered. In the second step, behavioural task-performance measures were entered. In the third step, ERP measures were entered. At this step, a data-driven forward-entry selection technique was used so that only those variables that added significant variance above and beyond that accounted for in the preceding steps were entered. In the final fourth step interactions between group and the CPT-AX measures were added to the model. Similarly, a data-driven forward-entry selection technique was used in this step so that only group-interactions that accounted for significant unique variance were entered into the final model.

4.3.3.3 Treatment of data

Data were examined for outlying values. Inspection of the ERP data revealed extreme scores (> +3 SD) for one term-born child for the cue-locked negativity, and for one very preterm child for P1 peak amplitude for cued targets, that were deemed to be the result of measurement error. As such, data from these participants were excluded from analyses involving the relevant components.

Assumptions for each statistical analysis were checked, and where appropriate, corrections of violations were applied and are reported. As always with a large number of comparisons, the risk of type one errors is increased. As the correlations were to guide variable selection for the regression analysis, it was decided that the application of Bonferroni corrected alpha levels was too conservative. Elsewhere, where appropriate, Bonferroni corrected alpha levels were applied and are reported. As in Chapter 3, the inflated risk for type one error rates was considered during the interpretation of findings.

4.4 Results

4.4.1 Section 1: Task-performance differences and task-related attentional modulation of ERPs

4.4.1.1 Behavioural results: Task performance differences

An initial MANCOVA was used to examine between group differences for the behavioural task performance measures. Age was entered as a covariate in order to account for the discrepancy in age between the groups. Using Pillai's Trace, multivariate tests showed that there was a significant main effect of age (V=0.141, F(4,77)=3.159, p=0.019, η_p^2=0.141) but there was no significant main effect of group (V=0.028, F(4,77)=0.545, p=0.703, η_p^2=0.028). As such, univariate tests were not investigated further.

As shown in Table 4.2, both term-born and very preterm children had high hit rates, averaging 89%. Commission errors were low, averaging 2% over a possible 360 no-go trials, including 40 presentations of the cue that were not followed by the target and 40 uncued presentations of the target stimulus.

Table 4.2: Age adjusted marginal means and standard errors for performance measures of term-born and very preterm children on the CPT-AX.

Measure	Very Preterm		Term	
	Mean	SE	Mean	SE
Hits (%)	90.30	1.93	88.13	2.00
Commission errors (%)	2.14	0.38	2.00	0.41
Median RT (ms)	442.20	11.98	453.79	12.44
SD RT (ms)	159.61	9.23	155.93	9.59

Note: RT = response time; SE = standard error.

These results are consistent with the hypothesis that group differences were not expected on hit rate, response time variability or commission errors, however they are contrary to the hypothesis that very preterm children would have faster response times.

4.4.1.2 ERP results

Cue-locked negativity: Attention during preparatory processing

Between-group differences

To investigate overall between-group differences in the cue-locked negativity, a mixed ANCOVA was conducted. The results demonstrated that there were no significant differences in amplitude between different time windows ($F(1,81)=2.276$, $p=0.135$, $\eta_p^2=0.027$), or groups ($F(1,80)=1.007$, $p=0.452$, $\eta_p^2=0.007$) and no interactions between time window and group ($F(1,80)=0.083$, $p=0.774$, $\eta_p^2=0.001$). Age adjusted group means are presented in *Table 4.3*.

Table 4.3: Age adjusted marginal means and standard errors (SE) of mean amplitude for the early and late cue-locked negativity for cues measured at CPz.

Measure	VP		Term	
	Mean	SE	Mean	SE
Mean amplitude – early window (µV)	-0.799	0.116	-0.620	0.117
Mean amplitude – late window (µV)	-0.868	0.112	-0.747	0.113

Assessment of task-related attentional modulation: relationships between cue-locked negativity and task performance

Partial correlations were conducted between mean amplitude and task-performance measures, controlling for age, across both groups and then split by group. Full correlation matrices are reported in Appendix 2. Associations with task performance for early and late windows are reported in *Table 4.4* and *Table 4.5* respectively.

Across groups, increased negativity in the earlier window (600-1000ms) was related to a higher hit rate, faster response time and less response variability, while in the later window (1000-1400ms), increased negativity was related only to faster response time.

When the correlations were repeated separately in the very preterm and term born groups different patterns emerged. The relationship observed across groups between increased negativity in the early window (600-1000ms) and higher hit rates

Table 4.4: Partial correlations between mean amplitude of cue-locked negativity during the early window measured at CPz and task performance.

	Mean Amplitude – Early (600-1000ms)		
Measure	Collapsed Across Groups	Very Preterm	Term
Mean Amplitude-Late	.236*	-.018	.466**
Hits	-.286**	-.424**	-.149
Commission Errors	.109	.294§	-.107
Response Time	.236*	.190	.343*
Response Variability	.381***	.498***	.189

Note: All correlations are controlled for the effect of age. **p*<0.05, ***p*<0.01, ****p*<0.001

Table 4.5: Partial correlations between mean amplitude of cue-locked negativity during the late window measured at CPz and task performance.

	Mean Amplitude – Late (1000-1400ms)		
Measure	Collapsed Across Groups	Very Preterm	Term
Mean Amplitude-Early	.236*	-.018	.466**
Hits	-.131	.040	-.210
Commission Errors	.060	-.005	.108
Response Time	.318**	.168	.392*
Response Variability	.101	.105	.106

Note: All correlations are controlled for the effect of age. **p*<0.05, ***p*<0.01, ****p*<0.001

and less response variability, was driven by significant associations in the very preterm group only. An additional trend (*p*<0.07) was observed in very preterm children whereby increased negativity in the early window was also related to fewer commission errors. Fischer's correlation comparisons demonstrated that the associations between early negativity and commission errors (*z*=-1.76, *p*=0.039) and hit rate (*z*=2.59, *p*=0.005) differed significantly between very preterm and term-born children, while the between-group difference for the association between response time variability and early negativity was marginal (*z*=1.53, p=0.063).

In the term-born children, increased negativity in both early (600-1000ms) and late (1000-1400ms) time windows was associated instead with faster response times, but Fischer's comparisons showed that these relationships were not significantly different from those seen in very preterm children (*p*>0.05). Furthermore, it should be noted that the mean amplitude of the early window was positively correlated with the mean amplitude of the late window (*z*=2.25, *p*=0.012) in term-born children only.

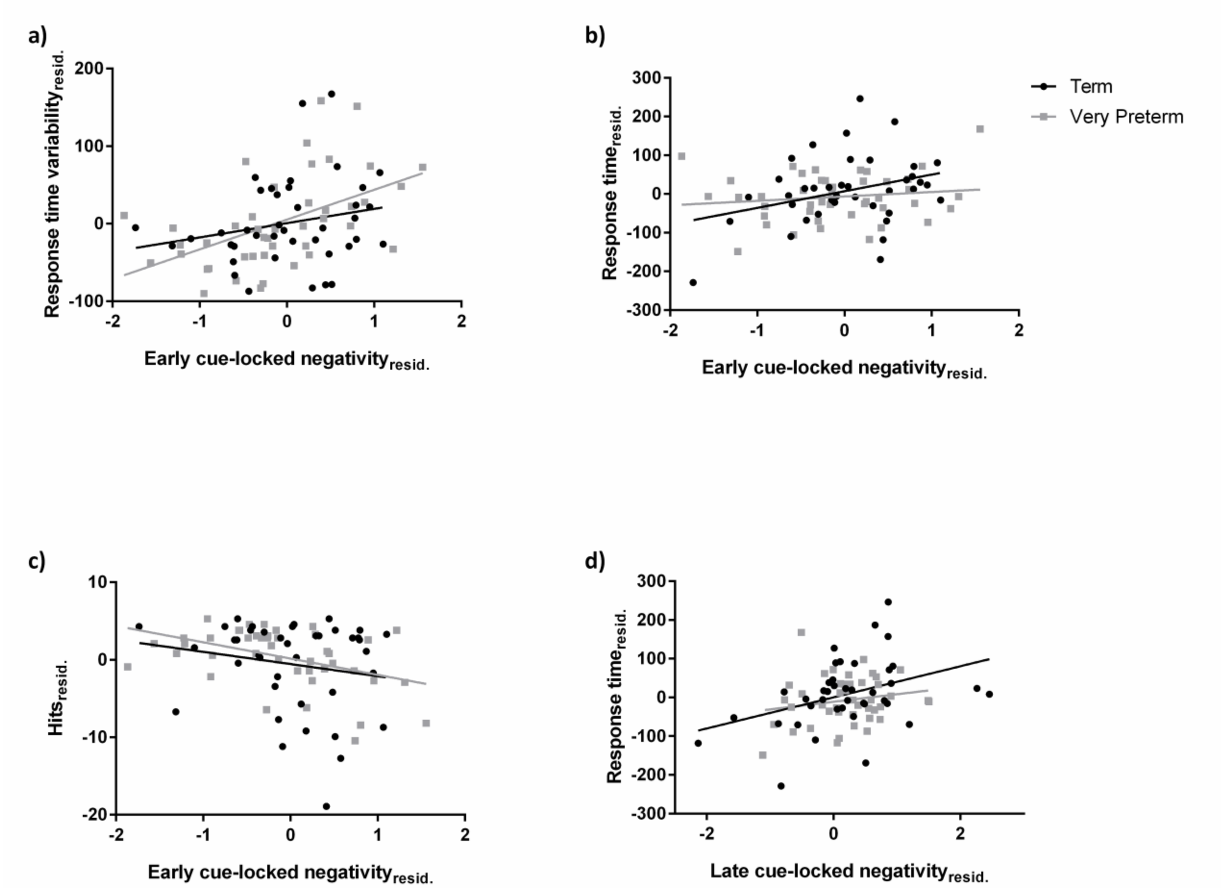

Figure 4.5: Scatter plots showing the association between (a) response time variability and early cue-locked negativity amplitude, (b) response time and early cue-locked negativity amplitude, (c) hits and early cue-locked negativity amplitude and (d) response time and late cue-locked negativity while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age.

Overall, the results concerning cue-locked negativity were partially consistent with my hypotheses. As expected, there were no group differences in amplitude, and larger amplitudes were associated with better performance. However the precise pattern of results and the difference between the associations present in the two groups were not as expected. It was hypothesised that the early cue-locked negativity would be associated with accuracy measures (hit rate and commission errors) while the late cue-locked negativity would be associated with response times and response time variability. Instead, it was found that increased cue-locked negativity in the early window was related to multiple task-performance measures in children born very preterm only, while in term-born children increased cue-locked negativity across both time windows was associated only with faster response times (see Figure 4.6).

P1 to targets: Attention during visual discrimination

An ANCOVA on peak amplitude of the P1 component at Oz was carried out with target type (cued or uncued) as a within-subject factor and group (very preterm, term) as a between subject factor, and with age entered as a covariate. There was no significant main effect of target type on P1 peak amplitude ($F(1, 80)=0.817$, $p=0.369$, $\eta_p^2=0.010$). As *Table 4.6* shows, values were similar for term-born and very preterm children and the ANCOVA confirmed that there was no significant effect of group on P1 peak amplitude ($F(1,79)=0.903$, $p=0.345$, $\eta_p^2=0.011$), and no significant interaction between target type and group ($F(1,79)=0.883$, $p=0.350$, $\eta_p^2=0.011$).

Table 4.6: Age adjusted marginal means and standard error for the P1 peaks for cued and uncued targets measured at Oz for each group.

P1 measurements at Oz	Very Preterm		Term	
	Mean	SE	Mean	SE
Peak Amplitude (µV)				
Cued Target	17.69	1.27	18.35	1.30
Uncued Target	17.63	1.36	20.14	1.40
Peak Latency (ms)				
Cued Target	127.50	3.45	133.72	3.54
Uncued Target	138.57	3.53	137.01	3.62

Following on from the analysis of P1 peak amplitude, a similar analysis was conducted investigating how the peak latency varied. It was found that overall P1 latencies peaked significantly earlier for cued targets than uncued targets ($F(1, 80)=11.834$, $p=0.001$, $\eta_p^2=0.129$; mean difference= 7.17ms). As *Table 4.6* shows, P1 peak latencies were similar for term-born and very preterm children, and the ANCOVA confirmed that they did not differ significantly between groups overall ($F(1,79)=0.254$, $p=0.616$, $\eta_p^2=0.003$), and that there was no significant interaction between group and target type ($F(1,79)=3.132$, $p=0.081$, $\eta_p^2=0.038$).

Although there was no evidence of the hypothesised increased amplitude for cued compared to uncued targets, the unexpected findings of shorter latency for cued compared to uncued targets was considered to be evidence of task-related attentional modulation. As hypothesised, task-related attentional modulation did not differ between groups.

P2 to targets: Attention during feature detection and stimulus categorisation

An ANCOVA on the peak amplitude of the P2 component was carried out with electrode (Fz and Cz) and target type (cued and uncued) as within-subject factors and group (very preterm and term) as a between subjects factor, with age entered as a covariate. Significantly larger P2 peak amplitudes were observed at Cz than at Fz ($F(1,81)=5.232$, $p=0.025$, $\eta_p^2=0.061$; mean difference = 1.12µV), and for cued targets compared to uncued targets ($F(1,81)=15.873$, $p<0.001$, $\eta_p^2=0.164$; mean difference = 1.41µV). In addition, there was a significant interaction between electrode and stimulus type ($F(1,81)=38.136$, $p<0.001$, $\eta_p^2=0.320$). Post hoc paired comparisons, with a Bonferroni adjusted alpha of 0.013 revealed that there was no difference in P2 peak amplitude between cued and uncued targets at Fz (mean difference = 0.685µV, $p=0.145$), but at Cz there was a larger amplitude for cued than uncued targets (mean difference = 3.512µV, $p<0.001$). Furthermore, while for cued targets, amplitudes were significantly larger at Cz than at Fz (mean difference =3.22µV, $p<0.001$), for uncued targets, amplitudes were not significantly larger at Fz than Cz (mean difference =0.98µV, $p=0.047$).

Regarding between-group differences, it was found that children born at term had marginally higher P2 peak amplitudes than those born very preterm ($F(1,80)=3.784$, *p*=0.055, η_p^2=0.045), as can be seen in *Table 4.7*, but the effect size was small and group did not interact with stimulus type or electrode.

Table 4.7: Age adjusted marginal means and standard error for the P2 peaks for cued and uncued targets measured at Fz and Cz for both groups.

P2 measurements	Very Preterm		Term	
	Mean	SE	Mean	SE
Peak amplitude at Fz (µV)				
Cued Target	3.45	0.78	5.20	0.81
Uncued Target	3.88	0.58	6.14	0.60
Peak amplitude at Cz (µV)				
Cued Target	7.27	0.75	7.82	0.78
Uncued Target	3.61	0.60	4.45	0.63
Peak latency at Fz (ms)				
Cued Target	207.40	3.09	208.39	3.21
Uncued Target	205.57	3.49	211.99	2.45
Peak latency at Cz (ms)				
Cued Target	216.28	2.36	206.86	3.62
Uncued Target	211.05	2.88	211.22	2.99

Next, a similar analysis was conducted investigating how the peak latency varied. It was found that the P2 component peaked significantly earlier in response to cued targets than to uncued targets (*F*(1,81)=12.447, *p*=0.001, η_p^2=0.133, mean difference=5.59ms), but latency did not differ between electrodes (*F*(1,81)=1.954, *p*=0.166, η_p^2=0.024) and there was no interaction between electrode and stimulus type (*F*(1,81)=0.320, *p*=0.573, η_p^2=0.004). As shown in *Table 4.7*, P2 peak latencies were similar for both groups and the ANCOVA confirmed that there was no main effect of group (*F*(1,80)=0.020, *p*=0.887, η_p^2=0.000) nor were there any interactions with group.

Thus, the P2 peak amplitude was maximal at Cz, and larger and earlier for cued targets than uncued targets. This difference in amplitude was consistent with hypotheses, and although the difference in latency was unexpected, it was considered to be further evidence of task-related attentional modulation. Furthermore, and also inconsistent with hypotheses, amplitude was marginally larger for term-born children than those born very preterm.

P3: Attention during evaluation of task-relevance

P3 amplitude was analysed at Pz using a mixed ANCOVA with target type (cued and uncued) as within-subject factor, group (term and very preterm) as a between subjects factor, and age entered as a covariate. As can be seen in *Table 4.8*, P3 peak amplitudes were significantly larger for cued targets than for uncued targets ($F(1, 81)=118.787$, $p<0.001$, $\eta_p^2=0.595$; mean difference = 6.69µV), but they did not differ between groups ($F(1, 80)=0.829$, $p=0.365$, $\eta_p^2=0.010$) and there was no interaction between group and stimulus type ($F(1, 80)=0.263$, $p=0.609$, $\eta_p^2=0.003$).

Table 4.8: Age adjusted marginal means and standard errors for the P3 peaks for cued and uncued targets measured at Pz for each group.

P3 measurement at Pz	Very Preterm		Term-born	
	Mean	SE	Mean	SE
Peak Amplitude (µV)				
Cued Target	14.11	1.99	12.74	1.04
Uncued Target	7.09	0.76	6.37	0.78
Peak Latency (ms)				
Cued Target	308.86	5.31	304.42	5.51
Uncued Target	294.45	4.39	293.16	4.56

P3 peak latencies were significantly later for cued targets than for uncued targets ($F(1,81)=9.517$, $p=0.003$, $\eta_p^2=0.105$; mean difference = 12.82ms). As can be seen in *Table 4.8*, latencies were similar in children born at term and those born very preterm, and the ANCOVA confirmed that there was no significant effect of group ($F(1,80)=0.253$, $p=0.617$, $\eta_p^2=0.003$) or interactions between stimulus type and group ($F(1,80)=0.129$, $p=0.720$, $\eta_p^2=0.002$).

Overall, P3 amplitudes were larger and peaked later for cued targets than uncued targets. As with the P2 results, the amplitude difference was consistent with hypotheses, and although not hypothesised, the latency difference was considered to be evidence of task-related attentional modulation. P3 characteristics did not differ between groups, consistent with hypotheses.

4.4.2 **Section 2: Relationships with parent-rated inattention**

4.4.2.1 Behavioural results

The pattern of association between parent-rated inattention and behavioural performance measures from the CPT-AX was investigated using correlational analysis. First, correlations were measured across groups and then for each group separately using Pearson's partial correlations controlling for the effect of age. Full correlation matrices are reported in Appendix 2. Associations with parent-rated inattention are reported in *Table 4.9* and scatter plots display these in Figure 4.7.

Table 4.9: Partial correlations between parent-rated inattention and task performance.

	Parent-Rated Inattention vs. Task Performance		
Measure	Collapsed Across Groups	Very Preterm	Term
Hits	-.297*	-.302*	-.308*
Commission Errors	.212*	.137	.281
Response Time	.080	.056	.155
Response Variability	.303*	.201	.397*

Note: All correlations are controlled for the effect of age. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Consistent with hypotheses, across groups it was found that fewer hits, a greater number of commission errors, and greater variability in response times were all related to greater parent-rated inattention. When the analyses were repeated for each group separately the pattern of associations was similar in both groups. However, with reduced sample sizes, and therefore less power, many no longer reached significance. The association between greater parent-rated inattention and fewer hits remained significant in both groups, while that of greater parent-rated inattention and greater response variability was only significant in the term-born children. Fischer's r-to-z coefficient comparisons revealed that for all relationships, there were no significant between-group differences in the strength of the association ($p>0.1$).

There was no evidence of the hypothesised association between slower response times and parent-rated inattention in children born very preterm.

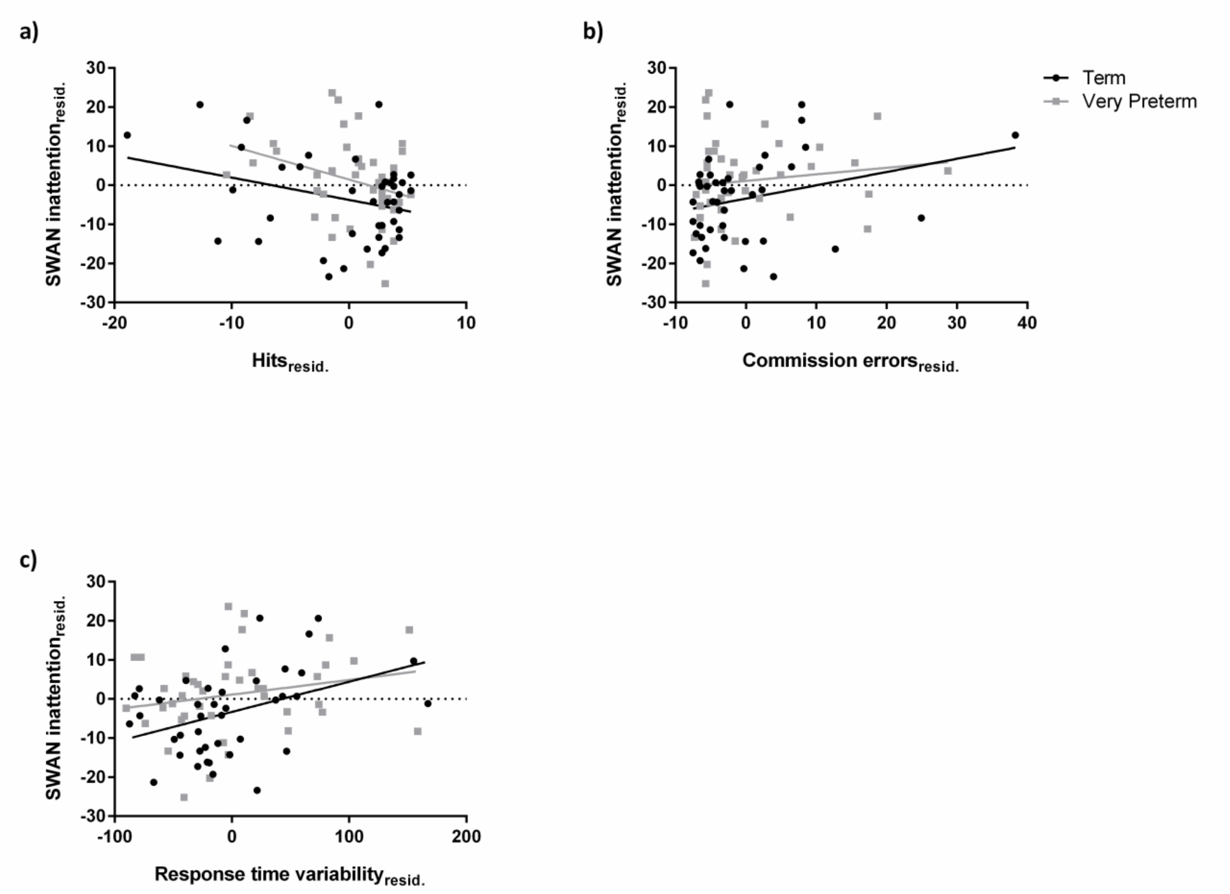

Figure 4.6: Scatter plots showing the association between SWAN parent-rated inattention and (a) hits, (b) commission errors, and (c) response time variability while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age. The dotted line represents ‘average’ attention, while positive scores indicate more severe ratings of inattention and negative scores indicate above average ratings of attention.

4.4.2.2 ERP results

Cue-Locked ERPs

The pattern of association between parent-rated inattention and mean amplitude of early and late portions of the cue-locked negativity, as measured at CPz, for cued and uncued targets, was investigated using correlational analyses. Correlations were assessed across groups and then for each group separately using Pearson’s partial correlations controlling for the effect of age. Full correlation matrices can be seen in Appendix 2. Associations with inattention are reported in *Table 4.10*.

Table 4.10: Partial correlations between parent-rated inattention and mean amplitude of cue-locked negativity measured at CPz.

		Parent-Rated Inattention vs. Mean Amplitude		
Component	Window	Collapsed Across Groups	Very Preterm	Term
Cue-locked negativity	Early	.132	-.002	.288
	Late	-.140	-.241	-.057

Note: All correlations are controlled for the effect of age. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Contrary to hypotheses, no significant associations were observed between parent-rated inattention and the mean amplitude of cue-locked negativity.

Target-Locked ERPs

Peak Amplitude

The pattern of association between parent-rated inattention and peak amplitude measures of each target-locked component (P1, P2 and P3) was investigated using separate correlational analyses. Correlations were assessed across groups and then for each group separately using Pearson’s partial correlations controlling for the effect of age. Full correlation matrices can be seen in Appendix 2. Associations with parent-rated inattention are reported in *Table 4.11*. The measures selected for each component were those identified as being maximal and assessed for group differences and evidence of task-related attentional modulation above with the following exceptions. For P1, amplitude was collapsed across cued and uncued targets as peak amplitude did not differ significantly between cued and uncued targets. For P2, correlations were restricted to the P2 amplitude as measured at Cz on the basis of the P2 being maximal and showing more evidence of task-related attentional modulation at this location.

It was found that there was an overall association between greater parent-rated inattention and smaller P2 amplitudes in response to uncued targets (see Figure 4.8).

The association between greater parent-rated inattention and smaller P2 amplitudes in response to uncued targets only reached significance in term-born children, but in children born very preterm the relationship was in the same direction and did not differ significantly from the term-born children according to Fischer's comparisons (*p*>0.1). No other significant associations were observed between component amplitudes and parent-rated inattention.

Table 4.11: Partial correlations between parent-rated inattention and peak amplitude of P1 measured at Oz, P2 measured at Cz and P3 measured at Pz.

		Parent-Rated Inattention vs. Peak Amplitude		
Component	Target Type	Collapsed Across Groups	Very Preterm	Term
P1	All targets	-.134	-.070	-.164
P2	Cued	.000	-.011	.020
	Uncued	-.307***	-.295	-.343*
P3	Cued	-.058	.094	-.285
	Uncued	-.042	-.067	-.052

Note: All correlations were controlled for the effect of age. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

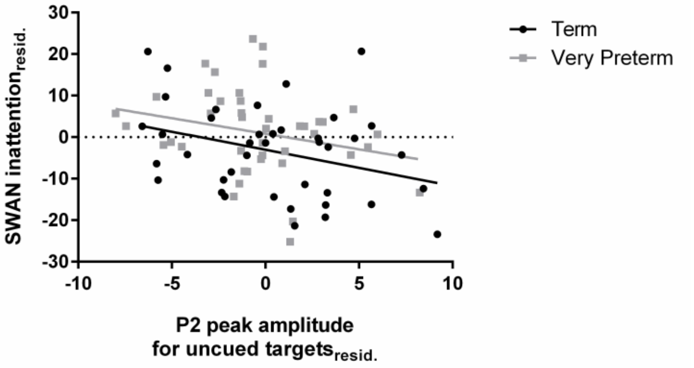

Figure 4.7: Scatter plots showing the association between SWAN parent-rated inattention and P2 peak amplitude for uncued targets while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age. The dotted line represents 'average' attention, while positive scores indicate more severe ratings of inattention and negative scores indicate above average ratings of attention.

These findings are partially consistent with my hypotheses. Although the association observed was in the hypothesised direction (smaller amplitudes associated with more severe parent-rated inattention), their presence only for the P2 component in response to uncued targets was not expected.

Peak Latency

The pattern of association between parent-rated inattention and peak latency measures of each component (P1, P2 and P3) was investigated using separate correlational analyses. Correlations were assessed across groups and then for each group separately using Pearson's partial correlations controlling for the effect of age. Full correlation matrices can be seen in Appendix 2. Associations with parent-rated inattention are reported in *Table 4.12*. The measures selected for each component were those identified as being maximal and assessed for group differences and evidence of task-related attentional modulation above with the following exception. For P2, correlations were restricted to the P2 latency as measured at Cz on the basis of the P2 being maximal and showing more evidence of task-related attentional modulation at this location.

Table 4.12: Partial correlations between parent-rated inattention and peak latency of P1 measured at Oz, P2 measured at Cz and P3 measured at Pz.

		Parent-Rated Inattention vs. Peak Latency		
Component	Target Type	Collapsed Across Groups	Very Preterm	Term
P1	Cued	-.179	-.272	-.063
	Uncued	-.174	-.205	-.160
P2	Cued	-.150	.131	-.459**
	Uncued	-.173	-.007	-.336*
P3	Cued	.018	.227	-.184
	Uncued	.064	.144	-.028

Note: All correlations control for the effect of age. *p<0.05, **p<0.01, ***p<0.001.

No overall associations were observed between parent-rated inattention and ERP latencies. However relationships in term born children emerged between greater parent-rated inattention and shorter P2 latency for both target types (see Figure 4.9), a direction contrary to expectations. Fischer's comparison confirmed that the association was stronger in term than preterm children, a finding that was significant for cued targets (*z*=2.75, *p*=0.003), although only marginal for uncued targets, (*z*=1.50, *p*=0.067). Contrary to expectations, no other significant associations were observed between component latency and parent-rated inattention.

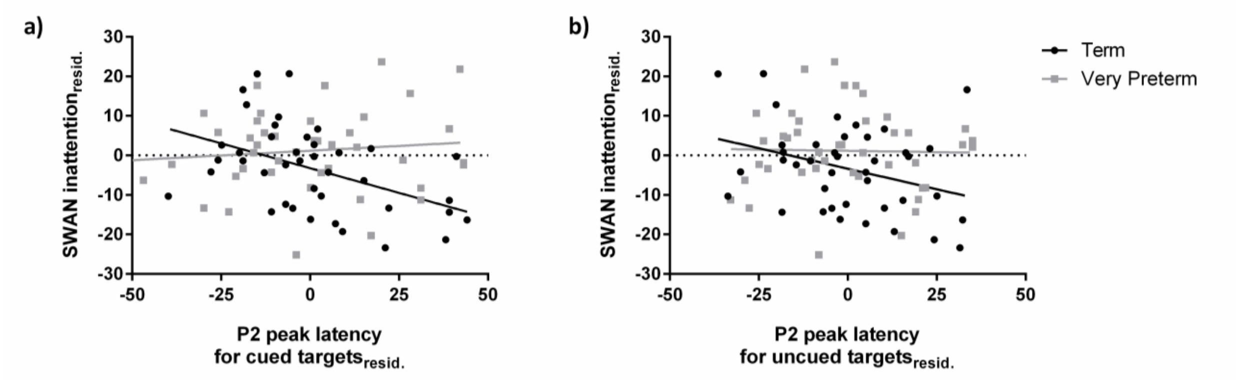

Figure 4.8: Scatter plots showing the association between SWAN parent-rated inattention and (a) P2 peak latency for cued targets, and (b) P2 peak latency for uncued targets while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age. The dotted line represents 'average' attention, while positive scores indicate more severe ratings of inattention and negative scores indicate above average ratings of attention.

Post-hoc correlations were performed to further investigate the unexpected association between shorter P2 latency to both target types and more severe parent-rated inattention, and explore how P2 components related to task-performance measures. One possible reason for this association could be that children who are more inattentive are also impulsive. It would thus be feasible that a component such as the P2, which is thought to represent stimulus categorisation, might be affected by impulsivity, and children who were less attentive might categorise stimuli quicker, and possibly less effectively. If this were the case, it would be expected that P2 latency would have a positive relationship with hit rate, and an inverse relationship with the number of commission errors. Results are reported in Table 4.13.

No significant associations were found between P2 characteristics and task performance measures. However, it should be noted that trends (*p*<0.07) suggestive of associations between shorter latency P2s and greater response time variability in term children, give some tentative support for the speculation that shorter P2 latencies in these children might be linked to poorer performance. This might help to explain the unexpected presence of shorter P2 latency in term-born children with higher levels of parent-rated inattention. It is interesting to note the presence of an opposite trend in children born very preterm (*r*=0.29, *p*<0.07), confirmed as significantly different from that in term-born children (z= -2.59, *p*=0.005).

Table 4.13: Partial correlations between task-performance and P2 latency measurements at Cz

	Very Preterm		Term	
	Cued Targets	Uncued Targets	Cued Targets	Uncued Targets
Hits	.065	-.016	.216	.213
Response time	.200	.102	.037	.117
Response variability	.287§	.219	-.288§	-.007
Commission errors	-.125	-.034	-.108	-.092

Note: All correlations controlled for age. § *p*<0.07, **p*<0.05, ***p*<0.01, ****p*<0.001.

4.4.2.3 CPT-AX behavioural and ERP predictors of parent-rated inattention

Overall, correlational analyses showed that at the behavioural level, more severe parent-rated inattention was associated with a lower hit rate, more commission errors and greater response time variability. These relationships did not differ between groups. Although the cue-locked negativity component showed evidence of task-related attentional modulation and was related to task-performance, it did not relate to parent-rated inattention in either group. Similarly, although the P1 and P3 components showed evidence of task-related attentional modulation, they were not related to parent-rated inattention in either group in terms of amplitude or latency. Meanwhile P2 amplitude was related to parent-rated inattention in both groups of children, but P2 latency was related to parent-rated inattention only in term-born children.

Relationships between CPT-AX indices and parent-rated inattention were explored further using a multiple hierarchical regression in order to assess the unique contribution of any of the specific measures that showed an association with inattention. This analysis also allowed me to test whether ERP measures explained additional variance beyond that explained by behavioural measures. Group and age were entered into the first step, behavioural measures were entered into the second step, ERP measures were entered into the third step and group interaction terms were entered into the final step. Results are displayed in Table 4.14.

Table 4.14: Regression model for ERP predictors of parent-rated inattention.

	Parent-Rated Inattention		
	Model 1 R^2 =.053 -	Model 2 R^2=.181 ΔR^2= .129*	Model 3 R^2=.237 ΔR^2 =.056*
Predictor	*β*	*β*	*β*
Group	$.222^{\S}$	.249*	.230*
Age	.023	.122	.072
Hits		-.195	-.179
Response variability		$.228^{\S}$	$.210^{\S}$
Commission errors		.043	.025
P2 Uncued Peak Amp			-.245*
P2 Cued Peak Lat			-
P2 Uncued Peak Lat			-
Group*Hits			-
Group*Response variability			-
Group *Commission errors			-
Group*P2 Uncued Peak Amp			-
Group*P2 Cued Peak Lat			-
Group*P2 Uncued Peak Lat			-

Note: § $p<0.07$,*$p<0.05$, - = did not meet criteria for forward entry model selection.

It was found that model 1 did not significantly predict parent-rated inattention ($F(2,78)=2.172$, $p=0.121$), explaining only 5.3% of the variance, with only group showing a trend towards contributing unique variance.

Model 2 significantly predicted parent-rated inattention ($F(5,75)=3.323$, $p=0.009$), explaining 18.1% of the variance. Group significantly contributed unique variance, while response time variability showed a trend towards this.

Model 3 introduced ERP components using the forward selection technique. Only the peak amplitude for uncued targets significantly improved the model, contributing unique variance in addition to the significant effect of Group, with the effect for response variability remaining marginal. This model significantly predicted parent-rated inattention (*F*(6,74)=3.836, *p*=0.002), explaining 23.7% of the variance, and significantly improving on Model 2 (ΔR^2 =0.056, *p*=0.023).

Similarly, the forward selection technique was used at a fourth step to introduce group interactions with cognitive and electrophysiological measures, however none of these improved the model significantly and thus were not included in the final model.

4.5 Discussion

This study found that children born very preterm and those born at term who were matched for levels of parent rated inattention performed equally well on the CPT-AX task, although term-born children showed a marginally greater amplitude for the P2 component. Moreover, both groups showed the same associations between poorer task-performance and higher ratings of parent-rated inattention. Similarly, the results suggested that, in both groups, smaller amplitude P2 related to higher ratings of inattention, however shorter P2 latency only showed this association in children born at term. Overall, it could be seen that although both latency and amplitude characteristics of the P2 ERP were associated with parent-rated inattention, only changes in the peak amplitude in response to uncued targets explained significant unique variance beyond that explained by behavioural measures. Of the behavioural measures associated with parent-rated inattention, only response variability showed a trend towards explaining unique variance. The findings were partially consistent with the study predictions, and are interpreted below in light of the hypotheses. Please refer to *Tables 4.15* and *4.16* for a summary of analyses, expected results and actual results relevant to ERP amplitude and latency respectively.

Table 4.15: Amplitude Predictions and findings

	Group Differences		Attentional Modulation		Associations with Inattention	
Component	Expected	Found	Expected [a]	Found	Expected	Found
Cue-locked negativity (CNV)	No basis to expect between-group differences	*Early*: VP=T *Late*: VP=T	*Early:* Positive correlation with commission errors and negative with hit rate *Late:* Positive correlation with RT and RTV	*Early:* Positive correlation with RTV (VP) and RT (Term), negative correlation with hit rate (VP). *Late*: Positive correlation with RT (Term)	Negative correlation in both VP & Term. Stronger effect for late component than early.	No correlations observed.
P1	No basis to expect between-group differences	*Cued*: VP=T *Uncued*: VP=T	Cued > Uncued	Cued = Uncued	Negative correlation in both VP & Term. Stronger effect for cued targets than uncued.	No correlations observed.
P2	No basis to expect between-group differences	*Cued*: VP=T *Uncued*: VP<T	Cued > Uncued	Cued > Uncued	Negative correlation in both VP & Term. Stronger effect for cued targets than uncued.	Negative correlation for uncued targets only (Term).
P3	No basis to expect between-group differences	*Cued:* VP=T *Uncued*: VP=T	Cued > Uncued	Cued > Uncued	Negative correlation with inattention (VP & Term). Stronger effect for cued targets than uncued.	No correlations observed.

[a] These findings were not expected to differ between groups.

Table 4.16: Latency Predictions and findings

	Group Differences		Attentional Modulation		Associations with Inattention	
Component	Expected	Found	Expected	Found	Expected	Found
P1	*Cued & Uncued:* VP<T[a]	*Cued:* VP=T *Uncued:* VP=T	No basis to expect between-stimulus differences	Cued < Uncued	Positive correlation in VP only, in both cued and uncued targets.	No correlations observed.
P2	*Cued & Uncued:* VP<T[a]	*Cued:* VP=T *Uncued:* VP=T	No basis to expect between-stimulus differences	Cued < Uncued	Positive correlation in VP only, in both cued and uncued targets.	Negative correlation to both cued and uncued targets (Term).
P3	*Cued & Uncued:* VP<T[a]	*Cued:* VP=T *Uncued:* VP=T	No basis to expect between-stimulus differences	Cued > Uncued	Positive correlation in VP only, in both cued and uncued targets.	No correlations observed.

[a] Expected on the basis of motor processing speed findings in Chapter 3.

4.5.1 **Behavioural Results**

Given that the groups were matched on parent-rated inattention, it is unsurprising that they did not differ on any CPT-AX performance measures. These findings were in line with hypotheses for hit rate, commission errors and response variability, however based on the increased processing speed in children born very preterm observed in Chapter 3, faster response time had been predicted in children born very preterm compared to the term born children. The absence of this group difference in a subset of the same larger sample[1], suggests that 'processing speed' is very task-dependent and the two tasks may not be measuring the same underlying construct.

As hypothesised, parent-rated inattention was related to fewer hits, more commission errors, and greater response variability across both groups. However, no relationship was observed between response time and inattentive symptoms, even in children born very preterm. The absence of this relationship with response time is commensurate with a recent meta-analysis of studies of CPT performance in children with ADHD compared to typically developing controls (Huang-Pollock et al., 2012). This meta-analysis revealed large effect sizes for lower hit rates, higher errors of commission and higher response time variability in ADHD populations compared to typically developing controls, with a smaller effect size for slower response time. However, given the direct relationship between processing speed and parent-rated inattention in very preterm children observed in Chapter 3 an association with response time was predicted. As noted above, the results led me to conclude that processing speed is a task-dependent measure, and that response time in extended computerised response paradigms may not be measuring the same construct as in the motor processing task used in Chapter 3. The absence of a relationship between parent-rated inattention and response time is in line with other studies using computerised response based measures (Aarnoudse-Moens, Duivenvoorden,

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[1] When using the subsample of participants used in this analysis, the children born very preterm are still significantly faster than those born at term on the measure of motor processing speed used in Chapter 3 analyses (mean difference = 0.51s, *F*(1,81) = 4.07, *p*=0.048).

Weisglas-Kuperus, Van Goudoever, & Oosterlaan, 2012; de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012). De Kieviet et al. (2012) even demonstrated that variability in responding caused by lapses in attention could be at the root of such findings in other populations, also consistent with this analysis, where associations with response time variability were present. However, these findings highlight the need for a more thorough investigation of processing speed in children born very preterm to understand the conditions under which speed of processing is important and on from which measures it can be accurately detected.

All relationships between task performance and parent-rated inattention observed were small-to-moderate and when investigated separately for each group, some no longer met the criteria for significance. However, as the patterns observed were the same in both groups and Fischer's comparisons revealed no significant differences in the relationships observed in term-born compared to very preterm children, no further implications should be read into slight differences in the sizes of the relationships observed, as it is likely they emerged due to decreased power with smaller samples.

4.5.2 **ERP results**

Overall, although all of the ERP components measured showed evidence of task-related attentional modulation, only characteristics of the P2 were associated with parent-rated inattention. The P2 component was also the only component that showed any difference between groups, with marginally larger amplitudes in term-born children than in very preterm children. It should be noted that none of the components showed the predicted relationship between longer latencies and more severe parent-rated inattention in children born very preterm. These relationships were expected on the basis of the association between parent-rated inattention and motor processing speed in children very preterm in Chapter 3, and assumptions that such relationships would also be observable in the latency of different component parts of processing. However given that there was also no relationship between inattentive symptoms and response speed in this task, it is unsurprising that no evidence of this association was observed in ERP components either. Findings are discussed in detail below.

4.5.2.1 Attention during preparatory processing

Contrary to expectations, although the results indicated that the cue-locked negativity reflected response preparation, it was not related to parent-rated inattention in either group. The cue-locked negativity seen in this study was of a smaller amplitude than the CNV components found in previous studies (e.g. Banaschewski et al., 2008; Jonkman, 2006; Spronk, Jonkman, & Kemner, 2008) and I was therefore hesitant to compare it directly to the CNV that has been described in other ERP studies of preparatory processing. Certain comparisons can be drawn however, such as the separation of early and late components and link to task-performance, and similarly small levels of negativity have been observed and referred to as the CNV in other studies (Ortega et al., 2013). The small amplitude of the cue-locked negativity may also be one reason why there was no association observed between this neural activity and inattentive behaviour. Possible reasons for such small amplitudes include the fact that visual inspection of averaged negativity for individual subjects revealed that many subjects showed amplitude fluctuations throughout the 600-1650ms time window following cue onset, which was interpreted to reflect high response time variability. However, on averaging, this is likely to result in overall lower mean amplitudes. Further, previous research has observed that the CNV is of smaller amplitude in children than in adults (Jonkman, 2006) and in ADHD samples than in typically developing controls (Banaschewski et al., 2008; Banaschewski et al., 2003; Ortega et al., 2013), thus perhaps we should not be surprised that the grand averages of a sample of children with varying levels of ADHD symptoms would show relatively small amplitudes of this late negativity. On reflection, a stronger preparatory response may have been elicited by using a paradigm where the cue was a stronger predictor of the subsequent target. The CPT-AX implemented in this study had 50% cue validity, thus on half of all trials following a cue stimulus it was necessary to respond, but on half it was necessary to withhold a response. It is clear from the small proportion of commission errors made overall that children were successfully able to withhold a response, perhaps indicating weaker response preparation. As such, amplitudes of the CNV would remain small in the task. This was not identified as a possible issue prior to the study as the CNV has been investigated using this paradigm in other studies (e.g. Jonkman, 2006; Banaschewski et al., 2008; Banaschewski et al., 2003) and prior studies have shown no effect of cue validity on CNV amplitude (Gajewski, 2008).

Regardless of nomenclature, the results showed that despite a lack of between-group differences in the mean amplitude of the negativity in either time window, associations with task performance measures emerged, supporting the idea that the cue-locked negativity represented preparatory processing. Contrary to hypotheses, different relationships emerged between the two groups. In children born at term, the mean amplitude in the early and late windows was strongly correlated, and in both windows smaller amplitudes were associated with slower response times. This suggests that in term-born children, the recruitment of more resources throughout the whole response preparation period (early and late windows) allowed for faster responding, as would be predicted on the basis of prior literature (e.g. Doehnert et al., 2013; Wright et al., 1995). Although these relationships with response time did not meet significance in children born very preterm, Fischer's comparisons indicated that the associations were not significantly different between groups.

In contrast, in children born very preterm the mean amplitudes of the negativity in the early and late time windows were not significantly correlated, suggestive of functional separation. Furthermore, associations between the mean amplitude in the early window and specific measures of task-performance were observed: smaller amplitudes were associated with less accurate performance and more response time variability, and it was confirmed that these associations were restricted to the very preterm group only. In these children, it appeared that the early and late portions of this wave could be functionally separated, echoing the separation of the O-wave (orientation) and the E-wave (expectation) in the CNV identified in previous studies (Loveless & Sanford, 1974; Rohrbaugh & Gaillard, 1983). Thus it could be interpreted that difficulty in orientation to the cue results in poorer performance on a test of sustained attention in children born very preterm, reflected in increased response time variability and reduced accuracy, although there was no association of this with inattentive symptoms. Differences between groups in associations between cue-locked negativity and task performance were not predicted and therefore these findings should be interpreted with caution and replication is required.

4.5.2.2 Attention during early sensory processing

For the P1 component, representing initial visual processing, there were no between group differences in amplitude or latency, as hypothesised. However, contrary to expectations, no relationships with parent-rated inattention were observed in either group. Despite this, there was evidence of task-related attentional modulation, in that the peaks were earlier for cued targets than uncued targets. This was interpreted as a facilitation of stimulus detection due to expectation of a target following the cue in comparison to the processing of uncued targets. The absence of any association between parent-rated inattention and amplitude or latency measures of P1 suggests that difficulty with initial visual processing of target stimuli, and modulation to facilitate visual processing of target stimuli following cues, is not related to parent-rated inattention in term-born or very preterm children. This is in line with studies that have found no differences in P1 components between ADHD and control groups (Brown et al., 2005; Jonkman et al., 1997; Oades, 1998; Steger et al., 2000; Strandburg et al., 1996). Furthermore, it is consistent with the finding of comparable P1s across VLBW and NBW children with and without ADHD (Potgieter et al., 2003).

In contrast, the P2 not only showed evidence of task-related attentional modulation, with larger amplitudes and shorter latencies observed for cued targets, and a more frontal topography observed for uncued targets, but differences in the P2 amplitude and how P2 characteristics related to parent-rated inattention emerged between the two groups. As with the P1, the presentation of the cue prior to the target resulted in shorter P2 latencies, which were not hypothesised, but this finding was interpreted as a priming effect where presentation of the cue enables quicker stimulus categorisation of the target than for uncued targets. Furthermore, the presence of the cue also appears to have resulted in the allocation of more resources during stimulus categorisation, in line with hypotheses based on previous literature showing enhanced P2s for attended-to stimuli compared to unattended (Luck & Hillyard, 1994). Correct stimulus categorisation following the cue stimulus is essential for successful task-performance, as although the response has been primed by the cue, the cue is only valid 50% of the time, so target categorisation is essential for the evaluation of its relevance to activate the appropriate response. As such, allocation of additional resources would aid correct categorisation. Moreover, the amplitude was marginally larger in children born at term than in children born very preterm. This was not expected, however it may suggest that term born children allocate more attention during stimulus categorisation, however as there were no behavioural differences or relationships between P2 amplitude and task-performance, the functional relevance of this difference is questionable, and it may merely reflect differences in the underlying neural architecture.

Interestingly, characteristics of the P2 showed associations with inattentive symptoms. Children with smaller amplitudes in response to uncued targets were more inattentive, suggesting that the best attenders allocate more neural resources during stimulus categorisation of potentially task-relevant stimuli even if they have not been cued. This relationship did not quite reach significance in children born very preterm when the groups were split, but as Fischer’s comparison showed that the trend was not statistically different, we may conclude that they showed a similar relationship. This is partially in line with hypotheses, and in line with other studies showing reduced P2 amplitude in children with ADHD compared to term-born controls (Brown et al., 2005; Johnstone et al., 2007), although in contrast to expectations there was no association with P2 amplitude to cued targets. In everyday terms, this may indicate that children who attend well are better at orienting towards, and allocating appropriate resources to, the processing of potentially important information without the need for a cue, while those who struggle with attention are still able to allocate sufficient resources, but only when cued.

Unexpectedly, in term-born children shorter P2 latencies for both cued and uncued targets were associated with greater parent-rated inattention. This initially appears contrary to the evidence that P2 components peaked earlier to cued targets than to uncued targets, indicative of effective orienting of attention. However it is likely that these findings relate to different mechanisms. Although cues orient processing so that it is faster across the board, it may be that term-born children who are better attenders spend longer categorising task-relevant stimuli to ensure correct categorisation, while those who are inattentive categorise quickly in a more impulsive fashion. As such, these findings may represent a dissociation between the exogenous and endogenous orienting of attention in good attenders, whereby stimulus driven orientation processes captured by the comparison of cued vs. uncued targets result in quicker stimulus categorisation following cues overall, but better top-down control results in spending longer during stimulus categorisation for good attenders. These results fit with the observation and interpretation of shorter P2 latencies in unmedicated children with ADHD compared to controls, which were normalised with methylphenidate administration (Sunohara et al., 1999). Post-hoc correlational analysis of the relation between P2 latency and task-performance measures was conducted to examine further the interpretation that in the term-born children shorter P2 latencies reflected faster, but not necessarily better stimulus categorisation. Results showed that the shorter P2 latencies were not associated with better performance in term-born children, and a trend provided tentative evidence of an association between shorter P2 latency and greater response variability, suggesting a link with poorer performance, and consistent with the interpretation above. Not only this, but the relationship between poorer parent-rated inattention and shorter P2 latency was restricted to term-born children, as was this association between shorter P2 latency and greater response variability, also consistent with this interpretation.

4.5.2.3 Attention during the evaluation of task-relevance

The P3 also showed evidence of task-related attentional modulation, but as with the P1, there was no evidence of an association between P3 characteristics and parent-rated inattention. Amplitudes were larger for cued targets than for uncued targets, in line with hypotheses and previous literature showing larger amplitudes for task-relevant 'go' stimuli (Spronk et al., 2008). Peaks were also later for cued targets than uncued targets, which was unexpected but could be interpreted as reflecting children spending longer evaluating the task-relevant stimuli, and making their decision of whether to respond. This is logical as the cue stimuli are only 50% valid, and thus evaluation of the stimulus following the cue is important to prevent commission errors, resulting in the allocation of more resources and longer evaluation. Conversely, when the same stimulus is presented in the absence of the cue the response has not been primed, thus decisions about relevance for uncued targets are less likely to require so much mental effort in spite of the context-dependent relevance of the target stimulus.

On the basis that the P3 represented working memory-type processes (Donchin & Coles, 1998), which were linked to parent-rated inattention in both groups in Chapter 3, it was expected that P3 characteristics would show similar associations with inattention in both term-born and very preterm children. However, no such relationships were observed, contrary to studies of children with ADHD where reduced P3s are seen in ADHD groups compared to typically developing controls (Overtoom et al., 1998; Strandburg et al., 1996). Conversely, the findings in this study are in line with Spronk et al. (2008), who found no difference in the P3 between typically developing controls and children with ADHD. It appears that in a straight-forward task such as this, with fairly low memory demands, evaluative processing is unrelated to inattention in both groups. However it could be that use of tasks with higher working memory demands, particularly in the visuo-spatial domain, could reveal different associations and this could be tested in further studies.

4.5.3 **Explained variance**

It is important to note that although the various cognitive and ERP measures reported here showed associations with parent-rated inattention, relationships were predominantly small to moderate, and taken together, the total explained variance was 23.7%. Furthermore, the regression analysis revealed that few of the measures contributed significant unique variance. It was interesting that although the model only containing group and age did not significantly predict parent-rated inattention, group itself continued to be a significant unique predictor when other indices of CPT performance were modelled. This suggests that in the reduced sample of children who completed the EEG testing, parent-rated inattention was less well matched between the groups when other factors (age and indices of CPT performance) were controlled. While this is somewhat undesirable given the intention to have groups matched for parent-rated inattention, both term-born and very preterm groups included children with similar ranges of SWAN scores, and SWAN score means were matched in comparisons not accounting for the influence of age and CPT performance[2]. As such I am confident that relationships with parent-rated inattention would have been captured in both groups. The findings relating to response variability build on existing research endorsing its promise in the study of inattention (Castellanos & Tannock, 2002), although its unique contribution was only marginally significant. This is likely to be due to the shared variance among other behavioural measures. Regarding ERPs, only the introduction of P2 amplitude to uncued targets significantly improved the model beyond the variance explained by the behavioural measures, and no group interactions improved the model. It was hypothesised that ERP measures would explain variance beyond that explained by behavioural measures, and thus the significant contribution of P2 amplitude is consistent with this idea, and suggests that the ability to isolate variance in

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[2] For the subsample of participants used in this analysis SWAN inattention did not differ between groups (term-born mean(*SD*) = -3.56 (12.88), very preterm mean(*SD*) = -1.15 (10.06); *p*=0.345) and the range of scores was similar in both groups (term-born -27 to 20; very preterm -26 to 21).

processing stages provides additional information not measurable in the behavioural response.

4.5.4 **Design limitations**

Although ERPs have been used extensively in the study of attention and ADHD, the growing body of literature proposing that *variability* in responding is a hallmark of inattention (Castellanos and Tannock, 2002) suggests that the use of a measure that averages across multiple trials may not be optimal. Indeed, the finding that response variability was the measure most highly associated with inattention and the only behavioural measure that showed a trend towards explaining unique variance in parent-rated inattention while controlling for all other measures from this analysis, supports this notion. In particular, latency jitter across trials is likely to reduce peak amplitude measurements for the averaged waveform, thereby exaggerating group differences between groups which differ in response time variability (Saville et al., 2011; n.b. the authors of this article found that the difference of interest was still present with latency-adjusted ERPs and was not entirely accounted for by latency jitter).

One alternative to using averaged ERPs would be to assess the EEG signal across single trials. Such data could be used to examine whether fluctuations in single-trial ERP components relate to behavioural performance on that trial, and to measure the level of variability in neural responses across trials to assess whether neural inter-trial variability is associated with task-performance and symptom scores. However, traditionally single-trial EEG analysis has been difficult due to both the noise recorded alongside the neural signal (in children with hyperactivity, movement artefacts can be a particular problem), and the fact that neural signals comprise both task-related and task-unrelated processes. Assuming that only the task-related neural signals will be consistent on each trial, the averaging process improves the signal to noise ratio, but without that, data are noisy. Several methods for facilitating single-trial EEG analysis have now been developed that all aim to isolate the task-related neural signal for analysis. These include the use of ICA (Milne et al., 2011), linear spatial integration (Parra et al., 2003), complex filtering (Salajegeh et al., 2004) and maximum likelihood estimation (Jaskowski and Verleger 1999). Although these techniques have not been fully utilised in the context of ADHD and inattention yet, their potential for assessing EEG inter-trial variability in clinical groups has been recognised in analyses such as Milne et al. (2011), which used ICA-derived single trial EEG analysis to illustrate greater EEG variability in adolescents with ASD compared to typically developing peers of the same IQ.

In a similar line of thinking, although the standard deviation of response time measures the variation around the mean response time, it assumes data are normally distributed and produces an average estimate of variability. In reality, the RT distribution is traditionally positively skewed (Luce, 1991) with a few longer RTs having a disproportionate influence on the mean, and subsequently, the SD. It is thought that these outliers represent lapses of attention, which are more frequent in individuals with poor attention, resulting in an exaggeration of the positive RT skew (Leth-Steensen et al., 2000). The use of global means and SDs can result in data that has either been heavily influenced by such outliers, or that has masked the important effects of the skew. In addition, it has been shown that if the difference between two conditions resides in the mean of the normally distributed data, but the data includes outliers, ANOVAs had a reduced ability to detect this difference (Ratcliff, 1993). When looking solely at the mean and SD, two very differently distributed sets of data could produce identical means and SDs.

One alternative method of investigating RT and RT variability is to perform an ex-Gaussian analysis. As opposed to producing two measures (mean and SD) based upon the dataset, an ex-Gaussian analysis separates the data into its estimated Gaussian (normally distributed) component, and the exponential (skewed) component. This produces 3 measures for each subject; μ, which represents the mean of the normally distributed part of the data and can be seen as a measure of processing speed, σ, which represents the standard deviation of the normally distributed part of the data and can be seen as a measure of variability, and τ, which represents the mean of the exponential component and can be seen as a measure of lapses in attention.

Not only do ex-Gaussian measures allow for a better description of results due to the improvement in the characterisation of the shape of the distribution of reaction times, but this also allows for better testing of hypotheses about underlying cognitive processes. Evidence has shown that they can reveal differences that cannot be detected using the mean and SD. Specifically, in ADHD using ex-Gaussian analyses it has been found that the τ component of the ex-Gaussian distribution can be used as a more suitable marker of inattention than the mean or SD. While between-group comparisons of the means and SDs indicated that a group of children with ADHD were as slow and variable as a group of young controls, but significantly worse than age matched controls, ex-Gaussian analysis revealed that in μ and σ (speed of processing and variability) the ADHD group had comparable performance to the age-matched controls, differing only in increased lapses in attention.

Intra-individual reaction time variability scores (tau) based on ex-Gaussian distributions have been proposed as being potential endophenotypes for ADHD (Lin et al., 2015). Unfortunately, due to the CPT-AX's focus being on infrequent responses, the number of 'go' trials does not meet minimum requirements for stable estimates using ex-Gaussian distribution estimation techniques (the CPT-AX has a maximum of 40 trials compared to the minimum of 100 suggested for ex-Gaussian analysis; Heathcote et al. 1991), therefore it was not possible to use this approach in the current study design. As such, a study design with a greater number of 'go' responses would be required in order to assess RT variability in greater depth.

Moreover, more advanced statistical analysis techniques such as multilevel modelling can be used in order to investigate these intra-individual variations and covariations. Such techniques are able to examine the extent to which measures from neuropsychological tasks or instruments such as EEG may differ within a task for a particular individual, and how fluctuations in one measure may relate to fluctuations in another domain, such that they can help us understand how neuropsychological processes can impact the magnitude of the outcome measure, the variation of that measure within and between groups, and the variation of that measure within individuals simultaneously (Hoffman, 2007).

4.5.5 **Conclusions**

Poorer accuracy and greater response time variability on the CPT-AX task, as well as smaller amplitude P2s to uncued targets, were related to higher levels of parent-rated inattention in both groups. In term-born children only, faster, perhaps rushed, stimulus categorisation was also associated with higher levels of parent-rated inattention. In addition, term-born children allocated more resources during the stimulus categorisation process overall, though it is unclear whether there was any functional benefit to this.

Contrary to expectations, this analysis did not find any relationship between measures akin to processing speed and parent-rated inattention in children born very preterm, neither at the level of the behavioural response (response time) nor in terms of the latency of any individual ERP component. This was unexpected given the association between motor processing speed and parent-rated inattention reported in primarily the same children in the Chapter 3 analysis[3]. This raises questions about what precisely constitutes ‘processing speed’, as these results would suggest that the measure of motor processing speed used (fingertip tapping) did not measure the same underlying construct as the measures of response time in the CPT-AX, or different neural processes. This emphasises the need for a thorough investigation of the issue of task dependency, with the comparison of different measures within the same children to elucidate precisely which elements of ‘processing speed’ are of importance. This is of special relevance in light of studies

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[3] When using the subsample of participants used in this analysis, the correlation between parent-rated inattention and motor processing speed (controlling for age) in very preterm children only is still observed, and in fact becomes stronger (preterm: r=0.585, p<0.001; term: r=0.133, p=0.418).

promoting the importance of processing speed in predicting educational as well as clinical outcomes (Mulder, Pitchford, & Marlow, 2011; Rose et al., 2011).

Overall the measures recorded on the CPT-AX in this sample were poor predictors of inattentive behaviour in the home environment. However, a recent systematic review of the use of different variants of CPTs in children and adults with ADHD suggested that the poor association between CPT measures and symptom rating scales may also indicate that the CPT measures aspects of ADHD that cannot be captured using rating scales (Hall et al., 2015). However the review concluded that mixed results across the literature prompt the need for further investigation about the clinical utility of CPTs in ADHD diagnosis and treatment. Our study suggested that some ERPs may provide additional explanatory power, but they are likely to be task-dependent, thus replication and further examination in larger and different samples is necessary. These results bring into question the diagnostic value of a cued-CPT, and particularly the measurement of ERPs.

Chapter 5: Functional connectivity and inattention

5.1 Background

5.1.1 The importance of connectivity

In recent years, neurobiological models of ADHD have begun to implicate the role of impaired functional connectivity rather than disruption in individual brain regions (Konrad & Eickhoff, 2010). Functional connectivity refers to the co-ordination of distinct assemblies of neurons for the efficient completion of a cognitive task or perceptual process (Fingelkurts, Fingelkurts, & Kähkönen, 2005). In preterm samples, atypical connectivity is also purported to be implicated in ADHD. However, such theories predominantly stem from neuroanatomical evidence implicating atypical structural connectivity. Structural connectivity refers to the presence of anatomical connections between different brain regions that are thought to support the relay of neural signals across the brain. Atypical structural connectivity has been a common theme in explanations of the neurocognitive (Nosarti et al., 2006; Woodward et al., 2012), neurobehavioural (Fischi-Gómez et al., 2015; Skranes et al., 2012), and academic (Mulder et al., 2010; Rose et al., 2011) difficulties observed in preterm children. A recent review of the literature demonstrated convincing evidence for altered structural connectivity and atypical development of white matter tracts, even in preterm children who do not appear to show any major brain injury or impairment (Ment et al., 2009). Other studies have provided links between atypical white matter growth and cognitive impairment (Edgin et al., 2008; Nosarti et al., 2006; Skranes et al., 2012; Soria-Pastor et al., 2008; Woodward et al., 2012) as well as ADHD symptoms (Skranes et al., 2007) in preterm populations.

Although it is assumed that structural connectivity supports functional connectivity, there has been less research directly assessing the impact of altered functional connectivity in preterm samples, particularly with relevance to inattention. Research utilising fMRI techniques has shown atypical functional connectivity in school-aged preterm samples (e.g. Gozzo et al., 2009; Mullen et al., 2011), with different neural networks activated during task completion relative to term-born peers, indicating that the risk of altered functional connectivity is a consequence of preterm birth. This research has been predominantly restricted to the language domain, but research in relation to other domains, including visual attention, is beginning to emerge (Finke et al., 2015). Interestingly, the study by Finke and colleagues of preterm-born adults revealed that individuals with more distinct connectivity differences in relation to term-born peers for visual and attentional neural networks were less impaired in visual short term memory. These findings suggest that the observed alterations to ‘typical’ connectivity may represent compensatory neural reorganisation that protected against adverse effects of preterm birth. However, research in this area is limited, particularly with relation to behavioural outcomes, and researchers have identified the need for more studies of neural connectivity and biomarkers to fully understand risk and protective factors for behavioural disorders in preterm children (Msall, 2010).

An investigation of functional connectivity could provide insight into further similarities or differences between the underlying causes of inattention observed in preterm and term-born samples. From the existing evidence reviewed above it seems likely that, despite different developmental pathways (gene-environment interactions vs. preterm birth), indices of poor functional connectivity may be associated with inattention in both preterm and term-born children. In the period following the presentation of the cue the brain needs to orient attention and co-ordinate sensory-motor regions for the successful execution of the correct response following the presentation of the upcoming target stimulus. Accordingly, investigation of this response preparation period provides an opportunity to investigate the initial recruitment of top-down attentional control networks that control this co-ordination across brain regions.

Electrophysiological measures of functional connectivity can tell us about the functional organisation of brain networks with millisecond resolution. Neural oscillations are rhythmic changes in cortical excitability that are characterised by their frequency, amplitude and phase. When oscillations among an ensemble of neurons are synchronised, they can be measured using EEG, or MEG (magnetoencephalography). MEG measures the magnetic fields generated through the same biophysical processes that generate the voltage measured by EEG, and thus is also sensitive to oscillatory activity, and some of the relevant literature reviewed below uses MEG methodology rather than EEG. Different frequency bands measurable in humans include delta (approx. 1-3Hz), theta (approx. 4-7 Hz), alpha (approx. 8-13Hz), beta (approx. 14-30Hz) and gamma (approx. 30Hz and above). It is believed that neural oscillations in different frequency bands reflect the neurobiological organisation of brain networks, and that these are reorganised in response to task demands (Mazaheri et al., 2010). Not only can relationships between spatio-temporal characteristics of oscillatory activity and task-performance or symptom expression be investigated separately for different frequency bands, but a recent surge of interest in cross-frequency coupling has begun to reveal more about how long range networks act. The current analysis investigated how one measure of cross-frequency coupling, involving frontal theta and occipital alpha frequencies measured during the cue-target interval, was related to task-performance and inattentive symptoms. Below I describe the literature for how frontal theta and occipital alpha each relate to attentional and cognitive processes, before discussing the chosen coupling method.

5.1.2 Theta

Theta waves oscillate at between 4-7Hz. Task-related theta observed in frontal regions is thought to reflect error monitoring and cognitive control processes (Clayton, Yeung, & Cohen Kadosh, 2015), with larger increases in theta associated with better cognitive control. For example, task-related frontal theta has been shown to increase with increasing memory load (Jensen & Tesche, 2002), following presentation of oddball stimuli (Mazaheri & Picton, 2005) and following errors, where post-error behavioural adjustments take place (Cavanagh, Zambrano-Vazquez, & Allen, 2012).

Task-dependent changes in theta have also been the focus of research within ADHD populations. McLoughlin, Palmer, Rijsdijk, and Makeig (2014) found evidence to suggest that power and phase of frontal theta relate to ADHD at the phenotypic and genetic levels. They found that smaller stimulus-related theta increases and lower stimulus-related phase synchrony were related to higher response time variability and greater symptom severity. The heritability observed in this study led the authors to suggest atypical theta dynamics as a candidate biomarker for ADHD.

To date, investigation of oscillatory activity in preterm samples has predominantly used spectral analysis to determine the presence of maturational delay in neural development during infancy (e.g. Grieve et al., 2008), rather than to investigate the relevance of oscillatory activity to goal-directed action or functional connectivity in older childhood. However, Doesburg et al. (2011) recognised the need for research in this area and investigated inter-regional phase locking of oscillatory activity within individual frequency bands during visual short term memory retention. Activity in theta, beta and gamma bands in very preterm children resembled that seen in term-born peers. Although this research indicated that theta phase locking was typical during a memory task, there is at present no published research reporting theta modulation during the response preparation period in a cuing paradigm within preterm samples. Given the research indicating that theta is important for attentional control (Clayton, Yeung, & Cohen Kadosh, 2015), which is also a particular area of weakness in children born preterm, coupled with evidence suggesting atypical theta dynamics are a biomarker for ADHD (McLoughlin et al., 2014), examination of theta with a focus on attentional processing in preterm populations is an important avenue for investigation.

5.1.3 Alpha

Alpha waves oscillate at between 8-14Hz. Alpha oscillations are prominent in sleep and were traditionally thought to represent an idling rhythm, suppressing neural activity related to active cognitive processing (Berger, 1929). More recently, it has been shown that alpha oscillations bias neural activity to facilitate processing of task-relevant stimuli by decreasing alpha activity in brain regions responsible for processing the task-relevant elements of stimuli. This has been demonstrated in visuo-spatial attention tasks, where stronger alpha decreases were observed contralateral to the attended location, facilitating processing of the attended location (Sauseng et al., 2005). Moreover, task-relevant stimulus processing is further facilitated through the increase of alpha activity in brain regions responsible for the processing of distractors to actively select against the processing of stimuli that need to be ignored (Foxe & Snyder, 2011). For example, when a cue indicated that participants were required to attend to the auditory component of a visual-auditory compound stimulus, alpha power increases were observed over the visual cortex to suppress visual processing (Fu et al., 2001). As such it has been implicated as the mechanism by which selective attention may work (Foxe & Snyder, 2011).

Previous studies have demonstrated that this alpha modulation is less effective in children with ADHD. Mazaheri et al. (2010), found that children with ADHD did not show such a strong alpha decrease compared to a control group of children without ADHD. Moreover, in contrast to controls, the larger alpha decreases did not relate to improved task performance. A further study showed that aberrant alpha modulation during a spatial cueing paradigm negatively affected task performance in adults with ADHD (Huurne et al., 2013). In particular a study comparing participants with different ADHD subtypes demonstrated that children with the predominantly inattentive subtype of ADHD had particular problems modulating alpha in response to cues (Mazaheri et al., 2014).

Despite the scarcity of task-dependent spectral analysis in preterm samples, the aforementioned study of visual short term memory revealed that long range task-dependent alpha phase *desynch*ronisation was observed in children born very preterm, in a striking contrast to the alpha phase *synch*ronisation observed in term-born children (Doesburg et al., 2011). Furthermore, the level of alpha synchronisation in the very preterm children was associated with task-performance and lower level visual perception, whereby higher levels of synchronisation (more similar to the patterns seen in term-born peers) was related to better recall and perceptual ability. These findings highlight the potential importance of task-related activity in the alpha band, suggesting that preterm birth may alter inter-regional alpha connectivity in a way that affects cognitive outcomes.

5.1.4 Theta-alpha cross-frequency coupling

Cross-frequency coupling refers to the interaction between oscillatory activity in different frequency bands, often in distinct separable brain regions, using evidence of interaction as an index of functional connectivity. Connectivity analyses using EEG and MEG can often be confounded by the problem of volume conduction, whereby the diffusion of the neural signal from its generator to the scalp where it is measured, through tissue, cerebrospinal fluid and the skull, means that the location of measurements of a signal may be spatially distant from the generator. When the same signal is measured in different electrodes, it may falsely appear as though distinct regions are synchronous. This can be a particular problem in the investigation of synchrony and interactions between signals measured across different regions of the scalp. However, investigating long-range cross-frequency interactions offers the opportunity to use simple methodology that avoids the problems of multiple comparisons, while simultaneously avoiding volume conduction problems, due to the low likelihood that a single neural generator would produce spatially distinct signals in distinct frequency bands.

Mazaheri et al. (2010, 2014, 2009) have conducted a series of studies on the role of theta-alpha cross-frequency coupling in cognitive control during response preparation. Their initial study found trial-by-trial coupling between increases in frontal theta power and decreases in occipital alpha power in adults following commission errors on a go/no-go task (Mazaheri et al., 2009). Frontal theta increases have been linked to higher-order cognitive processing such as focussed attention, while parieto-occipital alpha decreases are thought to represent increasing activation of the visual cortex. As such the authors interpreted the fronto-occipital theta-alpha coupling following erroneous responses as evidence of frontal cognitive control modulating the occipital visual system to facilitate more efficient future stimulus processing and avoid further mistakes. Further research utilising this approach in the investigation of ADHD has demonstrated that similar theta-alpha interactions during response preparation can be observed in typically developing children, but are not present in children with ADHD, suggestive of impaired fronto-occipital connectivity (Mazaheri et al., 2010). Moreover, this absence of theta-alpha interactions was found in children with both the combined ADHD subtype and the predominantly inattentive ADHD subtype (Mazaheri et al., 2014). This technique therefore provides a simple method for investigating one instance of long range functional connectivity representative of efficient cognitive control, and may be a potential biomarker for impaired functional connectivity in ADHD. As such, the current analysis aimed to replicate the association between impaired fronto-occipital theta-alpha interactions during the cue-target interval and inattentive behaviour in term-born children, and investigate whether similar impairment was related to inattention in children born very preterm.

EEG evidence of impaired functional connectivity is only just beginning to emerge in studies of children born preterm. Cross-frequency connectivity of the type studied by Mazaheri et al. (2010, 2014, 2009) has yet to be examined, but given the atypical alpha connectivity observed (Doesburg et al., 2011) and altered structural connectivity (Ment et al., 2009) in children born very preterm, along with the findings in children with ADHD, it is an avenue ripe for exploration.

5.1.5 The current analysis

The current analysis aimed to investigate whether cue-induced oscillatory activity in the theta and alpha bands, (i) differed between term-born and very preterm, and (ii) was related to task-performance and inattentive behaviour in term-born and very preterm children. Further, it aimed to use the principles demonstrated in Mazaheri et al. (2010, 2014, 2009) to replicate associations between trial-by-trial fronto-occipital theta-alpha coupling and inattentive behaviour in term-born children, and to investigate this in relation to children born very preterm. It was broadly hypothesised that better task performance and less severe parent-rated inattention would be associated with larger cue-induced theta increases, alpha decreases and stronger inverse correlations between trial-by-trial frontal theta and occipital alpha. Due to the scarcity of oscillatory research in preterm samples and matching of preterm and term groups on severity of parent-rated inattention, it was unclear whether groups would differ in the levels of theta, alpha or cross-frequency coupling observed, or whether associations of task-performance and inattention with oscillatory activity would differ between term-born and very preterm children.

5.2 Method

The sample, procedure and behavioural measures used in this analysis were as described in Chapter 4 (see Section 4.2, page 88).

5.1 Analysis

5.2.1 Spectral Analysis

5.2.1.1 Spectral pre-processing

All data pre-processing was conducted using FieldTrip software (Oostenveld, Fries, Maris, & Schoffelen, 2010). Data were epoched from -1000 pre-cue to 3300ms post-cue, time-locked to cue stimulus onset with time-domain baseline correction -1000ms pre-stimulus. Epochs were then downsampled to 250Hz. Artefact rejection was conducted using the method described in full in Chapter 4 (Section 4.3.1). Data from each trial were demeaned to avoid direct current offset. Time frequency representations for each trial for each participant were then calculated over a frequency range 2.5-40Hz. Each data segment was multiplied by a Hanning taper and spectral power was estimated every 100ms using a sliding time window of 500ms in 2.5Hz steps and log transformed to normalize the data.

For analysis of the alpha and theta frequency bands, single trials were baseline corrected from -750 to -500ms pre-stimulus to produce a measure of power relative to baseline, thus positive values represented an increase in power with respect to the baseline period, while negative values represented a decrease in power with respect to the baseline period. Grand averages were then computed and inspected.

Theta

Inspection of a topoplot of theta power (4-7Hz) relative to the pre-stimulus baseline (see Figure 5.1) demonstrated that the theta increase was maximal over electrode

AFz. In order to replicate the method used in Mazaheri et al. (2014), theta power was averaged over trials and time points for time windows of 0-500ms, 500-1000ms and 1000-1500ms for further investigation.

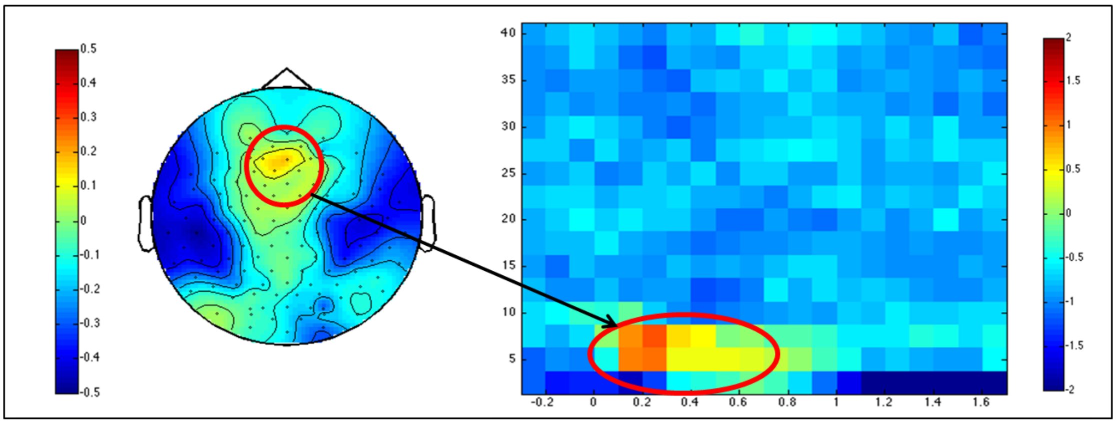

Figure 5.1: Frontally maximal topography of theta (4-7Hz) between 0-1000ms (left) and the time-frequency representation (TFR) of spectral activity measured in dB observed at AFz from 200ms pre-cue to 1.65ms post-cue. The red circles indicate the power increase in the theta band.

Alpha

Inspection of a topoplot of alpha power (9-13Hz) relative to the pre-stimulus baseline (see Figure 5.2) demonstrated that the alpha decrease was maximal over occipital electrodes, thus it was measured at midline occipital electrode Oz. In order to replicate the method used in Mazaheri et al. (2014), the alpha power was averaged over trials and time points for time windows of 0-500ms, 500-1000ms and 1000-1500ms for further investigation.

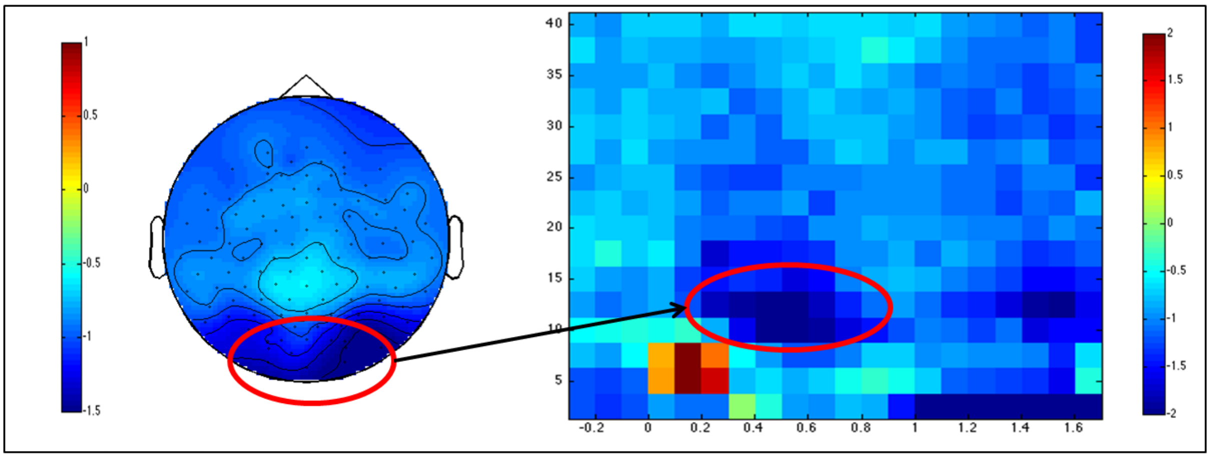

Figure 5.2: Occipitally maximal topography of the alpha (9-13Hz) between 0-1000ms (left) and the time-frequency representation (TFR) of spectral activity measured in dB observed at Oz from 200ms pre-cue to 1.65ms post-cue. The red circles indicate the power decrease in the alpha band.

Theta-alpha cross-frequency coupling

A measure of the relationship between the frontal theta increase and occipital alpha decrease following the cue (see Figure 5.3), henceforth referred to as theta-alpha cross-frequency coupling, was calculated for each participant. First, on each trial, power (relative to a pre-stimulus baseline) was extracted at the midline electrodes where power was maximal (theta AFz, alpha Oz), and averaged within the frequency band (theta 4-7Hz, alpha 9-13Hz) and over time points in the 0-500ms time window. This provided trial-by-trial measures of increases in theta power and decreases in alpha power for each participant, from which correlation coefficients representing the association between theta and alpha power over trials were calculated.

These theta-alpha cross-frequency coupling coefficients were initially calculated using the 0-500ms time window for both theta and alpha to enable direct comparison with the results reported in Mazaheri et al. (2014).

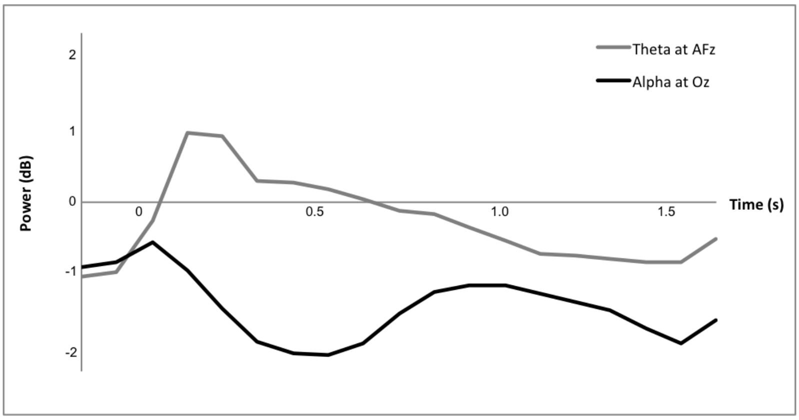

Figure 5.3: The timecourse of the increase in frontal theta and decrease in occipital alpha relative to a pre-stimulus baseline from the onset of the cue (0s).

5.2.1.2 Statistical Analysis of Spectral Data

Effects of time and group

In order to assess whether cue-induced oscillatory activity differed between groups, and how it changed over time, mixed-measures ANCOVAs were conducted for alpha power and theta power separately. Mean power following cue onset was assessed with a within subjects factor of time window (0-500ms, 500-1000ms, 1000-1500ms), and a between subjects factor of group (term-born vs. very preterm), with age entered as a covariate. Main effects for within-subject measures are independent of the covariate of age as all measures were collected in a single session. As such, pure within-subjects main effects are reported from analyses that exclude the covariate, thus degrees of freedom may differ for pure within-subjects effects compared to between-groups and interaction effects. This method has been used previously (Annaz et al., 2009).

In order to assess whether cross-frequency coupling (as measured at 0-500ms to allow direct comparison with the results of Mazaheri et al., 2014) differed between groups, a univariate ANCOVA with a between-subjects factor of group (term-born vs. very preterm) and age entered as a covariate was conducted.

Relationships with task-performance and inattention

To determine whether smaller changes from baseline in alpha and theta power related to poorer task performance and more severe parent-rated inattention, partial correlations were conducted between the mean power in the time window showing the strongest change from baseline (theta: 0-500ms, alpha: 500-1000ms) and task-performance measures and parent-rated inattention, while controlling for the effect of age. These analyses were also conducted using the cross-frequency coupling measure of the correlation coefficient between trial-by-trial theta and alpha to determine whether smaller inverse correlations related to poorer task-performance and more severe parent-rated inattention. All correlations were initially conducted collapsed across groups to maximize power for finding correlations that were consistent across both groups, and then repeated split by group to identify any relationships that were restricted to one group. The strength of the correlation coefficients were compared statistically between groups using Fischer’s r-to-z tests.

5.3 Results

5.3.1 Effects of time and group

5.3.1.1 Theta

A mixed ANCOVA was conducted on the measure of theta power relative to a pre-stimulus baseline at AFz, with a within-subjects factor of time window (0-500ms, 500-1000ms, 1000-1500ms), a between-subjects factor of group (term-born, very preterm), and age as a covariate. A significant effect of time window was found ($F(1.724, 141.403) = 43.160$, $p<0.001$, $\eta_p^2=0.345$). Post-hoc comparisons showed that the theta increase during the 0-500ms window was significantly larger than between 500-1000ms (mean difference = 0.214dB, $p=0.013$), or 1000-1500ms (mean difference = 0.826dB, $p<0.001$). Further, the theta increase during the 500-1000ms window was significantly larger than that during the 1000-1500ms window (mean difference = 0.612dB, $p<0.001$).

Theta power was similar in both groups as shown below in Table 5.1. Theta power did not differ significantly between groups ($F(1,81) = 0.150$, $p=0.700$, $\eta_p^2=0.002$), and nor did it interact between time and group ($F(1.756, 142.211) = 0.657$, $p=0.501$, $\eta_p^2=0.008$).

Table 5.1: Age adjusted marginal means and standard errors (SE) of mean theta power measured at AFz across the 3 time windows.

	Very Preterm		Term	
Mean theta power	Mean	SE	Mean	SE
0-500ms (dB)	0.17	0.14	0.22	0.15
500-1000ms (dB)	-0.10	0.12	0.06	0.12
1000-1500ms (dB)	-0.61	0.11	-0.66	0.11

5.3.1.2 Alpha

A mixed ANCOVA was conducted on the measure of alpha power relative to a pre-stimulus baseline at Oz, with a within-subjects factor of time window (0-500ms, 500-1000ms, 1000-1500ms), a between-subjects factor of group (term-born, very preterm), and age as a covariate. A significant effect of time window was found ($F(2, 82) = 5.950$, $p=0.003$, $\eta_p^2=0.068$). Post-hoc comparisons showed that the alpha decrease in the 500-1000ms time window was significantly larger than in the 0-500ms window (mean difference = -0.370dB, $p=0.001$), or the 1000-1500ms time window (mean difference = -0.308dB, $p=0.007$), which did not differ from one another (p=0631).

The two groups displayed similar levels of alpha power, as shown below in Table 5.2. Alpha power did not differ significantly between groups ($F(1,81) = 0.127$, $p=0.723$, $\eta_p^2=0.002$), and nor did it interact between time and group ($F(2, 162) = 2.182$, $p=0.116$, $\eta_p^2=0.026$).

Table 5.2: Age adjusted marginal means and standard errors (SE) of mean alpha power measured at Oz across the 3 time windows.

	Very Preterm		Term	
Mean alpha power	Mean	SE	Mean	SE
0-500ms (dB)	-1.35	0.16	-1.15	0.16
500-1000ms (dB)	-1.48	0.18	-1.75	0.18
1000-1500ms (dB)	-1.25	0.12	-1.37	0.12

5.3.1.3 Theta-alpha cross frequency coupling

Theta-alpha cross-frequency coupling was calculated only for the window 0-500ms in line with Mazaheri et al. (2014), and as such no effects of time were investigated in this analysis. A between-subjects ANCOVA was conducted on theta-alpha coupling coefficients with group as a between subjects factor (term vs. very preterm), and age entered as a covariate.

Theta-alpha coupling did not differ between groups ($F(1,82) = 0.007$, $p=0.931$ $\eta_p^2<0.001$). Not only did the two groups display similar levels of theta-alpha coupling, as shown below in Table 5.3, but it should also be observed that the mean value of theta-alpha coupling coefficients shown in both groups was positive with fairly narrow variance, indicating that on average, there was little evidence of theta-alpha coupling. Although the range indicates that some children did demonstrate the expected negative coefficients thought to index optimal cross-frequency coupling, the most negative coupling coefficients in both groups remained small (see Table 5.3) and many children demonstrated positive associations instead. The small standard error values indicate that the majority of children demonstrated theta-alpha coupling values very close to the group mean.

Table 5.3: Age adjusted marginal means and standard errors, and the unadjusted range of theta –alpha coupling coefficients over participants in each group.

Theta-Alpha coupling (*r*)	Very Preterm	Term
Mean (SE)	0.11 (0.02)	0.12 (0.02)
Range	-0.16 to 0.33	-0.13 to 0.49

5.3.2 Relationships with task-performance and inattention

Next, relationships between parent-rated inattention and power measures were assessed. Partial correlations between theta power and alpha power relative to pre-stimulus baselines, theta-alpha cross-frequency coupling and task-performance and parent-rated inattention measures, controlling for the effect of age were computed. For theta and alpha power, correlations were computed using the measure of mean power in the time window showing the strongest change from baseline for each frequency band (theta: 0-500ms, alpha: 500-1000ms). For analysis of cross-frequency coupling, theta-alpha correlations in the 0-500ms time window were used, in line with Mazaheri et al. (2014). These values were then correlated with task-performance and inattention measures, collapsed across both groups and then split by group. Results can be seen in Tables 5.4 and 5.5 respectively.

Across groups, it can be seen that although the theta increase did not relate to any task-performance measures, there was an association between smaller theta increases and more severe parent-rated inattention (see Table 5.4). However, measures of the decrease in alpha power, or of theta-alpha cross-frequency coupling were not associated with parent-rated inattention or any task performance measures.

Table 5.4: Partial correlations between inattention and task-performance measures and power measures

	Theta (0-500ms)	Alpha (500-1000ms)	Theta-Alpha Coupling (0-500ms)
Inattention	-.220*	-.016	.124
Hits	.091	.008	-.039
Commission errors	.090	-.071	-.055
Response time	-.151	.016	.041
Response variability	-.134	-.057	-.031

Note: All correlations were conducted across groups while controlling for age. **p*<0.05, ** *p*<0.01, *** *p*<0.001.

Table 5.5: Partial correlations between inattention and task-performance measures and power measures

	Theta (0-500ms)		Alpha (500-1000ms)		Theta-Alpha Coupling (0-500ms)	
	Very Preterm	Term	Very Preterm	Term	Very Preterm	Term
Inattention	-.397**	-.061	-.280	.219	.220	.052
Hits	.316*	-.030	.051	-.075	-.153	.021
Commission errors	-.012	.200	-.188	.032	-.177	.061
Response time	-.041	-.235	-.071	.082	.319*	-.164
Response variability	-.119	-.175	.079	-.197	-.042	-.009

Note: All correlations were conducted split by group, while controlling for age. **p*<0.05, ** *p*<0.01, *** *p*<0.001.

Different patterns emerged when the groups were split (Table 5.5). In the term-born children, theta was unrelated to both parent-rated inattention and task performance. On the other hand, in children born very preterm, a smaller increase in theta power was associated with a lower hit rate, and Fischer's r-to-z comparisons confirmed that this was significantly different to term-born children (*z*=1.65, *p*=0.05). Further, this analysis showed that there was a significant relationship between a smaller increase in theta and more severe parent-rated inattention, and although Fischer's r-to-z was only marginal (*z*= 1.3, *p*=0.09), the absence of a relationship in the term-born children (*r*=-.061) indicated that this was restricted to the children born very preterm (see Figure 5.4).

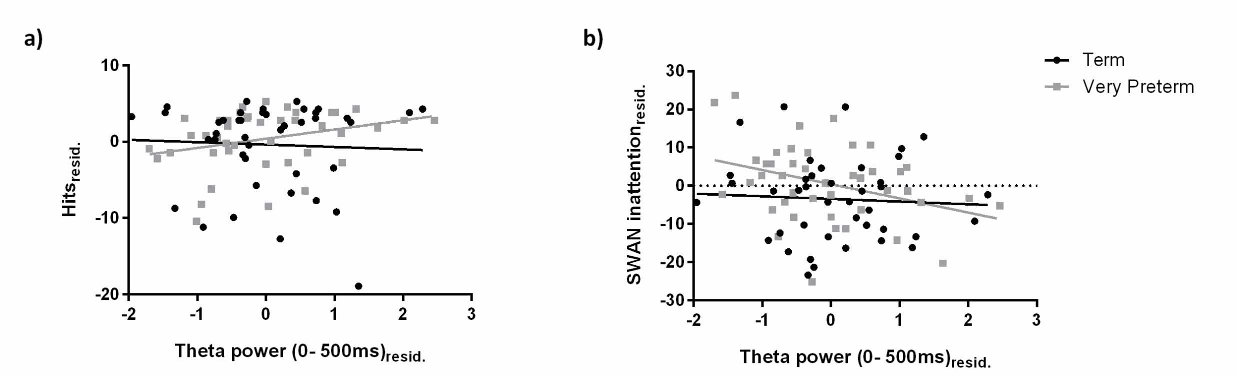

Figure 5.4: Scatter plots showing the association between mean theta power measured at AFz between 0-500ms relative to a pre-stimulus baseline and (a) hit rate, and (b) parent-rated inattention, while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age.

Additionally, faster response time was associated with a more negative theta-alpha relationship (i.e. stronger theta-alpha connectivity) in children born very preterm (see Figure 5.5). Fischer's comparison confirmed that the two groups showed significantly different associations (*z*=2.17, *p*=0.015).

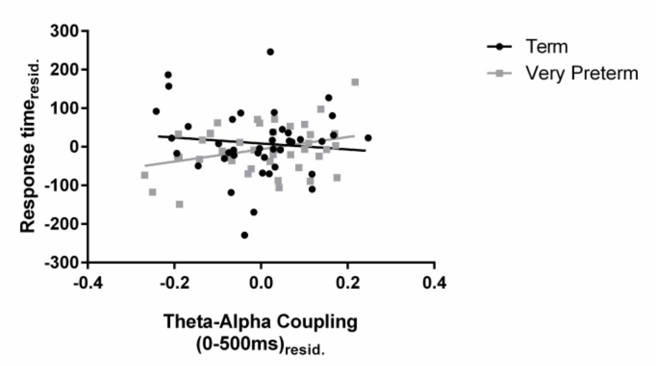

Figure 5.5: Scatter plots showing the association between theta-alpha cross-frequency coupling and response time while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age.

5.3.2.1 Secondary analysis of cross-frequency coupling

Theta-alpha cross-frequency coupling was initially calculated using power values extracted from the 0-500ms window, in order to compare results directly with Mazaheri et al. (2014). However, my data indicated that while the peak in theta power did occur in the 0-500ms time window, the alpha decrease was at its peak in the subsequent time window (500-1000ms). In order to explore the possibility that a measure calculated using the *peak* time windows for each frequency band may better reflect the extent of cross-frequency coupling, and may therefore relate to measures of parent-rated inattention, a secondary analysis was conducted. In this analysis, theta-alpha cross-frequency coupling was calculated in the same manner as before; by calculating the correlation between trial-by-trial theta and alpha power. Trial-by-trial theta was again extracted and averaged across time points in the 0-500ms time window, however this time trial-by-trial alpha was extracted and averaged across time points in the 500-1000ms time window.

A between-group ANCOVA with group (preterm vs. term) as a between-subjects factor and age entered as a covariate indicated that there were no differences between the level of theta-alpha coupling in term-born and very preterm children ($F(1,82) = 0.084$, $p=0.772$, $\eta_p^2=0.001$). As in the analysis using the previous measure of theta-alpha coupling, the mean correlation coefficient shown in both groups was very close to zero with fairly narrow variance (see Table 5.6), indicating that on average, there was little evidence of theta-alpha coupling. In this analysis however, the range included children with stronger negative correlations.

Table 5.6: Age adjusted marginal means and standard errors, and the unadjusted range of theta –alpha coupling coefficients

Theta-Alpha coupling (*r*)	Very Preterm	Term
Mean (SE)	0.08 (0.02)	0.08 (0.02)
Range	-0.17 to 0.28	-0.30 to 0.32

Note: These calculations used the coefficient calculated using different time windows for theta (0-500ms) and alpha (500-1000ms).

As before, theta-alpha cross-frequency coupling measures were then correlated with task-performance measures and parent-rated inattention, controlling for the effect of age. These were conducted collapsed across both groups and then split by group. Results can be seen in Table 5.7 and Table 5.8, presented alongside the correlations computed in the original analysis.

Table 5.7: Partial correlations between inattention and task-performance measures and theta-alpha coupling calculated in the two different ways

	Theta-Alpha Coupling (0-500ms)	Theta-Alpha Coupling (different windows)
Inattention	.124	.133
Hits	-.039	-.014
Commission errors	-.055	.037
Response time	.041	-.051
Response variability	-.031	.008

Note: All correlations were conducted across groups and while controlling for age. *p<0.05, ** p<0.01, *** p<0.001.

Table 5.8: Split-group partial correlations between inattention and task-performance measures and theta-alpha coupling calculated in the two different ways

	Theta-Alpha Coupling (0-500ms)		Theta-Alpha Coupling (different windows)	
	Very Preterm	Term	Very Preterm	Term
Inattention	.220	.052	.245	.035
Hits	-.153	.021	-.067	-.004
Commission errors	-.177	.061	-.030	.089
Response time	.319*	-.164	.363*	-.312*
Response variability	-.042	-.009	-.018	.041

Note: All correlations are controlled for age. *p<0.05, ** p<0.01, *** p<0.001.

Overall, correlations were very similar and non-significant regardless of the time windows used to calculate theta-alpha cross-frequency coupling. Across groups, no associations were observed between theta-alpha coupling and either task-performance measures, or parent-rated inattention.

When correlations were split by group, again faster response time was associated with a more negative theta-alpha relationship in children born very preterm. Use of this time window changed these associations only in that the correlation between faster response time and a more positive theta-alpha relationship in term-born children (the opposite direction to in preterm children) now reached significance (see Figure 5.6). Fischer's comparison confirmed that the two groups showed significantly different associations (*z*=3.08, *p*=0.001).

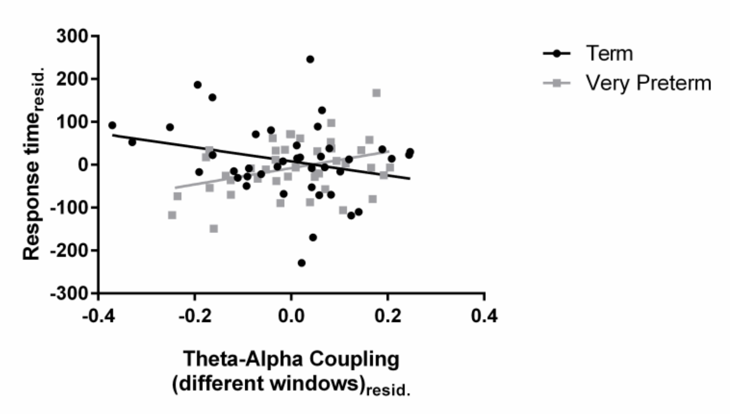

Figure 5.6: Scatter plots showing the association between theta-alpha cross-frequency coupling (calculated using different time windows) and response time while controlling for the effect of age. Values plotted are unstandardised residuals from regressing the variables against age.

5.4 Discussion

This analysis compared cue-elicited changes in theta and alpha frequencies, and the interaction between the two, between very preterm and term-born children. It also assessed how these changes related to CPT-AX performance and parent-rated inattention. Overall, none of the frequency measures differed between the groups. The theta power increase was strongest in the 0-500ms time window immediately following the cue, with the alpha decrease being strongest in the following 500-1000ms time window. Although this is somewhat contrary to the findings of Mazaheri et al. (2014), who observed the greatest alpha power decrease in the time window immediately following the cue onset, the authors also found that the theta increase preceded the alpha decrease in line with the current analysis. Despite no between-group differences in the strength of the theta power increase, alpha power decrease or level of theta-alpha coupling between term-born and very preterm children, associations of these measures with behavioural measures did differ between the groups. Theta increases were related to improved accuracy on the task and better parent-rated attention in very preterm children only, but alpha decreases were not related to task-performance or parent-rated inattention. Theta-alpha coupling, reflected in a negative correlation between theta and alpha power, was not observed in many children and associations that emerged should be interpreted with this in mind. Results are discussed in detail below.

5.4.1 Theta

In children born very preterm, smaller theta increases were associated with less accurate CPT-AX performance as measured by hit rate, and more severe parent-rated inattention. This suggests that initiation of top-down control following the presentation of a cue stimulus is a mechanism that partly explains poorer task performance in this sample and is also related to inattention.

Given that groups were matched on inattention it was hypothesised that these associations would be observed in both groups of children due to previous literature associating smaller theta increases with ADHD and increased response variability, another performance measure thought to provide an index of lapses in attention (McLoughlin et al., 2014). While the data from the children born very preterm fits the notion of theta increases representing cognitive control necessary for orienting attention and co-ordinating preparatory responses, it is unclear why similar relationships were not observed in term-born children. Other studies have failed also to find evidence of decreased theta in ADHD populations (Mazaheri et al., 2010, 2014). It may be that the mechanisms linking theta modulation, task performance and inattention differ between term-born and preterm children, but this requires replication in order to determine whether the absence of the association in term-born children is an anomalous result.

5.4.2 Alpha

Contrary to expectations, decreases in alpha power were unrelated to task-performance and parent-rated inattention in both groups. As alpha frequencies are associated with inhibition of processing, alpha decreases elicited by a cue stimulus over the occipital cortex are thought to represent a facilitation effect for the processing of the expected visual stimulus (Foxe & Snyder, 2011). In addition, findings have shown weaker alpha decreases in children with ADHD (Mazaheri et al., 2010), and specifically following the cue in children with the predominantly inattentive subtype (Mazaheri et al., 2014). Moreover, it has been shown that weaker alpha decreases in adults with ADHD can negatively affect task performance (Huurne et al., 2013). Therefore, it is surprising that no links were observed here between changes in alpha and task-performance or parent-rated inattention. A possible explanation for this will be discussed below as it has stronger relevance to the cross-frequency coupling findings.

5.4.3 Theta-Alpha Cross-Frequency Coupling

Very little evidence of trial by trial theta-alpha cross frequency coupling was observed, regardless of the time windows used for the calculation. As such, subsequent correlations between the level of coupling and behaviour should be considered with this in mind. Contrary to hypotheses built on the findings of other studies using this technique in case-control comparisons of ADHD samples (Mazaheri et al., 2010, 2014), there was no association between the level of cross-frequency coupling and inattentive symptoms. However, in terms of task-performance, term-born and very preterm groups showed opposite associations, with faster response time associated with stronger cross-frequency coupling in very preterm children, but with weaker cross-frequency coupling in children born at term. Assuming that these findings represent true effects, the children born very preterm would be considered to be displaying the expected relationship, suggesting that in these children, poor fronto-occipital connectivity is associated with slow responses. Meanwhile, the term-born children, poorer fronto-occipital connectivity appears to be associated with quicker responding, which could be interpreted as reflecting more impulsive responding. It is unclear why such a dissociation might emerge in samples of children matched on inattentive (and hyperactive-impulsive) symptoms. Such findings are tenuous and difficult to interpret in the absence of any association with inattentive symptoms, and given the weakness of any theta-alpha cross-frequency coupling.

Conversely, it is important to consider why theta-alpha coupling was not readily observed in this study. Visual inspection of the single trial measurements of theta and alpha showed a lot of variation across trials in individual subjects, and as such it is likely that cue trials were not consistently evoking the same neural responses. One reason for such inconsistency, even in good attenders, may stem from the cue validity, with the 50% validity used in the CPT-AX being far lower than in the paradigms used by Mazaheri and colleagues in their series of experiments. Haegens, Händel, and Jensen (2011) compared alpha lateralisation during a somatosensory cueing paradigm under different levels of cue validity, finding that at 50% validity alpha lateralisation to cues was virtually absent. The low validity of the cue may also explain the absence of relationships between behavioural measures and alpha decreases.

The original intention was to apply an established method in a hypothesis-driven approach to a new dataset, with the anticipation that if the theta-alpha coupling was a consistent effect, we would be able to replicate it and infer new information about the relation of fronto-occipital connectivity to inattention in children born very preterm. However, ultimately this method may not have been optimal for the study of functional connectivity in this sample and using the CPT-AX measure selected. With functional connectivity analysis using EEG still in its infancy, new techniques are continually being identified and the number of different approaches available is already vast. It was decided that the connectivity analysis should be restricted to fronto-occipital theta-alpha power-power coupling for several reasons. Although phase-power and phase-phase coupling approaches may offer opportunities for new insights, it has been argued that unlike power measures, cross-frequency *phase* synchrony measures are not optimal for the investigation of long range connectivity due to difficulty in the maintenance of the required timing accuracy for phase synchronisation across different frequencies and long distances (Bruns, Eckhorn, Jokeit, & Ebner, 2000; Jensen & Mazaheri, 2010). In addition, it has been shown in other cueing paradigms that only alpha power, and not alpha phase, can be modulated by attention and expectancy (van Diepen, Cohen, Denys, & Mazaheri, 2015). As such, the implementation of other connectivity analysis methods in order to further assess the nature of CPT-AX elicited functional connectivity and its relation to inattention in term-born and very preterm children would be of an exploratory nature and was not considered to be within the scope of this PhD. The use of the vast array of spectral analysis techniques presents a potentially informative avenue for future research into functional connectivity within preterm populations, however. Such studies utilising similar techniques should ensure that their paradigm consistently elicits the given connectivity index in typical samples before deriving any inferences from its absence in other samples.

5.4.4 Conclusion

Perhaps the most promising result in terms of practical applications was that in children born very preterm smaller theta increases, indicative of less top-down control, were associated with lower accuracy, as well as more severe inattention. It remains unclear why similar associations were absent in the term-born children. Reductions in alpha power following the cue did not differ between children born at term and those born very preterm, and were not associated with task-performance or inattention. This suggests that all children were equally able to modulate alpha oscillations in this task in order to facilitate processing of the target stimulus, but that variation in alpha modulation did not alter task-performance and did not vary across children with different levels of inattention. There was very little evidence of fronto-occipital theta-alpha power coupling even in term-born children who had above average levels of attention. Therefore, any relationships observed between the measure of coupling and behavioural indices require replication and should be interpreted with caution.

In summary, this analysis presents initial evidence that theta modulation is related to attentional processing in preterm children, and may represent an appropriate biomarker for future study. Such findings highlight the potential and importance for future studies of the role of functional connectivity in inattention in children born preterm in order to improve our understanding of how disrupted neural circuitry may impact on behavioural outcomes.

Chapter 6: General Discussion

6.1 Background

By middle childhood children born very preterm are at increased risk for inattention (Brogan et al., 2014; Johnson & Wolke, 2013; Jaekel et al., 2012; Johnson et al., 2010; Shum et al., 2008), in terms of both symptoms and disorders. The published literature to date has not directly compared whether the mechanisms underlying inattention are the same in term-born and very preterm children. This thesis aimed to determine whether cognitive and neural correlates of inattention differ in term-born and very preterm children. Analyses reported in Chapter 3 focussed on cognitive processes that are (i) known to be impaired following preterm birth and/or (ii) known to be associated with inattention. Chapters 4 and 5 aimed to use electroencephalography to identify new correlates of inattention in very preterm children, drawing upon the larger body of available literature assessing the neurobiology of ADHD. This discussion will outline the key findings from the analyses described in this thesis, identifying any converging themes, and will go on to discuss their practical implications. It will also consider the strengths, challenges and limitations of the study, and recommendations for future research, before drawing general conclusions.

6.2 Summary of results

6.2.1 **Chapter 3: Cognitive predictors of inattention**

In Chapter 3, it was found that children born very preterm displayed poorer memory (verbal and visuo-spatial short term memory, verbal working memory) and visuo-spatial processing, but better processing speed than children born at term. Poorer short term memory (visuo-spatial and verbal; storage only) and poorer visuo-spatial working memory (storage plus concurrent processing) were also identified as cognitive predictors of inattention shared by both term-born and very preterm children. However, slower processing speed was identified as a predictor of inattention unique to children born very preterm. Poorer interference control and verbal working memory were also associated with more severe inattention, but did not account for unique variance in inattention. It is important to note that the amount of variance in inattention explained by these cognitive predictors remained modest at 33.2%, suggesting that these differences in cognition were not the only factors involved in the aetiology of inattention in this sample.

6.2.2 Chapter 4: ERP predictors of inattention

In Chapter 4, there were no performance differences between term and very preterm children on behavioural measures of sustained attention. Poorer response time variability was identified as a behavioural predictor of inattention shared by both term-born and very preterm children. Other correlates were identified but did not account for unique variance in inattention; specifically a lower hit rate and a higher number of commission errors on the sustained attention task were both associated with more severe inattention.

Regarding ERPs, early and late cue-locked negativity (thought to reflect the CNV), and target-P1, -P2 and -P3 all showed evidence of attentional modulation in response to task demands. The target-P2 component was marginally larger in term-born than very preterm children, but there were no amplitude or latency differences between groups in other components. Furthermore, only characteristics of the P2 component were associated with inattention. Specifically, smaller amplitude P2s elicited by uncued targets were found to be a significant predictor of more severe inattention across both groups. It was also found that in term-born children only, shorter P2 latencies for cued and uncued targets were associated with more severe inattention, but did not account for unique variance in inattention.

As with the analyses reported in Chapter 3, it should be noted that only a small proportion of variance (23.7%) in inattention was explained by the behavioural and ERP measures derived from the sustained attention task, suggesting that other factors were involved in the aetiology of inattention in this sample.

6.2.3 Chapter 5: Functional connectivity and inattention

In Chapter 5, frequency changes elicited following the cue did not differ between term and very preterm children. Nonetheless, associations between smaller increases in cue-elicited theta and both more severe parent rated inattention and a lower hit rate were observed only in children born very preterm. No associations between inattention and alpha decreases or theta-alpha cross-frequency coupling were observed. There was some evidence of opposing associations between the level of theta-alpha cross-frequency coupling and response time in term compared to very preterm children. However, there was very little evidence of the expected cross-frequency coupling index in itself, thus this finding should be interpreted with this in mind.

6.3 Conclusions and theoretical implications

6.3.1 **Cognitive correlates of inattention**

Cognition was measured in terms of basic cognitive function and executive function in Chapter 3, and in terms of behavioural indices of sustained attention in Chapter 4. The conclusions and theoretical implications I am able to draw from these findings are discussed below.

6.3.1.1 Basic cognitive function

Of the basic cognitive functions assessed, there was evidence that more severe inattention was associated with poorer verbal and visuo-spatial short term memory in both term-born and very preterm children, and with slower motor processing speed only in children born very preterm, but it was not associated with basic visuo-spatial processing in either group.

Chapter 3 provides evidence that poor short term memory – both verbal and visuo-spatial – contributes to more severe inattention, extending the large body of literature that has implicated poor working memory in inattention in very preterm children (Aarnoudse-Moens et al., 2013; de Kieviet et al., 2012; Mulder et al., 2011b; Nadeau et al., 2001). In spite of evidence of poorer short term memory in children born preterm (Briscoe et al., 1998; Bull et al., 2008; Shum et al., 2008) and even some evidence linking it directly to inattention (Shum et al., 2008), previous research investigating inattention in preterm children has focussed more on higher order cognitive functioning at the executive level and thus on working memory. This is also true of the ADHD literature more generally, with a greater focus on executive level functioning in spite of evidence of impaired short term storage in tasks with no executive demands (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). The implication here is that studies that have failed to account for poor short term memory in their assessment of the relevance of working memory to inattention are flawed and may overestimate the amount of variance explained by working memory by ignoring the shared variance explained by more basic short term memory processes.

In line with previous literature (Mulder et al., 2011b), the analyses in Chapter 3 suggest an important role for slow processing speed in inattention in preterm children. Multiple studies have shown that children born very preterm are at increased risk of slow processing speed compared to term-born peers (Aarnoudse-Moens et al., 2012; Foulder-Hughes & Cooke, 2003; Luciana, Lindeke, Georgieff, Mills, & Nelson, 1999; Mulder et al., 2011), and this has also been linked to poorer executive function (Mulder et al., 2011a; Rose et al., 2011) and poorer academic attainment (Mulder et al., 2010) in preterm populations. Studies have linked the increased risk of poor processing speed to atypical white matter growth following preterm birth (Soria-Pastor et al., 2008), and it has been proposed that this could lead to a cascade of impairments resulting in inattention (Mulder et al., 2011a) and poor academic attainment (Rose et al., 2011). It is important to also note that in the analyses reported in Chapter 3, a main effect of faster processing speed in children born very preterm was observed, and this was driven by significantly faster processing speed in preterm children with above average parent-rated attention relative to term-born children with comparable attention ratings. This provides some preliminary evidence of an alternate neuro-protective role of processing speed whereby neuroplastic brain changes may allow for increased processing speed in order to compensate for widespread impairment in ways that are not apparent in term-born children. However analyses did show that the association between inattention and processing speed was driven by those very preterm children with more severe inattentive behaviour. Thus it would appear that in this sample of children born very preterm, slow processing speed was associated with a greater severity of inattention, but at the same time, in children with better than average attention, processing speed was faster than in similarly attentive term-born controls.

An important consideration when concluding that processing speed is of importance, however, is the assumption that the measure of 'motor processing speed' analysed in Chapter 3 reflects a domain-general construct independent of task demands. This is questionable since in Chapter 4, there was an absence of similar associations between more severe parent-rated inattention and slower processing speed as measured by slower response times or later ERP latencies in children born very preterm, both thought to also index processing speed. The discrepancies in results across chapters imply that processing speed measurements are highly task-dependent, and this may also account for variation in findings both across, and within studies. Across the literature, some studies report no association between inattention and processing speed in preterm samples (Aarnoudse-Moens et al., 2013; de Kieviet, van Elburg, Lafeber, & Oosterlaan, 2012) while others have reported results similar to our own (Mulder et al., 2011b). Moreover, within the results of Mulder et al. (2011b), it can also be seen that associations with inattention were stronger for the measure of verbal processing speed than for motor processing speed. The findings reported in this thesis are the first to show such a distinct difference in associations that could be expected to be similar within the same sample (strong associations with motor processing speed but no associations with response time or ERP latency), and these findings question the validity of a single construct of 'processing speed', or suggest that different tasks vary in their sensitivity to measuring the construct of processing speed. It is recommended that future research targets the question of how best to characterise or measure processing speed, and to further investigate the contexts under which processing speed may be predictive of inattention in preterm samples in Section 6.6.

6.3.1.2 Executive function

Of the executive functions measured, poorer verbal and visuo-spatial working memory and interference control were all associated with more severe inattention, but variance in task switching was not related to variance in inattention. This supports the view that inattention is not the result of poor global executive control, and instead can be linked to domain specific deficits.

The importance of memory at both short term and executive levels lends support to the view that the concepts of attention and memory are intimately related although they appear semantically distinct (Diamond, 2005). This overlap can be demonstrated at the most basic level in terms of similarities between the descriptions of the constructs. For example, one item that assesses inattentive symptoms in the SWAN questionnaire (Swanson et al., 2006) asks how well the child 'remembers daily activities'. Recently, it has been proposed that attention and memory interact (Astle & Scerif, 2011). Evidence has shown that not only does attention affect memory, but also that memory affects attention. For example, in Shimi, Nobre, Astle, and Scerif (2014), cues presented prior to encoding oriented attention to a particular location and improved recall in children, but equally, cues presented post encoding oriented attention to a particular internal representation held within memory and also improved recall. Moreover, when cue-validity was reduced, children no longer oriented attention in line with cues, indicating top-down control over this attentional biasing process. In terms of interactions between memory and attention in situations children are likely to encounter in daily life, observations of attention to tasks have indicated that children are more likely to disengage with tasks that exceed their short term memory capacity or that place greater demands on the central executive (Kofler, Rapport, Bolden, Sarver, & Raiker, 2009).

Chapter 3 analyses found that verbal working memory, although associated with inattention, did not account for unique variance in inattention when other cognitive predictors were modelled. Conversely visuo-spatial working memory significantly predicted inattention after controlling for other factors. This is in line with previous findings that visuo-spatial working memory has a stronger relationship with inattention and is impaired in ADHD (e.g. Castellanos & Tannock, 2002), and is in line with similar findings implicating visuo-spatial working memory over verbal working memory in inattention in preterm children (de Kieviet et al., 2012). The reason for this is not yet fully understood, but the absence of any association between inattention and poor visuo-spatial processing at a more basic level rules out suggestions that general visuo-spatial difficulties could account for greater difficulty with visuo-spatial rather than verbal working memory. One explanation is that visuo-spatial working memory tasks may simply be more demanding and/or less automatic as the modality is used less often for memory in daily life than the verbal domain (Martinussen et al., 2005). Alternative explanations refer to neuroimaging evidence that visuo-spatial working memory and attention processes use overlapping neural networks (Awh & Jonides, 2001). Studies have indicated that visuo-spatial memory tasks predominantly activate fronto-parietal networks in the right hemisphere (Astle et al., 2014; Smith, Jonides, & Koeppe, 1996); regions that have also been implicated in ADHD (for a review, see Giedd, Blumenthal, Molloy, & Castellanos, 2001), while verbal working memory tasks are left lateralised (Smith et al., 1996). It is not yet clear whether preterm children demonstrate lateralised neural disruption that could fit the ‘right-hemisphere’ explanation. One study has reported that in preterm infants scanned at term-equivalent age, right-hemisphere white-matter volumes in the parieto-occipital brain regions were reduced compared to those of term-born infants (Peterson et al., 2003). However, more research is needed in this area to confirm whether disrupted right-hemisphere circuitry may be responsible for working memory and inattention difficulties in preterm children.

Despite associations with inattention in very preterm children, variation in interference control did not account for unique variance in inattention. Few studies have investigated interference control, or the related skill inhibitory control, with relation to inattention in preterm children. Those that have report mixed results, with some studies finding evidence to support the notion that inhibitory processing is important for inattention in preterm children (Aarnoudse-Moens et al., 2012; Scott et al., 2012), while others have found it to be unrelated (Mulder et al., 2011b; Shum et al., 2008). It is interesting that no such relationship was observed in term-born children despite a wealth of evidence implicating inhibitory control in ADHD generally, and specifically as underpinning inattention (Chhabildas et al., 2001). Given that the results in Chapter 3 indicated interference control was not a significant predictor when other cognitive predictors were modelled, the association between interference control and inattention in children born preterm may be accounted for by variation shared across some different types of executive-level processing (including working memory), rather than linked to inattention directly. The presence of the association only in preterm children may be indicative of more widespread difficulties observed in children born very preterm compared to term-born peers, even those with similar levels of inattentive behaviour. This perspective may be further supported by the finding that children born very preterm had marginally poorer interference control, although the between-group comparison did not reach significance (p=0.085).

6.3.1.3 Sustained attention

In Chapter 4, indices of sustained attention derived from a cued-CPT task were also identified as correlates of inattention; specifically more severe parent-rated inattention was associated with a lower hit rate, a greater number of commission errors and greater response time variability. Although these relationships were stronger in the term-born children than the children born very preterm, the correlations did not differ significantly between the two groups. However, only response time variability emerged as contributing marginally significant unique variance in inattention, and the model including only these behavioural measures along with age and group explained only 18.1% of the variance.

Response time variability is considered a relatively stable marker of ADHD (Castellanos & Tannock, 2002; Hervey et al., 2006; Leth-Steensen, King Elbaz, & Douglas, 2000; Vaurio, Simmonds, & Mostofsky, 2009), with evidence showing that greater variability correlates with more severe inattention ratings in clinical and non-clinical populations (Gómez-Guerrero et al., 2010). Although it has been linked most consistently with inattentive symptoms in the literature, studies examining which symptom domain it relates to most strongly suggest that it is a non-specific marker, related to both inattention and hyperactivity/impulsivity (Tamm et al., 2012). In spite of its relation to inattention, it has been largely overlooked in the investigation of preterm samples. This is notable given the conclusion in studies of children with ADHD that response time variability is likely to be responsible for apparent slow average response times (Klein, Wendling, Huettner, Ruder, & Peper, 2006), and the proposed importance of processing speed in inattention in preterm children (Mulder et al., 2011a). De Kieviet et al. (2012) is the only study that investigated response time variability in relation to inattention in preterm children. This study implemented an ex-Gaussian analysis, which separates the data into its estimated Gaussian (normally distributed) component, and the exponential (skewed) component. This produces 3 measures for each subject; μ, which represents the mean of the normally distributed part of the data and can be seen as a measure of processing speed, σ, which represents the standard deviation of the normally distributed part of the data and can be seen as a measure of variability, and τ, which represents the mean of the exponential component and can be seen as a measure of lapses in attention. De Kieviet et al. (2012) found that τ, lapses in attention, were predictive of inattentive symptoms, but neither processing speed (μ), nor standard response time variability (σ) were. Given the small number of trials present in the sustained attention task used for the analyses in this thesis (maximum of 40 trials per individual), it was unfortunately not possible to implement ex-Gaussian response time analyses. However, de Kieviet's results suggest that response time variability and/or the proportion of attentional lapses may also be a key marker of inattention in preterm samples, and warrant closer investigation.

6.3.1.4 Cognitive correlates of inattention: Conclusion

In sum, it can be observed from these findings that at the cognitive level, mechanisms underlying inattention in very preterm and term-born children are predominantly overlapping. In particular, memory plays an important role in both groups. Short term memory measures should be incorporated in future studies that investigate the role of working memory, but visuo-spatial working memory is highlighted as an area of particular relevance to inattention. The role of processing speed in inattention appears to be unique to children born very preterm, demonstrating that although some mechanisms are shared, others are distinct. Moreover, the results here call for a deeper analysis of processing speed in children born very preterm to further understand the constraints under which this mechanism predicts adverse behavioural outcomes in preterm samples.

6.3.2 Neural correlates of inattention

Neural correlates of inattention were assessed in Chapters 4 and 5. Analyses in Chapter 4 of the cue-locked negativity ERP and in Chapter 5 of cue-locked frequency changes assessed the neural activity of response preparation, while the other ERPs assessed in Chapter 4 assessed neural activity of target processing. The conclusions and theoretical implications concerning the relation of response preparation and target processing that I am able to draw from these findings are discussed below.

6.3.2.1 Response preparation

Analyses of the cue-locked negativity ERP in Chapter 4 and of cue-locked frequency changes in Chapter 5 assessed the neural mechanisms thought to be responsible for response preparation. In both chapters, results implicated variation in the ability to co-ordinate responses as key to variation in CPT-AX task performance and/or inattention in children born very preterm. Specifically, smaller amplitudes of early cue-locked negativity were associated with multiple measures of poorer task performance (lower hit rate, greater response time variability and greater number of commission errors), and smaller cue-induced frontal-theta increases were associated with both a lower hit rate and more severe parent-rated inattention. These findings were restricted to children born very preterm, with term born children showing only an association between smaller amplitude cue-locked negativity (early and late) and slower response times. Findings in Chapter 5 concerning the association between theta-alpha cross-frequency coupling and response times were unexpected and require replication before confident conclusions can be drawn. Moreover, this index of cross-brain connectivity was not associated with parent-rated inattention, and as such these findings will not be discussed further.

Regarding parent-rated inattention specifically, it was apparent that greater symptom severity was only associated with smaller theta increases in children born very preterm, but not to any index of response preparation in term-born children. Frontal theta is considered to be a mechanism for top-down control (Cavanagh & Frank, 2014), thus smaller increases in frontal-theta following cue-presentation are thought to represent poorer instigation of top-down control. Stimulus-induced frontal-theta increases have previously been linked to ADHD symptom severity and response time variability and also to the genetic and phenotypic expression of ADHD (McLoughlin et al., 2014). The absence of this relationship in term-born children is at odds with the limited prior literature at hand and it is unclear whether this result was anomalous or indicative of differences in the mechanisms underlying inattention. Future replication with larger samples is required to further elucidate the presence of any differences in theta modulation between inattentive children born very preterm or at term.

While cue presentation oriented attention, participants were only required to respond on 50% of subsequent trials. The low predictive validity of the cue (50%) appeared to create a lot of trial to trial variability in terms of neural activity elicited by the cue, and this may have dampened out effects related to response preparation. Although cued-CPTs have been used to assess response preparation previously (e.g. Jonkman, 2006; Banaschewski et al., 2008; Banaschewski et al., 2003), it is likely that use of a paradigm with increased cue validity may allow for improved assessment of the neural mechanisms underlying response preparation. As such I cannot be confident that the absence of associations in my studies is meaningful. One possibility is that fewer associations are observed in term-born children due to poor predictive validity of the cue, but that the children born very preterm did not assess cue validity, or did not alter their cue processing as a result. Given the presence of associations between indices of response preparation and inattention in children born very preterm, this may be an avenue of research that is deserving of future investigation with a greater focus on only response preparation. Moreover, assessment of the use of cues with changing levels of cue-validity in children born very preterm may be of value.

6.3.2.2 Target processing

Evaluation of ERPs elicited by the presentation of cued and uncued targets revealed that the amplitude of the uncued target P2 was a predictor of inattention that was shared between term-born and preterm children. Conversely, the latency of both cued and uncued target P2s was only associated with inattention in term-born children and did not account for unique variance in explaining inattention when modelled with other behavioural and neural measures derived from the CPT-AX task.

The P2 is thought to represent the categorisation of stimuli, and the association between smaller P2 amplitude and more severe parent-rated inattention is in line with previous literature that reports smaller P2 amplitudes in children with ADHD/I than in age-matched controls (Brown et al., 2005; Johnstone et al., 2007). It is of interest that this association was only present in response to uncued targets, and suggests that children who are rated as having better than average attention allocate more processing resources during the categorisation of potentially task-relevant stimuli, even in the absence of a cue for orientation purposes. It is likely that these children are able to internally maintain attention throughout the task, and thus allocate more resources to the processing of uncued targets, while children with more severe inattention may not notice the presentation of uncued targets without the external aid of the cue to orient their attention. In contrast, the presentation of the cue stimulus may alert inattentive children to the relevance of the subsequent stimulus and thus allow for the allocation of similar levels of resources as attentive children during the categorisation of cued targets. The fact that P2 amplitude to uncued targets accounted for additional variance in inattention beyond that explained by the behavioural measures of the CPT-AX task alone is an example of the potential for examination of the neural underpinnings of inattention to help us to understand more about its aetiology.

The association between shorter P2 latencies and more severe parent rated inattention appears to be at odds with my hypotheses, as well as the direction of the difference in the comparison between cued and uncued targets (shorter latencies for cued targets than uncued). It was expected that longer latencies would be indicative of poorer attention, and this perspective was supported by the finding of longer latencies in response to uncued targets, than to cued targets. However, whilst this was true, it was also clear that term-born children with more severe inattention demonstrated overall shorter P2 latencies. This suggests that they may have categorised target stimuli faster overall, but these increases were not accompanied by better task performance; moreover a marginally significant association indicated that shorter P2 latencies in term-born children were associated with greater response time variability (poorer performance). This is in line with findings from Sunohara et al., (1999), who reported that unmedicated children with ADHD demonstrated shorter P2 latencies, which were normalised with the administration of stimulant medication.

6.3.2.3 Neural correlates of inattention: Conclusion

As with the exploration of cognitive mechanisms, the neural mechanisms underlying inattention in term-born and very preterm children are partially overlapping, but partially distinct. In both groups, inattentive children allocated fewer resources during stimulus categorisation to uncued targets than attentive children, as reflected by smaller P2 amplitudes. Variance in processing of cued targets was not associated with parent-rated inattention in very preterm children, suggesting orienting processes were unimpaired. In contrast, allocation of resources on uncued target trials did vary with inattention across both groups, indicating poor sustained attention on the CPT-AX task was related to parent-rated inattention.

Other associations observed were different in the two groups. There was more evidence of the functional relevance of impaired response preparation for sustained attention in very preterm children than of impaired target processing. In particular, smaller theta increases, indicative of less top-down control, were related to inattention and CPT-AX task-performance, and may provide a useful neural marker for inattention which warrants further investigation in preterm populations. Conversely, in term-born children, variation in preparatory processing did not appear to drive inattentive behaviour. Instead, shorter P2 latencies during target processing, indicative of more rapid stimulus categorisation, were associated with more severe parent-rated inattention. Interestingly, and contrary to expectations, P2 latencies were not associated with better task performance, indicating that although faster, the speed may have been sub-optimal.

It is particularly interesting that although both groups performed equally well on the CPT-AX task, and behavioural correlates did not differ between groups, differences in neural correlates of inattention emerged. This highlights the importance of dimensional studies in clinical populations for improving our understanding of how variation in cognitive and neural processing relates to behavioural outcomes. This design provides information that goes beyond identifying elements of processing that differ between term-born and preterm populations, by additionally providing an indication of the relevance of differences to inattentive behaviour. Correlates like these have the potential to be used in the assessment of symptom severity and in early identification of children at risk of developing inattentive symptoms. Practical implications are considered in greater detail in Section 6.4 below.

6.3.3 Do cognitive and neural mechanisms of inattention differ between term and very preterm children?

Overall, these results indicate that at the cognitive level, mechanisms underlying inattention in term-born and very preterm children were predominantly the same (verbal and visuo-spatial short term memory, visuo-spatial working memory), with the exception of processing speed, which was unique to very preterm children. Conversely, at the neural level, more of the mechanisms underpinning inattention were unique only to one group (cue-theta in children born very preterm; P2 latency to cued and uncued targets in term-born children) than were shared by both groups

(P2 amplitude to uncued targets). As yet the precise causes and practical consequences of such differences remain unclear.

6.4 Practical implications

Practical implications following these analyses primarily concern the identification of risk markers and intervention targets for inattention that can be used by parents, teachers and clinicians. Moreover, although some of the underlying mechanisms of inattention were shared between both term-born and very preterm children (memory and P2 amplitude to uncued targets), others were unique only to term-born children (P2 latency) or only to those born very preterm (motor processing speed and theta modulation). Such differences between these populations should be taken into account when considering practical implications, both in terms of identification of and intervention for those at risk.

6.4.1 **Identification of risk for inattentive behaviour**

Given findings that children born very preterm who have not been identified as requiring special educational needs often show increased inattention (Brogan et al., 2014), increased awareness of the association between inattention and preterm birth could help teachers recognise children who would benefit from intervention. Moreover, identification of the specific mechanisms underlying inattention in school age term-born and very preterm children presents a step closer towards the identification of particular areas of weakness. These areas of weakness may be detectable early in development, during the preschool period. The analyses reported here are cross-sectional, but longitudinal studies have shown that cognitive performance in children born very preterm aged two years can reliably predict cognitive ability throughout childhood and into adulthood (Breeman, Jaekel, Baumann, Bartmann, & Wolke, 2015b). Thus, if weaknesses in particular cognitive domains or neural processes underpin later-emerging inattentive behaviour, early identification of such risk factors may be possible. Identification of children at risk would be beneficial on two counts. First, it may highlight those children who might benefit from intervention. Intervention at an early age may be able to alter the developmental trajectories of those children at risk, and additional support or training may be able to facilitate cognitive development to improve behavioural and academic outcomes, either by directly reducing symptoms, or by providing compensatory support that indirectly reduces the risk of the consequences associated with poor attention. Candidates for intervention will be discussed further below in section 6.4.2. Secondly, identification of those at risk also holds value for future research that may advance our understanding of the full developmental pathway that leads from preterm birth to inattention. Directions for this future research are discussed further in section 6.6.2.

6.4.2 **Candidates for intervention**

Non-pharmacological treatment options for ADHD and inattention are gaining popularity. Cognitive training and neurofeedback have received scientific recognition as two potential intervention strategies for ADHD and are relevant to the results of this thesis. Cognitive training (sometimes referred to as 'brain training') typically targets executive functions such as working memory and inhibitory control, with the aim of improving these skills in order to have positive impacts in daily life. Neurofeedback is a method whereby real-time EEG recordings are used to train individuals to regulate their neural activity, with the similar aim of teaching individuals self-regulation techniques that can be implemented in daily life.

A prime candidate for cognitive training identified by this (and other) research is that of visuo-spatial working memory, given its interaction with attentional processing and inattentive behaviour. This is also an area that has received a considerable amount of scrutiny in recent years. Astle, Barnes, Baker, Colclough, and Woolrich (2015) demonstrated that training verbal and visuo-spatial working memory improved performance on similar but novel tasks. And perhaps more surprisingly, it also resulted in alterations in resting state neural networks that have been associated with working memory performance, with the greatest alterations observed in those children who showed the greatest working memory improvements from pre- to post- test. Although a previous meta-analysis of the effectiveness of verbal and visuo-spatial working memory training concluded that research prior to 2013 had failed to convincingly demonstrate far transfer effects (Melby-Lervåg &

Hulme, 2013), a more recent meta-analysis specifically investigating of the effectiveness of the CogMed working memory training program indicated that improvements in visuo-spatial and verbal working memory were associated with reduced ratings of inattention in daily life (Spencer-Smith & Klingberg, 2015). Similarly, working memory training has been shown to be effective in improving general cognitive functions across a range of domains in pre-school children born very low birth weight (Grunewaldt, Løhaugen, Austeng, Brubakk, & Skranes, 2013). On the basis of the developmental trajectories of the networks involved and the current research evidence, it has been proposed that application of working memory training programs to younger children is likely to result in more widespread transfer effects than can be observed when children reach school age and beyond (Wass, Scerif, & Johnson, 2012), further supporting the notion of early identification of risk and intervention. As such, building evidence suggests that visuo-spatial working memory training may be beneficial in reducing inattention, and more research needs to be conducted to demonstrate the most effective way to implement such interventions.

Slow cortical potentials (such as the CNV) and theta modulation are two of the most common candidates for neurofeedback training within current ADHD treatment (Arns, Ridder, Strehl, Breteler, & Coenen, 2009). These are also two of the neural mechanisms that were associated with sustained attention task performance, and in the case of theta modulation, with parent-rated inattention, particularly in children born very preterm. A meta-analysis reported that neurofeedback is effective for the treatment of inattention from investigation of aggregated evidence (Arns et al., 2009), however, a more recent review demonstrated that such findings are less convincing in studies where symptom-raters are blind to the intervention (Holtmann, Sonuga-Barke, Cortese, & Brandeis, 2014). Thus, while the efficacy of neurofeedback remains inconclusive, it presents as another alternative to medication-based interventions that is worthy of further exploration.

6.5 Strengths, challenges and limitations

The analyses reported here benefit from; (i) a term-born comparison group with a similar range of level of inattention to the very preterm group, ii) a very preterm sample representative of the population from which it was drawn in terms of birth weight, gestational age and gender, (iii) inclusion of basic cognitive processing measures in analyses assessing the influence of executive functioning, (iv) moderately large samples, (v) EEG measures to allow direct examination of neural activity and (vi) a dimensional approach. However, the project was also restricted in a number of ways, and I faced several challenges in the collection of data, particularly in the recruitment and testing phases of the study.

6.5.1 **Recruitment challenges**

NHS research ethics committee approval was required in order to identify eligible children born very preterm. Due to the comprehensive nature of the aggregation of all required documents for the NHS ethical approval applications and the length of the decision process, the start of the project was slightly delayed thus it was not possible to test the number of children initially proposed (80 per group). Recruitment of children born very preterm required identification of eligible births from hospital records, and the tracing of their residential address aged 8-10 years, all of which was time consuming, and it is possible that the addresses available were not all accurate meaning that some parents may not have received the recruitment pack. Testing required a 3-hour visit to the department and EEG recording. Such a commitment may not have been possible or appealing for all families, and this may explain why the children born very preterm that were tested were of significantly higher socio-economic status (SES) than the families of eligible births who did not complete testing. Additional recruitment challenges stemmed from attempts to recruit term-born children with an appropriate spread of inattention. In order to achieve this, it was necessary to screen a large number of term-born children for levels of parent-rated inattention prior to selection for testing. The departmental volunteer database from which families are often recruited is a skewed sample predominantly comprising children with above-average SES and attention. Accordingly, recruitment was supplemented by targeting families from wider socio-economic backgrounds.

This was achieved by advertising through schools and community centres in lower income areas, publishing a press release and participating in an interview on BBC Radio Nottingham.

In spite of the recruitment challenges, we gained consent from the parents of a total of 218[4] children. However, further challenges were experienced for the scheduling of testing sessions. Due to the length of testing sessions (3 hours per child), testing had to be restricted to school holidays to prevent interference with the child's education. This presented scheduling difficulties, and while every effort was made to ensure any available time-slot was filled, it was not possible to test all children for whom we had consent during the period of my PhD degree. Moreover, it was evident that the very preterm sample were representative of the cohort from which they were drawn on most key variables, namely; birth weight, gestational age and gender.

6.5.2 **Testing challenges**

A total of 113 children completed the testing visit, where further challenges were apparent. Where parents arrived late, it was not possible for the child to complete all study tasks as there were only short breaks between participants. Furthermore, although every effort was made to design the study session in a way to maintain engagement for children with the tasks, tiredness or boredom also resulted in some children not completing all study tasks. This was of particular concern considering the level of inattention in some of the children. However, missing cognitive data was found to be missing completely at random and there was no association between the level of inattention and failure to complete the cognitive tasks. There were also differences across children in their tolerance of the EEG procedure, which contributed to the decreased sample sizes of children who completed the EEG testing compared to those who completed behavioural testing. Although not painful, the set up of the EEG recording equipment can be uncomfortable and may elicit

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[4] This total includes term-born children who were not selected for invitation to the neurocognitive testing session, but whose parents' had completed the screening questionnaire.

anxiety, and the wellbeing of the children being tested was the key priority. Given the association between preterm birth and hypersensitivity (Buskila et al., 2003) and anxiety (Burnett et al., 2011) it is unsurprising that some children were not willing to complete the EEG testing. Indeed, it was observed that those who completed the EEG testing were of higher IQ and higher gestational age, which is likely to reflect fewer neurobehavioural problems. That said, samples of 40 children or more per group were large in comparison to other clinical EEG studies cited (Mazaheri et al., 2010; Potgieter et al., 2003), however replication of the results with larger samples is recommended. During testing, other challenges included attempts to minimise the impact of distracting noise from siblings in the waiting room next door, and from noise from building work that unfortunately coincided with one of the school summer holidays. Steps taken included discussions with workmen and families to encourage them to minimise any unnecessary noise, and ensuring children were wearing headphones for any task with audio elements.

6.5.3 **Study limitations**

This study was limited by a number of factors, many of which resulted from the challenges given above. To begin with, the sample was not as large as had been initially intended due to scheduling constraints. Given that some associations present across groups no longer met significance when term-born and very preterm groups were assessed individually, presumably due to a loss of power, this study may have benefitted from larger sample sizes to be confident that all effects were successfully detected and appropriately represented. Secondly, although the measures chosen to assess inattentive behaviour were carefully considered, with the use of the SWAN to capture both above and below average levels of attention, and the use of the Conners to provide a more clinically validated evaluation of the ADHD symptoms present in the sample, only parent-report measures were collected. Studies have shown that associations between cognition and inattention can differ between parent and teacher ratings (e.g. Mulder et al. 2011b; Aarnoudse-Moens 2012), however collection of teacher ratings was considered to be beyond the scope of the study within the given timeframe. Thirdly, the samples assessed were recruited through the community and primarily consisted of children with no diagnosis of ADHD. This recruitment method was intentional, particularly given evidence of increased inattention even in subclinical children born very preterm (Johnson & Marlow, 2011) and the decreased likelihood of referral to clinics for diagnosis in cases of ADHD/I (Willcutt et al., 2012). However, it assumes that clinical presentations of ADHD are extreme cases of behaviours that are apparent in varying levels across the general population and cannot directly provide evidence for clinically significant inattention.

While very preterm and term-born groups were well matched for most characteristics, and crucially, on inattention, the term-born children were younger and had higher IQ than the children born very preterm. The difference in age may be an artefact resulting from the selection of a term-born group of children with lower attention. Accordingly, all analyses were adjusted for age. The discrepancy in IQ was expected and is in line with the previous literature (Bhutta et al., 2002). It was not considered appropriate to adjust for IQ due to the overlap in the measurement of IQ and measurement of cognitive processes key to this study, thus adjustment for IQ would remove variance of interest (Taylor, 2006). However, the topic of whether it is appropriate and important to incorporate IQ into analyses of neurocognitive functioning is controversial, and it was recognised that investigation of the role of IQ may provide additional insight that could alter theoretical and practical implications of these finding. Similarly, although groups did not differ significantly on SES, it has previously been cited as a key mechanism underlying ADHD and may play a role in the aetiology of inattention. As such, I have included in Appendix 3 an exploration and discussion of the role of IQ and SES in the analyses examined across this thesis.

To summarise the findings outlined in Appendix 3, it was found that lower IQ, but not SES, was associated with more severe parent-rated inattention in both very preterm and term-born children. Moreover, although inclusion of SES in reanalyses did not alter results substantially, inclusion of IQ altered the pattern of findings relative to those reported in chapters throughout the thesis. The reanalyses indicated that, as expected, the IQ composite score shared variance with many of the more specific cognitive processes, masking relationships of interest between specific cognitive processes and inattention. Perhaps more importantly, these reanalyses also revealed that both visuo-spatial working memory and P2 peak amplitude to uncued targets predicted inattention independently from IQ. This further reinforces the strength of the evidence that visuo-spatial working memory is an important marker of inattention, and indicates that use of electrophysiological techniques may provide biomarkers that capture aspects of inattention missed in cognitive tests. IQ explained more variance than most other measures included in this thesis. In terms of practical implications, this indicates that IQ tests could be a more beneficial screening tool in the early identification of those at risk, particularly in children born very preterm, for whom IQ measured at two years of age remains stable and can reliably predict IQ at adulthood (Breeman et al., 2015). Moreover, these analyses demonstrate how even in situations where there is shared variance between cognitive processes of interest and IQ, analyses that assess the patterns of results with and without IQ incorporated can provide a deeper insight into the theoretical and practical implications of the study, and thus IQ should be considered as an important part of future examinations of neuropsychological mechanisms. See Appendix 3 for full details of analyses and a discussion of the implications.

The findings throughout the thesis may be limited somewhat due to the problem of multiple comparisons. As always with a large number of comparisons, the risk of type one errors is increased. However, many of the findings were consistent with existing literature and as such they can be interpreted with some level of confidence, but replication of findings would be advised where there is less supporting prior literature. In particular, given the conflicting findings with respect to processing speed and the variability of the measures that have been used across different studies, a more detailed analysis of its role in preterm inattention would be useful.

6.6 Future research

Perhaps one of the most important avenues for future research generated by the analyses reported in this thesis is the assessment of the construct validity of 'processing speed' and a closer investigation of its role in inattention in preterm children. In order to do this, it would be important to understand the relationships between the different methods of measuring processing speed. The speed of information processing may vary within an individual on the basis of stimulus modality (audio, tactile, visual), stimulus complexity, and presentation method (predictability, brief presentation, presentation of several stimuli at once). Moreover, its measurement may be affected by the response required, from the verbal description of shapes on a page, or the motor response of a button-press when measuring response time, to the speed of saccades using eye-tracking, and the latency of ERPs using EEG. At its most simple, perceptual processing speed could be measured by investigating the latency of ERPs elicited by the mere presentation of sensory stimuli in the absence of task demands, and compared across visual, audio and tactile domains. Further assessment of more complex measures of processing speed including saccadic measures, psycho-motor measures and decision speed would allow the evaluation of how basic perceptual and more complex measures of processing speed across a variety of domains might be related to one another. It is recommended that a multi-method approach may provide the best evidence for us to understand whether processing speed can be considered a domain-general construct, or whether there are differences within individuals in the speed particular aspects of processing. In the case of the latter option, it would be important to then establish which aspect of processing is of the most relevance to inattention. It would also be important to recognise the potential importance in the variability of processing speed across trials in different measures, given the importance of reaction-time based measures of response variability in inattention as reported in Chapter 4. Such analyses may be further enhanced with the use of ex-Gaussian response time analyses that allow for the separation of infrequent lapses in attention from 'normal' response times and response time variability, such as those employed by de Kieviet et al. (2012).

Analyses in Chapters 4 and 5 indicated that neural mechanisms underlying response preparation may present an opportunity to assess an alternate part of attentional processing. Further assessment of response preparation using a paradigm with higher predictive validity may help to elucidate the role of these mechanisms in inattention further, and assessment of the role of predictive validity in cue orientation in preterm samples may shed additional light on the findings reported in this thesis. Moreover, the promising evidence implicating cue-related theta changes and target-P2 characteristics in inattention indicates that more detailed investigation of these neural mechanisms may establish whether such measures could be useful biomarkers.

Although the analyses of a cross-frequency coupling correlate of inattention conducted in Chapter 5 were inconclusive due to an inability to establish the hypothesised coupling even in attentive term children, this is a promising avenue for further research. There is building evidence of impaired connectivity in both school-aged children born very preterm (Gozzo et al., 2009), and in children with ADHD (Konrad & Eickhoff, 2010), and new methodology to assess functional connectivity using frequency analysis is continually developing. In particular, assessment of possible disruptions to right-lateralised connectivity may further elucidate the neural basis for inattention in preterm children. As discussed previously, a right-lateralised fronto-parietal network has been associated with visuo-spatial memory (Astle et al., 2014; Smith et al., 1996), a predictor of inattention, and also directly with ADHD (Giedd et al., 2001). A study in typically developing children revealed that variation in theta modulation in this right fronto-parietal network was associated with trial-by-trial variation in memory performance (Astle et al., 2014). As such, exploitation of the wide array of methods to assess functional connectivity may prove valuable, with the caveat that the technique and paradigm used to assess inattentive samples should first show consistency in typical samples.

As acknowledged in the limitations above, term children recruited in the PATCH study were not recruited from clinical samples and neither term nor preterm children were assessed by trained clinicians for ADHD diagnosis, thus we cannot be certain that the patterns observed would apply to clinical cases of ADHD. One avenue for future research would be to assess the influence of the correlates of inattention observed here in samples of term and preterm children with clinically diagnosed ADHD.

Dimensional approaches using correlational analysis such as that implemented here are particularly viable for understanding relationships in groups displaying heterogeneity (Gabrieli et al., 2015). This makes them appropriate for assessment of outcomes following preterm birth, and for the assessment of children with ADHD, both heterogeneous populations. Such approaches can also be considered as more appropriate for studying preterm populations, in which the population shift in symptomatology means that many children have sub-threshold behavioural problems that may still impact on daily life. Associations are a first step towards finding cognitive and neural markers of inattention that might allow for the prediction of clinical and educational outcomes, as well as treatment responses (Gabrieli et al., 2015), however more research is necessary to link the correlates of inattention observed here to other outcomes.

Broadly speaking, many of the mechanisms underlying inattention were shared across the two groups, particularly at the cognitive level. The results described in this thesis, however, are only able to give us an indication of similarities and differences in mechanisms underlying inattention at a particular point in development (8-11 years of age). It remains unclear whether the developmental trajectories triggered by preterm birth that lead to these shared mechanisms are similar to those triggered in term children, or whether similarities observed at age 8-11 years have been reached via distinct pathways. In order to fully understand the similarities and differences in the causal pathways to inattention and ADHD in preterm and term-born children, more comprehensive studies are required. A prospective longitudinal study comparing the cognitive, neural and behavioural development of children born preterm to term-born children at high risk for ADHD (e.g. family member with ADHD) from birth, would allow for the comparison of the developmental trajectories that lead to ADHD symptoms in the two populations. In addition, assessment of perinatal characteristics (e.g. duration of respiratory support, brain abnormalities) associated with later development of inattention in preterm children may allow us to predict which children have the highest risk for developing inattentive behaviour from an early stage.

6.7 General conclusions

This thesis aimed to determine whether the cognitive and neural mechanisms underlying inattention are different in term-born and very preterm children, by comparing a group of 8-11 year olds born very preterm to term-born peers matched on the ranges of their levels of inattention. The strongest findings are commensurate with previous findings implicating poor visuo-spatial working memory as a shared mechanism underlying inattention in both term-born and very preterm populations, and slow processing speed as a mechanism underlying inattention only in children born very preterm. The results also go beyond the existing literature by demonstrating that both verbal and visuo-spatial short term memory are unique predictors of inattention in term-born and very preterm children. Moreover, they present ERP and spectral analyses that have not been previously examined in relation to inattention in preterm samples.

Although the findings did not present a coherent perspective for the role of processing speed due to the failure to find similar associations between behavioural and ERP indices of processing speed and inattention, they do suggest that some element of processing speed is particularly important in children born very preterm. It is important to further study the role of processing speed and to establish the context under which processing speed can be considered a mechanism underlying inattention.

Findings concerning neural mechanisms of inattention were less consistent with hypotheses, but suggested that there may be some differences in the mechanisms that are important for inattention in term-born and preterm children. In particular, characteristics of P2 and theta modulation were highlighted as candidate biomarkers for inattention. Converging evidence from a wider range of electrophysiological research into inattention in preterm children is required to improve our understanding of these mechanisms and the causes and consequences of differences between term-born and very preterm children.

In sum, this thesis indicates that inattention in term-born and very preterm children is underpinned by partially overlapping mechanisms, both at the cognitive and neural levels. The findings discussed here; (i) highlight the need for further research into the role of processing speed in inattention in preterm children, (ii) emphasise the potential benefit of further electrophysiological research into neural mechanisms of inattention, and (iii) strengthen the literature implicating visuo-spatial working memory as a shared mechanism in both term-born and very preterm children.

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Appendix 1: Timeline of PhD

The first year of my PhD (see Figure 1 below) predominantly consisted of study design based on a thorough examination of the literature, and the application for NHS Research Ethics Committee (REC) and Research and Development (R&D) approval. This included the development of all study advertising and recruitment materials (letters to schools, flyers, posters, website, press release, letters to parents of traced children born very preterm, information leaflets for parents and children). Tasks were programmed while awaiting NHS REC and R&D approval. Following approval in July 2013, recruitment of term-born children began. Testing of term-born children was conducted during the 2013 school summer holiday. Identification and tracing of eligible children born very preterm began din the same period. Alongside research work, I was required to complete 60 credits of advanced ESRC training modules between October 2012 and June 2013.

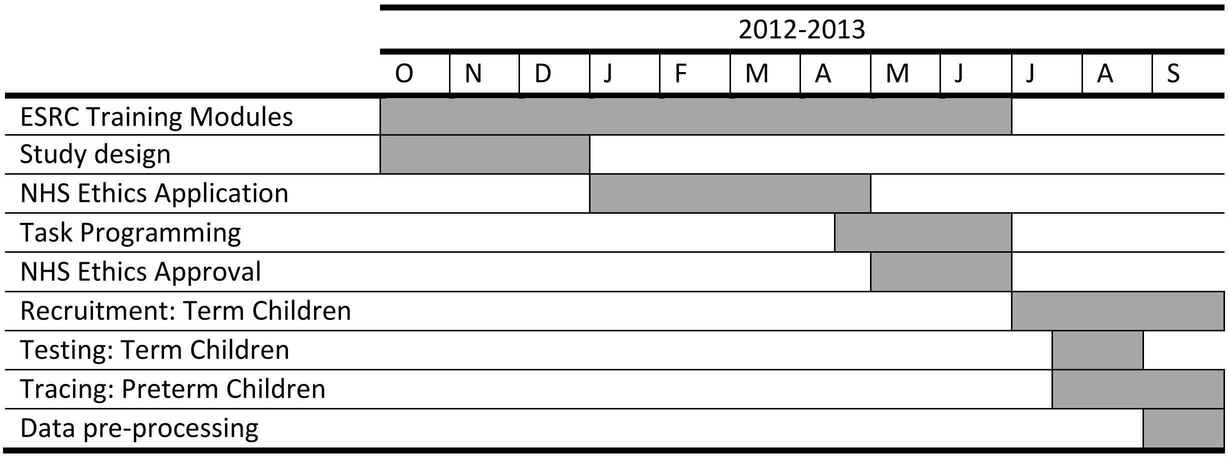

Figure 1. Gantt chart detailing the timeline of Year 1 activities from October 2012-September 2013.

During the second year of my PhD, I collected the bulk of my data and conducted some preliminary analyses (see Figure 2 below). Testing of term children continued in subsequent school holidays (October 2013, February 2014, Easter 2014, Summer 2014). Recruitment of children born very preterm began in Autumn 2013, and testing was conducted in the subsequent school holidays (February 2014, Easter 2014, Summer 2014, October 2014). Data pre-processing and recruitment and scheduling of participants for testing was ongoing between testing blocks. Preliminary data analysis was conducted for dissemination at internal and external conferences.

Appendix 1: Timeline of PhD

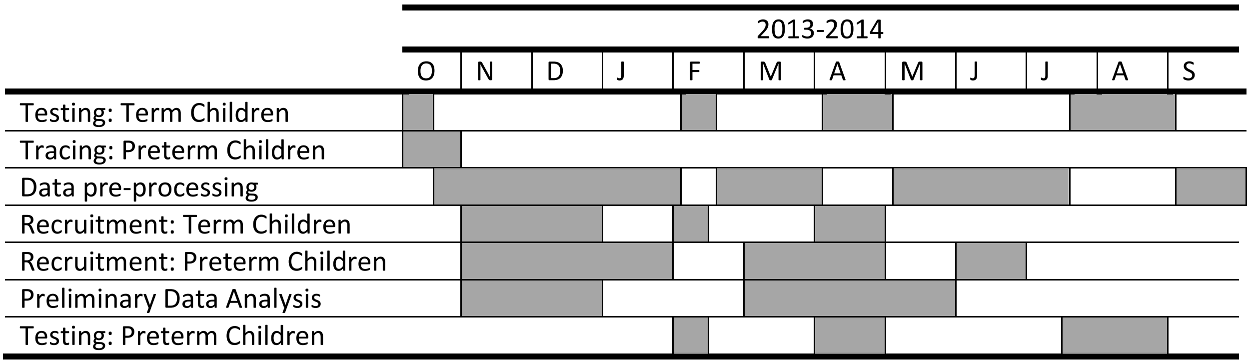

Figure 2. Gantt chart detailing the timeline of Year 2 activities from October 2013-September 2014.

My final year was spent preparing, analysing and interpreting the data (see Figure 3 below). The final period of testing was conducted in October 2014. After an initial period of final data entry and pre-processing, analyses for the experimental chapters were conducted in sequence. The general introduction was drafted prior to data analysis, and chapter drafts were written following each analysis. Analyses were completed in August 2015 and thesis chapters were refined.

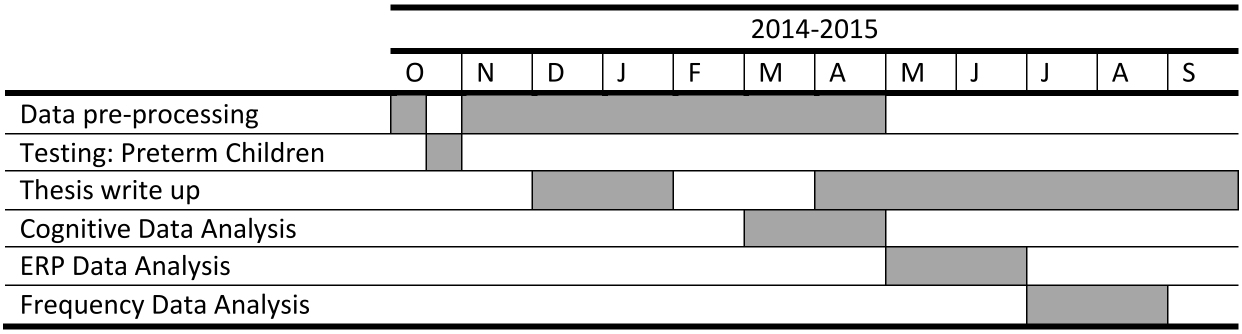

Figure 3. Gantt chart detailing the timeline of Year 3 activities from October 2014-September 2015.

Appendix 2: Full Correlation Matrices

i. Correlation matrices from Chapter 3

Below in Table 1 are the full correlation matrices expressing the overall partial correlations between inattention and task-performance measures, controlling for age, as described in Chapter 3. Those for split-group analyses are displayed in Table 2.

Table 1. Correlation matrix between inattention and task-performance measures controlling for age for both groups combined.

	IA	VS-P	MPS	VS-STM	VS-WM	V-STM	V-WM	LS	GS	IC
IA										
VS-P	-.130									
MPS	.160	.084								
VS-STM	-.332***	.200*	-.061							
VS-WM	-.400***	.218*	-.221*	.325***						
V-STM	-.370***	.173	-.028	.261**	.323***					
V-WM	-.256**	.166	-.041	.124*	.257**	.613***				
LS	.148	.116	-.051	-.060	-.109	-.094	-.207*			
GS	.091	.100	.082	-.050	-.018	-.060	.002	.411***		
IC	.186*	-.257**	-.017	-.092	-.085	-.154	-.114	-.047	.029	

Note: *p<0.05, **p<0.01, ***p<0.001. IA= parent-rated inattention; VS-P = visuo-spatial processing; MPS = motor processing speed; VS-STM = visuo-spatial short term memory; VS-WM = visuo-spatial working memory; V-STM = verbal short term memory; V-WM = verbal working memory; LS = local switching; GS = global switching; IC = interference control.

Table 2. Correlation matrix between inattention and task-performance measures controlling for age split by group

		Very Preterm									
		IA	VS-P	MPS	VS-STM	VS-WM	V-STM	V-WM	LS	GS	IC
Term-born	IA		-.108	.462***	-.225	-.478***	-.321**	-.227	.145	.120	.242*
	VS-P	-.097		.050	.256*	.214	.200	.134	.109	.050	-.237
	MPS	-.003	.006		-.124	-.277*	-.224	-.210	-.002	.109	.064
	VS-STM	-.366*	.068	-.167		.281*	.265*	.099	.064	.051	-.147
	VS-WM	-.272	.202	-.173	.346*		.431***	.281*	-.072	-.017	-.071
	V-STM	-.369*	.065	.070	.165	.091		578***	-.070	-.114	-.173
	V-WM	-.208	.118	-.007	.236	.130	.599***		-.217	.015	-.065
	LS	.140	.192	-.127	-.234	-.161	-.102	-.158		.418***	-.034
	GS	.070	.191	-.008	-.264	-.008	.023	-.067	.403**		-.022
	IC	.041	-.231	-.015	.087	-.025	-.023	-.069	-.145	.200	

Note: Very preterm data above the diagonal, and term-born data below. *p<0.05, **p<0.01, ***p<0.001. IA= parent-rated inattention; VS-P = visuo-spatial processing; MPS = motor processing speed; VS-STM = visuo-spatial short term memory; VS-WM = visuo-spatial working memory; V-STM = verbal short term memory; V-WM = verbal working memory; LS = local switching; GS = global switching; IC = interference control

ii. Correlation matrices from Chapter 4

i) Behavioural correlations

Below in Table are the full correlation matrices expressing the overall partial correlations between inattention and task-performance measures, controlling for age, as described in Chapter 4. Those for split-group analyses are displayed in Table 3.

Table 3. Correlation matrix between inattention and behavioural task-performance measures across both groups while controlling for age.

	IA	H	CE	RT	RV
Inattention (IA)					
Hits (H)	-.297*				
Commission errors (CE)	.212*	-.622***			
Response time (RT)	.080	-.091	-.120		
Response variability (RV)	.303**	-.398***	.228*	.295**	

Note: **p*<0.05, ***p*<0.01, ****p*<0.001.

Table 4. Correlation matrix between inattention and behavioural task-performance measures split by group while controlling for age.

		Very Preterm				
		IA	H	CE	RT	RV
Term Born	Inattention (IA)		-.302*	.137	.056	.201
	Hits (H)	-.308*		-.461**	-.201	-.372*
	Commission errors (CE)	.281	-.756***		.025	.239
	Response time (RT)	.155	-.041	-.219		.191
	Response variability (RV)	.397*	-.436**	.219	.413**	

Note: Associations for very preterm children are shown above the diagonal, and for term-born, below. **p*<0.05, ***p*<0.01, ****p*<0.001 .

ii) Cue-locked negativity correlations

Below in Table 5 are the full correlation matrices expressing the overall partial correlations between cue-locked negativity and task-performance measures, controlling for age, as described in Chapter 4. Those for split-group analyses are displayed in Table 6.

Table 5. Correlation matrix between mean amplitude of the negative-going component and behavioural task-performance measures across both groups while controlling for age.

	MA-E	MA-L	H	CE	RT	RV
Mean amplitude – early window (MA-E)						
Mean amplitude – late window (MA-L)	.236*					
Hits (H)	-.286**	-.131				
Commission errors (CE)	.109	.060	-.616***			
Response time (RT)	.236*	.318**	-.090	.121		
Response variability (RV)	381***	.101	-.383***	-.215*	.299**	

Note: As it is a negative-going component, smaller numbers represent larger magnitude amplitudes., **p*<0.05, ** *p*<0.01, *** *p*<0.001.

Table 6. Correlation matrix between mean amplitude of the negative-going component and behavioural task-performance measures split by group while controlling for age.

		Very Preterm					
		MA-E	MA-L	H	CE	RT	RV
Term Born	Mean amplitude – early window (MA-E)		-.018	-.424**	.294§	.190	.498***
	Mean amplitude – late window (MA-L)	.466**		.040	-.005	.168	.105
	Hits (H)	-.149	-.210		-.461**	-.201	-.372*
	Commission errors (CE)	-.107	.108	-.744***		.025	.239
	Response time (RT)	.343*	.392*	-.034	-.226		.191
	Response variability (RV)	.189	.106	-.400*	.190	420**	

Note: As it is a negative-going component, smaller numbers represent larger magnitude amplitudes. §*p*<0.07, **p*<0.05, ** *p*<0.01, *** *p*<0.001. Correlations for very preterm children are presented above the diagonal, for term-born, below.

iii) P1 correlations

Below in Table 7 are the full correlation matrices expressing the overall partial correlations between P1 characteristics and inattention, controlling for age, as described in Chapter 4. Those for split-group analyses are displayed in Table 8.

Table 7. Correlation matrix between inattention and P1 peak measurements across groups while controlling for age.

	IA	P-AT	L-CT	L-UT
Inattention (IA)				
Peak amplitude for All Targets (P-AT)	-.134			
Latency for Cued Targets (L-CT)	-.179	.283*		
Latency for Uncued Targets (L-UT)	-.174	.151	.631***	

Note: *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Table 8. Correlation matrix between inattention and P1 peak measurements while controlling for age.

		Very Preterm			
		IA	P-AT	L-CT	L-UT
Term Born	Inattention (IA)		-.070	-.272	-.205
	Peak amplitude for Cued Targets (P-AT)	-.164		.433**	.081
	Latency for Cued Targets (L-CT)	-.063	.081		.569***
	Latency for Uncued Targets (L-UT)	-.160	.246	.724***	

Very preterm are shown above the diagonal, term-born, below. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

iv) P2 correlations

Below in Table 9 are the full correlation matrices expressing the overall partial correlations between P2 characteristics and inattention, controlling for age, as described in Chapter 4. Those for split-group analyses are displayed in Table 10.

Table 9. Correlation matrix between inattention and P2 peak measurements at Cz across groups while controlling for age.

	IA	P-CT	P-UT	L-CT	L-UT
Inattention (IA)					
Peak for Cued Targets (P-CT)	.000				
Peak for Uncued Targets (P-UT)	-.307**	.431***			
Latency for Cued Targets (L-CT)	-.150	.200	.217*		
Latency for Uncued Targets (L-UT)	-.173	-.075	.040	.434***	

Note: *$p<0.05$, **$p<0.01$, ***$p<0.001$.

Table 10. Correlation matrix between inattention and P2 peak measurements at Cz while controlling for age.

		Very Preterm				
		IA	P-CT	P-UT	L-CT	L-UT
Term Born	Inattention (IA)		-.011	-.295	.131	-.007
	Peak amplitude for Cued Targets (P-CT)	.020		.196	.317*	.021
	Peak amplitude for Uncued Targets (P-UT)	-.343*	.557***		.086	-.122
	Latency for Cued Targets (L-CT)	-.459**	.127	.420**		.314*
	Latency for Uncued Targets (L-UT)	-.336*	-.136	.236	.579***	

Note: Very preterm are shown above the diagonal, term-born, below. **p*<0.05, ***p*<0.01, ****p*<0.001.

v) P3 correlations

Below in Table 11 are the full correlation matrices expressing the overall partial correlations between P3 characteristics and inattention, controlling for age, as described in Chapter 4. Those for split-group analyses are displayed in Table 12.

Table 11. Correlation matrix between inattention and P3 peak measurements at Pz across groups while controlling for age.

	IA	P-CT	P-UT	L-CT	L-UT
Inattention (IA)					
Peak for Cued Targets (P-CT)	-.058				
Peak for Uncued Targets (P-UT)	-.042	.537***			
Latency for Cued Targets (L-CT)	.018	.093	-.197		
Latency for Uncued Targets (L-UT)	.064	-.021	-.055	.259*	

Note: **p*<0.05, ***p*<0.01, ****p*<0.001.

Table 12. Correlation matrix between inattention and P3 peak measurements while controlling for age.

		Very Preterm				
		IA	P-CT	P-UT	L-CT	L-UT
Term Born	Inattention (IA)		.094	-.067	.227	.144
	Peak amplitude for Cued Targets (P-CT)	-.285		.537***	.192	-.184
	Peak amplitude for Uncued Targets (P-UT)	-.052	.537***		-.204	-.107
	Latency for Cued Targets (L-CT)	-.184	-.045	-.201		.297
	Latency for Uncued Targets (L-UT)	-.028	.143	-.017	.253	

Very preterm are shown above the diagonal, term-born, below. **p*<0.05, ***p*<0.01, ****p*<0.001.

iii. Correlations from Chapter 5

Below in Table 13 are the full correlation matrices expressing the overall partial correlations between inattention, task-performance measures, and power changes, controlling for age, as described in Chapter 5. Those for split-group analyses are displayed in Table 14.

Table 13. Correlation matrix between inattention, task-performance measures and power measurements while controlling for age

	IA	H	CE	RT	RV	Theta	Alpha	TA (0-500)	TA (DW)
IA									
Hits	-.288**								
CE	.230*	-.623***							
RT	.094	-.090	-.125						
RV	.305**	-.398***	.230*	.297**					
Theta	-.220*	.091	.090	-.151	-.134				
Alpha	-.016	.008	-.071	.016	-.057	.195			
TA (0-500)	.124	-.039	-.055	.041	-.031	-.116	-.166		
TA (DW)	.133	-.014	.037	-.051	.008	-.146	-.200	.787***	

Note: IA = Inattention. H = Hits. CE = Commission Errors. RT = Response Times. RV = Response Time Variability. TA = Theta-Alpha Cross-Frequency Coupling. DW = Different Windows.**p*<0.05, ***p*<0.01, ****p*<0.001.

Table 14. Correlation matrix between inattention, task-performance measures and power measurements while controlling for age.

		Very Preterm								
		IA	H	CE	RT	RV	Theta	Alpha	TA (0-500)	TA (DW)
Term-born	IA		-.317*	.171	.085	.202	-.397**	-.280	.220	.245
	Hits	-.308*		-.462**	-.200	-.372*	.316*	.051	-.153	-.067
	CE	.281	-.756***		.014	.243	-.012	-.188	-.177	-.030
	RT	.155	-.041	-.219		.195	-.041	-.071	.319*	.363*
	RV	.397**	-.436**	.219	.413**		-.119	.079	-.042	-.018
	Theta	-.061	-.030	.200	-.235	-.175		.290	-.020	.020
	Alpha	.219	-.075	.032	.082	-.197	.168		-.205	-.257
	TA (0-500)	.052	.021	.061	-.164	-.009	-.203	-.160		.795***
	TA (DW)	.035	-.004	.089	-.312*	.041	-.282	-.204	.784***	

Note: IA = Inattention. H = Hits. CE = Commission Errors. RT = Response Times. RV = Response Time Variability. TA = Theta-Alpha Cross-Frequency Coupling. DW = Different Windows. Very preterm are shown above the diagonal, term-born, below. *p<0.05, **p<0.01, ***p<0.001.

Appendix 3: The role of IQ and SES

3.1 Introduction

3.1.1 The role of IQ

IQ is thought to be a measure of general intelligence, a construct that measures an individual's aptitude and general ability. Low IQ has been shown to be linked both to very preterm birth (Bhutta et al., 2002), and to ADHD (Frazier et al., 2004), with both populations showing a 9-10 point decrement compared to typically developing peers. Given that IQ is relevant to both the population (children born preterm) and clinical symptoms (ADHD symptoms) of interest in this thesis, it is likely that IQ may play a role in the aetiology of inattention. Therefore, this appendix considers the ways in which IQ may relate to inattention, and whether this relationship may differ in term-born and very preterm children.

In Chapter 2, I asserted that it would not be appropriate to adjust for IQ in this thesis in spite of a 10 point difference in IQ between term and very preterm children in this sample. This decision was made for several reasons. The battery of tests that were used to assess neurocognitive functioning in our sample included neurocognitive tests of particular interest that are often included as part of a full scale IQ test battery (e.g. processing speed, working memory), but that had been explicitly chosen for inclusion in the current study for theoretical reasons. This design presented three concerns about the inclusion of IQ in analyses; (i) that variance of interest may be inadvertently masked due to a large amount of shared variance between performance in tasks of interest and performance on IQ tests, and (ii) it has been reported that deficits associated with very preterm birth are better described as selective deficits than global cognitive impairment (Johnson, 2007), and as such it was considered that investigation of the independent contribution of specific cognitions of interest would be most informative from a theoretical standpoint. A final concern regarded the inappropriateness of the commonly-used method of adjusting for IQ by using it as a covariate is described fully in Dennis et al. (2009), who point out in detail how IQ does not meet the requirements for a covariate in neurodevelopmental analyses on logical, statistical, nor theoretical grounds. However, the topic of whether it is appropriate and important to incorporate IQ into analyses of neurocognitive functioning is controversial, thus in this appendix I intend to explore and discuss the role of IQ in the analyses examined across this thesis.

In order to determine what IQ represents more clearly, it is essential to consider what IQ tests measure. IQ scores are a composite measure comprising scores from subtests within a test battery measuring different aspects of neurocognitive processing. These tend to include measures of non-executive skills such as processing speed, visuo-spatial processing and short-term memory (as included as separate subtests in the analyses in Chapter 3), along with vocabulary, and abstract reasoning, and executive skills such as working memory. In this study, IQ was measured using the two-subtest variant of the WASI. This estimates full-scale IQ from performance on two subtests; the vocabulary subtest and the matrices subtest. The vocabulary subtest is designed to measure both word knowledge and concept formation. The matrices subtest is designed to measure fluid intelligence, broad visual intelligence, classification and spatial ability, knowledge of part-whole relationships, simultaneous processing and perceptual organisation. Studies have shown that performance on this two-subtest battery correlates highly with the more comprehensive Wechsler Intelligence Scale for Children (WISC) IQ test performance (r=0.82; Salofske et al., 2000), suggesting that it is an accurate proxy for full-scale IQ in study designs where administration of the full-scale IQ test is not pragmatic.

3.1.2 The role of socio-economic status

Socio-economic status (SES) represents the demographic group of a child based on variables such as parental income, education, and employment. SES is thought to be a marker of several adverse environmental factors, including limited finances and low parental education (Loe et al., 2011), and greater family discord (Lindstrom et al., 2011) all of which may be individual risk factors for suboptimal neurodevelopment and subsequent neurobehavioural difficulties. In the general population, lower SES is consistently and robustly linked to increased ADHD diagnosis and increased levels of ADHD symptoms, and confounds such as increased labelling in lower SES families have been ruled out (Russell et al., 2014). However, other studies have shown that while low SES is associated with hyperactivity/impulsivity, it does not relate to the inattention domain (Counts et al., 2005).

In studies of children born preterm, many designs either match groups on SES (e.g. Johnson, 2007), or adjust for it statistically, rather than investigating it as a predictor in its own right. This is so common that a 2002 meta-analysis of risk for adverse cognitive and behavioural outcomes for preterm birth could not assess the role of SES due to a lack of data (Bhutta et al., 2002). Studies that have directly assessed the role of SES in behavioural outcomes following preterm birth report mixed results. For example, Conrad et al. (2010) found that SES did not contribute to behavioural outcomes in children with extremely or very low birth weight, while in contrast Lindstrom et al. (2011) found that in a Swedish cohort, SES modified the risk for ADHD caused by preterm birth. Given the strong links with ADHD, but inconsistent findings reported regarding inattention specifically and inattention in preterm populations, a second aim of this appendix was to investigate the association of inattention and SES in the current study and whether this relationship may differ in term-born and very preterm children.

3.1.3 The current analysis

This analysis aimed to assess the role of IQ and SES as mechanisms underlying inattention. The broad hypotheses were as follows; lower IQ and SES would be associated with more severe parent rated inattention, as well as poorer performance and atypical neural processing across the neurocognitive test battery. However, the hypothesis regarding SES was less certain given variability in the literature regarding preterm cohorts and the inattention domain. It was further hypothesised that the role of IQ and SES would be the same in term and very preterm children, given the lack of prior evidence to the contrary. Where associations been IQ and/or SES and neurocognitive test scores were present, analyses performed in earlier chapters were repeated in order to assess whether, and how, results may be altered by incorporating IQ and SES as predictor variables. Possible reasons for any alterations and the theoretical and practical implications were discussed.

3.2 Analysis

First, in order to limit the reanalysis to only those analyses which may be impacted by IQ and SES, partial correlations controlling for the effect of age were conducted between IQ, SES and all measures included in this thesis. These were conducted collapsed across groups to maximize power for finding correlations that were consistent across both groups, and then repeated split by group to identify any relationships that were restricted to one group. Subsequently, analyses that included any variables that were associated with IQ and/or SES were repeated using IQ and/or SES (dependent on the associations observed) as covariates and/or predictor variables. Where correlational analyses in the main body of the thesis had been conducted only in order to guide variable selection for subsequent regression analyses (Chapters 3 & 4), only the regression analyses were repeated. It should be noted that main effects for within-subject measures are independent of the covariate of IQ and SES as all measures were collected in a single session. As such, and in line with previous chapters in this thesis, pure within-subjects main effects are not reported as they would refer to analyses that exclude these covariates, and thus would not change in these reanalyses. The full results are reported only where the input of additional covariates changed the pattern of results, with a statement of no alteration given where the pattern of results was not altered by the covariates. In line with previous chapters in this thesis, all analyses below are controlled for age.

3.3 Results

3.3.1 Correlations between IQ, SES and performance measures

Partial correlations controlling for age were conducted between all measures included in the analyses in Chapters 3, 4 and 5 and IQ and SES in order to assess which measures were associated with IQ and SES. See *Table A3.1* for results.

3.3.1.1Inattention

More severe parent-rated inattention was associated with lower IQ both across both groups, and within each group individually, but it was not associated with SES. As such, all analyses involving inattention were repeated controlling for IQ. Parent-rated inattention was not associated with SES.

Table A3.1: Correlations between neurocognitive performance measures and IQ and SES

		IQ			**SES**		
Chapter	**Measure**	**Across**	**VP**	**Term**	**Across**	**VP**	**Term**
3, 4 & 5	Inattention	-.441***	-.453***	-.406**	-.139	-.225	-.053
3	VS-P	.295**	.258*	.242	.259**	.278*	.235
	MPS	.039	-.248*	.060	.157	-.123	.420**
	VS-STM	.290**	.258*	.198	.044	.078	.003
	VS-WM	.312***	.345**	.297*	.179	.177	.207
	V-STM	.412***	.344**	.465***	.126	.067	.192
	V-WM	.229*	.037	.409**	.134	.060	.222
	LS	-.095	-.069	-.099	.095	.140	.023
	GS	-.164	-.227	-.114	-.051	-.162	.147
	IC	-.356***	-.354**	-.263	-.105	-.096	-.119
4 & 5	Hits	.389***	.557***	.449***	-.020	.053	-.078
	Comm	-.197	-.212	-.231	.099	.030	.159
	RT	-.168	-.313*	-.197	-.009	-.011	-.013
	RV	-.323**	-.274	-.440**	-.012	.128	-.140
4	CLN-early	-.036	-.023	-.077	.183	.141	.274
	CLN-late	-.085	-.039	-.118	-.088	-.288	-.075

	P1 amp - cued	-.160	-.228	-.003	-.073	.012	-.225
	P1 lat - cued	.152	.023	.331*	.211	.437**	.025
	P1 amp - uncued	-.040	-.178	.042	-.003	.039	-.038
	P1 lat - uncued	.138	.038	.382*	.093	.219	-.027
	P2 amp – cued	-.002	-.016	-.024	-.074	-.115	-.032
	P2 lat – cued	.090	-.099	.427**	-.027	.014	-.085
	P2 amp – uncued	.156	.192	.166	-.070	.036	-.128
	P2 lat - uncued	.075	-.120	.407**	.115	.085	.134
	P3 amp – cued	-.118	-.284	.304	-.050	-.175	.070
	P3 lat – cued	-.114	-.231	.047	-.093	-.226	.009
	P3 amp – uncued	-.095	-.209	.154	.064	-.064	.180
	P3 lat – uncued	-.023	-.120	.176	.099	.129	.089
5	Theta – 0-500ms	.247*	.363*	.107	-.030	.110	-.162
	Theta – 500-1000ms	.303**	.408**	.163	.082	.206	-.017
	Theta – 1000-1500ms	.160	.128	.212	.025	.270	-.188
	Alpha – 0-500ms	.055	.042	.043	-.109	-.056	-.150
	Alpha – 500-1000ms	.042	.136	-.034	-.059	.030	-.191
	Alpha –	-.068	.050	-.210	-.041	.001	-.085

1000-1500ms						
Theta-alpha 0-500ms	.054	-.003	.137	.035	.008	.055

Note: All correlations are controlling for the effect of age.**p*≤0.05, ***p*≤0.01, ****p*≤0.001. IA= parent-rated inattention; IQ= intelligence quotient; SES= socio-economic status; VS-P = visuo-spatial processing; MPS = motor processing speed; VS-STM = visuo-spatial short term memory; VS-WM = visuo-spatial working memory; V-STM = verbal short term memory; V-WM = verbal working memory; LS = local switching; GS = global switching; IC = interference control; Comm = commission errors; RT = median response time; RV = standard deviation of response time; CLN = cue-locked negativity; P1 amp = P1 peak amplitude at Oz; P1 lat = P1 peak latency at Oz; P2 amp = P2 peak amplitude at Cz; P2 lat = P2 peak latency at Cz; P3 amp = P3 peak amplitude at Pz; P3 lat = P3 peak latency at Pz

3.3.1.2Chapter 3 measures

Across groups, lower IQ was related to poorer visuo-spatial processing, poorer verbal and visuo-spatial short term and working memory, and poorer interference control. Regarding basic cognitive processes, in very preterm children lower IQ was related to poorer visuo-spatial processing, slower motor processing speed, and poorer verbal and visuo-spatial short term memory, but only the association between verbal short term memory and IQ reached significance in the term-born children. Regarding executive functions, lower IQ was associated with poorer visuo-spatial working memory and interference control in very preterm children. In term children, it was similarly associated with poorer visuo-spatial working memory, but the relationship with interference control did not reach significance, and instead it was related to poorer verbal working memory. As such, analyses involving these variables were repeated incorporating IQ as a covariate or continuous predictor.

Across groups, lower SES was associated only with poorer visuo-spatial processing, and when correlations were repeated split by group, it was evident that this relationship only reached significance in very preterm children. Unexpectedly, and contrary to hypotheses, in term-born children, lower SES was related to faster processing speed. As such, analyses involving these variables were repeated incorporating SES as a covariate or continuous predictor.

3.3.1.3 Chapter 4 & 5 behavioural measures

The behavioural measures from the CPT-AX task that were included in analyses in Chapters 4 and 5 showed associations with IQ, but not with SES. Specifically, higher IQ was associated with a higher hit rate across and within both groups, with faster response time in children born very preterm, and with lower response variability across groups, and particularly in children born at term. As such, all analyses including these variables in Chapters 4 and 5 were repeated to assess the role of IQ.

3.3.1.4 Chapter 4 measures

Neither IQ nor SES correlated significantly with any measure of cue-locked negativity, any measure of the P3 component, and peak amplitude for P1 and P2. Higher IQ was associated with later P1 and P2 peak latency for both cued and uncued targets in term-born children. In addition, higher SES was associated with later P1 peak latency to cued targets in children born very preterm. As such, analyses involving P1 peak latency were repeated, adjusting for IQ and SES, while those for P2 peak latency were repeated adjusting for IQ only.

3.3.1.5Chapter 5 measures

Neither IQ nor SES correlated significantly with any measure of alpha or of theta-alpha coupling. Higher IQ was associated with larger increases in theta in the 0-500ms and 500-1000ms time window. SES was not associated with any frequency measure. As such, analyses involving theta increases were repeated, adjusting for IQ only.

3.3.1.6Repeated analyses

In summary, on the basis of these correlations, the following analyses were repeated in order to assess the role of IQ and/or SES:

1. Due to the presence of correlations between both IQ and SES and multiple performance measures that were used across all analyses in Chapter 3, all Chapter 3 analyses were repeated to assess the role of both IQ and SES, with the exclusion of correlations that were conducted to guide selection of variables for a regression analysis.
2. Due to the presence of correlations between IQ and multiple behavioural measures that were used across analyses in Chapters 4 and 5, Chapter 4 and

5 analyses including the behavioural measures were repeated to assess the role of IQ, with the exclusion of correlations that were conducted to guide selection of variables for a regression analysis.

3. Due to the presence of correlations between both IQ and SES and P1 peak latency measures, Chapter 4 analyses including these measures were repeated to assess the role of these variables, while analyses including P2 peak latency measures were repeated to assess the role of IQ only, with the exclusion of correlations that were conducted to guide selection of variables for a regression analysis.
4. Due to the presence of correlations between IQ and theta increases, Chapter 5 analyses including these measures were repeated to assess the role of IQ.

Where results showed an alteration to the pattern reported in the main body of the thesis, values are highlighted in yellow.

3.3.2 Reanalysis: Chapter 3

3.3.2.1 Between-group performance differences

Group differences in performance on cognitive tests and parent-rated inattention scores were examined using a MANCOVA with group (term-born or very preterm) as the between subjects factor and age, IQ and SES entered as covariates. Using Pillai's Trace, multivariate tests showed that although there was a significant effect of age (*V*=0.271, *F*(10,98)=3.638, *p*<0.001) and IQ (*V*=0.322, *F*(10,98)=4.650, *p*<0.001), there was no significant effect of SES (*V*=0.245, *F*(10,98)=1.656, *p*=0.102), thus the results reported here refer to the model corrected for age and IQ. There was a significant main effect of group when controlling for age and IQ (*V*=0.182, *F*(10,99)=2.204, *p*=0.023).

Levene's test indicated equality of error variances (*p*>0.05) for all variables except inattention (*F*(1,110)=5.060, *p*=0.026), local switch costs (*F*(1,110)=4.362, *p*=0.039) and global switch costs (*F*(1,110)=4.484, *p*=0.036). MANCOVA is robust to violations of homogeneity of error variance where the variance ratio is <3. The variance ratio for inattention was 1.21, for local switch costs was 1.60, and for global switch costs was 1.60, meeting this criterion, therefore univariate tests are reported in *Table A3.2* below. Further, violations of this assumption increase risk of a Type 1 error, and as can be seen below, this did not occur given that group effects relating to inattention, local switch costs and global switch costs were non-significant.

Table A3.2: Age adjusted marginal means and standard errors (SE) for performance measures of term-born and very preterm children.

Measure	VP		Term		Between-group differences		
	Mean	SE	Mean	SE	*F*	*p*	η_p^2
Parent-rated inattention	-2.14	1.34	-2.38	1.62	.012	.913	.000
Visuo-spatial processing	27.36	.48	28.05	.57	.767	.383	.007
Motor processing speed	6.46	.13	7.26	.16	13.385	<.001***	.110
Verbal short term memory	38.88	1.22	40.31	1.47	.493	.484	.005
Verbal working memory	21.72	1.29	25.83	1.55	3.699	.057	.033
Visuo-spatial short term memory	35.23	1.49	39.35	1.79	2.800	.097	.025
Visuo-spatial working memory	17.18	1.21	16.92	1.43	.018	.893	.000
Local switching	88.17	23.02	70.44	27.60	.218	.642	.002
Global switching	221.18	18.76	256.91	22.50	1.329	.251	.012
Interference control	189.26	13.17	181.18	15.80	.145	.704	.001

Note: Covariates appearing in the model are evaluated at the following values; age = 9.85, IQ = 105.42. * $p<0.05$, **$p<0.01$, ***$p<0.001$ and still significant using Bonferroni corrected alpha of $p<0.005$. VP= very preterm, η_p^2= partial eta squared.

When controlling for IQ in addition to age, the only between-group difference was that children born very preterm had faster processing speed. In contrast to the results reported in Chapter 3, differences in the domains of visuo-spatial processing, verbal short term memory, verbal working memory, visuo-spatial short term memory and visuo-spatial working memory no longer met the threshold for significance.

3.3.2.2Relationships with inattention

In the Chapter 3 analysis, correlations between performance measures and inattention were conducted in order to guide which variables to enter into a regression analysis. For consistency and comparability, I assessed the role of IQ and SES as predictors of inattention in the same models as were assessed in Chapter 3, thus these correlations were not repeated.

The roles of IQ and SES were assessed separately in order to limit the number of variables entered into the regression analysis.

The role of IQ

In order to assess the role of IQ in greater detail, the regression analysis of cognitive predictors of inattention reported in Chapter 3 was repeated, entering IQ into the model at the first step along with age and group. The results are shown in *Table A3.3.*

Table A3.3: Regression model with IQ into the first step for cognitive predictors of parent-rated inattention

	Parent-Rated Inattention			
	Model 1	Model 2	Model 3	Model 4
	R^2=.199***	R^2=.301***	R^2=.331***	-
	-	ΔR^2= .103**	ΔR^2 =.030*	-
Predictor	β	β	β	β
Group	.011	.029	.025	-
Age	.035	.139	.160	-
IQ	-.437***	-.307**	-.271**	-
Motor processing speed		.167	.126	-
Visuo-spatial STM		-.193*	-.151	-
Verbal STM		-.192*	-.155	-
Visuo-spatial WM			-.199*	-
Verbal WM			-	-

Interference control	-
Group*motor processing speed	-
Group*visuo-spatial STM	-
Group*verbal STM	-
Group*visuo-spatial WM	-
Group*verbal WM	-
Group*interference control	-
Group*IQ	-

Note: **p*<0.05; ** *p*<0.01;*** *p*<0.001. - = did not meet criteria for forward entry model selection.

In contrast to the results reported in Chapter 3, by adding IQ into the first step along with age and group, Model 1 explained a significant proportion of the variance in parent-rated inattention (19.9%; Model 1; *F*(3,108)=8.926, *p*<0.001), with IQ explaining significant unique variance.

With the addition of low level cognitive predictors in Model 2, the model explained 30.1% of the variance (Model 2; *F*(6,105)=7.553, *p*<0.001). As in Chapter 3, both visuo-spatial and verbal short term memory, but not motor processing speed, explained significant unique variance. IQ continued to be a significant independent predictor of variance in inattention.

Of the executive function predictors, only visuo-spatial working memory contributed enough unique variance to be entered into Model 3. The model was significantly improved (ΔR^2 =.030, *p*=0.034) and explained 33.1% of the variance in parent-rated inattention (Model 3; *F*(7,104)=7.356, *p*<0.001). In contrast to the equivalent Model 3 reported in Chapter 3 excluding IQ, only VSWM and IQ were significant independent predictors of parent-rated inattention.

In the final step, none of the interaction terms contributed enough unique variance to be entered into the model, thus no fourth model was reported. This contrasts with the model reported in Chapter 3, where the interaction between group and motor processing speed explained sufficient unique variance to meet the criteria for forward entry model selection.

The role of SES

In order to assess the role of SES in greater detail, I followed the same approach with SES. Adding SES into the first step made very little difference to the pattern of results relative to those reported in Chapter 3, only resulting in increasing the beta value for motor processing speed in Model 2 so that it was above the threshold for significance. The results are reported in *Table A3.4*.

Table A3.4: Regression model with SES entered into the first step for cognitive predictors of parent-rated inattention

	Inattention			
	Model 1 R^2=.052 -	Model 2 R^2=.242*** ΔR^2= .189**	Model 3 R^2=.278*** ΔR^2 =.036*	Model 4 R^2=.305*** ΔR^2 =.027*
Predictor	β	β	β	β
Group	.174	.118	.098	.109
Age	.033	.175	.194*	.140
SES	-.132	-.116	-.076	-.035
Motor processing speed		.191*	.136	.166
Visuo-spatial STM		-.227*	-.176	-.191*
Verbal STM		-.274**	-.226*	-.202*
Visuo-spatial WM			-.222*	-.214*
Verbal WM			-	-
Interference control				-
Group*motor processing speed				.181*
Group*visuo-spatial STM				-
Group*verbal STM				-
Group*visuo-spatial WM				-
Group*verbal WM				-
Group*interference control				-

Note: *p<0.05; ** p<0.01;*** p<0.001. - = did not meet criteria for forward entry model selection.

3.3.3 Reanalysis: Chapter 4

3.3.3.1 Behavioural results: Task performance differences

Group differences (term-born or very preterm) for the behavioural task performance measures were examined using a MANCOVA. Age, IQ and SES were entered as covariates. Using Pillai's Trace, multivariate tests showed that there was a significant main effect of age (*V*=0.201, *F*(4,74)=4.654, *p*=0.002), and IQ (*V*=0.278, *F*(4,74)=7.122, *p*<0.001), but there was no significant effect of SES (*V*=0.032, *F*(4,74)=0.608, *p*=0.658), thus the results reported here refer to the model corrected for age and IQ. In contrast to the results in Chapter 4, where IQ was not entered as a control variable, there was a significant main effect of group when controlling for age and IQ (*V*=0.123, *F*(4,75)=2.636, *p*=0.041).

Levene's test indicated equality of error variances (*p*>0.05) for all variables except hit rate (*F*(1,80)=11.523, *p*=0.001). MANCOVA is robust to violations of homogeneity of error variance where the variance ratio is <3. The variance ratio for inattention was 1.51, meeting this criterion, therefore univariate tests are reported below in *Table A3.5*.

Table A3.5: Age adjusted marginal means and standard errors for performance measures of term-born and very preterm children on the CPT-AX.

Measure	Very Preterm		Term		Between-group differences		
	Mean	SE	Mean	SE	*F*	*p*	η_p^2
Hits (%)	92.71	0.72	85.24	0.76	7.38	.008**	.086
Commission errors (%)	1.91	1.40	2.29	1.48	.414	.522	.005
Median RT (ms)	434.55	12.26	463.30	12.95	2.336	.130	.029
SD RT (ms)	152.21	8.98	163.38	9.48	.657	.420	.008

Note: Covariates appearing in the model are evaluated at the following values; age = 9.43, IQ = 107.28. RT = response time; SE = standard error. * *p*<0.05, ***p*<0.01 and still significant using Bonferroni corrected alpha of *p* <0.016. η_p^2= partial eta squared

Unexpectedly, when controlling for IQ and age, children born very preterm achieved significantly more hits than those born at term, but groups did not differ on any other score.

3.3.3.2 ERP results

Assessment of task-related attentional modulation: relationships between cue-locked negativity and task performance

As IQ correlated with some of the behavioural measures, partial correlations were conducted between mean amplitude and task-performance measures, controlling for age and IQ, across both groups and then split by group. Associations with task performance for early and late windows are reported in *Tables A3.6* and *A3.7* respectively.

Table A3.6: Partial correlations between mean amplitude of cue-locked negativity during the early window measured at CPz and task performance.

	Mean Amplitude – Early (600-1000ms)		
Measure	Collapsed Across Groups	Very Preterm	Term
Hits	-.223*	-.495***	.002
Commission Errors	.051	.296	-.190
Response Time	.161	.192	.178
Response Variability	.281**	.512***	-.004

Note: All correlations are controlled for the effect of age and IQ. **p*<0.05, ***p*<0.01, ****p*<0.001

Table A3.7: Partial correlations between mean amplitude of cue-locked negativity during the late window measured at CPz and task performance.

	Mean Amplitude – Late (1000-1400ms)		
Measure	Collapsed Across Groups	Very Preterm	Term
Hits	-.104	.073	-.157
Commission Errors	.085	-.014	.121
Response Time	.186	.164	.213

Response Variability	.131	.098	.178

Note: All correlations are controlled for the effect of age and IQ. *p<0.05, **p<0.01, ***p<0.001

The pattern of results, both across groups and split by group reflected the results observed in Chapter 4 in the main, with one exception. All relationships between cue-locked negativity amplitude and response time that previously reached significance were no longer significant. This included both the relationships with early and late cue-locked negativity, both across groups and in the term children independently. As a result, only relationships between the early cue-locked negativity and behavioural measures in preterm children remained significant.

P1 to targets: Attention during visual discrimination

An ANCOVA on peak latency of the P1 component at Oz was carried out with target type (cued or uncued) as a within-subject factor and group (very preterm, term) as a between subject factor, and with IQ and SES entered as covariates alongside age. The pattern of results did not differ from that reported in Chapter 4.

P2 to targets: Attention during feature detection and stimulus categorisation

An ANCOVA on the peak latency of the P2 component was carried out with electrode (Fz and Cz) and target type (cued and uncued) as within-subject factors and group (very preterm and term) as a between subjects factor, with IQ entered as a covariate alongside age. The pattern of results did not differ from that reported in Chapter 4.

3.3.3.3Relationships with inattention

In the Chapter 4 analysis, correlations between behavioural and electrophysiological CPT-AX measures and inattention were conducted in order to guide which variables to enter into a regression analysis. For consistency and comparability, I assessed the role of IQ and SES as predictors of inattention in the same models as were assessed in Chapter 4, thus these correlations were not repeated.

The roles of IQ and SES were assessed separately in order to limit the number of variables entered into the regression analysis.

The role of IQ

In order to assess the role of IQ in greater detail, the regression analysis of cognitive predictors of inattention reported in Chapter 4 was repeated, entering IQ into the model at the first step along with age and group. Results are reported in *Table A3.8*.

Table A3.8: Regression model with IQ entered into the first step for CPT-AX predictors of parent-rated inattention

	Parent-Rated Inattention		
	Model 1 R^2 =.239* -	Model 2 R^2=.272* ΔR^2= .033	Model 3 R^2=.315* ΔR^2 =.042*
Predictor	β	β	β
Group	.051	.079	.062
Age	-.015	.046	.002
IQ	-.470*	-.385*	-.373*
Hits		-.027	-.016
Response variability		.152	.130
Commission errors		.082	.059
P2 Uncued Peak Amp			-.216*
P2 Cued Peak Lat			-
P2 Uncued Peak Lat			-
Group*Hits			-
Group*Response variability			-
Group *Commission errors			-
Group*P2 Uncued Peak Amp			-
Group*P2 Cued Peak Lat			-
Group*P2 Uncued Peak Lat			-
Group*IQ			-

Note: § $p<0.07$,*$p<0.05$, - = did not meet criteria for forward entry model selection.

In contrast to the analysis reported in Chapter 4, it was found that Model 1 significantly predicted parent-rated inattention ($F(3,78)=8175$, $p<0.001$), explaining 23.9% of the variance, with IQ contributing unique variance.

Model 2 also significantly predicted parent-rated inattention ($F(6,75)=4.676$, $p<0.001$), explaining 27.2% of the variance, however it did not significantly improve on Model 1, and IQ remained the only significant independent predictor. Contrary to the results reported in Chapter 4, response variability did not show a trend towards being a significant independent predictor of inattention.

Model 3 introduced ERP components using the forward selection technique. Only the peak amplitude for uncued targets significantly improved the model, contributing unique variance in addition to the significant effect of IQ. This model significantly predicted parent-rated inattention ($F(7,74)=4.852$, $p<0.001$), explaining 31.5% of the variance, and significantly improving on Model 2 ($\Delta R^2 =0.042$, $p=0.036$).

In the same way as was observed in the Chapter 4 analyses, the forward selection technique was used at a fourth step to introduce group interactions with cognitive and electrophysiological measures, but none of these improved the model significantly and thus were not included in the final model.

The role of SES

In order to assess the role of SES in greater detail, I followed the same approach with SES. Adding SES as a control variable did not alter the pattern of results relative to those reported in Chapter 4.

3.3.4 Reanalysis: Chapter 5

3.3.4.1 Effects of time and group

Theta

A mixed ANCOVA was conducted on the measure of theta power relative to a pre-stimulus baseline at AFz, with a within-subjects factor of time window (0-500ms, 500-1000ms, 1000-1500ms), a between-subjects factor of group (term-born, very preterm), and age and IQ as covariates. The pattern of results did not alter from those observed in Chapter 5.

3.3.4.2 Relationships with task-performance and inattention

Next, relationships between parent-rated inattention and power measures were re-assessed with relevance to the role of IQ. Partial correlations between theta power and alpha power relative to pre-stimulus baselines, theta-alpha cross-frequency coupling and task-performance and parent-rated inattention measures, controlling for the effect of age and IQ were computed. For theta and alpha power, correlations were computed using the measure of mean power in the time window showing the strongest change from baseline for each frequency band (theta: 0-500ms, alpha: 500-1000ms). For analysis of cross-frequency coupling, theta-alpha correlations in the 0-500ms time window were used, in line with Mazaheri et al. (2014). These values were then correlated with task-performance and inattention measures, collapsed across both groups and then split by group. Results can be seen in *Tables A3.9* and *A3.10* respectively.

Table A3.9: Partial correlations between inattention and task-performance measures and power measures

	Theta (0-500ms)	Alpha (500-1000ms)	Theta-Alpha Coupling (0-500ms)
Inattention	-.101	-.018	.172
Hits	-.013	-.024	-.040
Commission errors	.164	-.053	-.055
Response time	-.164	.003	-.070
Response variability	-.047	-.052	-.025

Note: All correlations were conducted across groups while controlling for age and IQ. **p*<0.05, ** *p*<0.01, *** *p*<0.001.

Table A3.10: Partial correlations between inattention and task-performance measures and power measures

	Theta (0-500ms)		Alpha (500-1000ms)		Theta-Alpha Coupling (0-500ms)	
	Very Preterm	Term	Very Preterm	Term	Very Preterm	Term
Inattention	-.241	.002	-.316	.240	.288	.085
Hits	.169	-.134	-.014	-.130	-.171	-.005
Commission errors	.053	.290	-.183	.077	-.196	.064

Response time	.044	-.275	-.109	.072	.275	-.130
Response variability	-.033	-.096	.120	-.245	-.059	.037

Note: All correlations were conducted split by group, while controlling for age and IQ. **p*<0.05, ** *p*<0.01, *** *p*<0.001.

Although the direction of the associations was the same as observed in Chapter 5 analyses, covarying IQ removed any significant correlations.

3.4 Discussion

The analyses and reanalyses reported in this appendix indicate that as expected, IQ plays a substantial role in inattention, and that the inclusion of IQ in analyses altered the results relative to those reported in chapters throughout the thesis. Importantly, lower IQ was associated with more severe parent-rated inattention in both very preterm and term-born children independently, and collapsed across groups. In contrast, SES did not relate to inattention, nor to many of the other measures assessed in this thesis. Moreover, inclusion of SES into relevant analyses did not alter the results substantially relative to those reported in the main body of the thesis. This discussion addresses the results of the reanalyses and their implications by chapter, first for IQ, and then for SES.

3.4.1 The role of IQ

3.4.1.1 Chapter 3

IQ correlated with many of the variables for which between-groups differences were observed in Chapter 3; specifically visuo-spatial processing, verbal short term memory, verbal working memory, visuo-spatial short term memory and visuo-spatial working memory. This is not surprising given that the FSIQ-2 score used here is a proxy for a composite measure derived from administering a more comprehensive test battery that includes subtests that measure precisely these areas of cognition. Due to these associations the initial MANCOVA was repeated to assess whether the between-group differences remained when controlling for IQ. The results indicated that only the difference in processing speed remained significant. However, in theoretical terms, what does controlling for IQ in this instance mean? One interpretation is that children born very preterm have faster processing speed, but do not differ in other cognitive domains relative to term-born peers of the same level of IQ. However, this result embodies one of the arguments against using IQ as a covariate. Covarying IQ results in a comparison of groups at a value of IQ that is unrepresentative of the populations of interest. Because the variables that were no longer significant were positively correlated with IQ, and IQ was lower in very preterm children, equating IQ resulted in marginal means that were more equivalent across groups (i.e. IQ is lower in children born very preterm, if lower IQ is related to poorer performance, and the between group difference reported in Chapter 3 was that poorer performance was observed in children born very preterm, controlling for IQ will reduce this difference).The remaining significant between-group difference in processing speed, on the other hand, was further emphasised by adjusting means for IQ. This is because children born very preterm had lower IQ but faster processing speed, therefore, assessment of processing speed at equivalent levels of IQ only increased this between-groups difference. Although on the surface one could interpret that the other differences observed in Chapter 3 resulted from low IQ rather than preterm birth, because low IQ is an inherent group characteristic of children born very preterm, these differences cannot be causally disentangled from IQ (see Dennis et al., 2009 for a full discussion of this issue). The results reported in Chapter 3 are arguably more informative, indicating areas of relative strength and weakness across different specific cognitive domains that are masked by covarying IQ.

To assess the relation of IQ to inattention specifically, the FSIQ-2 score was entered into a regression between parent-rated inattention and cognitive performance measures. IQ was the strongest independent predictor of inattention overall, but in model two, visuo-spatial and verbal short term memory also emerged as independent predictors, and in model three, visuo-spatial working memory remained a predictor. It is interesting that VS-STM and V-STM only predicted significant unique variance in models where either IQ was entered as a predictor but not VSWM (as in

Model 2 in this appendix), or where VSWM was entered as a predictor but not IQ (as in Model 4 reported in Chapter 3). This suggests that the association of VS-STM and V-STM with inattention, shared variance with both IQ and VSWM. Another difference between the results reported here and those reported in Chapter 3 was that the interaction between group and processing speed no longer explained sufficient variance for entry into the model when IQ was modelled alongside other neurocognitive processes. This too, is likely to reflect shared variance between IQ and motor processing speed and their relationship with inattention in children born very preterm. Although neither VS-STM or V-STM, nor motor processing speed were measured explicitly in the IQ test administered during this study, the shared variance is not surprising. As mentioned above, the WASI FSIQ-2 is designed to be a pragmatic proxy for a more comprehensive test of neurocognitive functioning, and as such it would be hoped that there would be significant cross-over between the variance explained by the FSIQ-2 score, and by measures of specific cognitive skills that are included as subtests in longer IQ test batteries.

Perhaps the most important finding from these reanalyses is the fact that VSWM still emerges as a significant independent predictor of inattention even in analyses including IQ, lending strength to the conclusions about its importance in inattention in Chapter 3, and to the wider literature supporting this perspective in both term (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Gathercole et al., 2008) and preterm populations (Aarnoudse-Moens et al., 2012; Mulder et al., 2011b; Nadeau et al., 2001; de Kieviet et al., 2012).

3.4.1.2Chapter 4

Regarding the behavioural measures assessed in the CPT-AX, lower IQ was related to a lower hit rate in both groups, to lower response variability, particularly in term-born children, and to faster response times in children born very preterm. IQ did not correlate with many electrophysiological measures overall, but in term-born children low IQ was associated with shorter P1 and P2 latencies to both target types. In combination with the direction of findings in the behavioural measures, these results indicate that lower IQ was associated with faster processing speed on this task, contrary to expectations. This supports the speculation in the discussion of Chapter 4 findings that in some contexts short latencies in term-born children may represent less comprehensive early processing, rather than reflecting the ability to detect and categorise faster.

Unexpectedly, when controlling for IQ and age, children born very preterm achieved significantly more hits than those born at term, but groups did not differ on any other score. What does this mean in real terms? It could be interpreted to show that children born very preterm have better sustained attention relative to term-born peers of the same level of IQ. However, in the same way as the between-group comparisons of cognitive performance are difficult to interpret when using IQ as a covariate, this result is also comparing groups at a value of IQ unrepresentative of the populations of interest. Whereas in the Chapter 4 analyses (that did not include IQ) group means in hit rate were equivalent, here adjusting for IQ resulted in artificial inflation of hit rate in children born very preterm relative to those born at term because hit rate positively correlated with IQ and the preterm group had lower IQ. As argued above, this difference cannot be causally disentangled from IQ given that the IQ difference is an inherent group characteristic (again, see Dennis et al., 2009 for a full description of this argument).

The pattern of results observed in the reanalyses of attentional modulation for cue-locked negativity, P1 and P2 was generally as reported in Chapter 4, except that relationships between cue-locked negativity amplitude and response time that previously reached significance were no longer significant. This shows that when IQ was held constant, there was no longer a relationship between speeded responses and cue-locked negativity, suggesting that this finding is associated with individual differences in IQ. However it is interesting to consider from a theoretical angle whether response time – often taken as a measure of processing speed – would be considered as more low-level than IQ, and whether in fact the association between response time and IQ is better characterised as slower processing speed causing lower IQ. It is interesting that this relationship emerged given that processing speed was not itself part of the IQ test battery, but as discussed in relation to other elements of cognitive processing, the FSIQ-2 is designed to correlate highly with those other cognitive skills measured in more comprehensive test batteries.

With IQ entered into the regression models, results were altered, whereby only IQ and P2 peak amplitude were significant independent predictors of inattention. The trend for response variability to independently predict inattention observed previously in Chapter 4 was no longer present, indicating IQ differences accounted for this variance. One particularly interesting finding from these reanalyses is that P2 peak amplitude to uncued targets continued to be a significant independent predictor of inattention, predicting variance above and beyond that explained by IQ. This suggests that electrophysiological indices have the potential to provide a further measure of inattention that is not captured by IQ testing, and may represent useful biomarkers.

3.4.1.3Chapter 5

Of the Chapter 5 measures, only theta measured in children born very preterm was associated with IQ. Including IQ in between-group assessment of differences in theta did not alter the results found, however including IQ as a covariate in correlations between power measures and inattention and task performance measures did alter the results relative to those reported in Chapter 5. All associations previously observed between theta and inattention and CPT-AX measures in children born very preterm no longer met the threshold for significance. This is likely to be due to shared variance between IQ and theta, with correlations observed between measures of theta and IQ in very preterm children. Indeed, a study has previously associated increased frontal theta synchronisation during an encoding task with higher IQ (Capotosto et al., 2009). One interesting implication of this, is that in future research, task-related frontal theta could be evaluated as a marker for overall cognitive ability in this population.

3.4.1.4The role of IQ: Conclusions

The subtests used in IQ test batteries can be divided into those measuring executive and non-executive processes (Frazier et al., 2004), much like my division between ‘basic cognitive processes’ and ‘executive functions’ in Chapter 3. In this thesis, I chose to focus instead on specific processes for which there was a theory base rather than to assess a composite measure. The results from these reanalyses largely support the rationale for excluding IQ in the original analyses; namely that the IQ composite score shares variance with many of the more specific cognitive processes, thus masking relationships of interest between specific cognitive processes and inattention. That said, these analyses provide a deeper insight into the mechanisms underlying inattention in very preterm and term-born children.

In particular, the fact that both visuo-spatial working memory and P2 peak amplitude to uncued targets predicted inattention independently from IQ suggests that measurement of these markers may be beneficial for identifying children at risk, and give credence to research into working memory as an intervention target for inattention (Astle et al., 2015; Melby-Lervåg & Hulme, 2013; Spencer-Smith & Klingberg, 2015; Grunewaldt, Løhaugen, Austeng, Brubakk, & Skranes, 2013). The relationship between frontal theta and IQ indicates that future research into frequency markers of general cognitive ability may benefit from a focus on frontal theta. Moreover, the relationship of IQ to inattention was the same in both very preterm and term-born children, indicating that in spite of some variations in strengths and weaknesses across neurocognitive profiles, a composite of general cognitive ability has the same ability to predict inattention in both populations.

In practical terms, the variance explained by IQ is greater than that explained by most other measures, suggesting that it may be a more beneficial screening measure to assess those at risk for inattention than other measures reported in this thesis. Moreover, it has been shown that in very preterm samples, IQ remains stable and that IQ measured at two years of age, can reliably predict IQ in adulthood (Breeman et al., 2015). From a clinical standpoint, an IQ test at a very early age would allow for identification of those children most at risk for developing difficulties with inattention. This would complement the more specific analyses included in the main body of the thesis, by detecting those most at risk. Within those children, assessment of selective deficits for targeted intervention would then be possible.

3.4.2 The role of SES

SES was not associated with inattention, however it did show some associations with cognitive processes measured in this thesis. Specifically, lower SES was related to poorer visuo-spatial processing, faster motor processing speed in term-born children, and shorter P1 latency in children born very preterm. While the association with poorer visuo-spatial processing is in the hypothesised direction, it appears contrary that children with lower SES would be faster at processing, yet this was seen both in term-born children (motor processing speed) and in very preterm children (P1 latency). These findings are difficult to explain and require replication for a full understanding. It may be that these represent type one errors, the risk for which is inflated due to the number of correlations conducted. Alternatively, there may be an unidentified third confounding variable behind these relationships. It is difficult to find a theoretical explanation for this pattern of findings if they represent a true finding, but it is possible that children from higher SES are more considered in their processing, and thus processing speed is slower.

In the analyses repeated with SES included as a covariate or continuous predictor, results were in general unaltered relative to those reported in the main thesis, and any minor alterations did not have theoretical or practical implications.

3.4.2.1The role of SES: Conclusions

These results are in contrast with the general pattern of findings across the ADHD literature (Russell et al., 2014), which suggest ADHD is associated with lower SES, and with Lindstrom et al. (2011) who found that risk of ADHD in preterm children was modified by SES. This discrepancy may be due to the focus on inattention and recruitment from the community in the current study. As discussed in the general introduction of this thesis, there is a referral bias within ADHD, whereby children with more severe hyperactivity/impulsivity symptoms are more likely to be referred for clinical diagnosis and intervention. It may be that if SES is a greater risk factor for hyperactivity/impulsivity as was found in Counts et al. (2005), the type of behaviour that leads to this referral bias, associations are more likely to emerge in clinical samples with more extreme levels of hyperactivity/impulsivity. If this were the case, it may explain some of the inconsistency within the literature. For example, the cohort assessed in Lindstrom et al. (2011) consisted of preterm children who were receiving medication for ADHD, and thus were likely to have extreme levels of symptoms in both symptom domains, explaining the presence of an association with SES. Overall, these results suggest that SES is not an influential mechanism in the aetiology of inattention in community samples of term-born and very preterm children.

3.4.3 General summary and conclusions

IQ, but not SES, significantly predicted inattention in term-born and very preterm children. Inclusion of IQ in analyses reported earlier in the thesis substantially altered the results, while inclusion of SES did not. It has long been argued that use of IQ composite scores masks the more complex profiles of subtle dysfunction and relative strengths that may be observed in children born preterm (Aylward et al., 2002) and those with difficulties with attention (Dennis et al., 2009). The analyses reported here support that assertion. Consequently, IQ may also mask relationships between specific cognitive processes and inattentive behaviour. In spite of this, this analysis shows that IQ tests are relatively strong predictors of inattention in both term-born and very preterm children, thus may be appropriate to use as a first step in clinical and classroom contexts in order to identify children who develop difficulties with inattention. More detailed assessment of the relative strengths and weaknesses within a child by measuring specific skills, such as those included in the Chapter 3 analyses may then provide specific intervention targets.

Importantly, some variables measured in this study emerged as predictors of variance in inattention that were independent of the measurement of IQ. Firm conclusions regarding the potential usefulness of P2 amplitude require further replication, but the finding that it predicted inattention independent of IQ and other CPT-AX measures does indicate that electrophysiological recording can provide markers that are unrelated to IQ and warrant further investigation. More promising still, VSWM has a large body of literature supporting its importance as a mechanism underlying inattention, which these findings only reinforce. These conclusions follow both for term-born and very preterm children.