The Neural and Social Correlates of Automatic Behaviours

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Glossary of Terms

- ADHD – attention deficit hyperactivity disorder
- AQ – autism quotient
- ASD – autism spectrum disorder
- BA – Brodmann's area
- BAS – behavioural activation system
- BIS – behavioural inhibition system
- CS – conditioning stimulus
- CSE – cortico-cortical spinal excitability
- CY – contagious yawning
- EMG - electromyograph
- FDI – first dorsal interosseous
- FY – full yawn
- GABA – gamma-aminobutyric acid
- GTS – Gilles de la Tourette's syndrome
- hMNS – human mirror neuron system
- ICF – intracortical facilitation
- IO – input/output (slope of the TMS curve)
- IRI – interpersonal reactivity index
- ITI – inter trial interval
- LICI – long interval cortical inhibition
- MEP – motor evoked potential
- MH – motor hotspot
- MU – mean urge
- OCD – obsessive compulsive disorder
- pp-TMS – paired-pulse transcranial magnetic stimulation
- RMT – resting motor threshold
- RT – reaction time
- Si1mV – stimulus intensity resulting in 1 millivolt motor evoked potential
- SICI – short interval cortical inhibition
- sp-TMS – single-pulse transcranial magnetic stimulation
- SY – stifled yawn
- tDCS – transcranial direct current stimulation
- TES – transcranial electrical stimulation
- TMS – transcranial magnetic stimulation
- tRNS – transcranial random noise stimulation
- TS – test stimulus
- UPPS – urgency, premeditation, perseverance, sensation-seeking

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Abstract

The research in this thesis will focus primarily on the role motor cortex excitability has on social and non-social action behaviours, and in particular behaviours relating to; echophenomena, motor action, contagious behaviours, impulsivity, and action imitation. Inhibition and facilitation, specifically in relation to contagious behaviours, imitation, and impulsivity, will be explored to a greater extent in order to further understanding on how these might be altered in neurodevelopmental conditions. Initial studies chapter 3 to 5 investigated contagious yawning, a form of imitative behaviour related to echophenomena, in typically developed controls (TDC). Echophenomena is related to early social cognition and is altered in some neurodevelopmental conditions such as Autism spectrum disorders and Gilles de la Tourette's syndrome. The first study was a within subjects' design that utilised both physiological (TMS) measures of cortical activity alongside behavioural measures of contagious yawning. Subsequent studies were both within and between subjects' designs and sought to modulate motor cortex excitability during both automatic social and non-social behaviours. These same neurophysiological techniques were then used to explore the relationship between corticospinal excitability and impulsive behaviours. Measures of impulsivity were assessed using modified 'traffic light' behavioural paradigms.

Chapter 1 General Introduction

1.1 *Automatic Behaviour*

1.1.1 Imitation

Imitation is an automatic behaviour that frequently occurs among humans and easily recognised in day-to-day life. However, the underlying neural mechanisms that facilitate this behaviour appear to be far more complex than suggested (Hamilton, 2015). For example, a significant amount of knowledge comes from animal research, which often suggests that imitation is a unitary stimulus response behaviour. However, Hamilton (2015) posits that while the presence and significance of imitative behaviour among animals has been debated since the work of Charles Darwin, it is understood, even among these early theorists, that it does not encompass just a single behaviour. Moreover, animal research predominantly looks at how animals learn and adapt through imitation without addressing precisely how such research translates into understanding human social interaction. Therefore, imitation related to animal research will only feature in this review when it has directly featured in the human imitation research being discussed. The rationale for this decision is based on the premise that most animal researchers believe true imitation can only be produced among humans (Clay & Tennie, 2017; Zentall, 2001). Zentall (2001) suggests that simple learning through observation is simply not sufficient enough to suggest a being is truly imitating. Moreover, Zentall (2001) argues that true imitation can only be produced when behavioural, visual, and vocal mimicry is achieved, not simply the reproduction of exclusive behaviours as seen in some non-human animals.

Imitation among humans is referred to as an advanced behaviour where an individual observes and replicates the actions or behaviours of another. Moreover, the term ‘imitation’ typically refers to both conscious and unconscious behaviours, with unconscious imitation labelled as mirroring (Chartrand & Bargh, 1999). Bargh and colleagues (1999) refer to the nonconscious mimicry of mannerisms, facial expressions, postures and other behaviours displayed by our interactive partners, whereby one’s behaviour passively and unintentionally adapts to mirror that of other individuals in our immediate social environment, as the chameleon effect. Bargh et al., (1999) found that mere perception of other individuals’ behaviour automatically increased the likelihood of an observer engaging in that same behaviour themselves. Thus, imitation is considered a type of social learning that facilitates the development of our traditions, social rituals, and cultural norms (Hopper, 2010).

Hopper (2010) posits that imitation permits the transference of information, behaviours, and customs both between, and across, individuals and generations without the requirement of genetic inheritance. Moreover, and as noted earlier, the presence of imitation in humans is argued to be unique among animals (Clay & Tennie, 2017). Clay and Tennie (2017) compared children’s capacity to imitate behaviour with the same capacity as bonobo apes, human’s closest living ape relative. Results found that the bonobos do not copy actions as human children do, which highlights how unique imitation is to humans. The children were extremely willing to copy actions despite such action serving no obvious function, whereas bonobos were not (Clay and Tennie, 2017). The authors posit that the bonobos failure to imitate likely

demonstrates that even enhanced social orientation is simply not enough to facilitate human-like cultural learning behaviours. While some animals do show some ability to copy actions, the copying of actions that have no apparent function seems to be uniquely human and as such, is often cited as a scaffold for human social development (Bandura, 1962; Clay & Tennie, 2017; Miller & Dollard, 1941; Piaget, 1972).

1.1.2 Imitation in human development

Piaget (1932) earliest theory of cognitive development suggests that children construct a mental model of the world to understand and interact within it. He further argued that cognitive development occurs as a result of biological maturation and interaction within the environment (Piaget, 1932). His early perspectives also included theories regarding how children develop understanding through imitation (Piaget, 1964). Piaget (1964) found that children in a developmental stage, which he referred to as the sensorimotor stage, a period that lasts from infancy until approximately the second year of life, began to imitate the observed actions and behaviours of their caregivers. Piaget (1964) further stated that neonates are only able to imitate the actions of others that they themselves have been able to observe previously. Piaget (1964) went on to suggest that children develop schemas via the action of using individuals or objects as models for learning. He defined a schema as a mental representation related to an associated set of ideas, perceptions, and/or actions, and considered them as the scaffolding for thinking and learning (Piaget, 1964). Such behaviours are often referred to as social cognitive, or social learning theory (Bandura, 1962; Holt, 1933; Miller & Dollard, 1941).

1.1.3 Social learning theories of imitation

The conceptual origins of social cognitive theory began with Holt's idea that all animal action is based upon fulfilling basic psychological needs including, emotion, feelings, and desires (Holt, 1933). The most prominent element within Holt's (1933) theory is that a person cannot learn to imitate until they are imitated. Holt's theory was later revised with Miller and Dollard (1941) arguing that there are four factors that contribute to learning including; drives, cues, responses, and reward (Miller & Dollard, 1941). They suggest that one such driver is social motivation, which also encompasses imitative behaviour. They too classify imitation as a process whereby one matches an act to an appropriate cue, with the cue facilitating when and where to perform the act (Miller & Dollard, 1941). Moreover, whether a behaviour is imitated or not, is said to depend on whether or not a model encounters positive or negative response outcomes. Miller & Dollard (1941) further posit that if individuals' have the motivation to learn a specific behaviour, then that behaviour would be learned via pure observation, and in doing so, the observer would solidify the learned behaviour, and as such be rewarded via positive reinforcement (Miller & Dollard, 1941).

This proposal was later expanded and theorised upon by Albert Bandura using his unique Bobo doll experiments (Bandura, 1962). Bandura and colleagues conducted a battery of tests to examine whether children display aggressive behaviour's after observing an adult display violence towards an inflatable toy, which he named the bobo doll. The findings of these studies demonstrated that children imitated the observed behaviour and displayed aggressive action in the same manner as the adults they had observed. Bandura's (1962) research was

able to expand the view of how behaviours are acquired, which built upon Miller and Dollard's (1941) earlier theorising, and simultaneously demonstrated the value of modelling for acquiring novel behaviour. Bandura later emphasised the role that cognition plays in encoding and carrying out behaviours, suggesting that all human behaviour is influenced by personal, behavioural, and environmental factors (Bandura, 1986).

However, other research into human development has argued that imitation should be separated into two distinct constructs (Uzgiris, 1981). Uzgiris (1981) reviewed several studies of imitation, mainly during infancy, and argued that imitation may serve two functions; the first being emulation (the copying of goals), and second mimicry (the copying of familiar versus novel actions), as well as copying for learning about objects versus copying for social interactions. Uzgiris (1981) states that imitation helps facilitate understanding of confusing observations, as well as facilitating mutual communication and shared understanding among individuals. However, while these changes in cognitive understanding might influence imitation development, its occurrence in particular situations might be controlled by an interaction between the two separate functions imitation could serve (Uzgiris., 1981). This idea infers that research needs to contemplate, both the kinds of acts that are imitated at different levels of development, as well as the child's understanding regarding social interactions during which imitative behaviour is acquired, in order to clarify any age-related tendency towards imitation (Uzgiris, 1981).

However, while such theorising provides understanding of imitation at a cognitive level, it does little to elucidate understanding regarding the neural basis for imitation (Lyons, 2009). Lyons (2009) argues that such hypothesising

has been particularly hindered by oversimplifying imitation's complex cognitive reality. Lyon's (2009) proposes that the common coding of action perception, and action production, facilitated by human mirror neurons', raises exciting possibilities for generating knowledge regarding a neural basis of imitation.

1.2 *The Human Mirror Neuron System*

Mirror neuron activity was first documented following research on macaque monkeys during the early 1990s (di Pellegrino, Fadiga, Fogassi, Gallese, & Rizzolatti, 1992). Di Pellegrino and colleagues recorded from single cell neurons within the ventral motor cortex (area F5) whilst a monkey reached for and consumed food. Di Pellegrino and colleagues (1992) discovered that the neurons in this brain region fired when the monkey performed this particular action, and later observed within the same monkey, that the exact same neuronal firing occurred when the monkey observed other monkeys performing these same actions. Di Pellegrino et al (1992) suggested that this discovery made mirror neurons distinct for social learning and interaction, not only in monkeys, but also in humans.

Gallese & Goldman, (1998) supported di Pellegrino et al., (1992) view and went on to study human mirror neuron system (hMNS) functioning in human subjects using an experimental paradigm. Gallese & Goldman, (1998) observed, what they believed to be, similar neural firing in the human brain when a person performed a task, and when the same person watched someone else carry out the same task (Gallese & Goldman, 1998). The neural firing that they observed is purported to create a dynamic representation between perception, action, and experience (Gallese & Goldman, 1998). As a consequence of these and

similar postulations the neural activity of the hMNS has been claimed to be essential for; the ability to imitate (Williams, Whiten, Suddendorf, & Perrett, 2001); for emulation and motor mimicry (Bons et al., 2013; Hamilton, 2008), develop a theory of mind (Dapretto et al., 2006); develop empathy (Gallese, Rochat, Cossu, & Sinigaglia, 2009; Oberman & Ramachandran, 2007; Thagard, 2007), and the ability to understand social cues (Iacoboni, 2009). Thus, the function of the hMNS is said to provide a universal ideomotor framework for understanding these specific human mental abilities (Iacoboni, 2009).

Other research that used neuroimaging techniques have suggested that a similar observation-execution matching system is also present in the human cortex to that of primates (Grafton et al, 1996; Hari et al. 1998; & Nishitani & Hari, 2000). For example, Grafton et al, (1996) used positron emission tomography (PET) imaging of cerebral blood flow in order to establish which brain regions are involved in the representation of human hand grasp motor actions. Grafton et al. (1996) observed that cortical areas including; the left rostral superior temporal sulcus, left inferior frontal cortex (BA45), left rostral inferior parietal cortex (BA40), the rostral part of the left supplementary motor area (SMA), and the right dorsal premotor cortex, are active during a grasp observation condition.

However, brain areas including; the left caudal inferior parietal cortex (BA40, a greater response in the left rostral SMA, and left dorsal premotor cortex, are active during an imagined grasping condition. Grafton et al. (1996) also observed that the two conditions activated opposing areas of the right posterior cerebellar cortex. Grafton and colleagues (1996) suggest that brain regions activated during observation of the grasping action may well form a circuit that

facilitates the recognition of hand-object interactions. In contrast, they also suggest that areas active during the imagined hand grasp condition could be a human comparison to a similar circuit observed in non-human primates.

Similarly, Hari and colleagues (1998) used magnetoencephalography (MEG). to record neuromagnetic oscillatory activity from within the human precentral cortex, of 10 neurologically intact participants, Hari et al's (1998) task incorporated 3 conditions; 1) participants remained relaxed with no task to perform, or 2) they were asked to manipulate a small object with their right hand, and finally 3) they observed an experimenter perform an identical task, with the experimenter's right hand next to, and approximately parallel to, the participant's right hand. In addition, each participants left, and right, median nerves were stimulated using alternating patterns with stimulation intensities exceeding each subjects motor threshold. Each alternate pattern of stimulation was separated by an interstimulus interval of 1.5 seconds. Condition one was repeated without median nerve stimulation, for 60 seconds with eyes open and again with eyes shut, while simultaneously recording spontaneous cortical activity to assess signal replicability (Hari et al. 1998).Hari et al. (1998) were then able to calculate the post-stimulus rebound of the 15- to 25-Hz activity recorded in the vicinity of the Rolandic (central) sulcus. Hari et al. (1998) discovered that there was strong bilateral rebound suppression during object manipulation.

More intriguing however was that Hari and colleagues observed that the same rebound suppression was significantly reduced during action observation. Moreover, their control studies, whereby participants were asked to observe stationary or moving stimuli, helped confirm the precise neural mechanisms that

facilitate this suppression effect. Hari et al. (1998) reasoned that the human primary motor cortex is activated during both action observation and action execution. Hari and colleagues drew this conclusion from the knowledge that activity recorded at 15- to 25-Hz is known to originate predominantly from within the precentral motor cortex,

Later research by Nishitani and Hari (2000) was able to establish the temporal dynamics of cortical activation via neuromagnetic recordings during execution, on-line imitation, and observation of right-hand reaching movements which ended with a precise pinching grip of the tip of a manipulandum. Nishitani and Hari (2000) observed that the left inferior frontal cortex, also known as, Brodmann's area (BA) 44, was active first (250ms prior to the pinch) during action execution. This initial activation was followed by activation in the left primary M1 (BA4), and within 100–200 ms, but later,150–250 ms, in the right primary M1 (BA4). This sequence was also similar during both imitation and observation. However, this activation originated from the left occipital associated visual cortex (BA19).

Interestingly, Nishitani and Hari (2000) observed that this neural activity was always strongest during action imitation. Moreover, occipital activation was only identified when the participant observed the experimenter reaching with his hand in the absence of the pinch action. Nishitani and Hari's (2000) findings suggest that the left Broca's (BA44) is the predominant driver of the human "mirror neuron system" and is significantly involved in human action imitation. Nishitani and Hari (2000) posit that neurons in the mirror neuron system match both action execution and observation, and most likely provide humans with the ability to understand the actions of others.

Furthermore, since the hMNS is said to be directly associated with brain regions including, but not exclusive to, supplementary motor area, primary somatosensory cortex, premotor cortex, and the inferior parietal cortex (Molenberghs, Cunnington, & Mattingley, 2012), that the motor, communication, and socialisation difficulties faced by those with ASD, may be caused by dysfunctions in these areas (Perkins et al., 2010; Ramachandran, 2000b; Ramachandran, 2000). Indeed, it was Ramachandran (2000) who first theorised that a dysfunctional hMNS could be a single cause hypothesis for the complex symptoms seen in those with ASD. Ramachandran (2000) subsequently named this theory the 'broken mirror hypothesis of autism'.

Support for Ramachandran' (2000) theory, particularly from within the neuroscience community, soon followed. Indeed, neuroimaging studies have been able to show a strong association between physiological mechanisms of mirroring at both single-cell and neural-system levels (Keysers & Gazzola, 2010; Kilner, Neal, Weiskopf, Friston, & Frith, 2009; Mukamel, Ekstrom, Kaplan, Iacoboni, & Fried, 2010; Oberman et al., 2005; Oztop, Kawato, & Arbib, 2013). For example, Oberman et al., (2005) examined electroencephograph (EEG) recordings of 10 males with high functioning ASD and 10 age and gender matched typically developing control participants to investigate the hMNS. Their EEG data was analysed for mu rhythm suppression across all the participant groups (Oberman et al., 2005). Mu rhythm is a pattern of electrical activity in the brain that is suppressed or blocked when the brain is engaging in seeing, doing, or imagining action behaviours (Oberman et al. 2005). Oberman and colleagues

(2005) suggest that mu rhythm suppression correlates with activity within the hMNS and that this is evidence for its existence.

They also posit that the findings of their study offer support for Ramachandran (2000) dysfunctional hMNS hypothesis regarding individuals with ASD. Further support is found in the work of Oosterhof, Wiggett, Diedrichsen, Tipper, & Downing, (2010) who found *f*MRI activations in brain regions argued to contain mirror neurons during action performance and observation. Similarly, studies using *f*MRI (Martineau, Cochin, Magne, & Barthelemy, 2008), MEG (Nishitani, Avikainen, & Hari, 2004), and TMS (Cattaneo et al., 2007), have also suggested evidence for a dysfunctional hMNS in ASD. However, this evidence can be disputed as there are several limitations to these indirect measures of human cortical activity.

Nevertheless, a much more directed and convincing finding for the existence of the hMNS was found following single cell recordings of the human brain (Mukamel et al., 2010). Mukamel and colleagues (2010) point out that, although single cell recordings of MNS function in humans are far rarer than *f*MRI, they are considered a more direct and accurate measure of cortical activity (Mukamel et al., 2010). Mukamel and colleagues (2010) were able to obtain single cell recordings of the human brain and subsequently demonstrated that, not only do humans have mirror neurons, but that they are also present in more regions than previously thought. Mukamel et al., (2010) recorded extracellular activity from a total of 1177 single neuron' in 21 patients who were undergoing surgery for intractable epilepsy. During surgery these patients were conscious and able to view, and execute, both grasping actions and facial gestures in an observational task, whilst simultaneously observing various actions presented

to them on a laptop. In the execution task, the patients were prompted to perform an action from a word presented visually. Finally, in a control condition the same words were presented to them, but they were instructed not to execute any corresponding actions (Mukamel et al., 2010).

Mukamel et al., (2010) observations demonstrated ‘mirror’ spiking activity during action- observation and action- execution in the human medial frontal cortex, and in the human medial temporal cortex, the two cortical systems purported to contain mirror neurons (Hamilton, 2008). What makes this study so interesting is the fact that the mirroring responses they observed in these regions had not been recorded so directly before. Moreover, what was even more intriguing is that Mukamel and colleagues (2010) also noticed that a subgroup of these mirroring neurons exhibited opposing patterns of inhibition and excitation during both action- observation and action- execution. They suggest that this pattern of neural firing may help preserve a sense of body ownership over actions during execution, as well as exerting control over unwanted imitation during observation (Mukamel et al., 2010). They further suggest that their results provide evidence for; the existence of several systems within the human cortex that contain mirror neuron mechanisms, and state that these mechanisms may facilitate the flexible integration and variation of both motor and perceptual aspects of actions executed by the self and other individuals (Mukamel et al., 2010).

This strongly suggests that the hMNS may be directly involved in how empathy and theory of mind (TOM) are mediated. As a result of this, and similar arguments (Dapretto et al., 2006; Jacob, 2008; Oberman et al., 2005; Perkins et al., 2010), the function of the hMNS has since become the focus for explaining

‘mind blindness’, a term frequently associated with ASD (Rizzolatti & Fabbri-Destro, 2008). Difficulties with empathy along with the inability to understand that others have different emotions, perspectives, TOM, and thoughts, are considerable social obstacles in cases of ASD (Rizzolatti & FabbriDestro, 2008; Williams, 2008).

Thus, connecting these complex impairments in ASD to a dysfunctional hMNS does appear to make some semblance of sense. Indeed, human beings are primarily social creatures and successful socialisation relies heavily on one’s ability to detect, recognise, and understand the cognitive, motor, and emotional processes frequently displayed by those around us (Brüne & Brüne-Cohrs, 2006). This ability to infer another individuals’ mental state and emotions is what is frequently referred to as ‘theory of mind’ (TOM) (or mentalising) (Frith & Frith, 2005; Saxe & Kanwisher, 2003), and/or empathy (Shamay-Tsoory, 2011; Singer & Tusche, 2013). As noted earlier, both these human mental processes have been postulated to be mediated by the hMNS (Gallese et al., 2009; Oberman & Ramachandran, 2007; Thagard, 2007).

Empathy, despite being a multilevel construct (Singer & Lamm, 2009), is typically described as the capacity to infer and share the emotional experiences of others. TOM (or mentalising) on the other hand is described as the capability to attribute mental states such as; intentions, desires, or beliefs, to other individuals to understand, explain, or even predict their behaviours (Frith & Frith, 2005). These constructs relating to empathy and TOM appear to overlap considerably, and as such are highly correlated with each other. The consequence of this overlap means the two terms are used interchangeably and frequently represented as meaning the same thing (Blair, 2005). Such an

amalgamation of terms also means that there is no universal consensus regarding the constructs and definitions of both empathy and TOM.

For example, some researchers define empathy as a binary construct that consists of both an affective and a cognitive component (Reniers, Corcoran, Drake, Shryane, & Völlm, 2011). Similarly, Kalbe et al. (2010) also describe their TOM model as having two distinct components, namely affective and cognitive TOM. In support of this notion, Reniers, Völlm, Elliott, & Corcoran (2014) cite evidence from recent neuroscience literature that suggests empathy and TOM are mediated by similar underlying mechanisms which are apparent at the neural level. However, Blair (2005) postulates a three-component construct of empathy. Blair (2005) states that empathy should not be viewed as either a unitary or binary system, but instead should be seen as a loose collection of somewhat dissociable neurocognitive systems, which all work together to aid understanding of self and self-other representations. The result of this belief led Blair (2005) to add a motor element to his model of empathy. He added the motor component to reflect the propensity that individuals have for mirroring the motor responses of those they observe, and subsequently used the term ‘motor empathy’ to describe this phenomenon.

Motor empathy is defined as the propensity to automatically and synchronously mimic the postures, facial expressions, vocalisations, and/or movements of another (Hatfield, Cacioppo, & Rapson, 1994). However, adopting the postures of an observed other is also frequently referred to as ‘motor mimicry’, which also leads to an amalgamation of terms (Bavelas, Black, Lemery, & Mullett, 1986; Hamon-Hill & Barresi, 2010; Moody & McIntosh, 2011). Support for this also comes from neurocognitive accounts of motor empathy, which suggests that it

is a mechanism by which action representations modulate emotional activity (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003). Carr et al., (2003) posit that the superior temporal and inferior frontal cortices are essential regions for action representation, and further, that these areas are linked, via the insula, to the limbic system. This suggests that the insula may act as a crucial relay from action representation to emotional regulation (Carr et al., 2003).

Carr and colleagues (2003) used functional MRI (*f*MRI) to record subjects' responses while they were either observing or imitating emotional facial expressions. The result of this investigation demonstrates that observation and imitation of emotions activates a predominantly similar network of brain regions (Carr et al., 2003). In addition, Carr et al, (2003) noted that there was increased activity during imitation, when compared with observation of emotions, in areas related to the premotor system including; the inferior frontal cortex, the superior temporal cortex, amygdala and insula. This suggests that people can understand what another might be feeling by a mechanism of action representation and empathic modulation via limbic cortices (Carr et al., 2003).

According to this account, perception of another individual's mental state activates the observers corresponding motor representations of that state. Carr et al (2003) further posit that this then activates both autonomic and somatic responses at the anatomical level (Carr et al., 2003). Their conclusion is that the superior temporal cortex (STC) maps an early visual depiction of an action and subsequently relays this information to posterior parietal mirror neurons that code for the exact kinaesthetic feature of this action. These mirror neurons then transfer this information to other areas of cortex containing mirror neurons, namely the inferior frontal cortices (Brodmans area' 44 & 45), which are then

said to code the goal of the action. Carr and colleagues (2003) also posit that the connections from superior temporal, parietal, and inferior frontal cortices to the insula permit this representational information to produce emotional responses through corresponding limbic regions (Carr et al., 2003).

In sum, motor empathy appears to rely upon both the activation of neurons that code a movement description in the STC, and the activation of mirror neurons in the parietal and inferior frontal cortex, which all code for the execution of effective social imitation (Carr et al., 2003). This, along with converging evidence between cognitive models of imitative action, and constructs originating from social psychological research regarding motor mimicry, as well as empathy research (Heyes, 2011; Iacoboni, 2009; Oberman et al., 2005), all support the notion that the hMNS is heavily involved in modulating motor empathy and imitation (Heyes, 2011; Iacoboni, 2009; Oberman et al., 2005).

However, there remains hard to ignore cautious scepticism within the neuroscience community regarding the actual existence of the hMNS, and, to its reported role in empathy, TOM, and action understanding. This cautious scepticism led researchers to, not only investigate the existence of the hMNS and its role in action understanding, but also Ramachandran' (2000) ‘broken mirror’ theory of ASD (Dinstein, 2008; Hamilton, 2013). Hamilton’ (2013) systematic review of MNS research in autism suggests that the ‘broken mirror hypothesis of ASD’ cannot be supported in its current form. Support for Hamilton’s (2013) view is seen in research conducted by Dinstein et al., (2010) who found normally functioning hMNS among individuals with ASD. Dinstein et al., (2010) used fMRI to measure brain activity in subjects with ASD and in neurologically typical controls; they found that the MNS response in the ASD

subjects tested was not only strong but also surprisingly normal. Dinstein et al. (2010) suggest the reason for such conflicting results could be because previous testing for mirror neuron dysfunction among individuals with ASD might be skewed by a delay in their neurological responses.

Dinstein and colleagues suggest that the brains of individuals with ASD could be experiencing a delay in mirror neuron activity, which is consequentially misinterpreted as a dysfunction. Interestingly, they went on to offer an alternative theory to the mirror neuron hypothesis. Dinstein et al. (2010) suggestion is that the problem is not with any particular system of the brain, but rather the connections between them. Lead author Dinstein offers the idea of a 'global brain problem', which is said to be affecting the autistic mind. This theory appears to be a reasonable explanation considering the wide spectrum of effects that manifest in these disorders. To support this view Dinstein et al., (2012) presented evidence for poor evoked response reliability in ASD.

Dinstein and colleagues (2012) compared cortical response amplitude and reliability across individual trials in visual, auditory, and somatosensory cortices in individuals with high functioning autism and neurologically intact controls. Whilst mean response amplitudes were not statistically different across groups, trial-by-trial response reliability was far weaker in ASD. Notably, the group with autism presented smaller signal-to-noise ratios in all sensory systems. However, it is important to highlight here that the significant differences in response reliability were only observed during evoked cortical responses and not during ongoing resting state activity (Dinstein et al., 2012). Dinstein and colleagues' findings suggest that abnormally unreliable cortical responses, even those involving elementary non-social stimuli, could represent a physiological

alteration of neural processing among those with ASD, which does offer some support for their ‘noisy brain’ hypothesis. However, it can be seen from Dinstein and colleagues (2012) research that they do not refute the existence of the human MNS only that its function may be altered in ASD.

In contrast, Hickock (2009) argues that testing for the precise role mirror neurons play is merely speculative at best (Hickock, 2009). Hickock (2009) posits that the idea of mirror neurons being associated with action understanding is problematic due to, insufficient testing in monkeys, and because empirical evidence relating to neuropsychological and physiological double dissociations in humans refutes the existence of a hMNS altogether. Hickock (2009) further argued that following the discovery of mirror neurons in monkeys, not much progress has been made in regard to understanding mirror neuron functioning among humans. He suggests that this is a direct result of overemphasising action understanding theories, which he says further detracts research away from exploring other possible, and possibly more important, cortical functions.

Hickock (2009) makes a good point, given that action-execution, action-observation, and more specifically the control of unwanted imitation during observation, are important considerations, especially since these behaviours are often altered in neurodevelopmental disorders. For example, there is evidence of imitative anomalies, which involve issues with both copying another’s actions, and the ability to inhibit stereotyped mimicking behaviours of another, among individuals with neurodevelopmental disorders (Ganos, Ogrzal, Schnitzler, & Münchau, 2012; Williams, Whiten, Suddendorf, & Perrett, 2001). This suggests that not all imitative behaviour is intentional, and as such, could

be seen as the release of a predetermined motor pattern from an individuals' own repertoire of behaviour (Ganos et al., 2012). Indeed, there are many instances where it is considered pathological and indicative of an underlying neurological disorder (Ford, 1989). Ford (1989) referred to this pathological form of involuntary mimicking behaviour as echophenomena.

1.3 *Echophenomena in typical and atypical development*

Ganos and colleagues (2012) define echophenomena as automatic imitative behaviours without explicit awareness (Ganos et al., 2012). Echophenomena is also characterised by two distinct subtypes of stimulus driven 'mimicking' behaviours, namely echolalia and echopraxia (Ganos et al., 2012). Echopraxia is said to involve the automatic repetition of another person's goal directed motor actions (Ford, 1989). Echolalia on the other hand is said to be the non-communicative repetition of sounds and/or language which can be both immediate or delayed (Ganos et al., 2012; Volkmar, Lord, Bailey, Schultz, & Klin, 2004). It is also evident from the literature that repetition of another individual's action is to a large extent a normal feature of human behaviour, and clearly necessary for the development of prosocial behaviours, social cognition, empathy, and TOM, which makes echophenomena an essential component for normal development (Jones, 2009).

Jones (2009) discovered that an infant's echoing behaviour, specifically of those around them, begins just a few weeks after birth. However, in keeping with the 'wealth of stimulus theory', where a model regarding imitative development based on associative sequence learning is proposed (Ray & Heyes, 2011), Ganos et al. (2012) argue that the ability to distinguish between

automatic imitation, imitative learning, and echophenomena before the age of 2 is impossible. Ganos and colleagues (2012) further state that echophenomena and/or imitative behaviour develops over the first two years of life through Ray and Heyes (2011) hypothesised associative learning process. This process is said to promote communication, social interaction, and learning through the procurement and embodiment of transitive and intransitive catalogues of observed, and executed, motor actions (Want & Harris, 2002). It is also said to facilitate the modulation of emotions according to the emotional states of others, which can be observed in emotionally contagious behaviours (Shamay-Tsoory, 2011).

However, Jones (2009) and Ganos et al., (2012) both agree that for echophenomena to be considered a normal feature of development, it should be seen to decrease over time. For instance, it is recognised that preservation of imitative learning is essential for the development of healthy sensorimotor and social functioning moving into adulthood, and as such considered completely normal. However, as noted earlier, repetitive automatic imitation should gradually lessen over time and only occur infrequently throughout adulthood. For instance, contagious behaviours such as; coughing, smiling, itching, and yawning, all occur in healthy adults, and are known to be a normal and necessary feature for the promotion of social interaction with others (Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011).

However, if such behaviours persist into socially and emotionally less meaningful contexts they can then be considered pathological in nature (Ganos et al., 2012). Indeed, echophenomena are often reported as a clinical feature of many neurological conditions including; Gilles de la Tourette’s syndrome

(Ganos et al., 2012), ASD (Spengler, Bird, & Brass, 2010), some forms of aphasia (Hadano, Nakamura, & Hamanaka, 1998), and schizophrenia (Pridmore, Brüne, Ahmadi, & Dale, 2008). Moreover, Provine (1986) suggests that echophenomena might well be automatically generated by ethological releasing mechanisms that are ultimately responsible for activating stereotypical motor actions. This suggestion is wholly consistent with the development of self-regulatory mechanisms and reduced automatic imitation of observed actions (Ganos et al., 2012). Evidence for this account comes from observations of echophenomena occurring within a few weeks of birth but then diminishing from approximately three years of age (Ganos et al., 2012).

However, an example of atypical behaviour is when pathological echolalia, in the form of repetitive mimicking of sounds and/or vocalisations, persists beyond age 3, which is evident in some cases of ASD. There also exists the view that echophenomena is a pathological feature frequently seen in a variety of other clinical conditions (e.g., epilepsy, dementia, Tourette syndrome), and seemingly related to increased cortical excitability and/or decreased physiological inhibition (Ganos et al., 2012). Moreover, Ganos and colleagues (2012) argue that the propensity for echophenomena could well be associated with observed individual differences in motor cortical excitability.

Surprisingly, despite the repetitive nature of echophenomena, it is not seen in those with obsessive compulsive disorders (OCD) (Cath et al., 2001). For example, Miguel et al., (1997) assessed cognitive, sensory and autonomic phenomena preceding repetitive behaviours. Miguel et al (1997) found considerably more thought processing and autonomic anxiety behaviours, yet fewer sensory phenomena, in cases of OCD as compared to pure Tourette's.

Similar to the Tourette's group, the group co-morbid for OCD and Tourette's reported increased sensory phenomena and less thought processing than the OCD group. Miguel and colleagues (1997) conclude that the presence or absence of thought related cognitions, sensory phenomena, and autonomic anxiety, differentiates repetitive behaviours among those with OCD from patients with OCD plus Tourette's, and pure Tourette's. Indeed, prior to any compulsive behaviour being actioned, OCD type behaviours appear to involve a number of aberrant orbitofrontal thought processes, and as such are not outside of conscious awareness in the same way as some automatic behaviours are. Support for this notion can be found in a factor analytic study of 639 patients (Cavanna et al., 2011).

Cavanna et al., 2011) conducted a study that assessed individuals with obsessive compulsive disorders (OCD) and found that echophenomena originates in inhibitory and/or facilitatory neural systems and is not simply the result of behaviours facilitated by an OCD diagnosis (Cavanna et al., 2011). Moreover, it suggests that echophenomena may well be mediated by separate neural mechanisms, rather than those related to OCD type behaviours. In addition, this finding also provides further support for Ganos et al., (2012) postulations regarding increased cortical excitability and/or decreased physiological inhibition in neurodevelopmental and neuropsychiatric disorders.

What is more astonishing is that echophenomena, imitation, and contagious yawning, are all argued to fit under the umbrella term 'automatic imitation' (Heyes, 2011), which is said to be mediated by the hMNS. Thus, although these processes appear to elicit similar neural processes, the above literature suggests that something different, and distinctly separate, may well be going on

during episodes of contagious yawning and as such requires further investigation.

1.4 *Echophenomena – in the form of contagious yawning*

Yawning has long been observed as a contagious act (Provine, 2005). Provine (2005) describes yawning as a vigorous widespread act that can trigger the replication of the same act in its observers. Provine (2005) further states that this innate action bears the hallmark of human evolutionary origins. Moreover, contagious yawning is considered a unique and valuable tool for facilitating understanding regarding how the human brain operates (Walusinski, Meenakshisundaram, Thirumalaikolundusubramanian, Diwakar, & Dhanalakshmi, 2004). Walusinski et al., (2004) posits that uncovering which mechanisms underly contagious behaviours could help provide knowledge regarding what separates us from other animal species.

Contagious yawning affects approximately 60% of healthy human beings (Platek, 2010). It is also observed, to a lesser degree, in old world primates and some dogs. Platek (2010) summarises contagious yawning as an expression of social cognitive processing, more notably empathy. Furthermore, the susceptibility of an observer to the act of contagious yawning is significantly associated with the speed in which they recognise their own face, alongside theory of mind processing (Platek, Mohamed, & Gallup, 2005). It is also said to be linked with the activation of cortical regions known to be related to social cognitive processes (Platek, 2010). Platek (2010) posits that contagious yawning could be an evolutionarily ancient process that aided the production of higher levels of social cognition in some animal species.

In support of this notion, it is suggested that a neonate's assumed ability to imitate the facial expressions and/or gestures of their adult caregivers could well be the result of ethological fixed-action releasing mechanisms facilitated via sign stimuli (Provine, 1989). Provine (1989) goes on to suggest that contagious yawning among adults sets an example for facially fixed-action patterns (e.g. yawns) generated by a facial stimulus (e.g. observed yawns). Humans are highly social creatures who display significant skill when it comes to interpreting the facial expressions and/or gesticulations of other humans, as well as responding optimally to any expectations, signals and behaviours that might be encoded within these acts (Franzen, Mader, & Winter, 2018).

It should also be noted that there are many other acts that are considered contagious, such as laughing, itching, and coughing. However, none of these acts can surpass the act of contagious yawning in its power to facilitate an identical act in an observer. Simply reading, hearing, or thinking of the word yawn can make an observer succumb to the act of yawning themselves (Walusinski et al., 2004). In sum, although yawning is frequently considered a sign of boredom or tiredness, contagious yawns provide evidence of the development of human social ability and capacity to empathise with others. The inability to escape the transmission of contagious behaviours, not least yawning, demonstrates that humans are often unaware that they are neurologically preprogrammed social creatures. Thus, the investigation of the neural basis of contagious yawning could provide a convenient noninvasive way to understand how imitation, and mirroring phenomenon, among typically developed humans, are produced and controlled. The study of CY could also

provide insights regarding the neural genesis of automatic imitative behaviours, as well as the urge for action.

1.5 *Urge for Action*

At its most basic fundamental level the human brain is a simple carrot and stick biochemical system that essentially forces us into action. Moreover, prior to action execution, it is often argued that there is sometimes an overwhelming sensation of wanting to act, otherwise referred to as an urge (Jackson, Parkinson, Kim, Schüermann, & Eickhoff, 2011). Thus, an urge is defined as a strong desire or impulse to carry out a particular behaviour or action. Jackson et al., (2011) posit that many of our daily behaviours are characterised by internal body sensations. Further, according to Jackson and colleagues we experience these internal sensations as a desire or urge for action. For example, a tickle in one's throat may facilitate an overwhelming urge to cough or swallow which is impossible to voluntarily suppress (Jackson et al., 2011). However, the authors also state that not every urge for action is preceded by bodily sensations. For instance, while we might occasionally feel a strong urge to yawn, there are times when one simply finds oneself yawning without first experiencing a sensory trigger for the yawn (Jackson et al., 2011).

However, most social psychologists are in general agreement that almost all human behaviour is goal-directed (Aarts & Elliot, 2011; Custers, Eitam, & Bargh, 2012; Dijksterhuis & Aarts, 2012; Perugini & Bagozzi, 2001). Ajzen (1985) says that such behaviours are neither capricious or frivolous, and that human social behaviours are best described as the pursuit of more or less well-formulated plans. Most, if not all, human behaviours will be planned in advance

and their execution will occur as these plans unfold (Ajzen, 1985). Surety of action comes when a set sequence of acts becomes so familiar, or routine, that they are performed completely automatically, as is the case when driving a car or riding a bicycle for example. These highly developed cognitive skills no longer require the conscious construction of a set behavioral plan (Ajzen, 1985; Jackson et al., 2011).

Jackson and colleagues (2011) state that urges are oftentimes referred to as drives or impulses which compel us to act. However, it is also postulated that such acts can, and often do, occur in the absence of any conscious awareness of these drives or cues to act. As noted, one can simply find oneself acting out a behaviour without first feeling any bodily sensation or trigger for said behaviour (Jackson et al., 2011). Thus, it could be argued that these are reflex behaviours and not urges for action at all. That said, Jackson et al., (2011) suggest that a potential distinguishing facet of urges, which are separate to reflexes, are that they cannot be executed immediately and must be held under control until they can be released.

It would also appear that an urge is often described in the same context as a ‘desire’, which implies that every urge-for-action arises as a consequence of pleasant bodily sensations or desires. However, as Jackson et al., (2011) would attest, this is simply not the case in all instances of urge-for-action. For instance, it is known that many common neurodevelopmental and psychiatric conditions such as obsessive-compulsive disorder (OCD), Tourette syndrome (TS), autistic spectrum disorder (ASD), dementia, or schizophrenia, are frequently linked to unpleasant body sensations that precede movement

execution, and as such subsequently perceived as an urge for action (Jackson et al., 2011).

Currently, little is known regarding the neural basis of urge-for-action during episodes of echophenomena, and more interestingly contagious yawning. This is an important consideration given that many individuals report feeling an urge to yawn prior to an actual yawn being realised or stifled. In addition, there is some debate regarding whether the urge to yawn is mediated by the same brain region as the act of contagiously yawning itself. For example, (Nahab, Hattori, Saad, & Hallett, 2009) argue that the urge-to-yawn, via a contagion, as opposed to other non-contagious facial expressions, does not occur as a process of imitation or mimicry, but rather from a primeval motor program which is actuated by cortical regions and facilitated through well characterised brainstem and sub-cortical mechanisms. This suggests that the urge-to-yawn is a separate phenomenon and unrelated to imitation and the act of contagious yawning itself (Nahab et al., 2009). This is important particularly in respect of impulse control disorders whereby an urge-for-action typically precedes the expression of an action; an example of such would be premonitory urges followed by tic expression in Gilles de la Tourette's Syndrome.Thus, it would seem from the literature that the impulse, or urge to act out a behaviour, go hand in hand. However, that said, not all impulsive acts can be considered along the same axis as urges for action, nor can they be considered as conscious social acts. Indeed, impulsive actions are oftentimes automatic behaviours that also occur without explicit awareness or forethought (Evenden, 1999).

1.6 *Non-social automatic behaviour in the form of Impulsivity*

Impulsivity is frequently described as involving the propensity to display behaviours that are characterised by little to no forethought, reflection, or consideration of potential outcomes (Evenden, 1999). Moreover, this type of behaviour is often reported as; badly conceived, expressed prematurely, overtly risky, or inappropriate for a given situation, which can result in profound negative outcomes (Zermatten, Van der Linden, d'Acremont, Jermann, & Bechara, 2005). Impulsive actions are also typically said to impair long term goals and stratagems for success (Gregory Madden, Bickel Washington, & Perna, 2010). In addition, this maladaptive description of impulsivity, also commonly referred to as dysfunctional impulsivity, is frequently cited as a clinically important facet of many neuropsychiatric and neurodevelopmental conditions such as; ADHD (Anholt et al., 2010), Tourette's Syndrome (Cavanna et al., 2011), Autism Spectrum Disorders (Aman, Farmer, Holoway, & Arnold, 2008) Bipolar Disorder, (Victor, Johnson, & Gotlib, 2011), and Schizophrenia (Chamberlain & Sahakian, 2007; Kaladjian, Jeanningros, Azorin, Anton, & Mazzola-Pomietto, 2011) to name a few.

However, current research regarding impulsivity among the general population lacks a definitive consensus which is primarily due to disagreements regarding its underlying theoretical assumptions (Miller, Joseph, & Tudway, 2004). Miller et al (2004) suggest that such disagreements have led to confusion regarding how best to measure and define impulsivity. Initially the debate attracted a lot of attention from personality and behavioural theorists who argued that impulsive behaviours are related to an individuals' personality type (Barratt, 1959; Carver & White, 1994; Eysenck, 1952; Gray, 1970 & 1981; Patton, Stanford, & Barratt,

1995). These theorists suggested that those with certain personality types are quite likely to exhibit impulsive behavioural traits and not just those with neuropsychiatric disorders. However, these propositions have since fallen out of favour among psychologists. This is because personality test scores typically fall somewhere on a bell shaped curve as opposed to fitting into any distinct category or type (Bess & Harvey, 2002).

Bess and Harvey (2002) supported this view by directly comparing the Myers-Briggs Type Indicator (MBTI) (a *'type'* instrument), with the Neuroticism, Extraversion, Openness, Personality Inventory (NEO PI) (a *'trait'* instrument) and discovered that the trait measure was a better predictor of personality overall. Consequentially many researchers now argue that it is impossible to explain the diverse facets of human personality, or indeed impulsive behaviour, using just a small number of discrete types. As a result of this, many researchers have since revised their questionnaires using factor analysis in order to explain impulsivity as a multi-factorial construct, and not just as a facet of a given personality type (Patton et al., 1995). Indeed, the *Barratt Impulsiveness Scale,* particularly the behavioural inhibition system (BIS), one of the oldest personality questionnaires, has since become one of the most extensively used instruments to assess impulsive personality traits.

The instrument that is used today however is very different to Barratt' (1959) original BIS. Barratt and colleagues extensively revised the original BIS in order to achieve two main goals. The first goal was to ascertain a subset of 'impulsivity' items that were orthogonal to a subset of 'anxiety' items. While the second was to define impulsive behaviours within the structure of related personality traits (Barratt, 1959). Subsequently the BIS-11, which encompassed

30 separate items, was developed in 1995 (Patton et al., 1995). According to Patton et al (1995) there is now 3 subscales within the BIS-11 that include; 1: 'Attentional Impulsiveness', 'Motor Impulsiveness', and 'Non-Planning Impulsiveness' (Patton et al., 1995). However, Carver and White (1994) argue that the behavioural inhibition system (BIS), most likely relates to an individual's sensitivity to punishment.

Patton and colleagues further moot that these subscales encompass a further 6 factors. The six factors in question include; *1) attention (focusing on the task at hand), 2) Motor impulsiveness (spur of the moment action), 3) self-control (carefully planning and thinking ahead), 4) cognitive complexity (enjoyment of challenging mental tasks), 5) perseverance, (adhering to a consistent life style) and finally, 6) cognitive instability (racing thoughts and thought)* (Patton et al., 1995). However, despite impulsiveness being represented in many contemporary models of human personality such as that seen in the BIS-11, the ways in which these traits have been theorised and evaluated actually differ to such an extent that the combination of these findings often proves problematic (Stautz & Copper, 2013).

In an attempt to resolve this problem, researchers have endeavoured to reorganise impulsivity constructs into a range of separate, albeit connected, traits (Dawe & Loxton, 2004). Dawe and Loxton (2004) argued that it is better to conceive impulsivity as comprising two main facets characterised as rash impulsiveness and reward sensitivity, also known as 'reward drive'. In terms of *'reward sensitivity'* this is said to reflect a set of neuronal projections that are involved in incentive motivation and reward processing, and reactivity of a theoretical behavioural approach system (Stautz, & Copper, 2013). On the

other hand, rash impulsivity is best conceptualised as a failure to change or prevent a response even when such action might result in negative outcomes. Any individual differences, particularly found among those with this trait, are argued to reflect orbitofrontal and anterior cingulate cortex functioning (Dawe & Loxton, 2004).

With regard to reward sensitivity this can be evaluated with self-report questionnaires such as Carver and White's (1994) 'Drive and Reward Responsiveness subscales of the BIS/BAS scales' (Carver & White, 1994), and Torrubia, Avila, Molto, & Caseras, (2001) 'Sensitivity to Reward scale'. Carver and White's (1994) behavioural inhibition system (BIS) relates to an individual's sensitivity to punishment. In contrast, the behavioural activation system (BAS) refers to sensitivity to reward. Reports of an imbalance between these two motivational systems is often cited as being related to different forms of psychopathology. Scores from these methods are thought to reflect responsiveness to appetitive cues and the ability to engage relevant approach behaviours in situations where there is a probable reward (Stautz, & Copper, 2013). Stautz and Cooper (2013) posit that although higher reward sensitivity might not lead to frequent impulsive behaviours, individuals who have a higher degree of reward sensitivity might be more vulnerable towards positive reinforcement type stimuli, and as a consequence may well act with impulse in response to the conditioned cues that are fundamentally associated with said stimuli.

However in respect of measuring rash impulsiveness, this is arguably less straightforward than measuring reward sensitivity (Stautz, & Copper, 2013). This is because evidence from converging psychometric studies implies that

two dimensions are simply too inadequate to explain the multiple variations seen in impulsive actions. For example, Whiteside & Lynam (2001) employed factor analysis to investigate a variety of frequently administered self-report instruments of impulsiveness and derived four dimensions labelled; sensation seeking, lack of perseverance, urgency, and lack of premeditation (Whiteside & Lynam, 2001). Moreover these particular dimensions demonstrate diverse correlations with higher order traits from Costa and McCrae (1992) five-factor model (FFM), and as such can be evaluated by employing the UPPS Impulsive Behaviour Scale (Whiteside, Lynam, Miller, & Reynolds, 2005).

These four factors highlighted by Whiteside et al (2005) are said to be differentially related to psychiatric disorders that are typically characterised by impulsive behaviours (Heyes et al., 2012), and to the risk associated with engaging in such impulsive acts. Whiteside and Lynam (2001) UPPS questionnaire was created to measure impulsive behaviour across several dimensions of the Five Factor Model of Personality. Therefore, the UPPS model assists in clarifying the variations seen in behaviours characteristic of rash impulsiveness. However, it is important to note that the *'reward sensitivity'* facet of the *'two-factor model of impulsivity'* is not best characterised by the four UPPS dimensions (Stautz, & Copper, 2013). Stautz and Cooper (2013) argue that this is most likely because facets of this construct did not feature in the original factor analysis conducted by Whiteside and Lynam's (2001).

Another popular questionnaire for the examination of impulsive and risky behaviours is the BIS/BAS measurement. The BIS/BAS is a 24 item self-report tool created to measure two motivational systems; the behavioural inhibition system (BIS), which relates to motivation to avoid aversive outcomes, and the

behavioural activation system (BAS), which relates to motivation to approach goal-directed outcomes (Carver & White, 1994). Moreover, many theorists have argued that impulsivity can be understood as a combined function of both the behavioural approach (BAS) and behavioural inhibition (BIS) systems (Braddock et al., 2011). Braddock and colleagues (2011) discovered that the BIS/BAS reliably predicted both impulsivity and risky behaviours.

Thus, it is evident from the literature that self-report measures are a popular and frequently used tool for measuring impulsivity. However, despite their popularity they are in fact only subjective measures of impulsivity, and as such tell us nothing about impulsivity from a behavioural perspective. Empirical research in the form of experimental cognitive paradigms such as; delay discounting (Mobini, Grant, Kass, & Yeomans, 2007; Reynolds & Schiffbauer, 2004); probabilistic gambling (Upton, Bishara, Ahn, & Stout, 2011); and information sampling tasks (Banca et al., 2016; Clark, Robbins, Ersche, & Sahakian, 2006; Quiroga, Martínez-Molina, Lozano, & Santacreu, 2011), have however been employed to measure impulsive decision making behaviourally (Heyes et al., 2012). However, as Heyes et al., (2012) points out, in none of these tasks are subjects required to respond quickly under time constraints. Moreover, such rapid 'impulsive' decisions during these tasks are always considered suboptimal (Heyes et al., 2012). The only other widely used cognitive paradigm, that does require participants to respond swiftly to an imperative cue, is the '*stop signal*' task. However it is worth noting that the rapid responses elicited during this task are also used to measure inhibitory control which could be argued to be an entirely different construct (Logan, Schachar, & Tannock, 1997).

While such tasks provide insight into dysfunctional impulsivity, and the negative connotations associated with it, it is worth highlighting here that not all acts of impulsivity result in negative consequences or necessarily maladaptive in nature. For instance, there are some acts of impulsivity that can be conceptualised as having adaptive qualities (Dickman & Meyer, 1988; Dickman, 1990). Dickman and Meyer (1988) found that participants who were considered highly impulsive could occasionally outperform individuals with low trait impulsivity when undertaking a simple task while under time pressure. This observation led Dickman (1990) to conclude that there may well be two distinct forms of impulsivity namely, *'dysfunctional'* (as described above), and '*functional impulsivity'.*

Dickman (1990) highlighted that functional impulsivity, while still characterised by behaviours executed with little to no forethought, can frequently result in positive or optimal outcomes. Dickman (1990) suggests that the ability to respond in a quick and skillful manner, particularly in the absence of significant deliberation, can be both adaptive and beneficial in some situations. For instance, while in most situations prolonged and cautious deliberation might well appear to be the safe and sure option, in reality there are some situations whereby this approach would be incredibly detrimental to the overall outcome (Dickman, 1990). An example of such a situation would be when executing an emergency stop in a motor vehicle in response to an unexpected obstruction in the road.

In addition to this, Dickman (1990) was also able to show that not only are these two forms of impulsivity unrelated across individuals, but that they also harness different cognitive correlates. For example, although Dickman (1990)

found that *'functionally impulsive'* individuals performed quicker and more accurately on a rapid task that required straightforward perceptual judgments, than individuals who were considered lower on *'functional impulsivity'*, there were no differences between the individuals with high and low dysfunctional traits. Furthermore, latest empirical data has demonstrated that *'dysfunctional impulsivity'* is inversely related with the capability for inhibitory actions which are indexed by the *'STOP'* signal reaction time task (Heyes et al., 2012). In contrast, *'functional impulsivity'* measures do not exhibit the same inverse relationship (Colzato, van den Wildenberg, Van der Does, & Hommel, 2010). Heyes et al., (2012) argue that these are important considerations to bear in mind when developing new experimental paradigms to accurately measure these similar, but at the same time, seemingly very different constructs of impulsivity.

Indeed, it was this issue that led Heyes et al., (2012) to develop a manual *'traffic light'* behavioural paradigm to measure *'rapid'* decision-making while in search of time-sensitive risky rewards. Their goal was to develop a task that harnesses the range of '*functional impulsivity'* among healthy individuals while also having the capacity to track its changes during ageing or pathological states (Heyes et al., 2012). For each trial in Heyes et al., (2012) *'traffic light paradigm'*, subjects had to view a red light that sequentially turned from amber to green. Subjects were then asked to respond rapidly following the onset of the green *'go'* traffic light signal to acquire a reward (responding before green incurred a small fixed penalty). The value of the reward declined quickly with increasing reaction time from the onset of the green light; thus, the subjects' goal was to make responses within the minimum possible time following the

onset of the green light. However, the amber duration varied so that the temporal onset of the green light could not be predicted easily (Heyes et al., 2012).

Moreover, their subjects could not achieve the highest rewards if they passively waited, and simply responded *reactively* to the onset of the green light (Heyes et al., 2012). This is because the human sensorimotor decision-making system is subject to significant delay. For instance, basic human motor decisions take approximately 200ms to initiate a response to a go signal (Cardoso-leite, Gorea, & Mamassian, 2009; Taylor, Carpenter, & Anderson, 2006). In order to optimise reward subjects had to decide, during the amber fore period, whether to wait or to take a risk and initiate *anticipatory* responses in advance. These *'risky'* decisions could lead to responses being implemented just prior to the onset of the green light (penalised trials) or just after it (highly rewarded trials). Thus, in order to do well in Heyes et al., (2012) task subjects had to display a degree of *'functional impulsivity'* by making some risky anticipatory responses. Heyes et al., (2012) could then evaluate evidence of impulsive opportunistic responding in their model by counting the number of penalised trials and the overall reward attained. Heyes and colleagues also used a probabilistic model in order to characterise decision-making behaviour. Moreover, using these parameters Heyes et al., (2012) were able to explore whether there were any relationships between anticipatory behavior in the *'traffic light task'* and self-reported measures of impulsivity, as well as investigating whether any changes in the degree of *'functional impulsivity'* occur across aging.

Results of Heyes et al (2012) *'traffic light paradigm'* suggests that it is of benefit to respond in an *'impulsive,'* anticipatory manner. They posit that their task

"captures *'functional impulsivity,'* which is also adaptive within the current environment and balances the benefits of careful premeditation with those conferred by rapid opportunistic responding" (Heyes et al., 2012, pg. 3). This argument is in line with Dickman's (1990) thoughts regarding *'functional impulsivity'*. However, subjects who obtained greater scores on a specific subsection of self-reported impulsivity (UPPS lack of premeditation) demonstrated greater levels of anticipatory behaviour and therefore accumulated higher rewards. This suggests that this type of task could be used to support the findings of self-report measures and subsequently used in research investigating functional vs. dysfunctional impulsivity in healthy controls or clinical groups. Moreover, Heyes et al., (2012) findings demonstrate the usefulness of the *'Traffic Light paradigm'* for separating out any effects of individual differences when responding in an anticipatory manner and types of impulsive behaviour from the effects of slow reaction times.

1.7 *Research aims and summary*

Through a sequence of experiments the primary aim of this thesis was to ascertain the neural and behavioural basis for automatic behaviours, in the form of echophenomena and impulsivity, and how these could further our understanding regarding the atypical presentation of these behaviours often seen in neurodevelopmental disorders such as autism spectrum disorders (ASD) and Tourette's syndrome.

The first three research studies (chapters 3, 4, & 5) were designed to investigate the neural and behavioural basis of contagious yawning among neurologically typical individuals. TMS physiological measures of cortical

excitability, inhibition, and facilitation, and direct current electrical stimulation techniques, were utlilised in order to determine if the genesis of echophenomena is mediated by primary motor regions. I also sought to establish and identify individual subjective ratings of the urge for action in these paradigms.

In the fourth study (chapter 6) I explored positive and negative impulsive action in a group of neurotypical children aged 4-12 years. This study was conducted to ascertain whether there are age dependent effects of automatic impulsive behaviours. This paradigm was expanded to an adult cohort during experiment five (Chapter 7). However, this study included the same TMS physiological measures of cortical excitability, inhibition, and facilitation. It also incorporated an improved electrical stimulation protocol that was used in experiments 1 & 2. This study was conducted to investigate whether automatic impulsive action is mediated by the same neural networks as automatic imitation.

Within this thesis the following research questions are addressed:

1. What is the role of motor cortex excitability on the occurrence of echophenomena (e.g. contagious yawning)?
2. Does increasing excitability using electrical stimulation to motor cortical areas modulate contagious yawning?
3. Do subjective measures of urge for action correlate with subsequent behavioural expressions of echophenomena?
4. Do instructions to inhibit echophenomena alter perceived urge for action?

5. What is the role of the motor cortex during automatic non-social impulsive behaviours?
6. Are there two separate features of impulsive behaviour, namely dysfunctional and functional?
7. Can the application of electrical stimulation to SMA alter decision-making during a time sensitive impulsivity task?
8. How does knowledge regarding the neural and behavioural correlates of automatic social and non-social behaviour inform our understanding of echophenoma in typical development?

Chapter 2 Non-Invasive Brain Stimulation

2.1 *Transcranial Magnetic Stimulation (TMS)*

Luigi Galvani is understood to have laid the initial foundations in the field of electrophysiology and is considered the pioneer of bioelectromagnetic research (Horvath, Perez, Forrow, Fregni, & Pascual-Leone, 2011). Galvani undertook seminal research during the late 1700s regarding the effects of electricity on the body of animals (Whittaker, 1989). Galvani (1780) discovered that the leg muscles of dead frogs twitched when an electrical spark was accidentally applied to them (Whittaker, 1989). This discovery is recognised as one of the first ventures into the study of bioelectricity, a research area that explores electrical signals and patterns from biological tissues such as muscles and nerves even to the present day (Whittaker, 1989). However, the term bioelectricity is now referred to as electrophysiology in more contemporary literature.

Volta, an experimental physicist, peer, and oftentimes adversary of Galvani, was one of the first to repeat Galvani's experiments (Bresadola, 1998). Bresadola (1998) writes that while Volta initially embraced Galvani's ideas regarding animal electricity, he soon began to have reservations about what was causing the conductions observed. Volta no longer believed that the conductions were created via animal electrical fluid, which Galvani had suggested was central to the animals body parts, but rather to the metal cables Galvani had used to join the animals muscles and nerves in his experimental research (Bresadola, 1998). Indeed, while Galvani reasoned that the animal electricity came from muscles within the animals' pelvis, Volta opposed this,

believing it to be the result of physical phenomenon created by rubbing the frogs' skin. Volta suggested that animal electricity was no different to normal electricity insofar as, the cell potential created by biological electricity has the same chemical foundations as the current created between electrochemical cells, and as such could be recreated outside of the body. To support his theory Volta built the first ever known battery, and in doing so was able to disprove Galvani' postulations regarding the origins of 'animal electricity' (Bresadola, 1998; Horvath et al., 2011).

Following on from these early discoveries, it was Faraday who in 1831 found that all electrical currents yielded a corresponding magnetic field. Faraday was able to demonstrate that by changing an electrical current he could change the strength of its corresponding magnetic field. This discovery is often referred to today has Faraday's law of induction (Barth, 2000). These early discoveries then led to them being used to stimulate human tissue, most notably the human brain. By the 1930s electricity, in the form of electroconvulsive therapy (ECT) was originally created by Cerletti and Bini, both Italian physicians, to treat a range of mental health conditions (Horvath et al., 2011). ECT was highly effective and as such became regarded as a psychiatric cure-all and overused by clinicians. However, according to Horvath and colleagues (2011) contraindications of ECT, and the tendency for clinicians to overuse it, led to a significant backlash among the general population.

It was around the time of this backlash that Anthony T Barker, an engineer and medical physicist, began his studies on human magnetic nerve stimulation. Barker used his knowledge of magnetic nerve stimulation to explore the use of magnetic fields to change the electrical signaling within the human cortex

(Horvath et al., 2011). However, it was not until 1985 that Barker and his colleagues were able to produce muscle twitches in the human hand via magnetic stimulation of the motor cortex. This occurred in the opposite hemisphere, which corresponded to the control of movement in the targeted muscle (Barker, Jalinous, & Freeston, 1985).

Barker et al (1985) work demonstrated that transcranial magnetic stimulation (TMS), as it is now known, had the capacity to stimulate precise areas of the human cortex but without the pain that was associated with earlier electrical current stimulation. Barker et al (1985) research also helped to revolutionise the scientific field of non-invasive neurostimulation techniques, with TMS particularly growing in popularity over the last few decades. Moreover, TMS has since become an essential modality for the examination of cortical functions, and for assessment of human motor pathway integrity (Kobayashi et al., 2003). Indeed, since its introduction in the 1980s, TMS has become a widely used research tool in areas such as neurology, psychiatry, neuroscience, and clinical neurophysiology (Kobayashi et al., 2003). However, TMS has also gained in popularity over recent years, as a tool for therapeutic clinical interventions (Groppa et al., 2012).

TMS works on the same principals as Faraday's electromagnetic induction (Horvath et al., 2011). During a TMS session, a magnetic field generator, most commonly referred to as a 'coil, is applied to a targeted area of the scalp (Wagner, Valero-Cabre, & Pascual-Leone, 2007). Moreover, TMS machines can deliver TMS pulses via two different pulse configurations, namely monophasic and biphasic. The initial current produced by a monophasic machine is strong but is subsequently balanced via a dampening return current.

In contrast, the current produced by a biphasic machine begins with a rise in current. This current is then reversed but soon followed by an increase in current. Thus the direction of the current from a biphasic machine is twice reversed (Rossini et al., 2015).

Both mono and biphasic pulses have the capacity to induce fluctuating magnetic fields that run perpendicular to the TMS coil (Rossini et al., 2015). If the current of electricity passing within the TMS coil is of sufficient strength, and short enough duration, the coil can emit a rapidly changing magnetic pulse strong enough to penetrate the tissues of the head and reach the surface of the brain (Kobayashi, & Pascual-Leone, 2003b). The TMS pulse subsequently induces a secondary ionic current from within the human cortex (figure 2.1). This induced current then interacts with the cortical tissue, while simultaneously influencing electrical signaling of multiple neuronal populations, which then has the capacity to depolarise neurons or their axons (Hallett, 2007). Therefore, electrical stimulation will occur at the precise region where a spatial derived induced electric field is maximal (Kobayashi et al., 2003).

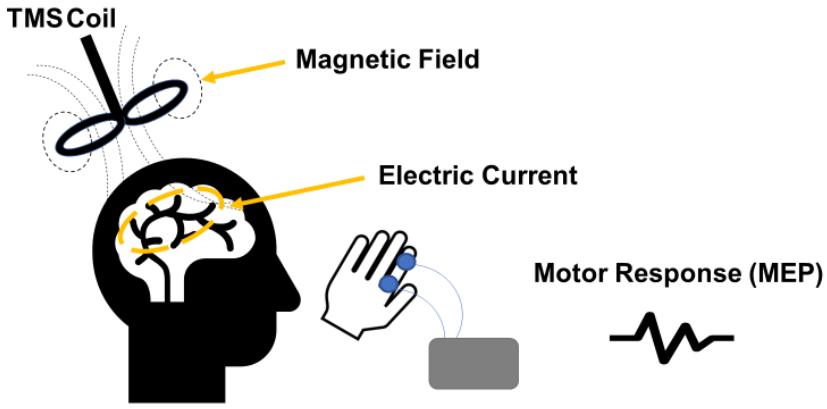


Figure 2-1: Basic principle of TMS. Schematic demonstrates the current flowing briefly in the coil which generates a changing magnetic field. This then induces an electrical current within the cortical tissue. Note the electrical current flows in the opposite direction to the magnetic field.

TMS operators can control the strength of the magnetic pulse by altering the level of intensity of the current that flows through the coil, and in doing so can change the magnitude of the corresponding magnetic field (Kobayashi & Pascual-Leone, 2003; Rossini et al., 2015). However, the primary focus of subsequent magnetic fields is dependent on the shape of the TMS coil. There are two commonly shaped TMS coils used, the circular shaped coil (figure 2.2), and the figure of eight coils. There are two main types of figure of eight coils the branding iron coil, and the flat iron coil (figure 2.3).

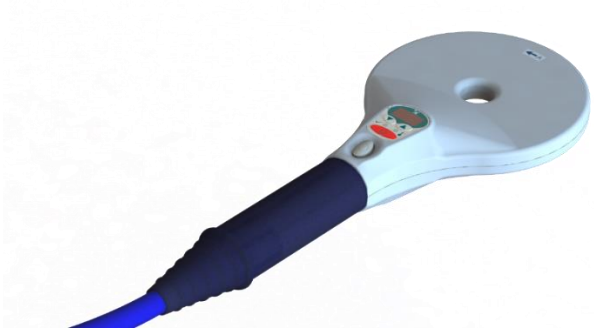


Figure 2-2: TMS circular coil - Image courtesy of Magstim.com

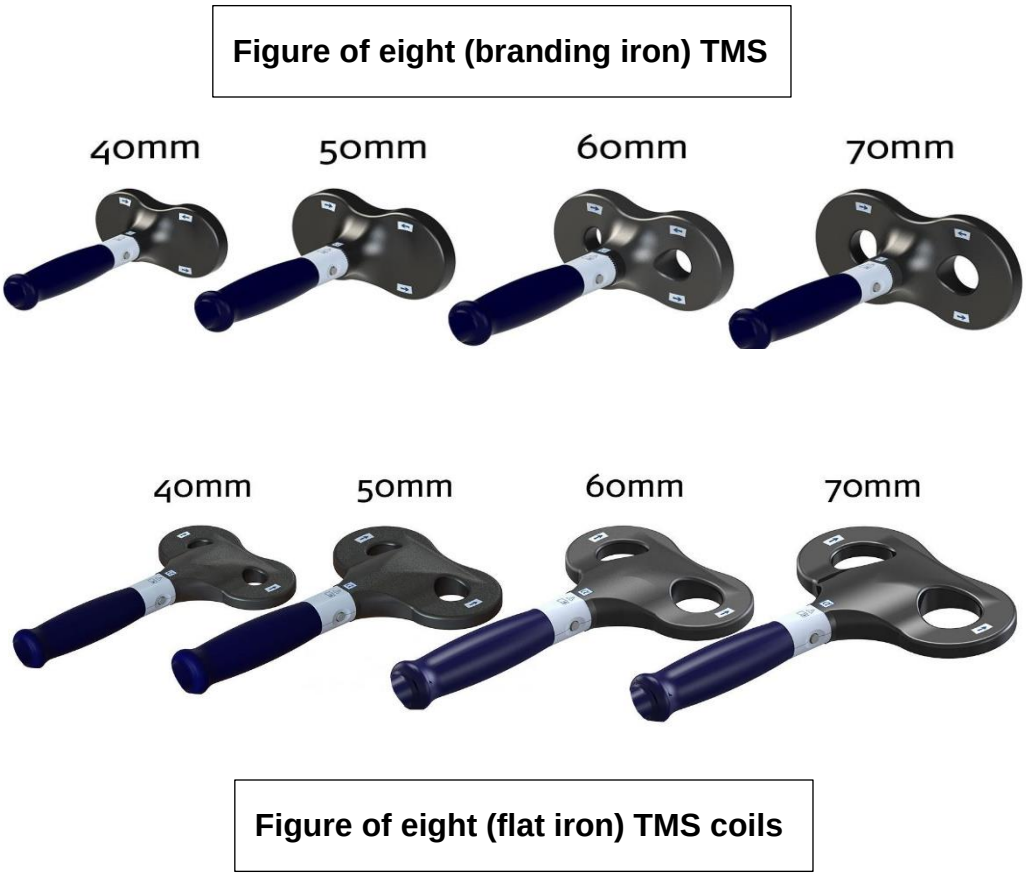


Figure 2-3: TMS figure of eight coils - Image courtesy of Magstim.com

The circular coil produces a wider distributed electrical field which facilitates bihemispheric stimulation which is typically used in studies of central motor cortex conduction latencies (Rossini & Rossi., 1998). In contrast, the branding iron coil facilitates a more focal stimulation that allows for a relatively detailed mapping of cortical representations (Hallett, 1997). In addition, operators can not only control intensity and focus, but also frequency of any administered stimuli, which in turn determines the overall effects of TMS pulses on the targeted brain area. However, it is important to acknowledge that the location of the TMS coil is also very much dependent on the TMS operator (Kobayashi et al., 2003). Moreover, different areas of the brain can be stimulated in order to

induce different behavioural effects. Exact anatomical localisation for stimulation can also be accomplished via the use of a frameless stereotactic system (Kobayashi et al., 2003).

TMS pulses preferentially activate pyramidal cells transsynaptically, which evokes indirect waves, or alternatively, stimulates directly at the neurons axon hillock to cause direct waves (Day, Dressler, & Maertens de Noordhout, 1989). In addition, axons that are fast-conducting (e.g. greater than 75m/s) have low thresholds for direct waves, while axons that are slow-conducting (e.g. less than 55m/s) have low thresholds for transsynaptic waves (Kobayashi et al., 2003). This makes TMS extremely well suited for the exploration of cortical excitability. As noted in chapter one, there are some neurodevelopmental and neuropsychiatric conditions that might include, or be produced by, impairments in cortical excitability (Finis et al., 2013; Ganos, Ogrzal, Schnitzler, & Münchau, 2012a; Pépés, Draper, Jackson, & Jackson, 2016). Moreover, any interactions between cortical and subcortical structures of the brain, that could also be altered, can be detected by TMS. TMS can also be employed to alter intracortical excitability, and activate along specific connections, distant cortical, subcortical, and epidural structures (Kobayashi et al., 2003).

2.1.1 The Motor Cortex, TMS and Motor Threshold

TMS is a popular brain imaging technique that is frequently used to study a wide variety of brain regions and/or functions. However, the motor cortex is thought to be by far the most popular brain region investigated. According to Kobayashi et al., (2003) TMS applied to this region, at suitable stimulation intensities, will facilitate motor evoked potentials (MEPs) from extremity muscles

contralateral to the stimulation site, quite easily. MEPs are neuroelectric signals elicited following direct stimulation of cortical areas corresponding to a targeted muscle. The neuroelectric signals that are generated during the subsequent muscle contractions are cortically driven and can be measured and recorded via electromyography (EMG) equipment. The MEPs are recorded via electrodes attached to the muscle of interest and amplified through an EMG recording device. Thus, MEPs provide a quantifiable measure of induced cortical activity non-invasively, and without the need for additional cognitive tasks and/or invasive paradigms (Kobayashi et al., 2003).

However, in order to quantify the afore mentioned measures the operator must first ascertain an individuals' resting motor threshold (RMT). RMT refers to the lowest TMS intensity necessary for facilitation of MEPs in the muscle of interest when single-pulse TMS stimuli are administered to the motor cortex (Hallett, 2007; Kobayashi et al., 2003). TMS research typically defines motor threshold as the lowest TMS intensity needed to yield MEPs greater than 50 μV peak-to-peak amplitudes in a minimum 50% of consecutive trials resulting from rested, or lightly contracted (activated), targeted muscles (Kobayashi et al., 2003; Rossini et al., 1994). Motor threshold is lower in the intrinsic hand muscles, such as the dorsal interossei, and higher in more proximal muscles of the upper and lower limbs (Brunoni et al., 2012). In addition, individual motor thresholds are thought to represent surface excitability of the corticospinal neurons and interneurons that project onto these neurons within M1 (Kobayashi et al., 2003). In addition to this, motor threshold is also said to reflect excitability of motor neurons from within the spinal cord, neuromuscular junctions, and muscle (Kobayashi et al., 2003).

Kobayashi et al., (2003) note that RMT have to relate to activity of neural inputs originating inside pyramidal cells, which in turn affect their membrane potentials (e.g. tonic inhibition and excitation that is driven onto cortical output neurons). Therefore, motor thresholds provide valuable insight into the effectiveness of synaptic sequences that originate from presynaptic cortical neurons to targeted muscles (Kobayashi et al., 2003). However, in order to quantify motor cortical spinal excitability, the brain region that facilitates MEPs in the targeted muscle, must first be established. Once this brain region is established it is often referred to as the 'hot spot'. The 'hot spot' is where the largest MEP responses are observed. It should be noted however that defining the 'hot spot' via high TMS intensities is not considered desirable, as higher pulse intensities, and the corresponding current spread, can invoke unwanted effects (Wagner, Rushmore, Eden, & Valero-Cabre, 2009).

It is important to note that accurate measures of RMT are essential for most TMS studies. However, the TMS intensity for each participant is typically adjusted according to their individual RMT. Therefore, inter-individual differences in RMT can vary according to multiple factors including; the distance between the scalp and cortex (Cukic, Kalauzi, Ilic, Miskovic, & Ljubisavljevic, 2009), the orientation of white matter fiber tracts (Danner et al., 2011), and/or inherited influences (Wassermann, 2002). Additional factors, other than structural differences, have also been cited as possible influences on RMT measures. For example, while almost all TMS studies recruit right handed participants, research regarding the impact of handedness on RMT has yielded inconsistent results (Goetz & Peterchev, 2012; Peterchev et al., 2012). Similarly, there is conflicting evidence regarding notable age dependent effects

on RMT measures (Smith, Ridding, Higgins, Wittert, & Pitcher, 2009). However, despite these reservations TMS still remains an important technique for yielding understanding regarding the structure and function of the human brain.

2.2 *Single Pulse TMS*

Single pulse TMS refers to the application of single pulses of TMS that are delivered in isolation to a targeted brain region. While numerous pulses can be administered to the target cortical area, inter-stimulus intervals, which are typically applied during all TMS protocols, prevents any associated interactive effects. Thus, single pulse TMS has been utilised in numerous research studies to establish accurate measures of global cortical excitability. Measures of global cortical excitability are typically assessed via motor cortical input-output recruitment curves. This involves measuring MEP amplitudes using a wide variety of TMS pulse intensities. The size of MEP amplitudes increase in a sigmoid pattern in direct response to the TMS pulse intensity (Bungert, Antunes, Espenhahn, & Thielscher, 2017). It is imperative that researchers randomise the order of the administered TMS intensities, accompanied by relatively short inter-trial-intervals (e.g. 4-5s). This is considered necessary as the typical ascending and descending order of TMS pulse intensities can shift the slope of the IO curve significantly (Sommer et al., 2018).

MEP amplitudes are also known to vary substantially in shape and size even when identical TMS pulses are administered to the same brain region (Ellaway et al., 1998; van der Kamp, Zwinderman, Ferrari, & van Dijk, 1996). Moreover, according to Devanne, Lavoie, and Capaday, (1997) the IO recruitment curve also results from two separate, yet distinct, components. The first is the bias

level, or threshold, and the second is the gain of the recruitment slope (Devanne et al., 1997). IO recruitment curves also have the capacity to measure activity from neurons that are much farther away from the centre of stimulus activation. To combat these issues measures of motor thresholds and cortical recruitment curves typically involve measuring multiple MEP amplitudes yielded via the same stimulus intensities. The resulting MEP amplitudes are then processed and averaged to provide an estimate of responses from the set intensity parameters.

2.3 *Paired Pulse TMS*

Since TMS was introduced further stimulation protocols have evolved in both research and medical settings, and stimulation can now include paired-pulse and repetitive TMS paradigms (Reis et al., 2008). These paradigms have provided researchers and clinicians the opportunity to examine, both excitatory and inhibitory mechanisms from within numerous cortical regions, and from within and across both cerebral hemispheres. Moreover, these TMS protocols have generated valuable insight into; the intra-cortical physiological processes that underly the functional roles of different cortical areas during a variety of cognitive processes, motor cortex control in both health and disease, and knowledge regarding the neuro-plastic changes and cortical function observed during recovery following brain injury (Bungert et al., 2017; Rossini et al., 2015).

Paired-pulse TMS also generates valuable information regarding the functional connectivity between various cortical areas when used in conjunction with other neuroimaging techniques (Reis et al., 2008). Moreover, Reis et al., (2008) states that such multimodal techniques provide crucial insight regarding the

relationship between many physiological processes and the anatomical constructs of specific cortical regions and associated pathways. In more recent years a developing interest, into how much these physiological processes can be modulated by different behavioural settings, has increased significantly. Indeed, a large part of this thesis utilised the use of paired-pulse TMS paradigms, and more specifically measures of cortical facilitation and inhibition, in order to explore the underlying neurophysiological processes during different behavioural settings.

Pulses delivered during ppTMS are typically applied using various inter-stimulus-intervals (ISI) between each one. The duration of the ISI is what determines whether the resulting effects are either excitatory or inhibitory. Shorter ISIs between 1 and 5 milliseconds (ms) usually lead to a corresponding increase in inhibition. Conversely, longer ISIs between 8 and 30ms tend to result in facilitation (O'Shea & Walsh, 2007). Strangely, if the ISI is increased to between 50 and 200ms then inhibition is also observed to occur. However, in order for longer ISIs to result in inhibition then it is vital that different conditioning stimulus intensities than those used for between 1 and 5 second intensities are used. The next section will discuss these different paired-pulse TMS protocols in more detail.

2.3.1 Measures of intracortical facilitation (ICF)

The facilitatory interactions that occur locally within the primary motor cortex (M1) can be examined through the application of paired-pulse TMS (pp-TMS) Paired-pulse TMS consists of two pulses being delivered via the same coil (or two coils overlapping each other), to the same brain region (Reis et al., 2008).

For example, intracortical facilitation (ICF) of test MEPs can be produced at inter-stimulus intervals (ISIs) between 6 and 25ms, whilst utilising a subthreshold conditioning stimulus (CS) in order to directly influence responses to subsequent supra-threshold test stimuli (TS). This phenomenon was first documented in a seminal article, whereby Kujirai et al., 1993) reported facilitation of test MEPs at intervals between 10–15ms. Kujirai et al., (1993) found that facilitation became stronger when the CS intensity increased. In contrast, others found that MEPs appeared to be considerably weaker with increasing TS intensities (Daskalakis, Christensen, Fitzgerald, Roshan, & Chen, 2002).

There is some debate regarding whether ICF is simply a rebound phenomenon elicited as a result of robust inhibition at short ISIs, or representative of a completely separate process entirely (Reis et al., 2008). Indeed, for ICF to be reliable the CS has to be induced in a posterior-anterior direction, whereas inhibitory TMS can be facilitated regardless of which direction the current is flowing (Ziemann, Rothwell, & Ridding, 1996). Ziemann and colleagues (1996) conclude that separate populations of neurons were most likely mediating intracortical inhibition and facilitation, and further state that while the mechanisms of ICF are not well understood, there is general agreement that ICF exams the excitability of excitatory neuronal motor networks and that this is distinctly different to those seen in the SICI network (Ziemann, 2013). Similar to ICF, SICI involves the administration of a sub-threshold conditioning stimulus (CS) followed by a supra-threshold TS. However, there is typically an inter stimulus interval (ISI) of between 1 and 5ms for SICI to occur. SICI will be addressed in more detail in the following section. Ziemann (2013) supported

this notion via neuropharmacological research which examined the effects of various medications on ICF. This research demonstrated that ICF, as measured while being influenced by various drugs, yielded different patterns of neuronal activity than results seen for SICI (Ziemann, 2013).

In addition, Ziemann previously found that excitatory glutamatergic interneurons inside M1, along with N-methyl-d-aspartate (NMDA) receptors, seem to also have an influence on measures of ICF (Ziemann, 2010). It has also been demonstrated that NMDA antagonists such as dextromethorphan eradicates ICF, or even reverses ICF via administration of memantine, when measured at 10 and 15ms (Schwenkreis et al., 1999). However, this issue is cloaked by the finding that ICF remains largely unaffected by ketamine, a non-competitive NMDA antagonist, specifically when dosage is administered at below typical anesthetic rates (Lazzaro et al., 2003). Moreover, ketamine reduces transmission at NMDA receptors and increases the release of glutamate and its transmission at AMPA synapses (Lazzaro et al., 2003; Reis et al., 2008). Thus, it would appear that ICF is largely modulated by both GABAergic and glutaminergic processes (Ziemann, 2013).

2.3.2 Short interval cortical inhibition (SICI)

Another well-established paired pulse TMS technique often used is short interval intracortical inhibition (SICI). Similar to ICF, SICI involves the administration of a sub-threshold conditioning stimulus (CS) followed by a supra-threshold test stimulus (TS). There is typically an inter stimulus interval (ISI) of between 1 and 5ms for SICI to occur. Both pulses are again delivered through the same, or overlapping coils, to a brain region of interest (Kujirai,

Caramia, Rothwell, Day, Thompson, Ferbert, Wroe, Asselman, & Marsden, 1993). SICI was first reported within Kujirai et al's., (1993) seminal TMS research paper. SICI TMS protocols are popular for the study of cortical inhibition in both patient groups and healthy controls (Cicinelli, Traversa, Bassi, Scivoletto, & Rossini, 1997; Daskalakis et al., 2002; López-Alonso, Fernández-del-Olmo, Costantini, Gonzalez-Henriquez, & Cheeran, 2015; Terao & Ugawa, 2002; Ziemann et al., 1996).

The conditioning pulse utilised in SICI protocols is generally considered to create a brief inhibitory postsynaptic action potential within corticospinal neurons via the initiation of lower threshold cortically driven inhibitory networks (Reis et al., 2008; Ziemann, 2013). According to Ziemann (2013) when this circuit is engaged it is believed to inhibit action potentials that have been created via the same collection of corticospinal neurons in direct response to the TS. Conversely, the subthreshold CS used in SICI in not believed to have any influence on spinal cord excitability. This is because such intensities do not seem to create identifiable spinal volleys when examined in isolation (Lazzaro et al., 2003; Rossini et al., 2015). Kujirai et al., (1993) did initially suggest, based on the minimal evidence available regarding the lack of change in epidural reflexes, that SICI most likely resulted from synaptic interactions occurring from within the primary motor cortex. However, later research that examined indirect (epidural) recordings of corticospinal volleys, was able to confirm that initial I_1-waves were dampened by the CS (Nakamura, Kitagawa, Kawaguchi, & Tsuji, 1997). I (indirect) waves are produced by single-pulse stimulation of the motor cortex and I1 waves in particular are associated with indirect activation of corticospinal neurons via monosynaptic corticocortical

connections (Ziemann & Rothwell, 2000). Thus, Nakamura and colleagues (1997) findings initially indicated that SICI appeared to be largely mediated at predominantly a cortical level. This notion was later confirmed when Di Lazzaro et al., (1998) demonstrated for the first-time direct evidence that SICI did indeed originate at the cortical level. During Di Lazzaro and colleagues' research, the subthreshold CS was observed to suppress the size of both epidural volleys and the corresponding MEP induced by the suprathreshold test stimulus. Moreover, this observed inhibition from the descending epidural volleys was more noticeable following an ISI of 1ms. Di Lazzaro et al., (1998) further observed that this effect disappeared after an ISI of 5ms.

2.3.3 Long interval cortical inhibition (LICI)

Long interval intracortical inhibition (LICI) is another inhibitory paired pulse protocol, which is often used in conjunction with ICF and SICI protocols. LICI is typically measured via two supra-threshold pulses that are separated by an ITI of between 50 and 200ms (Rogasch, Daskalakis, & Fitzgerald, 2013). Former research has demonstrated that when LICI is separated for longer ISIs than 50ms it is most likely mediated by the primary motor cortex (M1), as opposed to more subcortical structures (Nakamura et al., 1997). While Nakamura et al., (1997) research supports the notion that LICI relates to a reduced corticofugal excitability, there is still no clear understanding regarding whether the same populations of neurons mediate both SICI and LICI (Reis et al., 2008). Neuropharmacological research has suggested that LICI is most likely mediated via $GABA_B$ receptor activity (McDonnell, Orekhov, & Ziemann, 2006), whereas SICI is predominantly actioned via $GABA_A$ receptor activity (Ziemann, 2013). However, it is important to acknowledge that each receptor subtype may well

share neuronal populations, and as such mediate both inhibitory processes (Reis et al., 2008).

Prior research has demonstrated interactions occur between both LICI and SICI. For instance, it appears that SICI increases, whereby LICI appears to decrease when under the influence of high test MEP amplitudes (Chu, Gunraj, & Chen, 2008).This finding would suggest that neurons within M1 that are recruited at lower TS intensities are more prone to LICI than to SICI. Conversely, neurons that are recruited at much higher TS intensities seem to be most vulnerable to SICI than LICI (Reis et al., 2008). Reis et al., (2008) posits that these opposing effects suggests that different populations of inhibitory inter-neurons are most likely mediating SICI and LICI. Moreover, prior research has successfully demonstrated that SICI is much lower when in the presence of LICI, particularly when the size of the MEP test amplitude matches the test stimulus intensity. This suggests that an inhibitory effect of LICI on SICI is at work (Chu et al., 2008). In addition, most research that implemented ICF and SICI protocols typically report findings from distal hand muscle groups. However, it has also been demonstrated that fairly similar effects occur from more proximal arm regions (Bikmullina, Bäumer, Zittel, & Münchau, 2009; Gerloff, Corwell, Chen, Hallett, & Cohen, 1997; Sailer, Molnar, Cunic, & Chen, 2002).

Although LICI tends to be reported following ISIs of between 50 and 200ms, it would seem that the precise ISI chosen evokes subtle influences over the observed effects (Lazzaro et al., 2003). Higher intensities typically produce much later I waves, which are said to be associated with repeated discharge to corticospinal neurons via the action of presynaptic networks. Later I (indirect)

waves are produced by single-pulse stimulation of the motor cortex and refer to higher frequency, typically around 600Hz, repetitive discharge of corticospinal fibers (Ziemann & Rothwell, 2000). Indeed, when LICI occurs following an ISI of between 100 and 150ms a reduction in MEP amplitude is observed and the I_2 and later waves are suppressed (Lazzaro et al., 2003). Lazzaro et al (2003) suggests that this effect most likely originates from the cortex. However, when ISIs of 50ms were used in the same cohort, a reduction in the MEP amplitudes was observed, while the corresponding amplitude in the later I-waves appeared to increase. This finding would suggest that the inhibitory effects that occur with 50ms LICI might originate from more subcortical regions such as the spinal cord (Lazzaro et al., 2003). This initial finding as since prompted a significant amount of TMS research into using ISIs of 100ms or longer in order to examine the effects of LICI.

2.4 *Transcranial Electrical stimulation*

Transcranial electrical stimulation (TES) refers to another frequently used non-invasive brain stimulation technique, which involves the application of weak electrical currents, between 1 and 2 milliamps (mA), to the head for between 5 and 20 minutes (Nitsche, & Paulus, 2000). In contrast to TMS, TES delivers electricity directly to specific brain regions of interest via strategically placed electrodes (Nitsche & Paulus., 2000). While TES is a popular brain stimulation technique used in both clinical and research practices, it is not by any means a new discovery. For example, it is known that the ancient Egyptians were aware that catfish living in the Nile river had the ability to generate electricity. What is less certain however is whether or not they used these fish for medical purposes (Sarmiento, San-Juan, & Prasath, 2016). This knowledge was not

readily documented until some centuries later when the ancient Greek philosophers Plato and Aristotle noted that Torpedo fish had the ability to generate electricity. Moreover, both philosophers recognised this fish's potential for therapeutic application (Sarmiento et al., 2016).

However, despite this earlier knowledge, evidence of transcranial electrical stimulation to the human brain was not fully documented until the time of the Roman Empire. Sarmiento and colleagues (2016) report that Scribonius Largus, the Roman Emperor Tiberius' physician, had used a live torpedo fish to relieve a headache in one of his patients. It is documented that Largus placed the fish over the scalp of the patient, who then later reported relieve from their headache pain (Scribonius Largus, 1529, cited in Sarmiento et al., 2016). Similarly, Ibn-Sidah a Persian physician, reportedly used the electrical properties of Torpedo fish to treat epilepsy by placing the fish across the brows of his patients (Delbourgo & Dew, 2007; Priori, 2003). These sort of fish have an electrical organ that, when initiated by their brain, can produce a three-dimensional dipole field which surrounds their body. The fish then have the capacity to discharge a single cycle pulse of electricity from as low as 1Hz to approximately 65Hz at rest (Hopkins, 2010). However, the electricity produced by these fish was not direct current (DC) electricity. That said, it was still the first historical documented report regarding electrical stimulation of this kind. This discovery also led to the application of animal electricity becoming a popular method of electrical stimulation, particularly for therapeutic clinical practices, and remained so for over a thousand years (Sarmiento, 2016). The electrical properties of fish continued to be used to treat such conditions as epilepsy,

headaches, gout, and even, so called demonic possession (Fridriksson, Hubbard, & Hudspeth, 2012).

The medical use of electricity evolved alongside society's knowledge of conventional electricity. The first non-animal stimulation device known as an electrostatic generator, which consisted of a rudimentary crank operated friction machine, was invented in 1660 by the German scientist Otto von Guericke (Comroe & Dripps, 1976). Almost a century later, in 1767, the Middlesex Hospital was the first British hospital to acquire an electrostatic stimulation device for therapeutic use (Cambridge, 1977). The first device, with the capacity to store electricity, was also created around this time. Ewald Georg Von Kleist developed a device known as the 'Leyden jar', which consisted of a water-filled container of thin glass, that had the capacity to store the electricity generated from an electrostatic generator (Cherington, Yarnell, & Cherington, 1994; Jones, 2009). Subsequently, it was Benjamin Franklin and Anton de Haen who conducted research, which combined the Leyden Jar with an electrostatic generator, for therapeutic electrification experiments (Fridriksson et al., 2012; McWhirter, Carson, & Stone, 2015).

2.4.1 Contemporary electrical stimulation

Direct current (DC) electrical stimulation did not come about until the 18th century when, as discussed earlier, Galvani created the first DC battery (Bresadola, 1998). Direct current refers to electricity that flows without any fluctuations in the electrical charge (current). However, it was a nephew of Galvani, Giovanni Aldini, who was the first to use the DC battery in a medical setting, and began this work by first experimenting on himself (Sarmiento et al.,

2016). According to Sarmiento et al., (2016) Aldini used the DC battery on his first patient in 1801, a young Italian farmer who was admitted to the Santa Orsola Hospital, Bolonga, and who was found to be suffering with severe depression. Aldini observed that his patients mood and mental state steadily improved, and subsequently reported that the patient was completely cured following several weeks of his treatment (Parent, 2004). It was Aldini's pioneering research that helped to advance the use of DC brain stimulation for the treatment of both psychiatric and neurological disorders. It was during the 1880s that DC stimulation treatments became increasingly popular with German psychiatric practitioners. Indeed, it was German physicians who went on to pioneer and revolutionise electrotherapy, a predecessor of to the tDCS method seen today. Furthermore, during the 1950s DC stimulation became popular for a variety of uses including electrosleep therapies, and anesthesia research (Sarmiento et al., 2016). The discovery that Anodal DC stimulation helped facilitate better mood states, alertness, and motor activity, whilst cathodal polarisation facilitated a quieter state and apathy, helped create an interest in DC stimulation methods for research and clinical practice (Lippold & Redfearn, 1964). However, electrical stimulation was largely forgotten again following the introduction of neuropsychiatric medications during the 1970s.

2.5 *Transcranial Direct Current Stimulation (tDCS)*

It was not until the 1990s when interest, in the effects that direct current stimulation had on the human cortex, was reignited (Priori, 2003). Priori et al., (2003) examined the effects of direct current, specifically motor cortex excitability in the human primary motor cortex, via TMS techniques. It was also around this time that clinical researchers began to reevaluate the huge potential

that tDCS held for both research and clinical practices (Brunoni et al., 2012). tDCS has become increasingly popular among researchers and clinicians alike due to it being; cheap to administer, largely non-invasive, mostly well-tolerated, and carries with it only relatively minor adverse effects (Sarmiento et al., 2016). Another aspect of tDCS that has proved popular, particularly among researchers, is its capacity to cause cortical changes even when stimulation had finished. However, the length of any observed changes are largely dependent on the type, length, and strength of the stimulation administered (Utz, Dimova, Oppenländer, & Kerkhoff, 2010). Furthermore, there are several variations of tDCS including transcranial active current stimulation (tACS), transcranial pulsed current stimulation (tDCS), and transcranial random noise stimulation (tRNS). However, all these techniques fall under the umbrella term transcranial electrical stimulation (TES), for a full review see Ruffini et al., (2013).

The mechanism of action, whereby electrical stimulation changes to cortical function, is either through causing groups of neurons resting membrane potentials to hyperpoloarise or depolarise (Nitsche et al., 2000; Paulus, 2011). When positive stimulation, also referred to as anoldal tDCS, is administered, the current activates depolarisation of the resting membrane potential that simultaneously increases cortical excitation allowing for greater spontaneous neural firing. Conversely, when negative stimulation, also known as cathodal tDCS, is administered, the current produces hyperpolarisation of the resting membrane potentials. The action of cathodal stimulation reduces cortical excitability due to the corresponding decrease in spontaneous neural firing (Nitsche et al., 2000). Thus, tDCS has since been argued to facilitate both long-

term potentiation and long-term depression (Nitsche, 2012; Nitsche et al., 2000).

TDCS works when low direct currents are delivered to the scalp via electrodes encased in rubber and covered with sponge. When the electrodes are strategically positioned in a cortical region of interest, the electrical current creates a corresponding intracerebral current flow (Nitsche et al., 2008). Depending on whether anodal or cathodal stimulation is being delivered, the current flow either increases or decreases the neural excitation at the target site receiving stimulation. Nitsche and colleagues (2008) state that the resulting changes in cortical excitability leads to an alteration of brain functioning. Thus, these observed changes in cortical function can be used to provide information regarding the function of the human cortex, for research purposes, as well as for use in various different therapeutic applications (Nitsche et al., 2008). For example, cathodal tDCS has been used to treat psychological conditions that are typically caused by hyperactivity of specific regions of the brain (Nitsche et al., 2003). However, it should be noted that for research and clinical trial applications tDCS should always incorporate a sham stimulation control condition. Sham stimulation incorporates a brief duration of active stimulation but then switches off for the remainder of the testing session. The individual receiving the stimulation initially perceives the sensation believing that they are receiving prolonged stimulation for the duration of the test. The comparison of results from subjects who have received full anodal or cathodal stimulation and sham can then be explored (Nitsche et al., 2003).

There is no denying that tDCS is a promising technique for both clinical and research practices, however, it makes sense to be cautious when

communicating any findings. This is because while many findings appear positive, they are relatively few in number and consistency (Horvath, Forte, & Carter, 2015). Horvath et al., (2015) posit that tDCS does not have any significant, nor reliable neurophysiological effects, other than TMS specific changes. However, Horvath and colleagues received extensive criticism regarding the methods used in reaching their conclusions. Nevertheless, such debate only serves to highlight that the observed effects facilitated by tDCS are not always simple or predictable. Indeed, recent work conducted by Dyke et al., (2016) suggests that the precise mechanisms that underly the observed outcome of tDCS are not entirely certain. Moreover, their findings demonstrated that while 2 mA anodal tDCS effectively increased cortical excitability at a group level, the effects were not reliable across repeated testing sessions within the same individual subjects (Dyke, Kim, Jackson, & Jackson, 2016). Dyke and colleagues further suggest that 2 mA cathodal tDCS does not alter cortical excitability to a significant degree immediately after stimulation, and that poor reliability of this effect was observed within the same individuals across different testing sessions (Dyke et al., 2016). Thus, it would appear that there is still much to learn regarding issues related to tDCS such as parameter selection, setup, montage placement, and the stimulation protocols chosen.

Chapter 3 Echophenomena 1 – A pilot study investigating motor cortex excitability on contagious yawning

3.1 *Introduction*

Contagious yawning (CY) is a phenomenon that only occurs in humans, old world primates, and some dogs. It occurs in response to hearing, seeing, or even thinking about yawning (Platek et al., 2005). It is distinctly different to spontaneous yawning insofar as spontaneous yawning is an involuntary and stereotypical behaviour seen among most vertebrates (including humans) from in utero stages to adulthood (Helt, Eigsti, Snyder & Fein, 2010). Spontaneous yawning typically occurs as a result of many physiological changes including; boredom, hunger, changes in temperature, mood state, sleep/wake state etc. (for a full review see Guggisberg, Mathis, Schnider, & Hess, 2011). In contrast, where spontaneous yawning begins in utero, contagious yawning does not begin until early childhood (Platek et al., 2005).

This delayed start to contagious yawning has led to many researchers believing it to be linked with empathy and theory of mind (TOM) (Platek, Critton, Myers, & Gallup, 2003; Platek et al., 2005; Schürmann et al., 2005; Yoon & Tennie, 2010). Contagious yawning, as noted in the opening chapter, has also been linked to social development and automatic imitation, which subsequently places it in the spotlight for hMNS and empathy research. For example, Schürmann et al., (2005) used *f*MRI to investigate hMNS activity while subjects observed videos of contagious yawning and simple non-nameable mouth

movements in the form of mouth opening and closing. Schürmann and colleagues (2005) observed a significant increase in the blood oxygen level dependent (BOLD) signal in response to yawn viewing when compared with the viewing of non-nameable mouth movements. Activation was detected in the right posterior superior temporal sulcus (STS) and bilaterally in the anterior STS, which confirms a high affinity of STS to social cues (Schürmann et al., 2005). However, they saw no additional yawn-specific activation in Broca's area, a key area associated with the hMNS. Therefore, Schürmann et al (2005) conclude that CY may not be mediated by the hMNS. In contrast, Schürmann and colleagues did find that their participants' self-reported propensity to yawn did covary negatively with activation of the left periamygdalar region, which suggests a connection between CY and activation of the amygdala. This finding supports the suggestion that CY may be a form of empathy.

The link between CY and empathy can also be seen in both auditory (Arnott, Singhal, & Goodale, 2009) and visual (Platek et al., 2003) CY paradigms. In both these studies, subjects who had a greater propensity for contagious yawning also scored highly on ratings of empathy. However, these studies only looked at the frequency of CY in typically developing controls. This is a significant limitation because, as noted earlier, CY can be significantly diminished in those with neurodevelopmental or neuropsychiatric disorders such autism spectrum disorders (ASD) (Helt et al., 2010), schizophrenia (Platek et al., 2003; Rundle, Vaughn, & Stanford, 2015). For example, Helt et al (2010) tested susceptibility to CY in 120 children, aged 1-6 years, to identify any emerging time course during development. Their results suggest a significant increase in the occurrence of CY at 4 years of age onwards. In a second study,

the authors explored CY in 28 children with ASD aged between 6 and 15 years. The Children with ASD exhibited reduced vulnerability to CY as compared with two mental, and chronologically age matched control groups. Interestingly, they also found that children who were diagnosed with Pervasive Developmental Disorder, Not Otherwise Specified (PDD-NOS), which is a milder form of ASD, were more prone to CY than were children presenting with full ASD (Helt et al., 2010). The authors subsequently linked the implications of their results to theories regarding the development of mimicry and emotional contagion (Helt et al., 2010).

Similarly, Rundle and colleagues (2015) subjected 135 male and female students, who had completed the Psychopathic Personality Inventory-Revised (PPI-R), to a contagious yawning experiment. The experiment was intended to produce contagious yawns in these individuals. Further still, Rundle et al (2015) then subjected male participants to an emotion-related startle paradigm that was meant to assess their peripheral amygdala activation. They discovered that scores on the PPI-R subscale cold-heartedness could significantly predict a reduced propensity for contagious yawning. Rundle and colleagues (2015) further discovered that emotion-related startle amplitudes were also predictive of the occurrence of contagious yawning. Rundle et al (2015) argue that these findings suggest that psychopathic traits could be correlated with the empathic nature of CY among humans.

It is also clear from the literature that both empathy and CY are frequently linked with the actions of the human mirror neuron system (hMNS), which is also said to be directly linked to areas of motor cortex and limbic cortices (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Schürmann et al., 2005). Surprisingly

however, there remains no substantial research effort regarding the implication of motor cortex excitability on either empathy or CY in neurotypicals, ASD, or schizophrenia. Research regarding motor cortex excitability in Gilles de la Tourette's Syndrome (GTS) does exist however and suggests that an inhibitory cortical circuit deficiency exists in the motor system of those with this condition (Mink, 2001).

In support, studies by Jackson, Draper, Dyke, Pépés, & Jackson, (2015) and Pépés, Draper, Jackson, & Jackson, (2016) found that increased control over motor outputs in those with GTS is facilitated by local increases in 'tonic' inhibition, which in turn leads to a reduction in the 'gain' of motor excitability. Pépés et al., (2016) in particular found that both RMT and IO slopes among children and adolecents with TS differed significantly from controls and contrasted with findings regarding adults with TS. Pépés and colleagues (2016) results suggest that maturation of key brain networks in TS could be developmentally delayed. They also stated that the strength of neuronal activity, which progresses from presynaptic neurons and subsequently projects to the targeted muscles, does have a direct effect on subsequent motor behaviours. In addition, they further argue that RMT is thought to reflect such activity, and more importantly, that this activity depends on axonal membrane properties of corticospinal neurons at the TMS site and membrane properties of post synaptic neurons (Pépés et al., 2016).

Similarly, Orth, (2009) also used transcranial magnetic stimulation (TMS), to study the excitability of several different circuits in the human motor cortex in order to advance understanding regarding the pathophysiology of Gillies de la Tourette's (GTS). In contrast to Pépés et al., (2016) Orth (2009) discovered that

resting motor thresholds are comparable in both GTS patients and typically developed controls. However, he did find that recruitment of motor evoked potentials (MEPs) above threshold is much slower in those with GTS as compared to controls. Conversely, he then discovered that recruitment of MEPs during preactivation, along with the duration of the cortical silent period, are very similar across both groups (Orth, 2009). Orth, (2009) concluded that distribution of excitation in the corticospinal system of patient groups at rest is markedly different to that seen in typical controls.

Orth (2009) went on to support this notion with a correlation analysis, which demonstrated that lower levels of excitation at rest correlate with video ratings of complex tics, as well as hand and finger tics. He also found that less excitability predicts far fewer tics (Orth, 2009). However, what is interesting is that these correlations subsequently disappeared for measures made during voluntary activation. Orth (2009) posits that this is evidence of an adaptive response to aberrant basal ganglia-motor cortex inputs, and that this manifest in the patient groups as an effort to reduce unwanted motor outputs (Orth, 2009).

Furthermore, when compared to the typically developed control group, Orth (2009) observed that short intracortical inhibition (SICI) thresholds were similar. In contrast, above-threshold SICI recruitment and sensory afferent inhibition (SAI), a paradigm that examines sensory motor integration (SMI), were considerably lower in the GTS patient groups (Orth, 2009). This finding is in line with the consensus that lower levels of cortical excitability and inhibition is one facet that facilitates the difficulty GTS patients encounter when trying to suppress involuntary tics (Orth, 2009). Orth (2009) also concluded that reduced SAI indicates that; impaired intracortical inhibition may not be solely due to the

motor cortex alone but could also involve cortical circuits that link sensory input and motor output.

Although the findings of Jackson et al., (2015); Mink, (2001); Orth, (2009) and Pépés et al., (2016) all provide significant understanding regarding motor cortex abnormalities in GTS, they provide little evidence regarding the influence of motor cortex excitability on echophenomena or contagious behaviours. Indeed, despite the assumption that echophenomena is mediated by the hMNS and motor cortex (Ganos et al., 2012a; Mehta et al., 2013), there is very little empirical research evidence available that supports this. Moreover, there are very few studies to date that explore the role motor cortex excitability has on echophenomena more generally.

Studies that explore motor cortex resonance and imitation are also underrepresented in the literature. However a few studies in this area have provided some interesting findings (Obhi, Hogeveen, & Pascual-Leone, 2011; van Ulzen, Fiorio, & Cesari, 2013). For example, a study by Obhi et al., (2011) facilitated motor-evoked potentials using TMS during an action observation task, whereby subjects observed either independent or interdependent self-construal prime words. According to Obhi et al. (2011) self-construal refers to how an individual would view and make meaning of themselves. Obhi and colleagues (2011) identified two separate subtypes of self-construal, namely independent and interdependent. They posit that independent self-construal relates to a view of the self in the absence of others, while interdependent self-construal relates to a view of the self that includes relationships with others.

Results demonstrated that priming interdependent self-construal increased motor cortex activation, whereas priming independent self-construal did not when examined against a non-priming baseline condition (Obhi et al., 2011). Obhi et al., (2011) argued that these effects were most likely facilitated by changes in the mirror neuron system. They suggest that such action essentially tunes the individual to, or shields the individual from, social input. Moreover, the pattern of the self-construal-induced changes in the motor system observed by Obhi and colleagues substantiates previously observed self-construal effects on overt mimicking behaviours in social settings, and as such, provides robust evidence that motor resonance likely facilitates non-conscious mimicking behaviour in social settings (Obhi et al., 2011). Finally, they conclude that self-construal effects might lead to the creation of interventions for conditions of deficient or excessive social influence such as ASD and compulsive imitative disorders.

Similarly, van Ulzen, Fiorio, & Cesari, (2013) used TMS to probe motor resonance during a naturalistic mimicry paradigm. The aim of the study was to establish whether the motor system reverberates immediately with unobtrusive non-verbal behaviour of another individual (van Ulzen et al., 2013). Van Ulzen and colleagues measured corticospinal excitability in both the left and right hand while subjects watched sequences of video clips and static images. During each video clip an actor carried out numerous clerical tasks, while either discreetly touching their face, *face-touching* (FT) condition, or not, *no face-touching* (NFT) condition (van Ulzen et al., 2013). Van Ulzen et al., (2013) found that motor cortex excitability was greater in the FT condition as compared to the NFT and baseline conditions. Further still, their data demonstrated a greater degree of

excitation in the left motor cortex when compared to the right. Van Ulzen and colleagues (2013) posit that the observed hand to face gestures, even though they were not the primary focus of attention, and occurred inconspicuously throughout the ongoing action setting, could cause immediate motor resonance activity in the observer's motor system. This finding appears to support the notion of motor resonance involvement in mimicking behaviour and shows that this can be investigated via naturalistic mimicking paradigms. Moreover, motor resonance is frequently linked to activation in the motor system during action observation and as such is typically interpreted in the context of mirror neuron system functioning.

Support for the role that motor cortex excitability (CSE) plays in facilitating imitative behaviours, can be found in another study by Finis et al., (2013). Finis and colleagues (2013) used TMS to investigate and alter corticospinal excitability in order to investigate the occurrence of echophenomena in typically developing controls (Finis et al., (2013). Finis et al (2013) generated an experimental paradigm that utilised repetitive transcranial magnetic stimulation (rTMS) to alter corticospinal excitability in the supplementary motor area (SMA) in typically developing controls (TDC). The SMA is a brain region that acts as a relay between the primary motor area (M1), as well as brainstem motor regions. The SMA is primarily involved in programming skilled or complex motor sequences and argued to be involved in the genesis of echophenomena (Finis et al., 2013) and tics in Tourette's syndrome (Jackson et al., 2015).

Finis et al (2013) hypothesised that modification of neural activity within the SMA would evoke echophenomena. In order to test this hypothesis Finis and colleagues (2013) used both 5 Hz rTMS, which is said to temporarily facilitate

cortical activity, and 1 Hz rTMS, which is said to disrupt or attenuate neural activity. They presented video clips of either, a tic generated by a GTS patient, or a spontaneous movement of a TDC, to 30 TDCs both before and after rTMS stimulation. The subjects were split into two groups; group 1 were administered the 1 Hz rTMS, while group 2 were administered 5hz rTMS. Each video clip showed one single facial movement and participants were videotaped in order to observe the occurrence of echophenomena (Finis et al., 2013). Video films of the 30 TDCS responses (frequency of echophenomena) were then rated by two independent raters, which resulted in a moderate interrater reliability score Cronbach's alpha .745.

Their results revealed a significant increase in echophenomena following 5 Hz stimulation, but no significant effect following 1 Hz stimulation. Finis et al (2013) conclude that this finding implies that increased activation in SMA might mediate the occurrence of echophenomena. However, validity of their results is limited by the relatively small frequency of echophenomena that they observed. Moreover, Finis et al (2013) also observed significantly lower resting motor thresholds (RMT) for the 5 Hz rTMS group. Interestingly, the observed difference in RMT could hold some meaning for the occurrence of echophenomena but unfortunately Finis and colleagues (2013) did not explore this further.

The relevance of Gilles de la Tourette's to ASD and contagious yawning research is primarily due to both disorders sharing the core diagnostic feature of echophenomena. Moreover, many of those with ASD are also reported to suffer from involuntary tics. However, these tics can also be the occurrence of 'stims' (self-stimulatory behaviours) instead of actual involuntary tics. The two are

difficult to distinguish from each other and as such, involuntary tics often get mistaken for voluntary execution of 'stims' (Williams, 2016). Williams (2016) suggests if this misunderstanding happens and attention is drawn to the 'stims', or there are constant attempts to suppress what are actually tics, the tics generally become engrained and significantly more severe. Understanding the difference between the occurrence of involuntary tics and voluntary stims in ASD is therefore essential (Williams, 2016). This is because voluntary stims are self-soothing behaviours typically generated in response to anxiety symptoms and not via cortical regions associated with the genesis of tics.

Moreover, it is important to establish a more thorough understanding regarding the neural foundations of contagious yawning. This is particularly important for the understanding of human behavioural and communication mechanisms and could help elucidate why some populations develop absent or unusual forms of social mimicry (Arnott et al., 2009; Rogers, Hepburn, Stackhouse, & Wehner, 2003). It was with all these factors in mind, along with the fact that the hMNS has been suggested as a mediator of; echophenomena (Ganos et al., 2012a), and contagious yawning (Platek et al., 2005), that this first of many research studies was proposed. Furthermore, given the underexplored possibility that differences in RMT (Finis et al., 2013) and motor cortex excitability might mediate the occurrence of echophenomena, it seemed reasonable to assume that RMT and/or motor cortex excitability might also mediate the occurrence of contagious yawning. Based upon this assumption the following pilot study will investigate the role of motor cortex excitability on the occurrence of contagious yawning in typically developed controls.

3.2 *Method*

3.2.1 Study design

This study is a mixed method within subjects' design comprising of a single pulse TMS (sp-TMS) physiological protocol followed by a contagious yawning behavioural paradigm. The first method in this paradigm consisted of physiological TMS measures of both resting motor thresholds (RMT) and cortical excitability (CE). Measures of cortical excitability for each subject was then ascertained via TMS induced input-output curve (IO) measurements of motor evoked potentials (MEP). The second method involved a behavioural measure of contagious yawning. This behavioural method utilised a 2x2 (yawn condition v yawn response) ABBA blocked (x4) design. The primary aim of this study was to examine whether the number of stifled and full yawns displayed during the resist the urge to yawn condition could be predicted by measuring both RMT and CSE. The purpose of this is to ascertain what role RMT and/or CSE might have on the occurrence of contagious yawning. The other two conditions ('*full yawn in free' & 'stifle yawns in free*') were to also act as a baseline measure of contagious yawn propensity and a measure of how well subjects followed the behavioural task instructions respectively. The independent variable (IV) was TMS intensity, and the dependent variable (DV) in the physiological task was MEP response. For the behavioural task the IV was yawn condition, which had 2 levels, resist versus free, whilst the DV was the yawn response, which also had 2 levels, stifled versus full.

3.2.2 Ethics

Ethical approval for this study was sought and granted by the University of Nottingham ethics committee. (Ethics Approval Number=219).

3.2.3 Participants

Thirty-six subjects aged 18-26 years (mean age=20 ± SD=1.56), were recruited via opportunity sampling from the University of Nottingham. Prior to participation in this experiment all subjects were provided with a study information sheet. Inclusion criteria stipulated that all subjects needed to be pre-screened prior to being accepted onto the study in order to ascertain their suitability for the TMS procedure.

In addition, all subjects completed two questionnaires; the Autism Quotient (AQ) questionnaire (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001) and the Davis interpersonal reactivity index (IRI) empathy scale (Davis, 1980). Prior to the study commencing all subjects were taken through the appropriate TMS screening questionnaire again before signing it and a study consent form. A total of 7 subjects were excluded from the study; 3 for poor quality video recordings preventing reliable assessment of yawn/stifle counts; 2 for not following instructions in the behaviours task; and 2 withdrew their behavioural data before statistical analysis. All subjects were financially compensated for their time and participation in this study.

3.3 *Procedure*

3.3.1 TMS Procedure

An unpaired Magstim Bistim 2^{TM} TMS machine, with a 70mm figure of eight coil, was used to administer single pulse TMS (sp-TMS) to the motor hotspot (left M1) in an area that corresponds to the first dorsal interosseous (FDI) muscle of the right hand. Motor hotspot was found by positioning the TMS coil over each subjects' left motor cortex (M1) at approximately 45° in order to induce a posterior-anterior electromagnetic field for optimal stimulation of M1. The location of MH was located, and continuously tracked throughout the study, via *BrainSight^{TM} version 2.0',* (Rogue Research Inc. ©, 2016). *BrainSight^{TM} version 2.0* is a neuronavigation software program that facilitates the optimal positioning of the TMS coil via tracking equipment that either aligns specific external anatomical landmarks on the subjects' head, or through individual subjects structural MRI data. However, in respect of this study external trackers (one on the subjects' forehead and the other on the coil) were used to detect anatomical landmarks including the subjects'; tip of their nose, left and right preauriculars, and nasion. The tracking equipment and BrainSight software uses automatic curvilinear reconstruction to create a virtual head on-screen; this ensures that the TMS coil is always placed directly over the target site during the duration of testing.

Following localisation of motor hotspot resting motor threshold (RMT) was then obtained. Each subject's RMT was determined as the minimum TMS intensity needed to reliably elicit an FDI generated MEP of at least 150–200 μV in a minimum of 5 out of 10 trials. Only when the motor hotspot and RMT were

reliably determined, could the TMS coil be secured using the Manfrotto arm device. The TMS coil was continuously monitored by the researchers and adjusted where necessary during trial breaks to ensure the coil was positioned over the target area throughout the duration of testing. In order to record the FDI muscle twitch, disposable electromyography (EMG) electrodes (diameter 5 mm) were placed onto the FDI muscle in a standard *'belly-tendon'* configuration. Subjects were asked to keep their hand relaxed for the entire duration of the study. This was to prevent tension in the FDI muscle inflating the MEP amplitudes. The EMG responses, corresponding to the TMS protocol, were recorded using BrainVision Recording software at a sampling rate of 5000 Hz, and a sampling interval of 200 μS.

3.3.2 TMS Measurement of CSE recruitment curves (IO)

Each subject rested their chin on a chin rest while receiving 90 trials of single pulse TMS (sp-TMS) at different percentages of their individual RMT. The TMS intensities administered ranged from 100% - 150% of their RMT and delivered in 10% increments, which resulted in 6 TMS intensities. The sp-TMS pulses were triggered automatically through a Matlab script that was running on a Samsung laptop via a National Instruments Data Acquisition Device. The sp-TMS pulses, for each of the specified intensities, were subsequently delivered in blocks of fifteen in a pseudorandomised order. There was also an inter-trial interval (ITI) of 4s between each pulse. The 90 sp-TMS trials were organised into 4 blocks of 20 trials and 1 block of 10 trials. At the end of each block of trials the researcher checked to ensure the subject was tolerating the procedure well and gave them the opportunity to take a short break if they so wished. The equipment was also checked to ensure the coil was still optimally positioned

over the target area. The FDI EMG signals were recorded and saved for processing and later statistical analysis.

3.4 *Behavioural task procedure – facilitating contagious yawning*

Directly following the single pulse TMS (sp_TMS) data acquisition procedure the subjects were taken to a separate laboratory for completion of the contagious yawning behavioural task. Subjects were given instructions regarding a 30-minute video they were about to see and what they were required to do during the procedure. For example, each subject was asked to pay close attention to the video and answer four questions relating to the actors they were about to see such as, ‘how many actors were wearing glasses. The answers they provided were later used to confirm that each subject was paying attention to the video clips appropriately.

The video itself comprised of four 7-minute blocks of video clips (total 52 clips) with each clip ranging from 11-20 seconds approximately. All videos were shown on an Apple Macintosh MacBook air laptop via VLC media player software. Instructions appeared on screen immediately before and after each block of clips. Prior to the start of each of the 4 blocks subjects were instructed to either ‘resist the urge to yawn’ or to ‘yawn freely’. This made up the yawn response conditions stifle versus full yawns.

To avoid order effects the 4 blocks were counterbalanced using an ABBA design. For example, 50% of the subjects saw the videos in a (yawn freely, resist, resist, yawn freely) configuration while the other 50% saw videos displayed in a BAAB configuration (resist, yawn freely, yawn freely, resist). The

ABBA and BAAB block designs made up the yawn condition, resist versus free, measured in this study. A one-minute time window separated each block to allow the subjects to answer the question regarding the block they had just viewed.

The video clips featured either a male or female actor, age range 20-28 years, spontaneously yawning. The clips were shown to each subject in a randomised order with no clip repeated more than once for the duration of the 30-minute video. Subjects were recorded unbeknown using Open Broadcaster Software so that the yawn responses could be counted prior to analysis. Following participation all subjects completed a follow up TMS safety questionnaire, were debriefed, and given information about the covert recording.

3.4.1 Yawn count procedure

Two naïve raters were chosen to watch the covert video recordings and count the number of full yawns (FY) and stifled yawns (SY) displayed by the subjects during each video block. The recordings were blinded in order to prevent the display of either the actors or the block condition to the raters. The two raters were also required to follow a strict yawn count protocol in order to ensure consistency and reliability.

3.4.2 Inter-rater reliability

A two-way random intraclass correlation coefficient (ICC) analysis was conducted in IBM SPSS version 22 to assess inter-rater reliability for the behavioural count data collated by the two raters. There was a high degree of agreement between raters for the ‘’full yawn in free’ condition, with an ICC of .988 and with a 95% confidence interval (CI) ranging .975-.995 *f* (28)

=86.128, p<.001). A similar degree of agreement was yielded for both ’full yawn in resist’ and ‘stifled yawns in resist’ conditions; ICC .956 with a 95% CI ranging from .961-.991, *f* (28) = 22.911, p<.001 and ICC .982 with a 95% CI ranging from .961-.991, *f* (28) =54.862, p<.001 respectively. For the ’stifled yawns in free’ condition there was a moderate degree of agreement with an ICC of .700 and a 95% CI ranging from .361-.859, *f* (28) =3.335, p=.001. This result is still within an acceptable degree of inter-rater reliability.

3.5 *Results*

3.5.1 EMG pre-processing

The EMG signals that were recorded during the sp-TMS procedure were analysed using EEGLAB in MATLAB. The peak-to-peak amplitude of the MEP was measured for each individual trial. Data for each of these trials was also inspected visually to check for contaminated electrical activity, (e.g. tension in the muscle would artificially inflate MEP amplitude), and all contaminated trials were excluded from analysis.

3.5.2 TMS corticospinal excitability IO Data

MEP amplitudes for each individual subject were then mapped to show his or her individual CSE IO curves. These were then combined to show the overall spread of the MEP data for all 29 subjects. Both RMT and input/output (IO) slopes were found to be normally distributed (RMT: Mean=38.75, SD=4.74; & IO: Mean=65.08, SD=37.57). Finally, a repeated measures ANOVA of MEPs at each TMS intensity level was then conducted in IBM SPSS version 22. Results revealed a significant effect of TMS intensity on MEP response *f* (5, 140) = 57.718, p<.001.

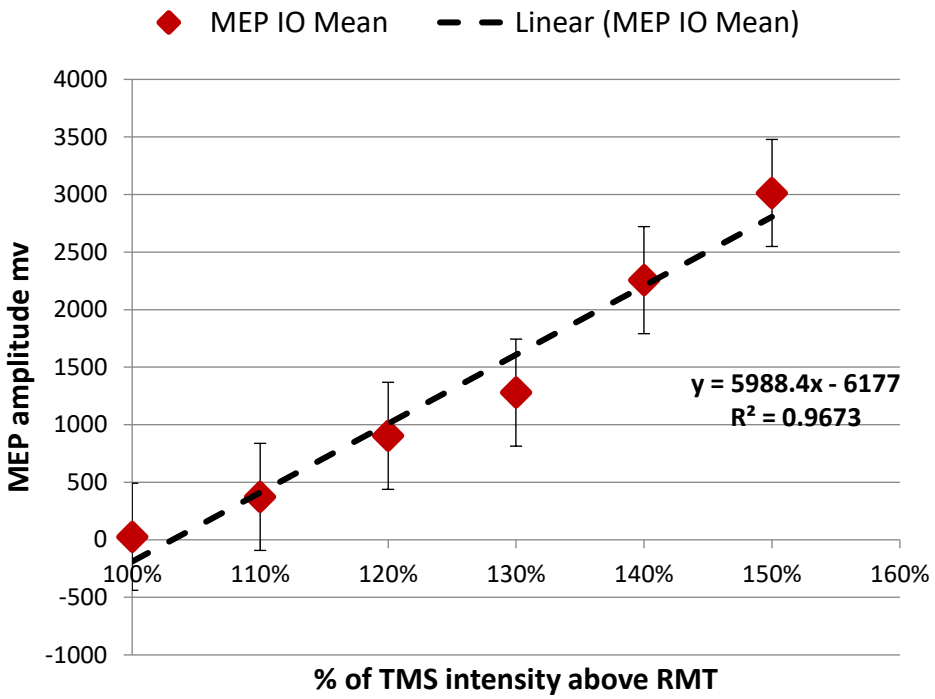


Figure 3-1: Graph depicting data (N=29) of TMS recruitment curves (the mean of individuals' mean MEP values, measured in microvolts) for each TMS stimulate output intensity, as a percentage of each individual RMT.

3.5.3 Behavioural data

In order to ensure the behavioural task protocol worked two-way repeated measures ANOVA of yawn response (Stifle v Full) frequency x yawn condition (Free v Resist) was conducted in IBM SPSS version 22. Results revealed significant effects of yawn response f (1, 28) = 15.119 p<.001 and yawn condition f (1, 28) = 13.716 p<.001. A significant interaction between yawn response and yawn condition was also found f (1, 28) = 21.111 p<.0001.

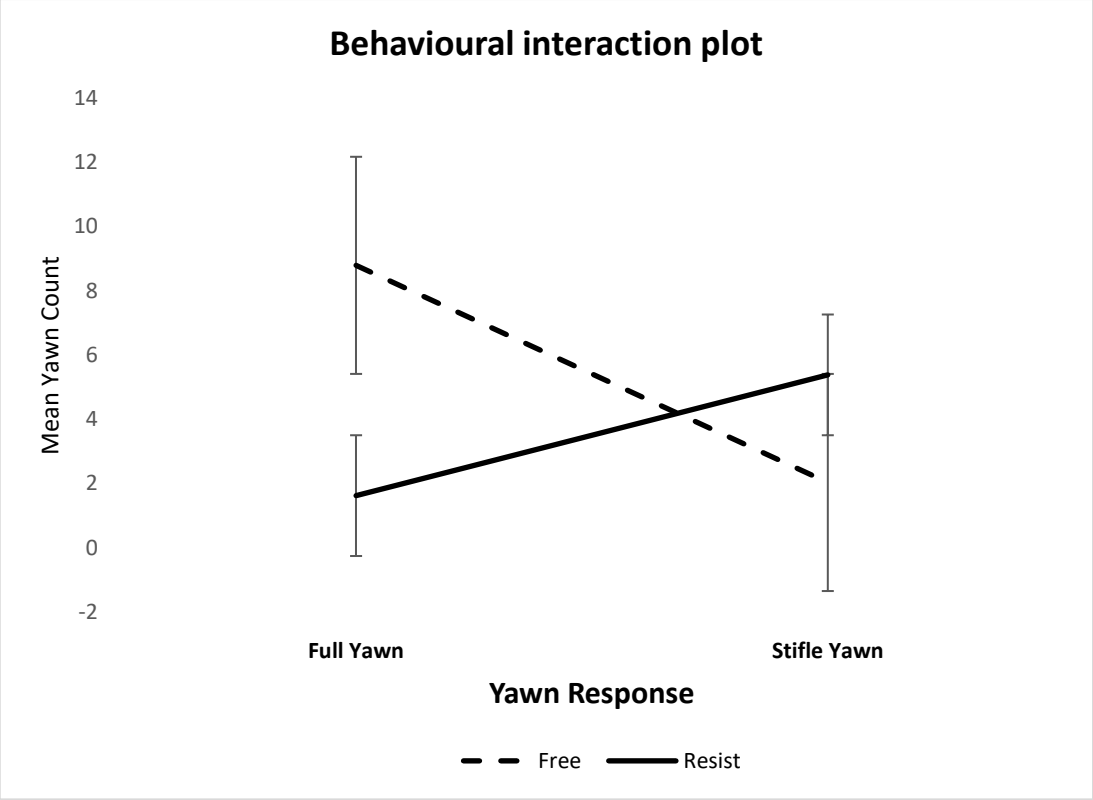


Figure 3-2: Graph depicting the behavioural task interaction plot between yawn condition (Resist v Free) and yawn response (Full v Stifle) and the mean yawn count across conditions.

Further Wilcoxon Z comparisons tests demonstrated significant effects for full yawn in free v stifle yawn in free, W (1, 28) = 4.199, p<0.001; full yawn in resist v stifles yawn in resist, W (1, 28) = 3.384, p=0.001; full yawns in free v full yawn in resist, W (1, 28) = 4.003, p<0.001; full yawns in free v stifled yawn in free, W (1, 28) = 2.351, p=0.019; and for stifled yawns in free v stifled yawns in resist, W (1, 28) = 3.644, p<0.001. As expected there was no significant effect of stifled yawns in free v full yawns in resist, W (1, 28) = 1.368, p=0.171 Results demonstrate that subjects understood the task and responded according to instructions.

Comparison	Wilcoxon Z	P-Value
Full in Free v Stifle in Free	4.199	<0.001
Full in Resist v Stifled in Resist	3.384	0.001
Full in free v Full in Resist	4.003	<0.001
Full in Free v Stifle v Resist	2.351	0.019
Stifled in Free v Full in Resist	1.368	0.171
Stifled in Free v Stifled in Resist	3.644	<0.001

Table 1: Behavioural task Wilcoxon Z test comparisons table

3.5.4 Relationships between both RMT and IO slope on contagious yawning

The count data for each block was then subjected to further analysis using a repeated measures Poisson regression to test whether there was a relationship between both RMT and IO curves on the occurrence of contagious yawning. Poisson regression is well suited for analysing count data insofar as; count data is not normally distributed with a high degree of positive skew, has numerous zero counts, and no negative integers. Moreover, when the mean count is very small and zero is the most common value in the dataset it is impossible to normalise using a log transformation (Gelman & Hill, 2006). The Poisson distribution is used to model the probability of a given number of events occurring in a fixed interval of time. Poisson has a single parameter lambda (λ),

also known as the rate. Thus, if x is a Poisson random variable its probability mass function is formulated as;

$$\mathbf{P(x = k|\lambda) = e^{-\lambda} \frac{\lambda^k}{k!}}$$

The symbol *P* denotes the probability that *k* (the number of times an event occurs in an interval), will happen, and *k* can take values from 0, 1, 2, n. The average number of events in an interval is designated as λ (lambda), *e* is the number 2.71828… also known as Euler's number, which is the base of the natural logarithms, or the mathematical constant.

In any regression problem, our data are (y_1, X_1), (y_2, X_2) ... (y_n, X_n), where each y_i is modelled as a stochastic function of X_i (X_i=x_{1I} … x_{Ki}). In Poisson regression, we assume that each y_i is a Poisson random variable rate λ_i and formulated as;

$$\mathbf{log(\lambda i) = \beta_0 + \sum_{k=1}^{K} \beta_k X_{ki}}$$

Log refers to the likelihood of each Poisson random variable rate λi occurring. Where β_0 … β_K are the unknown regression coefficients (Gelman and Hill 2006, p. 111). The regression coefficients are estimated via the method of maximum likelihood (MLE). The predicted values, along with the sum of squared errors, are also calculated using MLE.

In addition, there is an assumption in Poisson regression that the mean and variance are approximately equal. Thus, to check whether the data in this study met this assumption the four blocks of count data were subjected to goodness-of-fit chi square tests prior to further analysis.

The goodness-of-fit chi square tests are required to return non-significant results if the residual differences are small enough to meet the assumption required for Poisson regression. Results of the goodness-of-fit chi square tests revealed a non-significant result for model 1 the *'stifled yawns in the free block'* X^2 (26, N = 29) = 26.68, p =0.43 which meant this model fit the assumption needed for Poisson regression analysis. However, for the other three models the results are as follows; there were significant results for *'full yawns in free'* X^2 (26, N = 29) = 125.851, p <0.001; for *'full yawns in resist'* X^2 (26, N = 29) = 172.475 p <0.001; and for *'stifled yawns in resist'* X^2 (26, N = 29) =51.816, p <0.001. The results for these three blocks show that the variance is much greater than the mean, which demonstrates that there is a high degree of over dispersion for each of these blocks of data.

Therefore, the alternative analysis in this instance was to conduct negative binomial regressions on these datasets. Negative binomial regression is typically used when count data is over-dispersed, whereby the conditional variance exceeds the conditional mean, such as found in some of the data in this study. It can be thought of as a generalisation of Poisson regression because it has the same mean structure as a Poisson regression. However, negative binomial models the over-dispersion by incorporating an extra parameter. Moreover, if the conditional distributions of the outcome variables are over-dispersed, the corresponding confidence intervals for the negative binomial regression are expected to be far narrower than results seen from a Poisson regression model. Having said that, negative binomial regression is still suggested as the most appropriate alternative to Poisson regression when the count data is over dispersed in this way (Gelman & Hill, 2006).

3.5.5 Poisson regression results for model 1 'stifled yawns in free'

The Poisson regression results for model 1 demonstrated that neither RMT nor IO Slope could significantly predict the number of stifled yawns observed in the free to yawn condition (χ^2 [1, N=29] = -0.024, p= 0.35), IO slope (χ^2 [1, N=29] = -0.004, p= 0.21).

3.5.6 Negative binomial regression results for model 2 'full yawns in free.'

The negative binomial regression results for model 2 demonstrated that IO slope significantly predicts the number of full yawns observed in the free to yawn condition (χ^2 [1, N=29] = -0.006082, p<0.001). However, the model demonstrated that RMT did not significantly predict the number of full yawns in the free to yawn condition (χ^2 [1, N=29] = -0.010573, p=0.163).

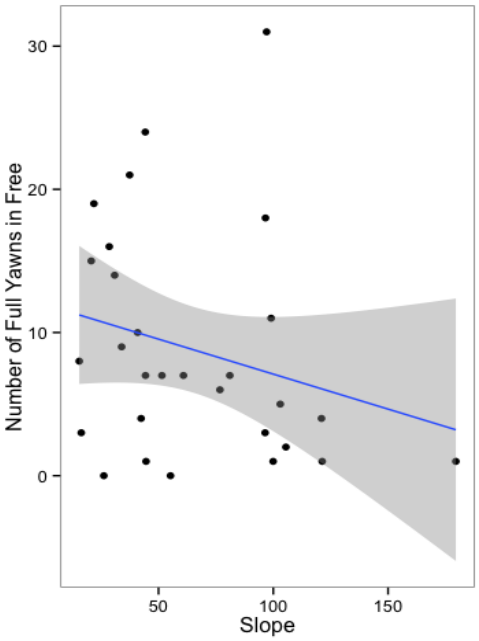


Figure 3-3: Graph depicting the significant association between IO Slope and the total number of Full yawns in the Free to Yawn condition. Please note that the blue line (best fit, linear regression) and the grey confidence interval are for visualisation purposes only.

3.5.7 Negative binomial regression results for model 3 'full yawns in Resist.'

The negative binomial regression results for model 3 demonstrated that neither IO slope (χ^2 [1, N=29] = 0.005918, p=0.07) nor RMT (χ^2 [1, N=29] = 0.017348, p=0.61) predicted the number of full yawns in the resist the urge to yawn condition. However, there is a trend towards IO slope predicting the numbers of full yawns in resist for this model.

3.5.8 Negative binomial results for model 4 'stifle yawns in Resist.'

The negative binomial regression results for model 4 demonstrated that IO slope (χ^2 [1, N=29] 0.002140, p=0.29) was not a significant predictor of stifled yawns in the resist condition. In contrast, RMT was found to significantly predict the number of stifled yawns in the *'Resist the urge to yawn'* condition (χ^2 [1, N=29] =-0.045786, p=0.004) please see figure 3.4.

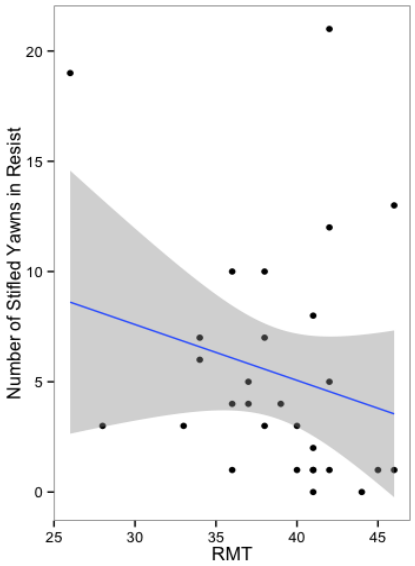


Figure 3-4: Graph depicting the association between RMT and the number of stifled yawns in the resist the urge to yawn condition. Please note that the blue line (best fit, linear regression) and the grey confidence interval are for visualisation purposes only.

3.5.9 Empathy and Autism Quotient questionnaires

There were no significant correlations between individual constructs, or total scores, on the Davis IRI empathy questionnaire and the incidence of contagious yawning $p>0.05$. Nor were there any significant correlations between scores on the autism quotient and measures of empathy, or the occurrence of contagious yawing all $p>0.05$. In addition, neither measures of empathy, or autism quotient scores, could predict the incidence of contagious yawning $p>0.05$.

3.6 *Discussion*

This study used a mixed physiological sp-TMS and behavioural paradigm to directly assess the role that motor corticospinal excitability and RMT may have on the occurrence of contagious yawning. The key aim of this study was to explore whether the number of full and stifled yawns in the *'resist the urge to yawn'* condition could be predicted by either RMT and/or CSE IO slopes. Full yawns in the *'free to yawn'* condition provided us with a baseline measure of each subject's propensity to contagiously yawn while the *'stifle yawns in free'* condition provided a measure of whether the subjects followed the behavioural task instructions appropriately.

3.6.1 Physiological task results

The physiological sp-TMS paradigm yielded significant results, which demonstrate that this method was highly effective. The physiological sp-TMS protocol clearly demonstrated that as TMS intensity increased, there was a significant increase in MEP amplitudes, which indicates a corresponding rise in

neuronal recruitment. This result was also consistently seen across all subjects in the study regardless of their starting RMT level (RMT range 26-46).

3.6.2 Behavioural task results

The contagious yawning behavioural task was also found to be highly effective. There was a significant effect of yawn condition on yawn response with a significant interaction between yawn condition and response. For example, there were significantly more *'full yawns'* in the *'free to yawn'* condition than in the *'resist the urge to yawn'* condition, and significantly more *'stifled yawns'* than '*full yawns'* in the *'resist the urge to yawn'* condition. In addition, the non-significant results for the, *'stifled yawns'* in the '*free to yawn'* versus the *'full yawns'* in the *'resist the urge to yawn'* condition, demonstrate that the task instructions were followed correctly.

The findings of the current behavioural task supports those of Schürmann et al., (2005), who also found that viewing videos of actors yawning naturally increases the likelihood of contagious yawning episodes in the viewing subjects. However, Schürmann et al., (2005) compared the likelihood of yawning, when subjects viewed actors yawning, or when they viewed actors performing non-nameable mouth movements (e.g. tongue in cheek) and found that the yawning movements elicited significantly more episodes of contagious yawning in the subjects than the "control" movements. However, unlike Schürmann et al., (2005) the current study did not include a control condition. The primary aim of this study was to explore whether the number of full and stifled yawns could be predicted by cortical excitability measures. Thus, the significantly greater number of *'full yawns'* than '*stifled yawns'* in the *'free to yawn condition*', acted

as a baseline measure of the subjects' propensity to contagiously yawn. Moreover, our behavioural results clearly demonstrate that the behavioural task instructions caused the subjects to significantly modify their behaviour, which were also consistent with the task instructions.

3.6.3 RMT and the occurrence of contagious yawning

The results for models 1, 2, and 3 demonstrated that RMT could not significantly predict the number of *'stifled yawns'* observed in the '*free to yawn'* condition, for *'full yawns'* in the *'free to yawn'* condition, nor for *'full yawns'* in the *'resist the urge to yawn'* condition. This result suggests that the strength of MEP activity, which progresses from presynaptic neurons, which then project to the targeted muscle, does not have a direct effect on a subjects' propensity to fully yawn, or stifle their yawns while being instructed to yawn freely. Nor were they able to predict individual's propensity for full yawns in the resist the urge to yawn condition. RMT is known to reflect the core of the corticospinal projections to the target muscles and arises from this excitability in individual neurons and their local density (Goetz & Peterchev, 2012). RMT also very much depends on the axonal membrane properties of corticospinal neurons at the site of TMS and the membrane properties of post-synaptic neurons (Orth, 2009; Pépés et al., 2016).

However, and as noted in chapter 1, accurate measures of RMT are essential for most TMS studies. For example, TMS intensity for each participant is typically adjusted according to their individual RMT. Thus, inter-individual differences in RMT can vary according to multiple factors including; the distance between the scalp and cortex (Cukic, Kalauzi, Ilic, Miskovic, & Ljubisavljevic,

2009), the orientation of white matter fiber tracts (Danner et al., 2011), and/or inherited influences (Wassermann, 2002). Additional factors, other than structural differences, have also been cited as possible influences on RMT measures. For instance, while almost all TMS studies recruit right handed participants, research regarding the impact of handedness on RMT has yielded inconsistent results (Goetz & Peterchev, 2012; Peterchev et al., 2012). Similarly, there is conflicting evidence regarding notable age dependent effects on RMT measures (Smith, Ridding, Higgins, Wittert, & Pitcher, 2009).Nonetheless, TMS remains an important technique for harnessing understanding regarding both structure and function of the human brain.

Surprisingly, this was not the case for the stifled yawns in the resist condition in our study. Significant effects of RMT were found regarding the occurrence of stifled yawns in the resist the urge to yawn condition. This result suggests that lower motor thresholds are associated with reduced ability to stifle yawns in the resist the urge to yawn condition. It appears that the instruction to inhibit yawning behaviour had a profound effect on how this behaviour was expressed.

Another surprising finding of this study, even though we were not assessing cultural influences on contagious yawning, was that we observed several of our subjects, who were of Chinese or Southeast Asian origin, either did not yawn at all, or for those that did, tended to cover their face or stifle them more often than our European subjects. It is suggested that Western and Eastern cultures assign different meanings to many elements of non-verbal communication, particularly those closely related to empathy (Walusinski et al., 2004). Unfortunately, there is currently no literature regarding individual differences and the occurrence of contagious yawning across cultures. Furthermore, it is

difficult to draw any definitive conclusions in this study, this is mainly because our sample is relatively small, and that this observation only occurred because of our sampling and not as a direct result of our methodology. Nevertheless, this is an interesting finding that could warrant further investigation in the future.

3.6.4 Corticospinal excitability and the occurrence of contagious yawning

The main purpose of this study was to assess whether the number of stifled and full yawns displayed during the *'free to yawn'*, and more importantly the *'resist the urge to yawn',* conditions could be predicted by corticospinal excitability (CSE) input output (IO) curves. First, we observed that shallower CSE IO curves significantly predicted the number of full yawns in the *'free to yawn'* condition. In addition, we found a near significant trend in the *'full yawns'* in the *'resist the urge to yawn'* condition *(*p=0.07). We suspect that this may be due to a lack of statistical power, or that there were five subjects who did not yawn in any of the four conditions. When we remove these from analysis the *'full yawns in resist'* condition become highly significant (p=0.01). However, it was felt that removing these subjects would have a detrimental effect on the transparency and validity of this study so opted to keep them.

Nevertheless, our findings do appear to suggest that lower motor cortex excitability results in a reduction in the ability to stifle yawns in the *'resist the urge to yawn'* condition. Also, the trend observed in the full yawn in resist condition demonstrates that there is at least some influence of CSE on the direction of contagious yawning outcomes. As noted, similar observations were discovered by Obhi et al., (2011), who also used TMS to elicit MEPs during an

action observation task. Their findings suggest that priming interdependent self-construal increases motor cortex output, whereas priming independent self-construal does not when compared with their non-priming baseline condition (Obhi et al., 2011). Interestingly, the pattern of the self-construal-induced changes in the motor system seen by Obhi et al., (2012) also supports the findings of previously observed self-construal effects on obvious mimicking behaviours in social settings. Obhi et al. (2011) describe self-construal as, how an individual views and makes meaning of themselves. Obhi and colleagues (2011) identified two separate subtypes of self-construal, namely independent and interdependent. They note that independent self-construal refers to a view of the self in the absence of others, while interdependent self-construal refers to a view of the self in relation to others.

It appears that our significant finding regarding the role of CSE in the '*stifled yawns in resist'* condition, as well as those by Obhi et al., (2012), provides some evidence that motor cortex excitability could well be mediating nonconscious mimicry in social settings. Interestingly, Obhi et al., (2011) further argued that these effects are most likely facilitated by changes in the human mirror neuron system, which given our own findings, suggests that contagious yawning may well be a form of social imitation also mediated by the hMNS. This is an intriguing suggestion, and as such, it seems wholly reasonable to interpret motor cortex excitability as a reflection of hMNS activity in this context. This idea is supported by Haker, Kawohl, Herwig, & Rössler, (2013) *f*MRI study that found that the hMNS plays a key role in the occurrence of contagious yawning.

Haker et al., (2013) objective was to test the theory that visually perceived yawning activates the hMNS. Haker and colleagues (2013) used *f*MRI to

evaluate cortical activity during episodes of contagious yawning (CY). They compared signal-dependent changes in blood oxygen levels (BOLD) when participants observed videotapes of yawning faces, and while they observed faces with neutral expressions (Haker et al., 2013). In response to the yawning stimuli, Haker et al' (2013) participants demonstrated unilateral activation in Brodmann's area 9 (BA 9), a portion of the right inferior frontal gyrus (IFG). Importantly, this is a region postulated to be part of the hMNS (Hamilton, 2008). Haker and colleagues (2013) argue that their findings mean; that two individuals could share physiological and related emotional states based on perceived motor patterns. Interestingly, they also imply that this is related to one component of empathy, particularly motor empathy, which was also proposed by (Blair, 2005). Moreover, this is said to subsequently underlie the development of cognitive empathy.

Haker et al., (2013) finding also appears to emphasise the connection between the hMNS and higher order cognitive empathic functions, including mentalising. This is an important consideration because motor cortex excitability appears to somehow influence imitative behavioural outcomes. In addition, BA 9 is also active during tasks requiring mentalising abilities, as well as during observations of contagious yawning. Thus, it seems feasible that individual differences in CSE could also be at the centre of altered contagious yawning and imitative behaviours in neurodevelopmental disorders.

Evidence that CSE is significantly related to the occurrence of imitative behaviours is also demonstrated by van Ulzen, Fiorio, & Cesari, (2013). Similar to the current study, Van Ulzen and colleagues utilised a TMS procedure in order to probe motor resonance during a naturalistic mimicry paradigm. The

objective of their study was to establish whether the motor system resonates immediately with unobtrusive nonverbal behaviour of another individual (van Ulzen et al., 2013). Van Ulzen et al., (2013) used TMS to measure CSE in both the left and right hand while subjects observed video clip sequences and static images with both face touching (FT) and non-face touching (NFT) conditions.

Van Ulzen et al., (2013) discovered that CSE was higher in the FT condition as compared to the NFT and baseline conditions. Furthermore, their data demonstrated a greater degree of excitability in the left motor cortex relative to the right motor cortex. Van Ulzen and colleagues (2013) report that the observed hand to face gestures could cause instantaneous motor resonant activity in the observer's motor system despite being away from the primary focus of attention and occurring inconspicuously throughout the ongoing action setting. Furthermore, Van Ulzen and colleagues (2013) also posit that motor resonance is linked to activation in the motor system during action observation and as such should be interpreted in the context of mirror neuron system functioning. Our finding that CSE is most likely involved in mediating the occurrence of contagious yawning supports Van Ulzen et al., (2013) notion that motor resonance is involved in mediating mimicking behaviours. Moreover, both the current study and that of Van Ulzen et al., (2013) demonstrate that this can be investigated using a combination of physiological TMS and naturalistic mimicry paradigms.

Support for the role that motor cortex excitability (CSE) plays in facilitating imitative behaviours was also demonstrated by Finis et al., (2013). As discussed in chapter one, Finis and colleagues (2013) used repetitive TMS (rTMS) to explore and modify corticospinal excitability while subjects viewed

videos of echophenomena. Finis et al (2013) used rTMS to alter CSE in the supplementary motor area (SMA) in typically developing controls (TDC). Finis and colleagues hypothesised that modification of neural activity in the SMA would evoke echophenomena in typically developed controls. To explore this theory Finis and colleagues (2013) used both 5 Hz rTMS, which is said to temporarily facilitate cortical activity, and 1 Hz rTMS, which is said to disrupt or attenuate neural activity. Their results demonstrated a significant increase in echophenomena following 5 Hz stimulation, but no significant effect following 1 Hz stimulation. Finis et al (2013) conclude that this finding implies that increased activation in SMA might mediate the occurrence of echophenomena. In sum, Finis et al., (2013) study demonstrates that non-invasive electrical stimulation of the SMA can produce tic-like movements (echophenomena) and an urge to move in individuals without tics. This appears to add evidence regarding the role of SMA in premonitory urges, a key feature of those with Tourette's syndrome.

Support for this idea can be found in a meta-analysis conducted by Jackson, Parkinson, Kim, Schüermann, & Eickhoff (2011). They used quantitative ALE meta-analytic techniques to explore the functional anatomy of the urge-for-action in the context of swallowing and micturition. The results of this analysis demonstrated that brain activations associated with these behaviours overlapped in two brain regions; the right insula and the dorsal anterior cingulate cortex. Furthermore, they were able to show that functional activations associated with the urge to tic in individuals with Tourette's syndrome, along with the urge to yawn in neurologically healthy individuals also overlapped within these same two brain regions. These two brain areas have also been

described as the limbic sensory and motor areas respectively (Jackson et al., 2011), and have also be associated with the occurrence of contagious yawning (Schürmann et al., 2005). The relevance of GTS to contagious yawning and research among those with ASD is primarily due to both disorders sharing the core diagnostic feature echophenomena.

3.6.5 Limitations

This study is the first to investigate the role of CSE on the occurrence of echophenomena in the form of contagious yawning. As with any new study we inevitably encountered several methodological issues. Firstly, our study did not include a control condition. The lack of a control condition leaves us open to criticism insofar as we cannot compare the incidence of contagious yawning against non-yawning stimuli. For example, it could be argued that we cannot differentiate between spontaneous and contagious yawns without a control condition. This criticism would be intensified by the knowledge that our subjects were sat alone in a dark room following a lengthy period of TMS measures.

Indeed, it is entirely possible that our subjects also spontaneously yawned during the behavioural task. One way we could improve the validity of the contagious yawning paradigm would be to assess the temporal window between the actors yawning and the occurrence of yawning in our subjects, a feature that was included in the study by Haker et al., (2013). However, one limitation of this protocol would be that, since contagious yawning does not always occur immediately following a yawn observation, the introduction of a temporal time window may reduce the reliability of the study. For instance,

contagious yawns might well be dismissed if they were to occur either side of this window.

Another issue relates to inter-rater reliability. For example, although the counting of full yawns yielded a high degree of agreement, the counting of stifled yawns did not. The moderate level of reliability for stifled yawns was reported by the raters to be due to difficulty in determining whether the subjects were stifling a yawn or simply covering their mouth. Since mouth covering is a frequent feature during the occurrence of yawns it seemed fair to assume that this was a stifle and was added to the rater protocol. However, as evident from the moderate degree of reliability this cannot be relied upon alone. Therefore, our future studies will also include a means of measuring each subject' urge to yawn as opposed to simply relying on video data alone.

As already noted, Jackson et al., (2011) explored the timing of conscious awareness of an urge relative to the conscious suppression of a yawn. Jackson and colleagues (2011) postulated that such an urge might not occur prior to a yawn, but rather a result of conscious attempts to stop the yawn. Indeed, if this were the case, the modified version of our behavioural task would yield a greater number of urges in the *'resist the urge to yawn'* condition. This modified version would also enable us to cross-validate the number of stifled yawns counted by our raters and the number of urges reported by our subjects. In addition, we could also explore the relationship between the number of urges and measures of CSE. Finally, given that our study encompasses elements of inhibitory processing (e.g. 'resist yawning condition') it is important for us to measure physiological measures of inhibition as well as excitation in subsequent studies.

3.6.6 Concluding comments

The results of the current study provide tentative evidence for the role of motor cortex excitability on contagious yawning. These findings could also go some way towards supporting the hypothesis that the hMNS is a primary mediator of both echophenomena (Ganos et al., 2012a), and contagious yawning (Platek et al., 2005). Moreover, the link between imitation, individual differences in motor cortex excitability, and the occurrence of contagious yawning, is an important consideration and as such will form a large part of our future research endeavours going forward. Given the evidence that individual differences in RMT and motor cortex excitability might mediate the occurrence of echophenomena, it seems wholly reasonable to assume that CSE might also mediate the occurrence of contagious yawning.

Chapter 4 Echophenomena 2 – A Neural Basis for Contagious Yawning

Some of the work in this chapter has been previously presented in: Brown, B.J., Kim, S., Saunders, H., Bachmann, C., Thompson, J., Ropar, D., Jackson, S.R., and Jackson, G.M. (2017). A Neural Basis for Contagious Yawning, *Current Biology, 27,* 2713-2717.

4.1 *Introduction*

The results of the previous study provided tentative evidence for the role of motor cortex excitability on contagious yawning. Moreover, these initial findings could go some way towards supporting the hypothesis that motor cortex excitability is a primary mediator of both echophenomena (Ganos et al., 2012a), and contagious yawning (Platek et al., 2005). More importantly, the link between automatic imitation, individual differences in motor cortex excitability, and the occurrence of contagious yawning is an important consideration and warranted additional investigation.

As already discussed elsewhere, contagious yawning (CY) is a phenomenon that only occurs in humans, old world primates, and some dogs. It is a contagion that is facilitated in response to, hearing, seeing, or for humans, even thinking about yawning (Platek, Mohamed, & Gallup, 2005). However, it is distinctly different to spontaneous yawning insofar as, spontaneous yawning is an involuntary and stereotyped behaviour observed in most vertebrate species (including humans) from foetal stages to adulthood (Guggisberg, Mathis, Schnider, & Hess, 2011; Helt et al., 2010). Spontaneous yawning also typically

occurs as a result of many physiological changes including; boredom, hunger, changes in temperature, mood state, sleep/wake state etc. (for a comprehensive yawning review see Guggisberg et al., 2011). Moreover, where spontaneous yawning begins in utero, contagious yawning does not begin until early childhood (Platek et al., 2005).

This delayed start to contagious yawning has led many researchers linking it to difficulties with empathy and theory of mind processes (TOM) (Platek, Critton, Myers, & Gallup, 2003; Platek et al., 2005; Schürmann et al., 2005; Yoon & Tennie, 2010). Contagious yawning has also been associated with social development and automatic imitation, which subsequently places it in the spotlight for hMNS and empathy research. It is for this reason that CY has frequently been researched in relation to the actions of the hMNS (Platek et al., 2005; Schürmann et al., 2005), which as noted previously, is thought to play a significant role in empathy, action understanding, and the synchronisation of group social behaviour (Rizzolatti & Craighero, 2004). However, functional magnetic resonance imaging (fMRI) research has produced diverse results regarding this proposal, noting that core regions of the hMNS are not in fact activated during CY (Platek et al., 2005; Schürmann et al., 2005) and is most likely related to amygdalar activation and empathy processing.

Conversely, Bartholomew & Cirulli, (2014) offer an opposing view and argue that CY is not correlated with empathy scores at all. They also state that while the propensity for CY varies across individuals, it is largely stable over time (e.g., across testing sessions). However, it is worth noting that these observed sensory signals may well trigger actions outside of conscious awareness (Cavanna, Black, Hallett, Voon, 2017). Actions triggered outside of conscious

awareness are typically referred to as urges-for-action (Jackson et al., 2011). Jackson and colleagues (2010) state that urges-for-action are primarily associated with actions that cannot be facilitated immediately, and consequently, their execution deferred until a more appropriate time, only then can these actions be released.

Interestingly, the word ‘urge’ is frequently described in the same context as ‘desire’. However, as Jackson and colleagues (2011) suggested, this distinction would imply that every urge-for-action arises as a consequence of pleasant bodily sensations or desires, which is not the case in all instances of urge-for-action. For example, it is understood that many common neurodevelopmental and psychiatric disorders such as obsessive-compulsive disorder (OCD), Tourette syndrome (TS), autistic spectrum disorder (ASD), or schizophrenia, are typically associated with unpleasant body sensations prior to movement execution, and as such subsequently perceived as an urge for action (Jackson et al., 2011).

Currently, little is known regarding the neural basis of urge-for-action during episodes of echophenomena, and more interestingly contagious yawning. As noted in the opening chapter, this is an important consideration given that many individuals report feeling an urge to yawn prior to an actual yawn being realised or stifled. In addition, there is some debate regarding whether the urge to yawn is mediated by the same brain region as the act of contagiously yawning itself. For example, (Nahab, Hattori, Saad, & Hallett, 2009) suggest that the urge-to-yawn, through a contagion as opposed to other non-contagious facial expressions, does not occur through a process of imitation or mimicry, but rather from a primitive motor program which is actuated by the cortex and

facilitated through well characterised brainstem and subcortical mechanisms. This suggests that the urge-to-yawn is a separate phenomenon and unrelated to imitation and the act of contagious yawning itself (Nahab et al., 2009). This is important particularly in respect of impulse control disorders whereby an urge-for-action typically precedes the expression of an action; an example of such would be premonitory urges followed by tic expression in Gilles de la Tourette's Syndrome (GTS). Research regarding motor cortex excitability in Gilles de la Tourette's Syndrome (GTS) suggests that an inhibitory cortical circuit deficiency exists in the motor system of those with this condition (G. M. Jackson, Draper, Dyke, Pépés, & Jackson, 2015; Mink, 2001; Orth, 2009; Pépés, Draper, Jackson, & Jackson, 2016)

However, as noted in chapter one, while this provides understanding regarding motor cortex abnormalities in GTS, it provides little evidence regarding the influence of motor cortex excitability on echophenomena or contagious behaviours. Indeed, despite the assumption that echophenomena is mediated by the hMNS and motor cortex excitability (Ganos et al., 2012; Mehta et al., 2013), there is very little empirical research evidence available that supports this. Moreover, there are very few studies to date that explore the role motor cortex excitability might have on echophenomena more directly. For instance, a comprehensive literature search yielded only one such study that supports the role that motor cortex excitability (CSE) might play in facilitating imitative behaviours (Finis et al., 2013). Finis and colleagues (2013) used TMS to investigate and alter corticospinal excitability to investigate the occurrence of echophenomena in typically developing controls (Finis et al., (2013).

As noted in the previous chapter, Finis et al (2013) generated an experimental paradigm that utilised repetitive transcranial magnetic stimulation (rTMS) to alter corticospinal excitability in the supplementary motor area (SMA) in typically developing controls (TDC). They hypothesised that modification of neural activity in the SMA would evoke echophenomena. Finis et al (2013) concluded that their finding implies that increased activation in SMA might mediate the occurrence of echophenomena. Furthermore, Finis et al (2013) also observed significantly lower resting motor thresholds (RMT) for the 5 Hz rTMS group. Interestingly, the observed difference in RMT could hold some meaning for the occurrence of echophenomena but unfortunately Finis and colleagues (2013) did not explore this further. However, it is hoped that this novel finding can be further addressed in this chapter and subsequent research studies.

It would appear from the literature that a more thorough understanding regarding the neural foundations of contagious yawning is needed. Moreover, while both empathy and CY are frequently associated with the actions of the hMNS, which is also said to be directly associated to areas of motor cortex and limbic cortices (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003; Schürmann et al., 2005), there still remains no clear consensus among researchers. Harnessing more accurate knowledge in this area would be particularly important for the understanding of human behavioural and communication systems more generally. More importantly, further understanding in the area of CY research could help elucidate why some individuals share absent or aberrant forms of social mimicry (Arnott, Singhal, & Goodale, 2009; Rogers, Hepburn, Stackhouse, & Wehner, 2003). As noted previously, the relevance of

contagious yawning research to conditions such as GTS and ASD is primarily due to both disorders sharing the core diagnostic feature of echophenomena.

It was with all these factors in mind, along with the fact that the motor cortex excitability has been suggested as a mediator of echophenomena (Ganos et al., 2012), and contagious yawning (Platek et al., 2005), that the current research was extended. In addition, if urge-for-action occurs prior to a behavioural expression, whether that be a tic or a contagious yawn, and is wholly mediated by another brain region, then further knowledge regarding this is also required. Furthermore, given the underexplored possibility that differences in RMT (Finis et al., 2013) and motor cortex excitability (Ganos et al., 2012) might mediate the occurrence of echophenomena, it seemed reasonable to assume that RMT and/or motor cortex excitability might also mediate the occurrence of contagious yawning.

Taking this, and the evidence from our pilot study, whereby it was found that individual differences in RMT and motor cortex excitability might mediate the occurrence of echophenomena, into account, it seemed sensible to extend the research to include measures of cortical excitability and physiological inhibition. It is hypothesised that both these measures might mediate the occurrence of echophenomena. Based upon this assumption the following study will investigate further the role that these might play in the occurrence of contagious yawning. We will also investigate the neural basis for CY using non-invasive brain stimulation [NIBS] in an attempt to modulate this behaviour via the supplementary motor area (SMA). The SMA is a brain region previously associated with the genesis and occurrence of Echophenomena (Bohlhalter et al., 2006; Finis et al., 2013).

Transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS) will be used in an attempt to alter the excitability of neurons within the SMA. Collectively these techniques are often referred to as transcranial electrical stimulation (TES) or NIBS. The application of TES has been shown to modulate cortical excitability, also referred to as anodal TES, in humans. Conversely, the same techniques can be used to reduce, or inhibit, cortical excitability, also known as cathodal TES. Anodal TES is achieved by placing the anode electrode over the region of interest, e.g. SMA, while cathodal stimulation is achieved by placing the cathode electrode over the region of interest. Excitatory anodal tDCS and tRNS were chosen for the purposes of this and subsequent studies. The rationale for using both excitatory tDCS and tRNS was due to each technique using different mechanisms of application in order to induce cortical excitability. Where tDCS imparts a continuous train of electrical stimulation at a set parameter, tRNS delivers random electrical stimulation at an amplitude and frequency of between 0.1 or -0.1, to as high as 2mA (figure 4.1). It is hypothesised that tRNS will influence cortical oscillations leading to changes in cortical excitability far more readilythan tDCS. It is felt that the random delivery of electrical stimulation to the SMA will increase the sensitivity of the neurons in this region and lead to modulation of the cortical response via the repeated opening of sodium channels (Paulus, 2011).

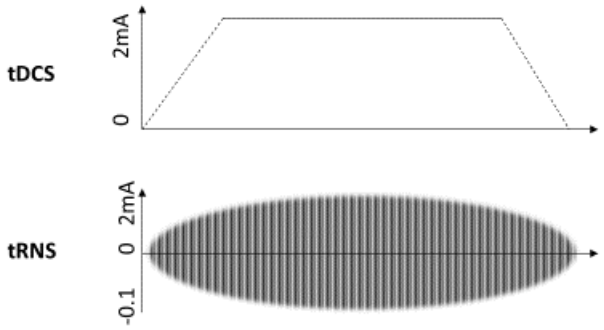


Figure 4-1: Transcranial electrical stimulation techniques. While tDCS uses constant current intensity, tRNS uses an oscillating current. The Y axis represents the current intensity in milliamp (mA), while the X axis shows the time-course

4.2 *Methods*

4.2.1 Ethics

Ethical approval for this study was sought and granted by the University of Nottingham ethics committee. Ethical approval number 219.

4.2.2 Participants

Thirty-six young adults aged 18-26 years (mean age=20 ± SD=1.56), were recruited via opportunity sampling from the University of Nottingham.

Prior to the study all participants were taken through appropriate TMS and TES screening and informed consent was obtained. Further informed consent regarding the video recording of the participants during the behavioural task was also obtained. All participants were financially compensated for their time and participation in this study.

4.3 *Study Design*

A within and between subjects' mixed methods experimental design was employed. The first method in this paradigm consisted of physiological TMS measures of resting motor thresholds (RMT), motor cortical excitability (MCE), and physiological inhibition and facilitation. Measures of cortical excitability for each subject were ascertained via TMS induced input-output curve (IO) measurements of motor evoked potentials (MEP). Physiological inhibition was determined via 1 and 3-millisecond short interval cortical inhibition (SICI), and 100-millisecond long interval cortical inhibition (LICI). Cortical facilitation was determined via 12-millisecond intracortical facilitation (ICF). The behavioural measures of contagious yawning utilised a 2x2 (yawn condition v yawn response) ABBA blocked (x4) design, while participants' perceived urge-to-yawn was measured using a custom-made continuous response metric slider mechanism.

We also utilised anodal transcranial direct current [a-tDCS] and random noise [tRNS] electrical stimulation (relative to sham stimulation) to increase the cortical excitability of the supplementary motor area [SMA] during the second half of the behavioural task. The primary aim of this part of the study was to examine whether contagious yawning could be moderated by excitatory stimulation, and to ascertain whether the SMA is involved in the genesis of echophenomena as proposed by Finis et al., (2013). In addition to this, measures of participants' subjective perceived urge-to-yawn ratings will be examined. Finally, the first two behavioural blocks will also act as a baseline measure of contagious yawn propensity, and a measure of how well subjects followed the behavioural task instructions respectively.

4.4 *Procedure*

The design of the experimental task is illustrated in Figure 4.2. Participants watched video clips that depicted another individual yawning and, in separate blocks, were either instructed to resist yawning or to allow themselves to yawn freely. Blocks 1 and 2 of the behavioural paradigm were completed without non-invasive brain stimulation, but during blocks 3 and 4 non-invasive brain stimulation was delivered continuously to the SMA region of the scalp.

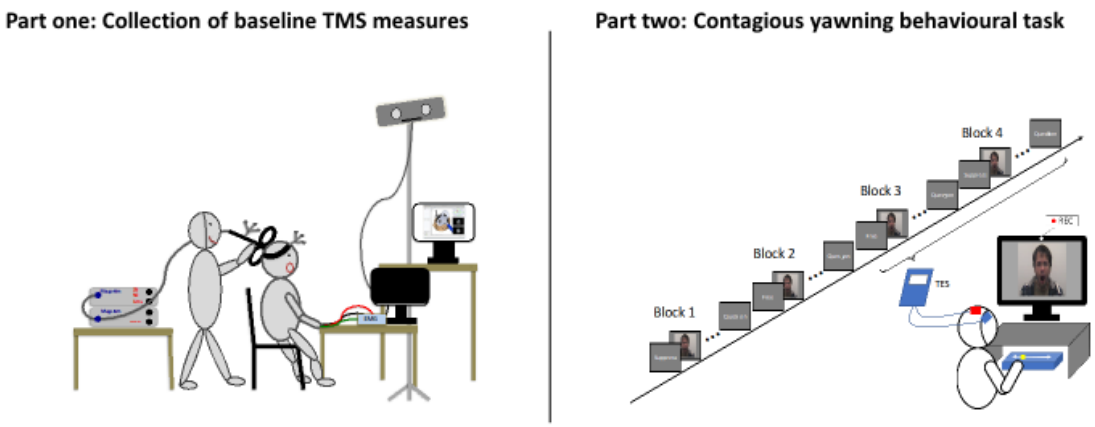


Figure 4-2: Illustrates the design of the task. Part one illustrates collection of the baseline measures of cortical excitability and inhibition. Part two illustrates the contagious yawning behavioural task. Participants viewed video clips depicting another individual yawning and, in four separate blocks, were instructed to either resist or allow themselves to yawn. Participants were videoed throughout, and their yawns or stifled yawns counted thereafter. During the latter two blocks (3 & 4) excitatory non-invasive electrical brain stimulation (Anodal-tDCS or tRNS) was delivered continuously to the cortical SMA region (contrasted with sham stimulation). To ensure that participants paid attention to the videos they were required to answer a question (e.g., How many people in the videos wore glasses?) after each block.

All participants were assigned randomly to one of three experimental conditions comprising of: anodal-tDCS stimulation, tRNS stimulation, or, sham stimulation. Participants were videoed throughout the duration of the task and their yawns and stifled yawns were counted. In addition, participants were asked to register their perceived urge-to-yawn ratings. These ratings were continuously recorded using a custom-made slider mechanism (Figure 4.3).

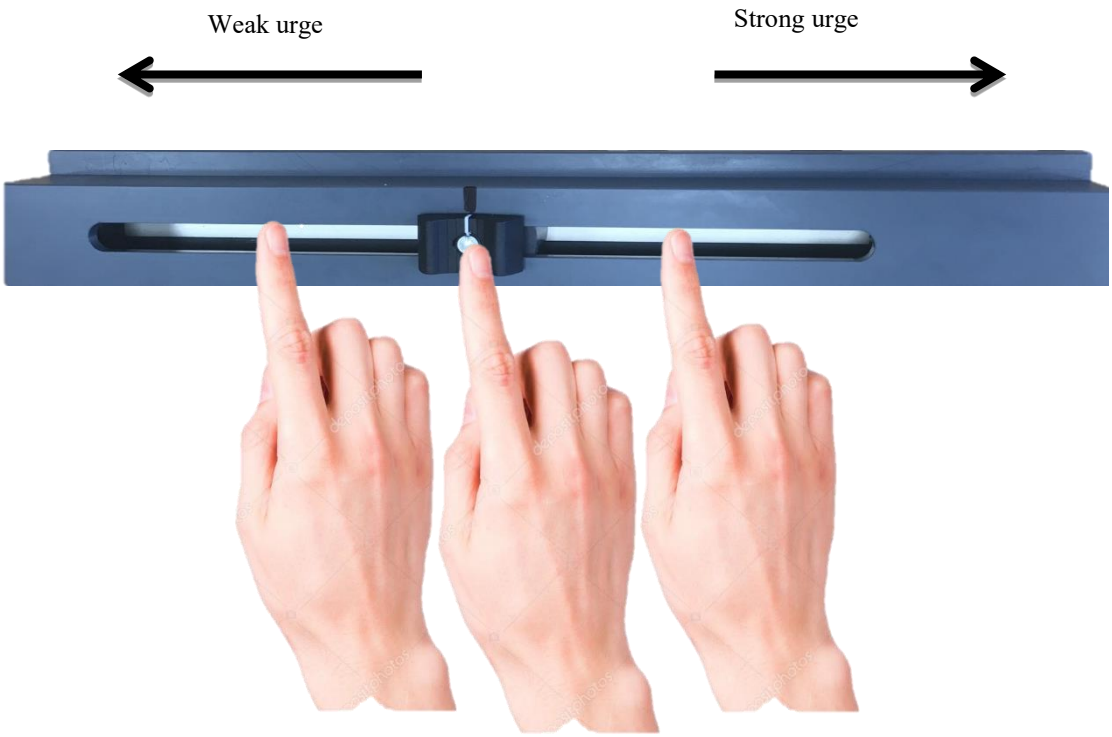


Figure 4-3: Illustrates the slider device used to continuously record each participant's self-estimate of their current urge-to-yawn (see text for details). Movement to the right represents a weak to no urge to yawn, whereas movement to the right represents stronger urges to yawn.

The intensity of each participants perceived urge-to-yawn ratings were captured throughout the duration of the behavioural task. The participants' operated the mechanism by using their right index finger. This device delivered a continuous voltage signal that indexed change over time in self-estimated intensity in the

perceived urge-to-yawn. Representative data from one individual are presented in Figure 4.4.

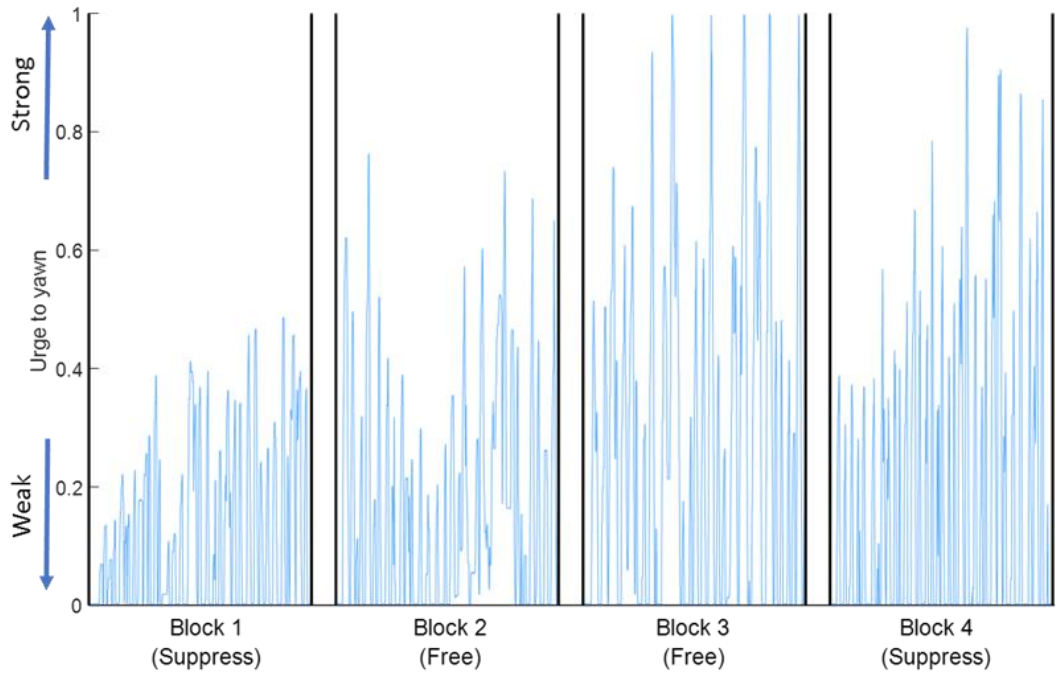


Figure 4-4: Depicts a representative example of one individual's self-estimated perceived urge-to-yawn across the four separate blocks of the behavioural task.

4.4.1 TMS

A Magstim Bistim 2^{TM}, with a 70mm figure of eight coil, was used to administer TMS to the left M1 in an area corresponding to the first dorsal interosseous (FDI) muscle of the right hand. Motor hotspot was defined as the coil location that elicited maximal MEP responses in FDI by positioning the TMS coil over each subject' left motor cortex (M1) at approximately 45° (Pascual-Leone et al., 1994). The coil location was continuously tracked throughout the study, via BrainSightTM version 2.0 (Rogue Research Inc. ©, 2016). EMG responses

were recorded using BrainVision Recording software at a sampling rate of 5000 Hz and band pass filtered (10-2000 Hz). Disposable Ag-AgCl surface electrodes were placed onto the FDI muscle in a standard 'belly-tendon' configuration.

4.4.2 RMT, Si1Mv, and IO curves

Following localisation of motor hotspot resting motor threshold (RMT) was then obtained. Each subjects RMT was determined as the minimum TMS intensity needed to elicit an FDI generated MEP of at least 150–200 μV in a minimum of 5 out of 10 trials. Once RMT was obtained each subjects Si1mV threshold was then calculated. Si1mV threshold was determined as the amount of TMS intensity needed to elicit an FDI generated MEP of approximately 1mV in size in a minimum of 5 out of 10 trials. Si1mV threshold is typically approximately15% of RMT. Si1mV threshold is required in order to facilitate paired pulse TMS protocols. Single pulse TMS intensities administered ranged from 100% - 150% of RMT and delivered in 10% increments resulting in 6 TMS intensities with an inter-trial interval (ITI) of 5s. The IO curve measurements were estimated by calculating the median intra-individual MEP amplitudes for each of the TMS intensities (i.e., 100–150% of RMT). A linear fit was then applied to the resulting values. Median values were calculated as opposed to the mean to limit the effect of non-standard distribution of individual data.

4.4.3 Paired pulse TMS (SICI, LICI, & ICF)

Paired pulse TMS (ppTMS) was performed at four inter-stimulus intervals (ISIs); 1 ms, 3 ms (SICI), 12 ms (ICF) and 100 ms (LICI). For 1 and 3 ms SICI the conditioning stimulus (CS) was set as 55% of RMT, ICF at 75%, and LICI at

RMT. The test stimulus was set at SI 1mV for all conditions (20 trials per stimulus condition). There were also 60 unconditioned stimuli (total 140 trials). All conditions were delivered in a pseudo-randomised order with an ITI of 6s. Paired pulse TMS measures were reported at a ratio to unconditioned responses (i.e. conditioned MEP/unconditioned MEP).

4.4.4 Behavioural task procedure – facilitating contagious yawning

Directly following TMS procedures the participants completed the contagious yawning behavioural task. Participants were instructed to watch a 40-minute (4 blocks) video of actors yawning. They were asked to pay close attention to the screen and answer four questions relating to the actors they would see such as, 'how many actors were wearing glasses. Answers provided were later used to confirm that they were paying attention to the video clips appropriately. Each question was asked after each block and prior to the next block.

The video was produced in-house and comprised four 9-minute blocks of video clips (total 52 clips) with each clip ranging from 11-20 seconds in length. Each video clip featured either a female or male actor (aged 20-28 years) spontaneously yawning. Each block of videos was also collated into 12 randomised video sets, which were then counterbalanced across all participants. All videos were shown on an Apple Macintosh desktop via VLC media player software. Prior to the start of each of the 4 blocks subjects were instructed to either 'resist the urge to yawn' or to 'yawn freely'. In each block both stifle and full yawns were measured.

The 4 blocks were counterbalanced in an ABBA/BAAB order (i.e. yawn freely, resist, resist, yawn freely or resist, yawn freely, yawn freely, resist). The first two

blocks in the ABBA/BAAB design acted as a baseline measure of contagious yawn propensity and a measure of how well participants followed the behavioural task instructions respectively. The capacity for these videos to induce contagious yawning was assessed in our previous study.

Video clips were played continuously throughout the 9 minutes duration with no interval between each clip. However, each block was separated by a 45 second interval. At the end of each block, participants had this 45-second interval to answer the question corresponding to that particular block. For the duration that the video' recording was playing each subjects face was recorded using Open Broadcaster Software.

Participants were also instructed to record their subjective urge to yawn by continuously adjusting a button on a custom-made slider mechanism throughout the duration of each video. The length of the slider mechanism was 195mm, which was scaled to give urge readings between 0 (left end-no urge) and 1 (right end-maximum urge), at a sampling rate of 32Hz. The slider was controlled via a data acquisition device (DAQ), and a Matlab script version 2010b.

4.4.5 Transcranial Electrical Stimulation (TES)

This study utilised three separate TES techniques, tDCS, tRNS and sham. Participants were randomly assigned to one of the three TES conditions. Stimulation was administered during blocks three and four of the yawn videos.

TES was administered via a DC-stimulator plus (NeuroConn, GmbH, Ilmenau, Germany). Stimulation was administered via two rubber electrodes each measuring 35cm^2. Each electrode was contained within a sponge applicator,

which was saturated in saline solution (concentration 0.9% sodium chloride (NaCI) to water)

The anodal electrode was positioned on the supplementary motor area (SMA) as determined by the electroencephalography (EEG) 10-20 system. The EEG 10-20 system locates SMA as 15% of the distance between nasion to inion, from preauricular to preauricular, anterior to Cz (Jurcak, Tsuzuki, & Dan, 2007). The cathodal electrode was positioned above the contralateral right orbital region. The position of each electrode was maintained by using cobalt self-adhering bandage. Anodal tDCS was delivered at a constant stimulation output of 2mA for 20 minutes with a ramp up & ramp down of 15 seconds. The tRNS stimulation was administered at a HF noise mode at 2mA, with the offset set to zero. For sham an identical set-up to that used for tDCS was used but the current was applied for 15 seconds with a ramp up & down of 15 seconds.

4.4.6 Analysis

The number of full yawns (FY) and stifled yawns (SY) displayed by the participants during each video block were counted using a yawn count protocol used in our previous study. Yawn counts were collated for each instruction (free & resist) and condition (full & stifled yawns).

4.5 *Results*

4.5.1 EMG pre-processing

All EMG signals that were recorded during the sp-pp-TMS procedures were analysed using EEGLAB in MATLAB. Peak-to-peak amplitudes of the MEPs were measured for each individual trial. Data for each of these trials was also

inspected visually to check for contaminated electrical activity, (e.g. tension in the muscle would artificially inflate MEP amplitude), and all contaminated trials were excluded from analysis. Less than 5% of trials were excluded in any given individual dataset.

4.5.2 TMS corticospinal excitability IO Data

MEP amplitudes for each individual subject were then mapped to show his or her individual CSE IO curves. These were then combined to show the overall spread of the MEP data for all 36 subjects (see figure 4.5). Both RMT and input/output (IO) slopes were found to be normally distributed (RMT: Mean=48.31, SD=7.96; IO: Mean=61.03, SD=46.36). Finally, a repeated measures ANOVA of MEPs at each TMS intensity level was then conducted in IBM SPSS version 22. Results revealed a significant effect of TMS intensity on MEP response f (5, 175) = 55.301, p<.001.

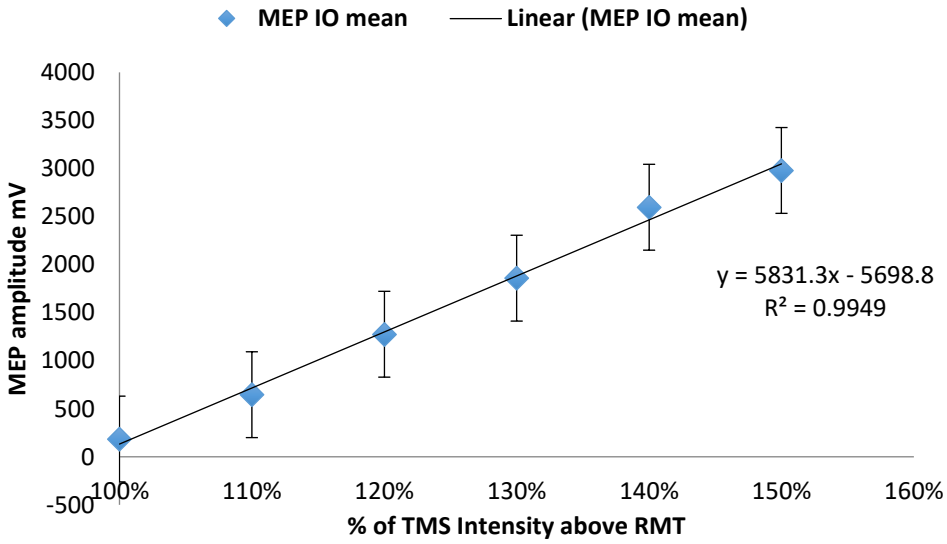


Figure 4-5: Graph representing TMS recruitment curves (the means of individuals' median MEP values, measured in microvolts), data (N=36), for each TMS stimulated output intensity, as a % of each individuals' RMT.

4.5.3 Pre-stimulation: Effects of instruction on yawning behavioural expression

In order to ascertain whether the instruction to resist yawning had any effect on yawning behaviour, we examined the number of full and stifled yawns observed during the first two (pre-stimulation) blocks of trials. Data were analysed using a two-way repeated-measures ANOVA with the factors Instruction condition (allow vs. resist yawning) and Yawn response (full vs. stifled yawns). The ANOVA revealed no significant main effects (maximum $F(1,34) = 2.22$, $p > 0.14$) but a significant Instruction x Response interaction ($F(1,34) = 54.29$, $p < 0.0001$). Relevant means are presented in Figure 4.6. The simple effects of this interaction demonstrated that whereas full yawns were substantially reduced following the instruction to resist yawning (Means: Allow condition = 5.23, Resist condition = 0.17; $t(34) = 6.31$, $p < 0.0001$; effect size [Hedges' G] = 1.46), stifled yawns were significantly increased by this instruction (Means: Allow condition = 0.11, Resist condition = 3.86; $t(34) = 5.51$, $p < 0.0001$; effect size [Hedges' G] = 1.28). This result demonstrates that the instruction to suppress contagious yawning was only partially successful and as such led to a significant decrease in full yawns, but an increase in the number of stifled yawns observed. (Means: full yawns = 0.17, stifled yawns = 3.86; $t(34) = -5.13$, $p < 0.0001$; effect size [Hedges' G] = -1.25). Hedges' G was used as the preferred measure of effect size because it outperforms Cohen's' D when group sizes are below 20.

To further establish whether the instruction to resist yawning influenced yawning behaviour, examination of the combined total of full and stifled yawns observed during the first two (pre-stimulation) blocks of trials was also conducted. This analysis revealed that the means were not significantly different from one

another (Resist = 4.03, Allow = 5.34; t(34) = -1.489 p > 0.05). This outcome indicates that the instruction to resist yawning significantly increases subjective urge-to-yawn ratings and alters how stifled yawns may be expressed, but it does not alter the individual's propensity for contagious yawning more generally.

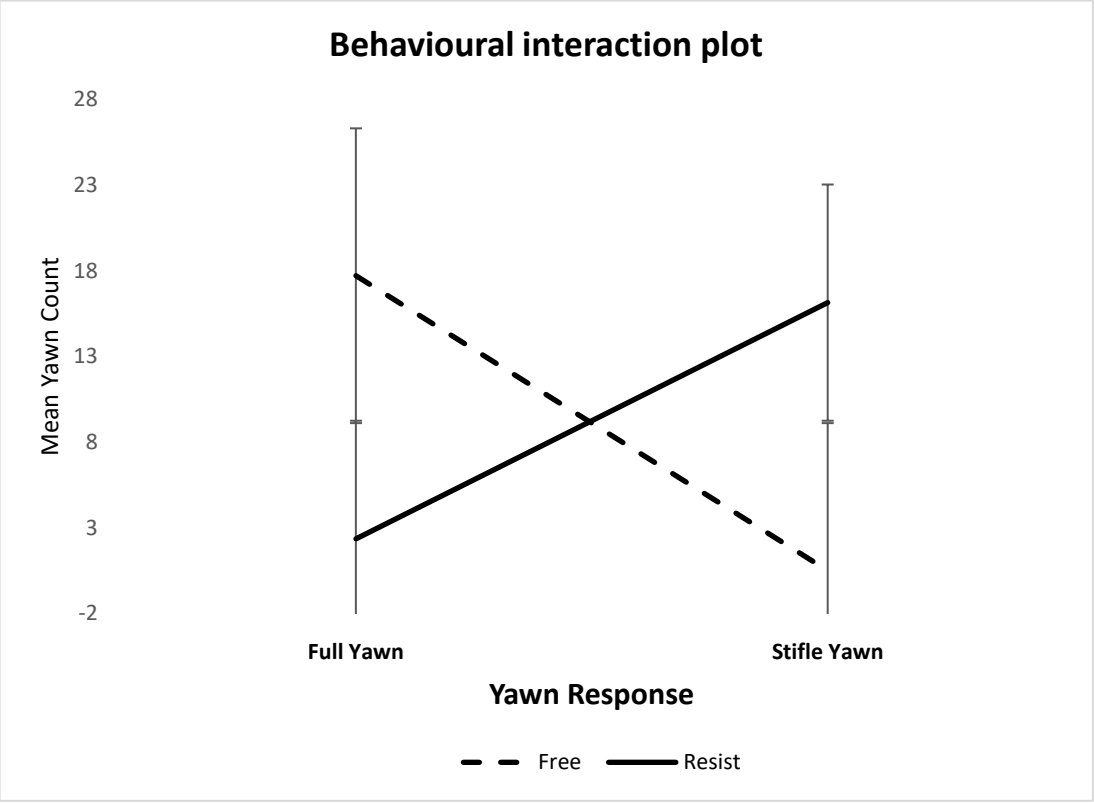


Figure 4-6: Illustrates the effect of instructing participants to either allow themselves to yawn or resist yawning on the mean number of full and stifled yawns observed. Error bars represent the standard error of the mean (SEM).

4.5.4 Pre-stimulation: effects of instruction on subjective urge-to-yawn ratings

To evaluate whether the instruction to resist yawning led to an increase in perceived urge-to-yawn ratings, we compared mean self-reported urge-to-yawn ratings in the 'allow' versus 'resist' blocks of the pre-stimulation period (e.g., blocks 1 and 2). A within-subject t-test revealed that estimates of mean urge-to-

yawn ratings increased significantly when participants were instructed to resist yawning compared to when they were allowed to yawn freely (Pre-stimulation block means: Allow = 0.15 units (0-1), Resist = 0.18 units (0-1); $t(35) = -1.85$, $p < 0.04$).

4.5.5 Pre-stimulation: effects of motor excitability and physiological inhibition on propensity for contagious yawning

To directly establish whether individual differences in measures of cortical motor excitability and/or physiological inhibition predicted individual variability in the propensity for CY, a separate stepwise regression analyses of the number of full yawns observed from each participant in the allow condition, and the number of stifled yawns observed in the resist blocks were conducted. Note, only data collected prior to the onset of electrical stimulation (Blocks 1 & 2) were analysed. The stepwise regression analysis demonstrated that a model based upon three factors: LICI, RMT, and SICI, could significantly predict and account for close to 50% of the individual variability in the number of full yawns recorded in the Allow condition ($F = 10.71$, $p < 0.001$). The order of entry into the model for these factors was as follows: LICI (coefficient = 4.15; t statistic = 3.89; $p = 0.0005$), $F = 6.81$, $p = 0.014$, R-squared value (Rsq) = 0.18, adjusted R-squared value (Adj-Rsq) = 0.15; RMT (coefficient = 0.38; t statistic = 4.33; $p = 0.0002$), $F = 8.65$, $p = 0.001$, Rsq = 0.36, Adj-Rsq = 0.32; and SICI (coefficient = 6.78; t statistic = 3.14; $p = 0.004$), $F = 10.71$, $p < 0.001$, Rsq = 0.52, Adj-Rsq = 0.47. (Figure 4.6). Please note that in this stepwise regression, the R-squared values for RMT and SICI are calculated on the residual variance remaining after the LICI and LICI plus RMT fits, respectively, have been accounted for.

For complete transparency we combined the number of full and stifled yawns across the resist and allow conditions to obtain a total yawning score for each individual. These data were then re-analysed to assess whether the above finding held for the combined number of yawns and stifles. The analysis confirmed that the TMS measures were not a significant predictor of the total number of yawns recorded in the resist condition (all $p < 0.1$). Conversely, the following TMS measures: RMT ($t=-4.1$, $p=0.0003$), 100ms LICI ($t=3.91$, $p=0.0005$), and 3ms SICI ($t=-3.28$, $p=0.0026$), were all significant predictors of the total number of yawns observed in the allow condition ($F = 10.48$, $R^2 = 0.50$, Adj-$R^2 = 0.46$, $p < 0.0001$).

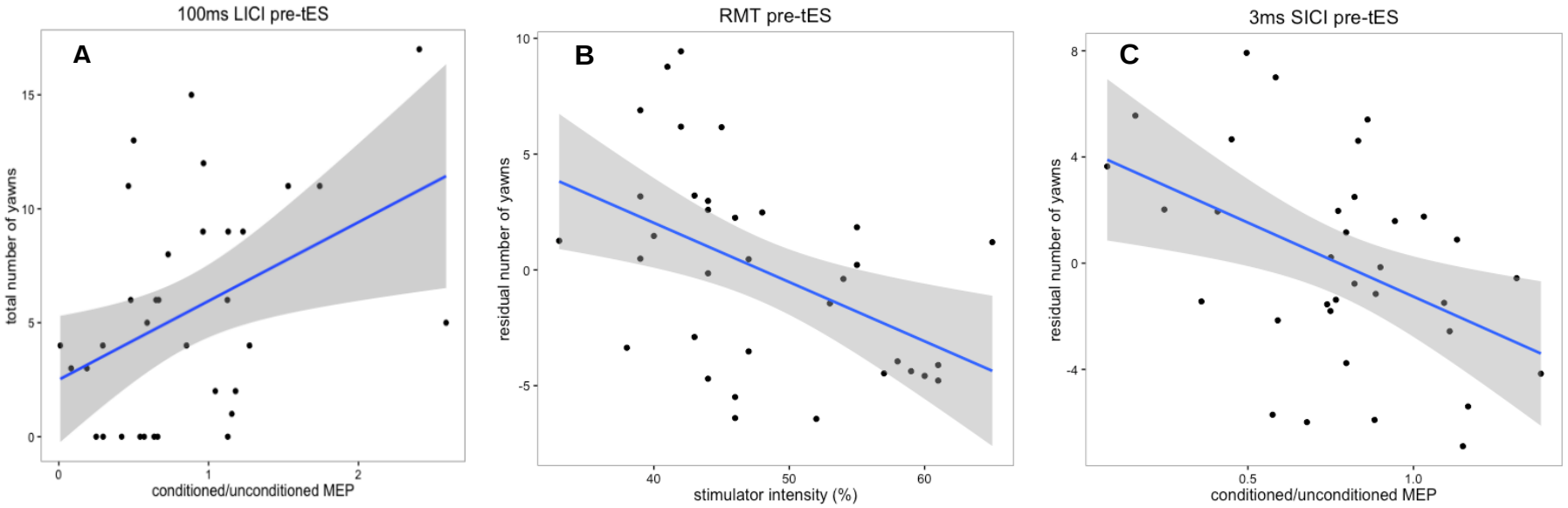


Figure 4-7: A. Scatter plot depicting the association between 100ms LICI values (x axis) and the total number of yawns recorded in the Allow condition (y axis). Note a ratio value of < 1 represents an inhibitory effect of the conditioning pulse. Please note that approximately half of the data illustrates an inhibitory effect. This is due to individual differences in cortical response to the LICI parameters set (see text for more details). B. Scatter plot depicting the association between resting motor threshold (RMT) (x axis) and the residual number of yawns (stifled + full) recorded in the Allow condition (y axis). Note that increased excitability is indexed by a lower RMT value. The grey shaded areas represent 95% confidence intervals for the regression. C. Scatter plot depicting the association between 3ms SICI values (x axis) and the residual number of yawns recorded in the Allow condition (y axis). Note a ratio value of < 1 represents an inhibitory effect of the conditioning pulse (see text for further details).

4.5.6 RMT and contagious yawning

The relationship in the current study between RMT and contagious yawning is shown in Figure 4.7a above. This figure plainly illustrates that lower motor thresholds are associated with an increased number of yawns.

4.5.7 LICI and contagious yawning

The relationship in the current study between LICI and yawning is illustrated Figure 4.7b. Review of this figure plainly illustrates that increased physiological inhibition (e.g., conditioned/unconditioned MEP ratio trial values less than 1) are associated with a reduction in the residual number of yawns observed. However, please note that approximately half of the data illustrates an inhibitory effect. This is most likely due to individual differences in cortical responses to the LICI parameters set.

4.5.8 SICI and contagious yawning

In the current study the findings for SICI were found to be in contrast to the findings for LICI. Inspection of figure 4.7c demonstrates that increased SICI was positively associated with an increase in the residual number of yawns observed (Figure 4.7c).

4.5.9 Effects of motor excitability and physiological inhibition: predicting the effects of instruction

The stepwise regression analyses revealed that none of the TMS measures were statistically significant predictors of the number of stifled yawns observed in the resist blocks (all $p > 0.1$). However, to investigate this issue further an additional stepwise regression was performed. Analysis regarding whether the

pre-stimulation TMS measures predicted the difference in the total number of yawns (full + stifled yawns) exhibited in the resist versus allow conditions was performed. This analysis revealed a marginally significant effect for RMT ($F = 3.97$, $p < 0.055$, Adj-$R^2 = 0.08$). This indicates that those individuals with a more excitable motor cortex (lower RMT values) tended to exhibit greater differences in the residual number of yawns observed in the resist – allow subtraction. This is in line with the findings of the previous study whereby lower RMT was able to predict the occurrence of stifled yawns in the resist the urge to yawn condition.

4.5.10 Pre-stimulation: effects of motor excitability and physiological inhibition on subjective urge-to-yawn ratings

A stepwise regression was conducted in order to determine whether any single pre-stimulation TMS measures (e.g., SICI, ICF, LICI, IO Slope, or RMT), or combination of these, were significant predictors of the urge-to-yawn ratings. The findings were that none of the TMS measurements could significantly predict the urge-to-yawn (all $p > 0.05$).

4.5.11 Effects of excitatory non-invasive brain electrical stimulation on the propensity for contagious yawning

The effects of non-invasive electrical stimulation, which included effects of A-tDCS and tRNS relative to sham stimulation, on CY were assessed separately. Firstly, the difference in the number of full yawns observed in the 'allow' condition was calculated for each individual (post-stimulation – pre-stimulation) and the between group differences (active stimulation vs. sham stimulation) were assessed. Second, gain scores in relation to the number of stifled yawns recorded in the 'resist' condition (post-stimulation – pre-stimulation) were

calculated for each individual. In addition, gain scores in relation to the between group differences (active stimulation vs. sham stimulation) were also assessed. Statistical analyses in the form of a priori planned independent-group t-tests were then conducted. These analyses demonstrated that there were no statistically significant effects of either A-tDCS or tRNS stimulation, relative to sham stimulation, in the 'allow yawning' instruction condition for full yawns, or mean urge-to-yawn estimates (maximum t-value < 1.0, p >= 0.29). Conversely, analyses for both excitatory A-tDCS and tRNS led to a significant increase in the number of stifled yawns observed in the resist yawning instruction condition relative to the control condition (sham stimulation) (Means: Sham stimulation = -1.36; A-tDCS stimulation = 1.83, t(21) = -1.69, p = 0.05, effect size = -0.68; tRNS = 1.0, t(21) = -2.24, p < 0.02, effect size = -0.9).

Interestingly, it should be noted that in the current study neither A-tDCS or tRNS had any significant effect on mean perceived urge-to-yawn ratings, relative to those recorded for the sham control condition (Mean: sham stimulation = -0.01 units (0-1), A-tDCS = 0 units (0-1), t(21) = 0.095, p = 0.46; tRNS = 0.03 units (0-1), t(21) = -1.04, p = 0.16).

4.5.12 Analysis of TMS measures of motor cortical excitability and physiological inhibition obtained prior to stimulation

In order to investigate individual variability in the efficacy of non-invasive electrical brain stimulation (NIBS), as well as determining the effects of NIBS on the existing level of excitability within primary M1 prior to stimulation, we used multiple regression analysis to examine whether the TMS measures of motor cortical excitability and physiological inhibition obtained predicted the scale of

any subsequent behavioural changes in CY, more specifically, the increased number of stifled yawns seen in the resist condition following stimulation. It should be noted that this particular analysis was only conducted on those participants who had received active stimulation (A-tDCS and tRNS groups). The analysis revealed that the slope of the TMS recruitment curve (IO slope) was a statistically significant predictor of the subsequent change in the number of stifled yawns recorded following active stimulation (post – pre-stimulation: coefficient = 0.02, t-statistic = 2.12, $p < 0.05$; $F=4.49$, adjusted-$R^2 = 0.14$). The relevant data from this analysis are depicted in Figure 4.8. Inspection of this figure indicates that increased motor excitability prior to stimulation, as indexed by the slope of the TMS recruitment (IO) curve, is associated with an increase in the number of stifled yawns recorded post stimulation.

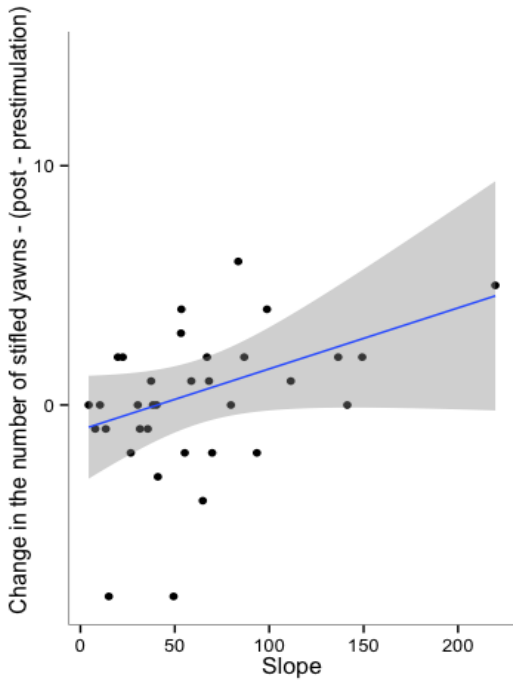


Figure 4-8: Scatterplot depicting the association between the slope of the TMS recruitment (IO) curve recorded prior to stimulation with tES (x axis) and the stimulation induced change in the number of stifled yawns recorded (post-pre-stimulation) following delivery of tES. A + value on the y-axis represents.

4.6 *Discussion*

In the present study, the hypothesis that the propensity for contagious yawning may be positively associated with motor excitability was explored. Firstly, the delivery and effects of excitatory non-invasive brain stimulation (A-tDCS and tRNS) to the supplementary motor area (SMA) was examined. The SMA is a cortical brain region thought to be associated with the volitional control of motor action (Bonini et al., 2014; Cunnington, Windischberger, & Moser, 2005; Tanji, 1994), and effector-specific control of motor outputs at a subconscious level (Sumner et al., 2007). Moreover, according to Finis et al., (2013) the SMA is a brain area frequently associated with the incidence and genesis of echophenomena. Thus, it seemed feasible that active stimulation to an area of the scalp corresponding to the SMA would likely increase the propensity for CY in healthy adults, relative to a control condition (sham stimulation).

Next, converging evidence was sought for this proposal via two TMS protocols, namely single- and paired pulse-TMS respectively. This investigation was conducted to ascertain whether individual differences in baseline measurements of motor cortical excitability and physiological inhibition were associated with the propensity for CY. Prior to the commencement of the CY experiment, TMS measurements of cortical excitability and physiological inhibition were recorded from the left primary motor cortex (M1) of each participant. Subsequently, these measurements were used to predict participants' propensity for CY. However, please note that it is not currently possible to measure cortical excitability and physiological inhibition from the SMA directly.

While this point could be argued as a significant study limitation, it is wholly justifiable as there is convincing evidence which demonstrates that the activity of the SMA and M1 are highly associated. For instance, Grefkes and colleagues (2008) conducted a dynamic causal modelling study and provided evidence of effective connectivity within the cortical motor networks. Grefkes et al., (2008) research was able to show a strong positive intrinsic coupling between the ipsilateral SMA and M1. Moreover, Grefkes et al., (2008) found that this positive intrinsic coupling increases during unimanual contralateral, and bimanual hand movements. Further support is also offered via research that used a dual-coil TMS paradigm, whereby TMS is delivered to both SMA and M1 simultaneously. This research demonstrated that stimulation to an area corresponding to SMA results in a faciliatory effect on the size of motor evoked potentials (MEPS) from primary M1 (Arai, Lu, Ugawa, & Ziemann, 2012a). In addition, magnetic encephalography (MEG) recordings have also demonstrated an increase in the coherence of oscillatory brain activity between SMA and M1 during the preparation and execution of hand movements (Franzkowiak et al., 2012).

More importantly, such findings are wholly consistent with previous investigations, which suggest that, while contagious yawning is variable across individuals, an individual's propensity for contagious yawning remains largely consistent over time (Bartholomew & Cirulli, 2014). It is also consistent with the finding of the current study insofar as; each individual's motor cortex excitability was found to be a significant predictor of the propensity for contagious yawning. For example, it was discovered that the instruction to resist yawning significantly increased participants perceived urge-to-yawn ratings, and as such altered how their subsequent yawns were expressed (stifled yawns rather than full yawns).

However, it was also observed that their overall propensity for contagious yawning remained unchanged. Furthermore, and as reasoned elsewhere, such sensory signals may well trigger actions outside of conscious awareness. This is postulated as a distinguishing feature of urges-for-action, which are chiefly related to actions that cannot be realised immediately. Consequently, these actions must be held under control until an appropriate time whereby they can then be released (Jackson et al., 2011). In the current study, it was discovered that participants perceived urge-to-yawn ratings increased significantly when they were instructed to resist yawning as compared to when they could yawn freely. Thus, this discovery is consistent with Jackson et al., (2011) notion that awareness of urges-for-action increases during times when actions are suppressed, or their execution delayed.

To further explore the idea that the propensity for Echophenomena, such as CY, might be associated with individual variability in motor cortex excitability several single and paired-pulse TMS protocols were utilised. This allowed measures of cortical excitability and physiological inhibition within the primary motor cortex (M1) of the left hemisphere (contralateral to the dominant right hand) for each participant to be obtained. These measurements comprised of resting motor threshold RMT, which is the minimum intensity of TMS stimulation required (expressed as a percentage of maximum stimulator output) to reliably elicit a motor-evoked potential MEP of a predefined size (typically 50-100 μV) from a resting target muscle. RMT is thought to reflect the excitability of corresponding corticospinal neurons with the lowest excitation threshold that project to the targeted muscle (Hallett, 2007), and the TMS-induced excitability of cortical-cortical fibre axons (Ziemann, 2013). In addition, RMT is known to be

highly variable between, but not within, individuals (Cicinelli, Traversa, Bassi, Scivoletto, & Rossini, 1997; Mills & Nithi, 1997). Interestingly, Cicinelli and colleagues (1997) found that RMT was not just representative of skull to cortex distance, as many believe. As noted earlier, RMT is dependent on multiple factors including; inter-individual differences in the orientation of white matter fiber tracts (Danner et al., 2011), and/or inherited influences (Wassermann, 2002). Additional factors, other than structural differences, have also been cited as possible influences on RMT measures. For example, while almost all TMS studies recruit right handed participants, research regarding the impact of handedness on RMT has yielded inconsistent results (Goetz & Peterchev, 2012; Peterchev et al., 2012), as have age dependent effects on RMT measures (Smith, Ridding, Higgins, Wittert, & Pitcher, 2009).

Moreover, recent studies suggest that RMT reflects properties of cerebral white matter microstructures (Klöppel et al., 2008), and that this can subsequently mediate cognitive functions (Roberts, Anderson, & Husain, 2013). However, it is important to note that, how properties of white matter microstructures mediate contagious yawning is beyond the scope of this thesis, but it is recognised as a research avenue worth pursuing in the future. Nevertheless, the correlation between RMT and yawning in the present study cannot be ignored. Indeed, the findings do suggest that lower RMT values represent an increase in motor cortex excitability, and as such a corresponding increase in the occurrence of CY. This is consistent with the finding of our previous study, and that of Finis et al (2013), who observed significantly lower resting motor thresholds (RMT) for their 5 Hz rTMS group. Despite Finis and colleagues (2013) not exploring this finding further, the current study's findings suggest that the observed difference

in RMT could account for increases in the occurrence of echophenomena in some individuals.

The additional physiological measures that were also found to significantly predict the occurrence of CY in this study were, 100ms LICI and 3ms SICI. LICI is a paired-pulse TMS protocol whereby two supra-threshold TMS pulses are delivered through a single coil with an inter-stimulus interval (ISI) of 50-200ms (see Methods). LICI typically leads to a reduction in the size of MEPs evoked from a standard TMS pulse and is typically reported as the ratio of the conditioned over an unconditioned test MEP amplitude. Moreover, LICI is taken to reflect physiological inhibition and is thought to be mediated by GABA-B receptors (Ziemann, 2013). However, individual differences in the cortical responses to the LICI parameters set demonstrates that not all individuals' responses are inhibitory. Visual inspection of pp-TMS parameters (see table – appendices 1) show that this difference is more apparent in female during the online TMS protocol. This difference could be due to the fixed set of parameters used in this study. Indeed, Orth, Snijders and Rothwell (2003) found that individual response variability to paired pulse transcranial magnetic stimulation was likely attributable to the use of a fixed conditioning stimulus interval (CSI). Orth et al. (2003) noted that the variability in their experiments was higher when a single CSI was used to compare the percentage of intracortical facilitation between participants. This finding held true between subjects and testing sessions (Orth et al. 2003). Orth et al. (2003) suggest that the ratio between CSI and motor thresholds are a robust and useful additional measure for assessing the integrity of the neural mechanisms involved in inhibition and facilitation.

SICI on the other hand is a paired-pulse TMS protocol whereby two TMS pulses are delivered in rapid succession (1-5ms ISI) through a single coil. However, in contrast to LICI, SICI protocols involve a standard supra-threshold TMS pulse preceded by the delivery of a sub-threshold conditioning pulse. SICI typically leads to a reduction in MEP amplitudes, and this is thought to reflect the operation of GABA-A mediated inhibitory interneurons acting upon corticospinal neurons (Ziemann, 2013).

The relationship between LICI and contagious yawning in this research suggests that increased physiological inhibition is associated with a corresponding reduction in number of yawns observed. In contrast, the findings for SICI show a positive association between SICI measurements and a corresponding increase in the number of yawns counted. This result is consistent with the key role that GABA-$_A$ mediated inhibition is thought to play in the control of movement-related brain oscillations (Hall et al., 2011). Hall et al., (2011) were able to demonstrate that movement-related beta oscillation de-synchronisation, which is related to the initiation of movements, facilitates increased GABA-$_A$ mediated inhibition. Thus, this suggests that LICI and SICI reflect quite different mechanisms of physiological inhibition.

Further still, the present study found that TMS measures of motor cortical excitability, specifically the slope of each individual's TMS recruitment curve measure prior to electrical stimulation, was a significant predictor of the scale of behavioural change (increased number of stifled yawns) observed in the resist condition following stimulation. However, it is acknowledged that while statistically significant, the size of the observed effect is relatively small with only 14% of the variance being explained. Fundamentally however, our overall

TMS findings suggest that while motor cortical excitability is a significant predictor of the propensity for contagious yawning, it is not a significant driver of, or associated with, the urge-to-yawn. As noted earlier, this finding appears to be consistent with Jackson et al., (2012) previous acknowledgement regarding the urge-for-action being most likely associated with upstream brain areas such as the anterior insular cortex and the cingulate motor cortices.

Further support for the findings of the present study, and for the notion that increased motor cortex excitability is linked to the occurrence of echophenomena in neurological disorders (Ganos et al., 2012), can be found in work conducted by Jackson, Draper, Dyke, Pépés, & Jackson, (2015) and Pépés, Draper, Jackson, & Jackson, (2016). These researchers recently discovered that increased control over motor outputs in those with Tourette's Syndrome (TS) is brought about by local increases in 'tonic' inhibition, which in turn leads to a reduction in the 'gain' of motor excitability. As noted earlier, Pépés et al., (2016) found that both RMT and IO slopes among children and adolecents with TS differed significantly from controls and contrasted with findings regarding adults with TS. Pépés and colleagues suggest that there could be a developmental delay in the maturation of key brain networks in TS. They also stated that the strength of neuronal activity, which progresses from presynaptic neurons and subsequently projects to the targeted muscles, does have a direct effect on subsequent motor behaviours. In addition, they further suggest that RMT is thought to reflect such activity, and more importantly, that this activity depends on the axonal membrane properties of corticospinal neurons at the site of TMS and the membrane properties of post synaptic neurons (Pépés et al., 2016). Such findings appear to be consistent with the

current, and other studies findings, whereby RMT, cortical excitability, and inhibition can predict the occurrence of motor actions.

4.6.1 Motor cortex excitability and the hMNS

In the current, and preceding studies, we demonstrated a direct association between areas related to the hMNS and the incidence of CY, a form of Echophenomena. In support of this notion previous studies, related to the hMNS and behavioural mimicry in social settings, have also revealed some interesting findings (Obhi, Hogeveen, & Pascual-Leone, 2011; van Ulzen, Fiorio, & Cesari, 2013). As noted previously, Obhi et al., (2011) facilitated motor-evoked potentials using TMS during an action observation task. Their results demonstrated that priming interdependent self-construal increased motor cortex output, whereas priming independent self-construal did not, when compared with a non-priming baseline condition (Obhi et al., 2011). Obhi et al., (2011) argued that these effects were most likely mediated by changes in the human mirror system. They suggest that such action essentially tunes the individual to, or shields the individual from, social inputs. Interestingly, the pattern of the self-construal-induced changes in the motor system observed by Obhi and colleagues corroborates with previously observed self-construal effects on overt behavioural mimicry in social settings, and as such, provides robust evidence that motor resonance likely mediates non-conscious mimicry in these situations (Obhi et al., 2011). Finally, they conclude that self-construal effects may lead to the development of interventions for disorders of deficient or excessive social influence such as ASD, TS, or other neurological disorders that encompass compulsive imitative features.

In further support, van Ulzen, Fiorio, & Cesari, (2013) used TMS to probe motor resonance during a naturalistic mimicry paradigm. The aim of the study was to ascertain whether the motor system resonates instantaneously with unobtrusive nonverbal behaviour of another person (van Ulzen et al., 2013). Van Ulzen and colleagues measured corticospinal excitability in both the left and right hand while subjects viewed sequences of video clips and static images. During the video clips an actor performed numerous clerical tasks, while either inconspicuously touching his face, face-touching (FT) condition, or not, no face-touching (NFT) condition (van Ulzen et al., 2013). Van Ulzen et al., (2013) found that motor cortex excitability was higher in the FT condition as compared to the NFT and baseline conditions. Furthermore, their data demonstrated a greater degree of excitability in the left motor cortex relative to the right. Van Ulzen and colleagues (2013) suggest that the observed hand to face gestures, even though they were outside the primary focus of attention, and occurred inconspicuously throughout the ongoing action setting, could cause instantaneous motor resonant activity in the observer's motor system. Moreover, motor resonance is frequently linked to activation in the motor system during action observation and as such is typically interpreted in the context of mirror neuron system functioning. This finding also supports the notion of motor resonance involvement in mimicry and demonstrates that this can be investigated using naturalistic mimicry paradigms. It is also consistent with our research findings thus far and the role the hMNS could play during unconscious mimicry, or in this case CY.

4.6.2 Non-Invasive Brain Stimulation (NIBS) to SMA

The SMA is a cortical brain area that has been associated with the volitional control of action (Nachev, Wydell, O'Neill, Husain, & Kennard, 2007) and non-conscious effector-specific control of motor outputs (Sumner et al., 2007). It is particularly associated with the genesis and occurrence of echophenomena (Bohlhalter et al., 2006; Finis et al., 2013). Moreover, it should be noted that there are dense connections between the SMA and the hand area of the primary motor cortex (Luppino, Matelli, Camarda, & Rizzolatti, 1993; Muakkassa, & Strick, 1979); electrical stimulation of the monkey SMA induces action potentials in motor cortex pyramidal tract neurons (Aizawa & Tanji, 1994); and dual-site TMS studies demonstrate that in humans there are predominantly faciliatory connections from the SMA to the hand area of primary motor cortex (Arai, Lu, Ugawa, & Ziemann, 2012b). Furthermore, functional MRI studies demonstrate that effective connectivity between SMA and the hand area of motor cortex is increased during hand movements (Grefkes et al., 2008). Finally, previous studies using NIBS have demonstrated that inhibitory stimulation (1Hz repetitive TMS) of the SMA can reduce motor tics in Tourette syndrome for prolonged periods after stimulation has ended (Kwon et al., 2011; Mantovani, Leckman, Grantz, King, Sporn, 2007). In addition, and as noted earlier, excitatory stimulation (5Hz repetitive TMS) of the SMA has been seen to induce echophenomena in neurologically healthy controls (Finis et al., 2013).

In the present study, we also investigated directly whether excitatory NIBS of the SMA region could increase the propensity for CY when compared against sham stimulation. Participants were randomly assigned to one of three stimulation conditions: A-tDCS, tRNS, or sham stimulation, and were blind to

the type of stimulation they would receive. Stimulation was delivered continuously throughout the second half of the experiment (Blocks 3 and 4). Excitatory transcranial direct current stimulation (tDCS) and transcranial random noise stimulation (tRNS) was used in an attempt to alter the excitability of neurons within the SMA. Both techniques can be used to reduce, or inhibit, cortical excitability, also known as cathodal TES. Anodal TES is achieved by placing the anode electrode over the region of interest, e.g. SMA, while cathodal stimulation is achieved by placing the cathode electrode over the region of interest. Excitatory anodal tDCS and tRNS were chosen for the purposes of this study. The rationale for using both excitatory tDCS and tRNS was due to each technique using different mechanisms of application in order to induce cortical excitability. Where tDCS imparts a continuous train of electrical stimulation at a set parameter, tRNS delivers random electrical stimulation at an amplitude and frequency of between 0.1, or -0.1, to as high as 2mA (figure 4.1). It is hypothesised that tRNS will influence cortical oscillations leading to changes in cortical excitability far more readily than tDCS. It is suggested that the random delivery of electrical stimulation to the SMA will increase the sensitivity of the neurons in this region to modulation via the repeated opening of sodium channels (Paulus, 2011). Application of tRNS with an offset is thought to lead to an increase in cortical excitability in a similar way to that produced by tDCS. Furthermore, tRNS with an additional offset appears to be more effective than tRNS without an offset in producing changes in cortical excitability (Ho, Taylor, & Loo, 2013).

However, it was found that delivering NIBS to the SMA had no effect on the number of yawns observed in the allow condition, but significantly increased the

number of stifled yawns in the resist condition. This finding suggests that the instruction to suppress yawning might alter the physiological properties of the motor system (alter motor excitability or physiological inhibition), and that this may well be further modulated by tES. This finding suggests that while the propensity for CY is increased by excitatory non-invasive stimulation of the SMA, this is not accompanied by any significant increase in the consciously perceived urge-to-yawn.

Moreover, this result is consistent with Provine (1986) view that CY may be triggered automatically by ethological releasing mechanisms, which suggests CY may well be an instinctive primitive behaviour that an individual has little control over This notion is further supported by Sumner et al., (2007) research which demonstrated that SMA is associated with non-conscious effector-specific control of motor outputs. However, it should also be noted that previous research has also demonstrated considerable individual variability in the efficacy of non-invasive electrical brain stimulation (Wiethoff, Hamada, & Rothwell, 2014). Moreover, Murakami et al., (2012) further suggested that a key factor in determining the effects of NIBS might be determined by existing levels of excitability of the targeted brain region prior to stimulation, which is also wholly consistent with the findings of the current study, and previous study.

4.6.3 Limitations

One key limitation of the current study was the introduction of the experimenter during the contagious yawning task. The presence of the experimenter could have influenced the number of yawns or stifles executed. Indeed, there does appear to be less yawns and stifles in this study compared to the pilot. It is well

documented that social presence diminished the occurrence of contagious yawning in the laboratory (Gallup, Church, Miller, Risko, & Kingstone, 2016). However, given the loss of data in the preceding study due to volunteers not following task instructions it was deemed necessary to have an experimenter present.

4.6.4 Conclusions

To summarise, the neural basis for contagious yawning (CY), which is purported to be an example of echophenomena, was investigated using converging non-invasive brain stimulation techniques TMS and NIBS. It is known that CY can be triggered by seeing, hearing, or thinking about another individual yawn (Guggisberg, Mathis, Schnider, & Hess, 2010; Platek et al., 2005), but that the propensity for CY, while stable over time, is known to vary across individuals (Bartholomew & Cirulli, 2014). In this study converging evidence was obtained which then demonstrated that CY might well be triggered automatically.

Moreover, the hypothesis that the propensity for contagious yawning (CY) was explored and found to be associated with the balance of cortical excitability and physiological inhibition within the primary and secondary motor cortex areas, which is consistent with Ganos et, (2012) earlier proposals. TMS measures of baseline cortical excitability and physiological inhibition, from within primary M1, were found to significantly predict behavioural expression in the form of CY. In addition, NIBS (anodal-tDCS and tRNS) were used to increase the cortical excitability of the SMA, a brain area previously associated with the occurrence of echophenomena. Subsequent changes in the propensity for CY post-

stimulation was compared to change observed following a sham stimulation control condition.

The key results of the present study indicate; i) that instruction to resist yawning only proved to be partially successful; ii) that the behavioural task instructions led to a significant decrease in the number full yawns observed; iii) that in contrast to the previous result, there was a significant increase in the number of stifled yawns recorded; iv) that when the number of full and stifled yawns were combined into one measurement, the difference between the resist and allow condition was not statistically significant; v) that participants perceived urge-to-yawn ratings did increase significantly when they were explicitly asked to resist yawning; vi) that an individual's propensity for contagious yawning is strongly predicted by individual variability in TMS measures of cortical motor excitability and physiological inhibition; vii) that excitatory NIBS to the SMA could lead to a significant increase in the number of stifled yawns when participants were explicitly instructed to resist yawning; viii) that excitatory NIBS of the SMA does not lead to significant increases in the consciously perceived urge-to-yawn ratings; ix) that the scale of SMA stimulation induced change, in the number of stifled yawns observed in the resist condition, was predicted by individual variability in baseline measures of motor cortical excitability as indexed by the slope of the TMS recruitment (IO) curve.

Taken together these findings suggest that increased baseline motor excitability is associated with increases in the propensity for CY. Further still, that the instruction to resist yawning significantly increases urge-to-yawn ratings, and as such alters how the stifled yawns might be expressed; yet not changing an individual's propensity for contagious yawning. Moreover, how instruction

changes behavioural expression at the neural level is currently unknown, and as such will be focus of the next research study. It is also proposed that the findings of the current research may well be important for understanding the association between motor excitability and the occurrence of echophenomena more generally. Echophenomena are frequently observed in a number of neurodevelopmental conditions such as ASD, TS; and neuropsychiatric disorders including schizophrenia, dementia, and some aphasia', and thus warrant further exploration.

Chapter 5 Echophenomena 3 - Administration of online TMS to investigate the neural basis of instruction processing and social inhibitory control during episodes of contagious yawning.

5.1 *Introduction*

In the previous chapter it was found that the instruction to resist yawning proved to be only partially successful. However, the same behavioural task instruction also led to a significant decrease in the number of full yawns observed in this condition. In contrast to the previous result, there was a significant increase in the number of stifled yawns recorded in this condition. In addition, when the number of full and stifled yawns were combined, the difference between the resist and allow yawning conditions, was not statistically significant. Interestingly, when participants were explicitly asked to resist yawning their perceived urge-to-yawn ratings increased significantly. It was also found that an individual's propensity for contagious yawning is strongly predicted by individual variability in baseline TMS measures of cortical motor excitability and physiological inhibition.

In line with the findings of Finis et al., (2013), excitatory non-invasive brain stimulation (NIBS) to the SMA was also found to significantly increase the number of stifled yawns when participants were expressly instructed to resist yawning. Conversely, excitatory NIBS of the SMA did not lead to significant increases in their conscious self-estimated perceived urge-to-yawn ratings. Finally, the scale of SMA stimulation induced change, in the level of

echophenomena observed, is predicted by individual variability in baseline measures of motor cortical excitability (Finis et al., 2013), and indexed by the slope of the TMS recruitment (IO) curve (Brown et al., 2017).

These previous findings suggest that increased baseline motor excitability is associated with increases in the propensity for contagious yawning, and that the instruction to resist yawning significantly increases urge-to-yawn ratings. This is thought to alter how the subsequent yawns might be expressed. However, while yawn expression was observed to be altered, an individual's propensity for contagious yawning was not. While this finding is an interesting discovery, precisely how these instructions changes behavioural expression at the neural level is currently unknown, and as such will form the basis for this next research study.

Evidence for the neural origins of echophenomena is currently underrepresented in scientific literature. Contemporary views suggest that echophenomena occurs as a result of natural neurodevelopment, and is particularly important for the acquisition of normal social interactions and functioning (Ganos, Ogrzal, Schnitzler, & Münchau, 2012b). This is evidenced in previously noted research, whereby echophenomena is considered normal behaviour for infants but diminishes around age three (Ganos et al., 2012). However, empirical and theoretical data does not provide sufficient evidence to support any single theory regarding its origin or purpose (Guggisberg et al., 2011). One often cited theory does suggest that yawns are primarily driven by social functioning as opposed to any physiological advantages (Guggisberg, Mathis, Schnider, & Hess, 2010). Although echophenomena, such as contagious yawning, is argued to be a form of natural neurodevelopment, and

significantly altered in many neurological and neuropsychiatric conditions such as Tourette's syndrome (Ford, 1989), there is very little empirical knowledge regarding what facilitates contagious yawning (Bartholomew & Cirulli 2014), nor the neural mechanisms that may underly the genesis of echophenomena.

The purpose of the proposed study is to further establish how cortical excitability and physiological inhibition relate to the propensity towards contagious yawning and self-estimated urge-to-yawn ratings. However, in this study a novel online-TMS paradigm will be employed in order to measure these specific neural correlates whilst simultaneously measuring contagious yawning behaviourally. Due to the occurrence of echophenomena among those with the neurological condition ASD, a self-report measure, the Autism Quotient, will be included to ascertain whether there is a relationship between the TMS measures, contagious yawning, and AQ scores. It is proposed that the findings of this further research study may well be important for understanding the association between motor excitability and the occurrence of echophenomena more generally. Echophenomena is frequently observed in a number of neurodevelopmental conditions such as ASD, TS; and neuropsychiatric disorders including schizophrenia, dementia, and some aphasia', and thus warrants further examination.

5.2 *Methods*

5.2.1 Ethics

Ethical approval for this study was sought and granted by the University of Nottingham ethics committee. Ethical approval number S9973R.

5.2.2 Participants

28 young adults aged between 19-25 years (14 males) (mean aged 20.6 ± SD1.52), were recruited via opportunity sampling from the University of Nottingham.

Prior to the study all participants were taken through appropriate TMS and TES screening and informed consent was obtained. Further informed consent regarding the video recording of the participants during the task was also obtained. All participants were financially compensated for their time and participation in this study.

5.3 *Study Design*

A within and between subjects' mixed methods experimental design was employed. An online TMS paradigm was used in this study and consisted of physiological TMS measures of resting motor thresholds (RMT), motor cortical excitability (CSE), and physiological inhibition and facilitation. Measures of cortical excitability for each subject were ascertained via TMS induced input-output curve (IO) measurements of motor evoked potentials (MEPs). Physiological inhibition was determined via 1 and 3-millisecond short interval cortical inhibition (SICI), and 100-millisecond long interval cortical inhibition (LICI). Cortical facilitation was determined via 12-millisecond intracortical facilitation (ICF). The behavioural measures of contagious yawning utilised a 2x2 (yawn condition v yawn response) ABBA blocked (x4) design, while participants' perceived urge-to-yawn was measured using the same custom-made continuous response metric slider mechanism as before.

5.4 *Procedure*

The design of the new online TMS task is illustrated in Figure 5.1. Participants watched four blocks of video clips that depicted another individual yawning and, in separate blocks, were either instructed to resist yawning or to allow themselves to yawn freely. Participants were videoed throughout the duration of the task and their yawns and stifled yawns were counted. In addition, participants were asked to register their perceived urge-to-yawn ratings. These ratings were continuously recorded using the same custom-made slider mechanism used in chapter 4 (figure 4.2). The intensity of each participants perceived urge-to-yawn ratings were captured throughout the duration of the task. The participants' operated the mechanism by using their left index finger. This device delivered a continuous voltage signal that indexed change over time in self-estimated intensity in the perceived urge-to-yawn.

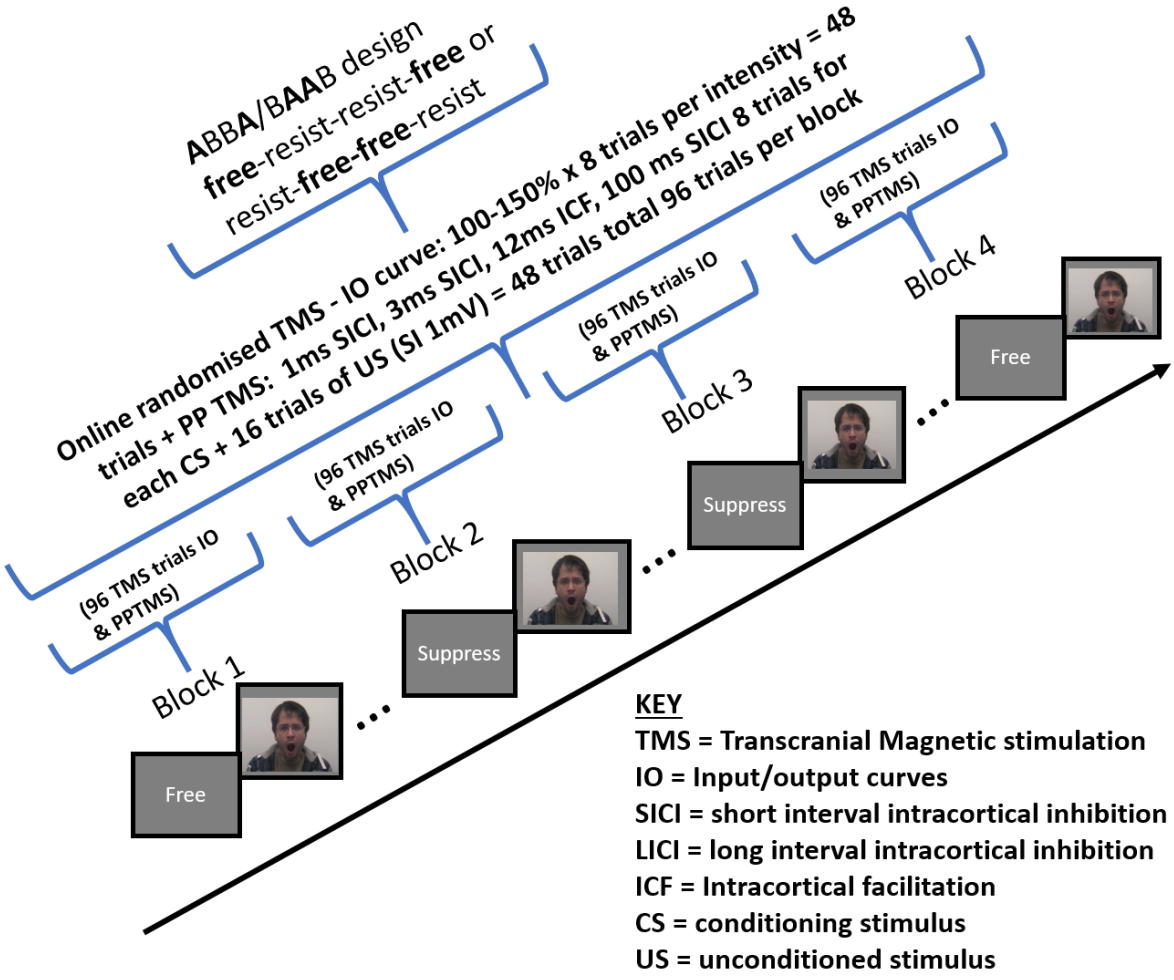


Figure 5-1: Echophenomena 3 online TMS task design and parameters

5.4.1 TMS

A Magstim Bistim 2™, with a 70mm figure of eight coil, was used to administer TMS to the left M1 in an area corresponding to the first dorsal interosseous (FDI) muscle of the right hand. Motor hotspot was defined as the coil location that elicited maximal MEP responses in FDI by positioning the TMS coil over each subject' left motor cortex (M1) at approximately 45° (Pascual-Leone et al., 1994). The coil location was continuously tracked throughout the study, via BrainSightTM version 2.0 (Rogue Research Inc. ©, 2016). EMG responses

were recorded using BrainVision Recording software at a sampling rate of 5000 Hz and band pass filtered (10-2000 Hz). Disposable Ag-AgCl surface electrodes were placed onto the FDI muscle in a standard 'belly-tendon' configuration.

5.4.2 RMT & Si1mV thresholding

Following localisation of motor hotspot resting motor threshold (RMT) was then obtained. Each subjects RMT was determined as the minimum TMS intensity needed to elicit an FDI generated MEP of at least 150–200 μV in a minimum of 5 out of 10 trials as before. Once RMT was obtained each subjects Si1mV threshold was then calculated. Si1mV threshold was determined as the amount of TMS intensity needed to elicit an FDI generated MEP of approximately 1mV in size in a minimum of 5 out of 10 trials. Si1mV threshold is approximately 15% of RMT. Due to individual differences in the response to TMS intensities between participants, it is imperative that accurate Si1mV thresholds are ascertained in order to facilitate paired pulse TMS protocols. If it were assumed that all participants Si1mV thresholds were all at 15% of their individual RMT, and they were not, it would be impossible to yield accurate paired pulse TMS calculations of SICI, LICI, and ICF.

5.4.3 Online TMS and Behavioural Task procedure

Directly following TMS thresholding procedures the participants completed the online TMS contagious yawning task. Participants were instructed to watch a 40-minute (4 blocks) video of actors yawning. They were asked to pay close attention to the screen. The questions relating to the actors being viewed was

omitted during this study as it was evident from the video recordings from the previous chapter that participants attend to the video stimuli appropriately.

The video stimuli consisted of the same in-house video clips used in the previous study and comprised of four 9-minute blocks of video clips (total 52 clips). Each clip ranged from 11-20 seconds in length and featured either a female or male actor (aged 20-28 years) spontaneously yawning. Each block of videos was collated into 12 randomised video sets, which were then counterbalanced across all participants. All videos were shown on an Apple Macintosh desktop via VLC media player software. Prior to the start of each of the 4 blocks subjects were instructed to either ‘resist the urge to yawn’ or to ‘yawn freely’. In each block both stifle and full yawns were measured.

The 4 blocks were counterbalanced in an ABBA/BAAB order (i.e. yawn freely, resist, resist, yawn freely or resist, yawn freely, yawn freely, resist). The contagious yawning blocks in the ABBA/BAAB design acted as measures of contagious yawn propensity and a measure of how well participants followed the behavioural task instructions respectively. Further analysis of yawn response for all four blocks demonstrated that yawn propensity was consistent across time and block order. There was no order, nor temporal affects found (see appendices). The capacity for these videos to induce contagious yawning was also assessed in our previous studies and shown to be reliable.

Video clips were played continuously throughout the 9 minutes duration with no interval between each clip. However, there was a one-minute break between blocks in order to cool the TMS coil, and to allow the participants a short break.

For the duration of the task each subjects face was recorded using Open Broadcaster Software.

Participants were also instructed to record their subjective urge to yawn by continuously adjusting a button on a custom-made slider mechanism throughout the duration of each video. The length of the slider mechanism was 195mm, which was scaled to give urge readings between 0 (left end-no urge) and 1 (right end-maximum urge), at a sampling rate of 32Hz. The slider was controlled via a Matlab script version 2010b. To further ensure the participants used the slider mechanism appropriately a pre-task training session was incorporated. How to use the slider mechanism was explained during a pre-study training session. During training a tone was played to the participants to indicate how their urges might wax and wane in intensity and duration (e.g. louder faster tone equaled greater urge to yawn, while a low slow tone indicated less urge to yawn, and finally, no tone represented no urge to yawn). The duration of the tone was 45 seconds in length. The participants were then asked to demonstrate how they would use the slider prior to commencement of the study. Participant's operated the sliding mechanism with their left hand during the online TMS protocol.

An Apple Macintosh laptop (screen size 15 inches) was used to display the video clips and to record the participants simultaneously. The laptop was positioned on top of, and centered upon, a custom-made laptop stand. The size of the stand measured 14cm high, by 75.5cm wide, by 45cm depth. The stand allowed the laptop to be raised to eye-level, as well as acting as a shield for the slider mechanism, which was placed underneath, and to the left of the laptop stand. Participants were sat in a fully adjustable TMS chair, which was adjusted

by the participant in order to ensure they were comfortable and sat in the optimal position for data collection. The laptops built in webcam was used to record the participants via Open Broadcast Studio (OBS) media software, While VLC media player was used to play the behavioural task videos. A black curtain was hung between the behavioural task equipment and Brainsight computer in order to obscure the view of this equipment. This was to prevent any distractions to the participants during data collection. Once ready, all lights were turned off as the light from the laptop proved to be sufficient for recording purposes. The task procedure is illustrated in figure 5.2.

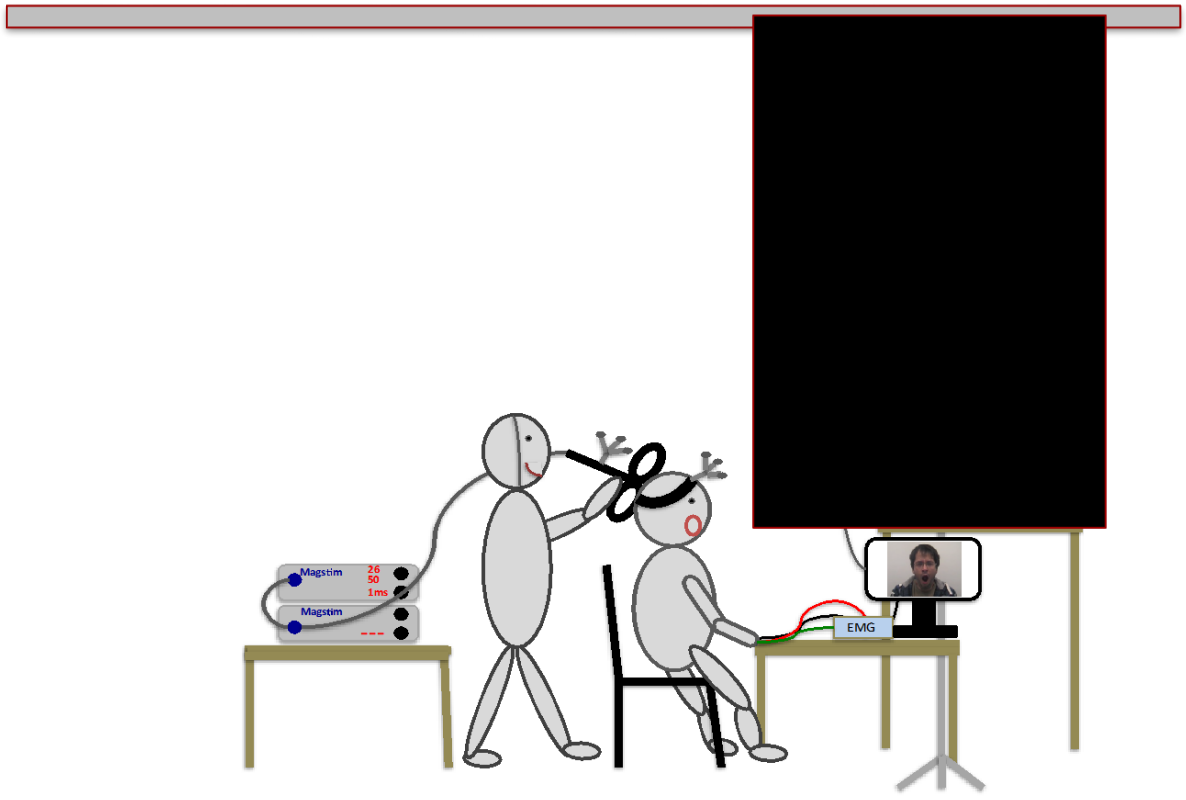


Figure 5-2: Graphical representation of the echophenomena 3 online TMS task procedure. Please note participants' operated the sliding mechanism with their left hand (not visible).

5.4.4 Online TMS procedure

During the behavioural task procedure participants underwent online TMS to their left motor cortex (M1) corresponding to the first dorsal interosseous (FDI) muscle of the right hand simultaneously. Online TMS consisted of 96 trials of sp-TMS and pp-TMS pulses administered during each 9-minute video block. The 96 trials consisted of 8 trials for each of the IO curve parameters (e.g. TMS intensities administered ranged from 100% - 150% of RMT and delivered in 10% increments resulting in 6 TMS intensities with an inter-trial interval (ITI) of 5-6s). There were also 8 trials of each of the pp-TMS parameters (e.g. 1 ms, & 3 ms SICI, 12 ms ICF, and 100 ms LICI). For 1 and 3 ms SICI the conditioning stimulus (CS) was set as 55% of RMT, ICF at 75%, and LICI at RMT. The unconditioned stimulus was set at SI 1mV for all conditions with 16 trials per block. All trials were pseudorandomised and delivered with a randomised inter-stimulus interval of 5-6s. There were a total number of 384 trials across the four blocks of the behavioural task.

The IO curve measurements were estimated by calculating the median intra-individual MEP amplitudes for each of the TMS intensities (i.e., 100–150% of RMT). A linear fit was then applied to the resulting values. Median values were calculated as opposed to the mean to limit the effect of non-standard distribution of individual data. Paired pulse TMS measures of SICI, LICI, and ICF, were reported at a ratio to unconditioned responses (e.g. conditioned MEP/unconditioned MEP).

Participants were also instructed to record their subjective urge to yawn sensations by continuously adjusting a button on the custom-made slider

mechanism throughout the duration of each video. The slider was controlled via a data acquisition device (DAQ) and Matlab script version 2010b. A representative example of one participant's mean urge to yawn is depicted in figure 5.3.

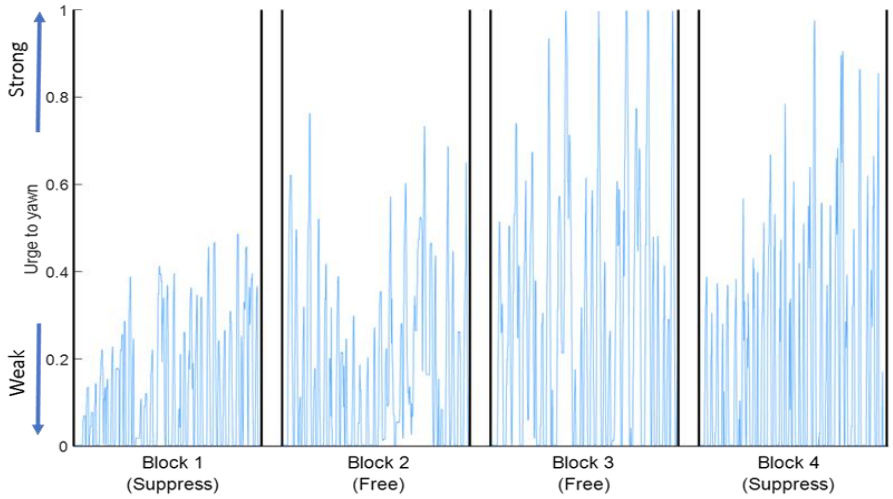


Figure 5-3: Representative example of one participant's mean urge to yawn

5.5 *Analysis*

The number of full yawns (FY) and stifled yawns (SY) displayed by the participants during each video block were counted using the same yawn count protocol used in the previous studies. Yawn counts were collated for each instruction (free & resist) and condition (full & stifled yawns).

5.6 *Results*

5.6.1 EMG pre-processing

All EMG signals that were recorded during the TMS procedure were analysed using EEGLAB in MATLAB. Peak-to-peak amplitudes of the MEPs were

measured for each individual trial. Data for each of these trials was also inspected visually to check for contaminated electrical activity, (e.g. tension in the muscle would artificially inflate MEP amplitude), and all contaminated trials were excluded from analysis. Less than 3% of trials were excluded in any given individual dataset.

5.6.2 TMS corticospinal excitability IO Data

MEP amplitudes for each individual subject were then mapped to show his or her individual cortical spinal excitability (CSE) IO curves. A representative example of one participants MEP data is depicted in figure 5.4. These measures were then combined to show the overall spread of the MEP data for all 28 subjects. CSE IO slopes were calculated in each yawn instruction condition (see figure 5.5). RMT and input/output (IO) slopes were found to be normally distributed (RMT: Mean=42.07, SD=6.78; IO slope (allow) Mean=9.25, SD=4.36); & IO slope (resist) Mean=9.45, SD= 4.67.

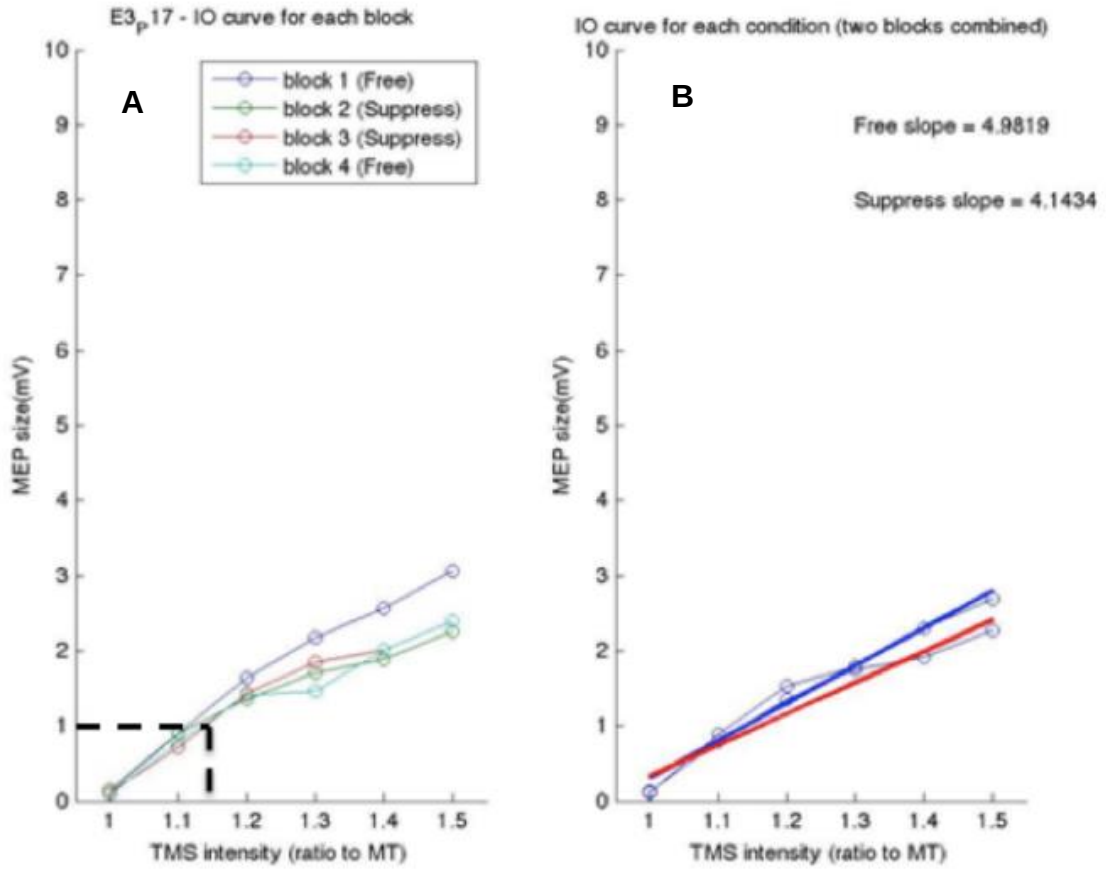


Figure 5-4: A: Graphical representation of one participants IO slope calculated for each of the 4 blocks of yawning videos. B. IO curve for each of the yawn instruction conditions (blue=Free, red=Resist). Dotted box area illustrates Si1mV threshold which is approximately 15% of RMT. Si1mV is required in order for ppTMS parameters to facilitate accurate measures of SICI, LICI & ICF.

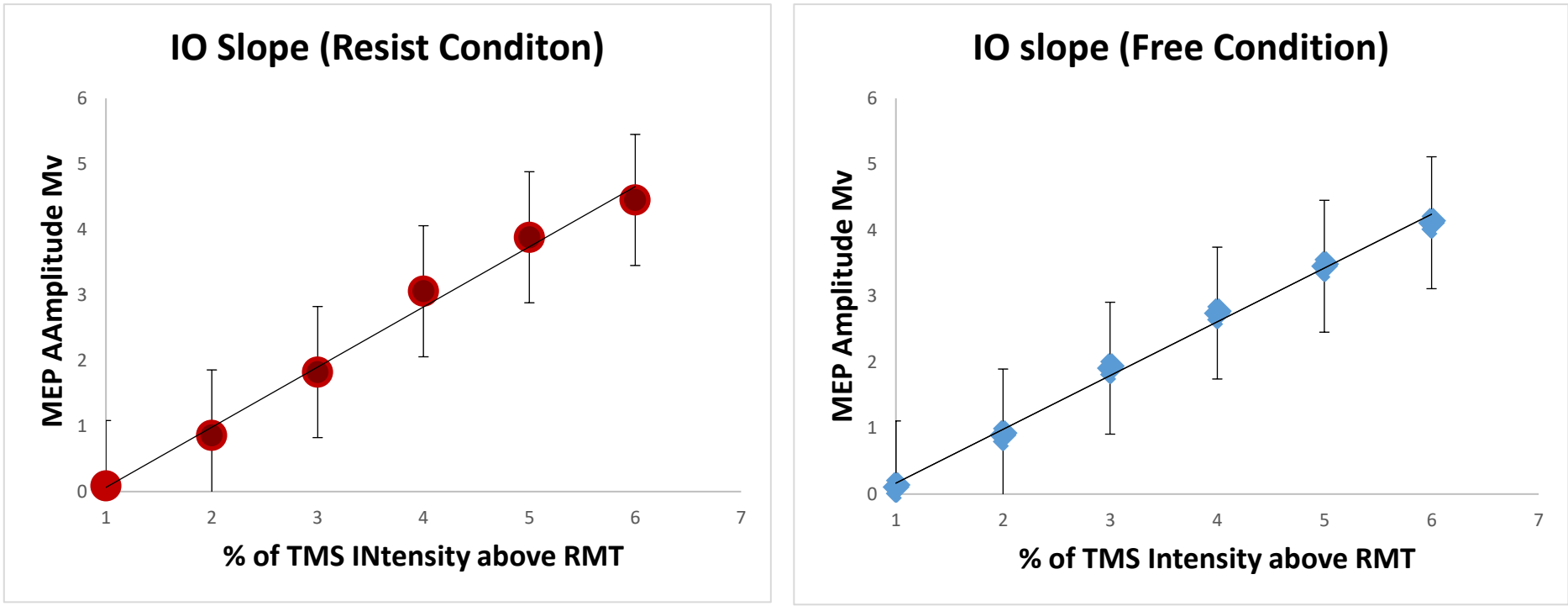


Figure 5-5: Graphs depicting data (N=28) of TMS recruitment curves (the means of individuals' median MEP values, measured in microvolts) for each TMS stimulated output intensity, as a percentage of each individuals' RMT for both yawn instruction conditions allow and resist

Visual inspection of the IO slopes for each yawn instruction demonstrated that they looked similar in presentation. However, further statistical analysis was conducted to establish whether there were any significant differences between the group IO slopes for each yawn instruction. A paired samples t-test was conducted to compare the IO slopes between the resist yawning condition and the free to yawn condition. There was no significant difference found between the group IO slope in the resist condition (M=9.453, SD=4.67) and the group IO slope in the free condition (M=9.25, SD=4.36); t(27)=-0.699, p=>0.05.

5.6.3 Effects of instructions on yawn behavioural expression

In order to establish if the instruction to resist yawning had any effect on yawning behaviour, we examined the number of full and stifled yawns observed during the four blocks of yawning videos. These data were analysed using a two-way repeated-measures ANOVA with the factors Instruction condition (allow vs. resist yawning) and Yawn response (full vs. stifled yawns). The ANOVA revealed no significant main effect for the allow condition ($F(1,27) = .283$, $p = 0.59$); and no significant main effect for the resist condition ($F(1,27) = 1.79$, $p = 0.19$). However, there was a significant Instruction x Response interaction ($F(1,27) = 39.69$, $p < 0.0001$). Relevant means are presented in figure 5.6. The simple effects of this interaction demonstrated that whereas full yawns were significantly reduced following the instruction to resist yawning (Means: Allow condition = 17.50, Resist condition = 0.50; $t(27) = 6.22$, $p < 0.001$; effect size [Cohen's d] = 1.176), conversely stifled yawns were significantly increased by the instruction to resist (Means: Allow condition = 2.32, Resist condition = 16.46; $t(27) = -5.32$, $p < 0.001$; effect size [Cohen's d] =

-1.007). This result demonstrates that the instruction to suppress contagious yawning was again only partially successful and as such led to a significant decrease in full yawns, but an increase in the number of stifled yawns observed.

To further ascertain whether the instruction to resist yawning influenced yawning behaviour, exploration of the combined total of full and stifled yawns, observed during each instruction condition of the contagious yawning videos, were also conducted. This analysis revealed that the means were not significantly different from one another (Resist = 18.50, Allow = 18.21; t(27) = -.532 p=0.59). This outcome indicates that yawn instructions, either freely yawn versus resist yawning, does not alter the individual's propensity for contagious yawning. However, it is evident from the analyses that there is a greater number of yawns and stifled yawns elicited during the online TMS protocol. This would suggest that the administration of TMS to primary motor cortex (M1) increases the incidence of contagious yawning. This is an intriguing finding and requires further exploration in order to ascertain why the occurrence of contagious yawning increases during online TMS.

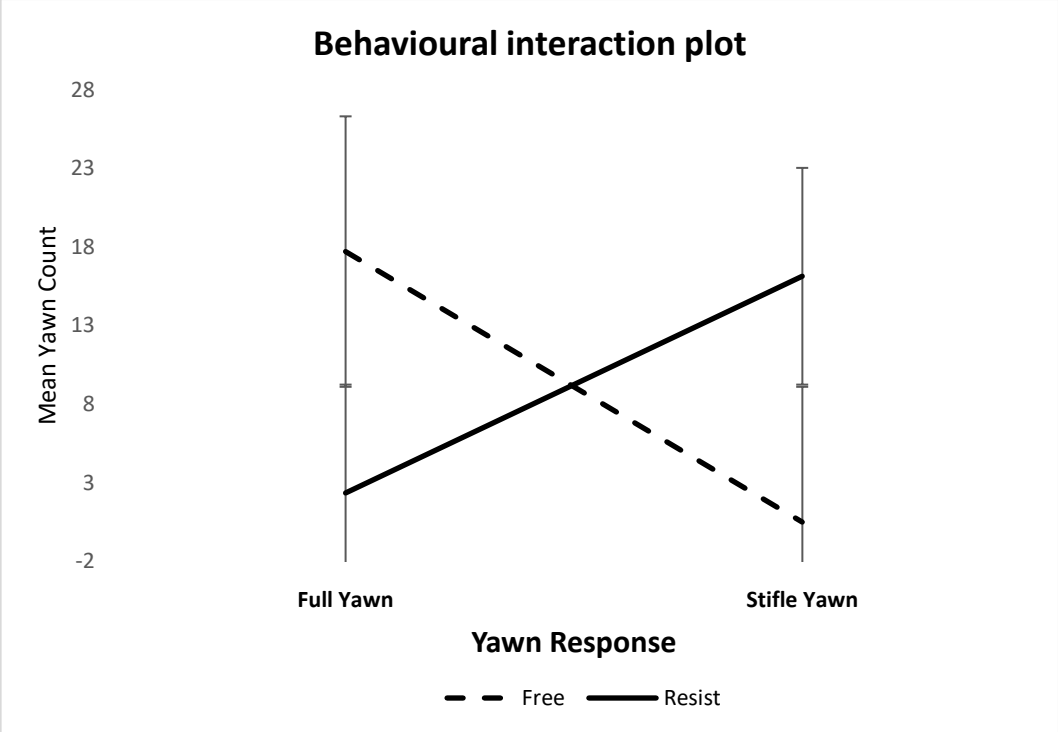


Figure 5-6: Illustrates the effect of instructing participants to either allow themselves to yawn or resist yawning on the mean number of full and stifled yawns observed. Error bars represent the standard error of the mean (SEM).

5.6.4 Effects of Yawn Instruction on Subjective Urge-to-Yawn Ratings

To determine whether the instruction to resist yawning during the online-TMS paradigm would lead to an increase in participant' subjective urge-to-yawn, the urge-to-yawn ratings in both the 'allow' versus the 'resist' blocks of yawning videos were examined. A Within-subjects t-tests was conducted to compare the mean urge-to-yawn ratings in both the resist yawning condition, and the free to yawn condition. Results demonstrated no significant difference between subjective urge-to-yawn ratings for either the free to yawn (M=.21, SD=.24); and resist yawning (M=23, SD=.24), conditions, t(27), -1.33, p=0.19 during online-TMS.

However, in order to further establish if any of the online-TMS measures of cortical excitability and physiological inhibition could predict the subjective urge to yawn ratings in either, the 'free to yawn', or the 'resist yawning' conditions, individual stepwise regression analyses were performed. The first stepwise regression analysis of cortical excitability and physiological inhibition on the subjective mean urge-to-yawn ratings in the 'allow condition' demonstrated that a model based upon a single factor; the IO slope, could significantly predict and account for close to 20% of the individual variability in the mean urge-to-yawn ratings recorded in the Allow condition ($F = 7.05$, $p < 0.01$, adjusted-$R^2 = 0.195$) (figure 5.7).

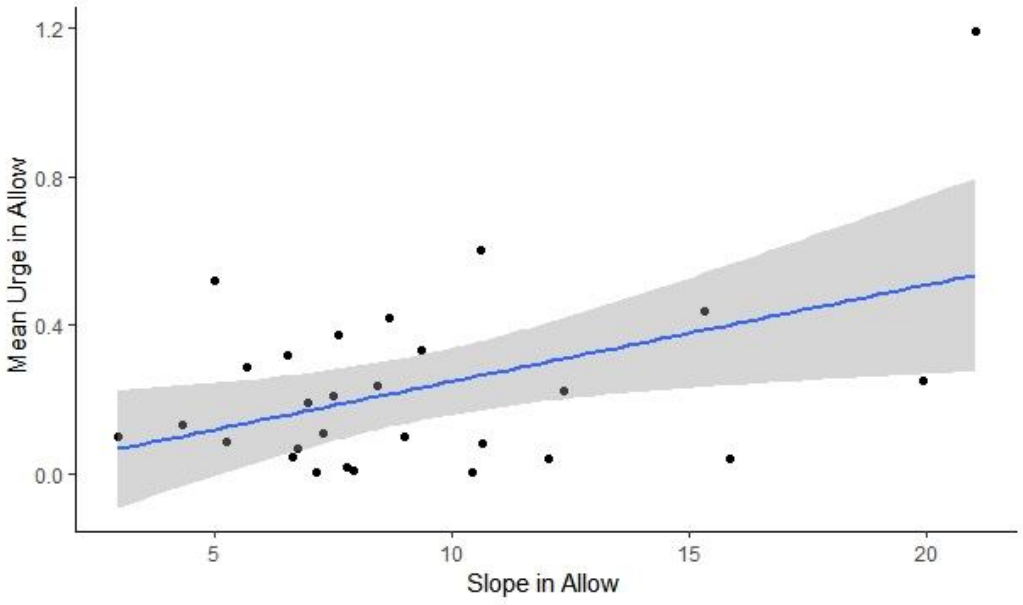


Figure 5-7: Scatterplot depicting the association between the slope of the TMS recruitment (IO) curve in the allow to yawn instruction condition (x axis) and the subjective urge-to-yawn ratings (y axis). An increase in cortical excitability as referenced by the slope of the recruitment curve corresponds to an increase in the subjective urge-to-yawn ratings in the allow condition.

A further stepwise regression analysis of cortical excitability and physiological inhibition on the subjective mean urge-to-yawn ratings, for the 'resist yawning' condition, demonstrated that a model based upon four factors; IO slope, 1ms

and 3ms SICI, and Autism Quotient (AQ) scores could significantly predict and account for close to 56% of the individual variability in the mean urge-to-yawn ratings recorded in the resist yawning condition ($F = 9.14$, $p < 0.0001$, adjusted-$R^2 = 0.556$).

The order of entry into the model for these factors was as follows: IO Slope (coefficient = -0.23, t-statistic = 2.60, $p < 0.01$; $F=6.80$, adjusted-$R^2 = 0.18$); 1ms SICI (coefficient = 3.98, t-statistic = 2.72, $p < 0.01$; $F=8.00$, adjusted-$R^2 = 0.35$); AQ (coefficient = -0.01, t-statistic = -2.76, $p < 0.01$`; $F=9.34$, adjusted-$R^2 = 0.49$); and 3ms SICI (coefficient = 0.24, t-statistic = 2.09, $p < 0.0001$; $F=9.14$, adjusted-$R^2 = 0.556$) (Figure 5.8 a, b, c, d).

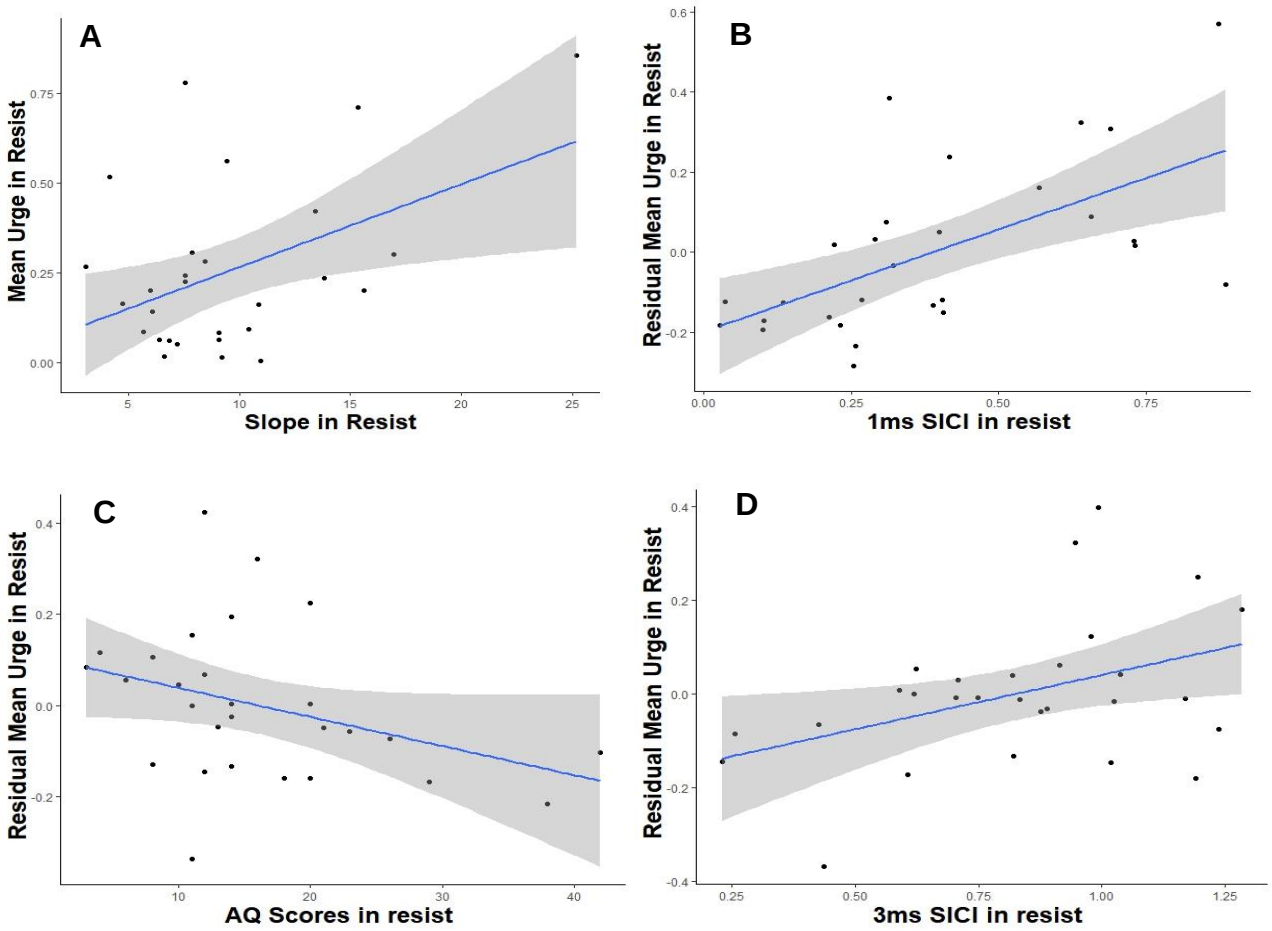


Figure 5-8: A. Scatter plot depicting the association between IO Slope in the resist yawning condition (x axis) and the mean urge-to-yawn ratings in the resist condition (y axis). Note that increased excitability indexes a greater mean urge-to-yawn value. The lighter dotted lines represent 95% confidence intervals for the regression. B. Scatter plot depicting the association between 1ms SICI values (x axis) and the residual mean urge-to-yawn ratings recorded in the resist condition (y axis). Note a ratio value of < 1 represents an inhibitory effect of the conditioning pulse (see text for more details). C. Scatter plot depicting the association between AQ scores (x axis) and the residual mean urge-to-yawn ratings recorded in the resist condition (y axis). D. Scatter plot depicting the association between 3ms SICI values (x axis) and the residual mean urge-to-yawn ratings recorded in the resist condition (y axis). Note a ratio value of < 1 represents an inhibitory effect of the conditioning pulse (see text for further details).

5.7 *Effects of motor cortex excitability and physiological inhibition on contagious yawning*

In order to establish if motor cortex excitability and physiological inhibition could predict the propensity for contagious yawning during the online-TMS protocol, further stepwise regression analyses were conducted for both the 'free to yawn' and the 'resist yawning' instruction conditions. Results demonstrated that none of the online-TMS measures of cortical excitability or physiological inhibition could significantly predict, the number of full yawns in the free to yawn condition, the number of stifled yawns in the resist condition, nor the number of total contagious yawns in either of the yawn conditions.

5.8 *Post-hoc analyses: Sex differences and echophenomena*

5.8.1 Between groups analyses

Considering the observed sex differences seen among those with neurological conditions that present with echophenomena such as, Autism spectrum disorders or Gille's de la Tourette's syndrome, post hoc analyses on the data were conducted. Independent samples t-tests revealed that there were no significant differences in age between females (mean age= 20.92 years, SD=1.33), and males (mean age=20.35 years, SD=1.69). Nor were there any significant differences found between the sexes for, RMT, IO Slope in either the free or resist conditions, self-estimated mean urge-to-yawn ratings in either the free or resist conditions, full yawns in free, nor the stifled yawns in resist, all $p>0.05$.

Further independent t-test analyses were performed for online-TMS measures of cortical excitability and physiological inhibition. Results revealed no significant differences between the sexes for 3ms SICI in the free condition, and 1ms SICI in the free condition, 1ms SICI in the resist condition, 12ms ICF in resist, all $p>0.05$. However, significant differences were found for 12ms ICF between males (M=0.514, SD=0.143) and females (M=1.613, SD=0.894); t(26), 2.98, p=0.006), and 100ms LICI males (M=0.676, SD=0.331) and females (M=1.260, SD=0.478); t(26), 0.352, p=0.001), in the free condition. Trends approaching significance was also found for 3ms SICI in the resist condition males (M=0.917, SD=0.298) and females (M=0.738, SD=0.246); t(26), 0.633, p=0.09.

5.8.2 Within sex-groups analyses

In order to establish if there were any differences in contagious yawning during online-TMS within the groups, further analyses were conducted. Paired samples t-tests demonstrated no significant differences between the number of full yawns in the free condition and the number of stifled yawns in the resist condition for males or females, all $p>0.05$. There was also no significant difference between the mean urge-to-yawn in the free to yawn condition (M=0.241, SD=0.293) and the mean urge-to-yawn in the resist yawning condition (M=0.241, SD=0.213); t(13), .879, p=0.39, for females. In contrast, there was a significant difference between the mean urge-to-yawn in the free to yawn condition (M=0.150, SD=0.169) and the mean urge-to-yawn in the resist yawning condition (M=0.242, SD=0.262); t(13), -2.823, p=0.01, for males.

5.8.3 Within sex-groups differences in cortical excitability and physiological inhibition

Initial analyses demonstrated no significant differences for the TMS generated recruitment curves for either the male or female groups. However, while not significant, visual inspection shows that IO slopes appear to go in opposite directions according to yawn instruction for females and males (figure 5.9).

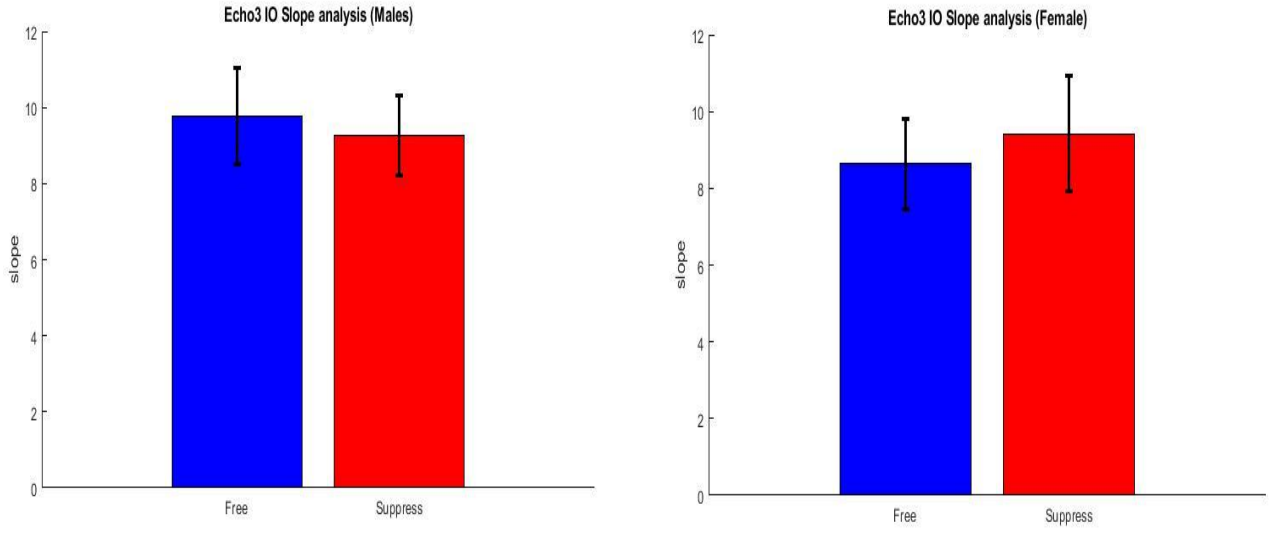


Figure 5-9: TMS generated IO recruitment curves for Males and Females in each of the contagious yawning behavioural instructions

To further establish whether there were any significant within groups differences for males and females in cortical excitability and physiological inhibition on the propensity for contagious yawning further stepwise regression analyses were conducted for females and males respectively.

5.8.4 Free to Yawn Condition – Female Results

Results revealed that RMT could significantly predict and account for 30% of the individual variability in the number of full yawns in the free to yawn condition for females ($F=6.67$, $p=0.02$, adjusted-$R^2=.30$). Similarly, a model based on two

factors; IO slope and 12ms ICF could significantly predict and account for close to 66% of the individual variability in the mean urge-to-yawn ratings in the free condition for females ($F = 13.35$, $p < 0.001$, adjusted-$R^2 = 0.655$). The order of entry into the model for these factors was as follows: IO Slope (coefficient = -0.053, t-statistic = 3.75, $p < 0.002$; $F=14.13$, adjusted- $R^2 = 0.50$); and 12ms ICF (coefficient =-0.139, t-statistic = 4.71, $p < 0.0001$; $F=13.49$, adjusted- $R^2 = 0.655$) (figure 5.10).

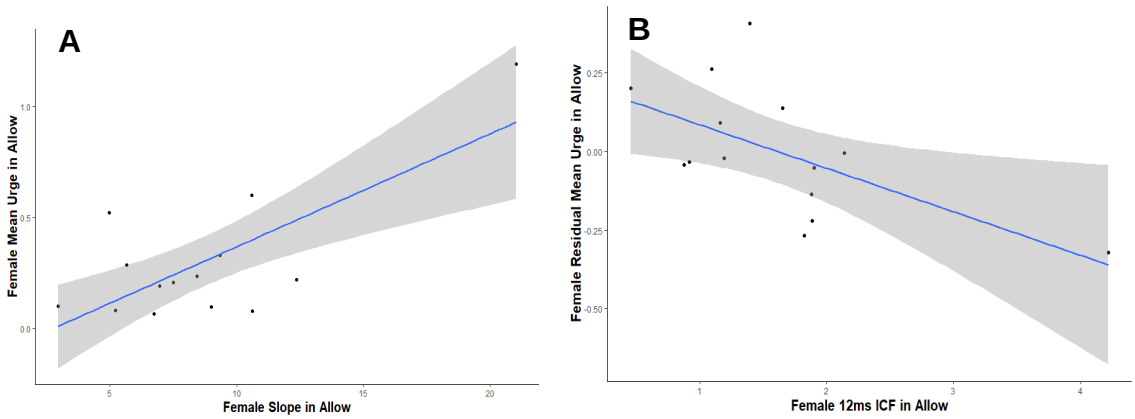
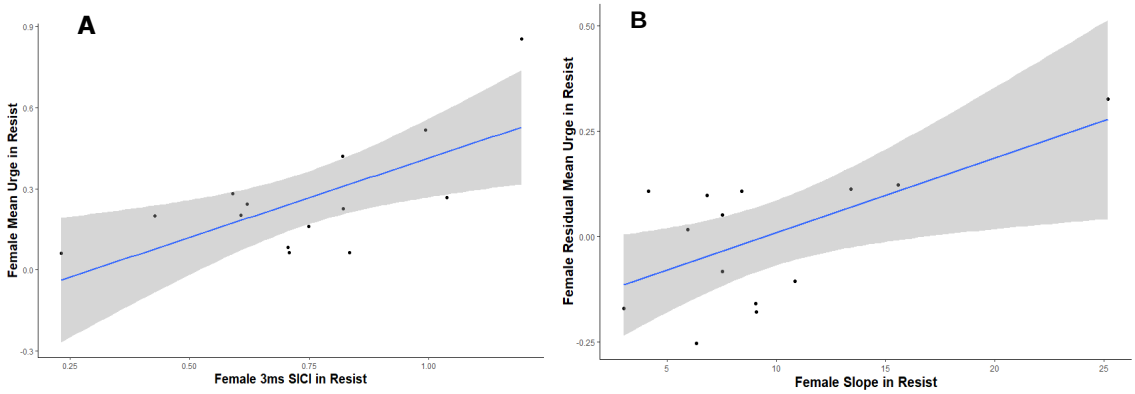


Figure 5-10: A. Scatter plot depicting the association between IO Slope in the free to yawn condition (x axis) and the mean urge-to-yawn ratings in the free condition (y axis) for females. Note that increased excitability indexes a greater mean urge-to-yawn value in the free to yawn condition for females. B. Scatter plot depicting the association between 12ms ICF values (x axis) and the residual mean urge-to-yawn ratings recorded in the free condition for females (y axis).

5.8.5 Resist Yawning Condition – Female Results

Stepwise regression results revealed that none of the online-TMS measures of cortical excitability and physiological inhibition could significantly predict the number of stifled yawns in the resist yawning condition for females. In contrast, further stepwise regression analysis yielded significant findings for the residual mean urge-to-yawn ratings in the resist condition in this group.

Results demonstrated that two factors; 3ms SICI in the resist condition, and IO slope in resist could significantly predict and account for close to 61% of the individual variability in the mean urge-to-yawn ratings in the resist condition for females ($F = 11.10$, $p < 0.002$, adjusted-$R^2 = 0.608$). The order of entry into the model for these factors was as follows: 3ms SICI (coefficient = 0.58, t-statistic = 3.11, $p < 0.008$; $F=9.71$, adjusted- $R^2 = 0.40$); and IO slope (coefficient =0.018, t-statistic = 2.71, $p < 0.02$; $F=11.10$, adjusted- $R^2 = 0.608$) (figure 5.11).



5.8.6 Free to Yawn Condition – Male Results

Figure 5-11: A. Scatter plot depicting the association between 3ms SICI in the resist yawning condition (x axis) and the mean urge-to-yawn ratings in the resist condition (y axis) for females. B. Scatter plot depicting the association between IO Slope in the resist yawning condition (x axis) and the mean urge-to-yawn ratings in the resist condition (y axis) for females. Note that increased excitability indexes a greater mean urge-to-yawn value in the resist yawning condition for females

Stepwise regression results demonstrated that 100ms LICI in the free to yawn condition could significantly predict and account for 34% of the individual variability in the mean urge to yawn ratings in the free condition for males (coefficient=32.56, t statistic=2.783; $F = 7.74$, $p < 0.01$, adjusted- $R^2 = 0.34$) (figure 5.12).

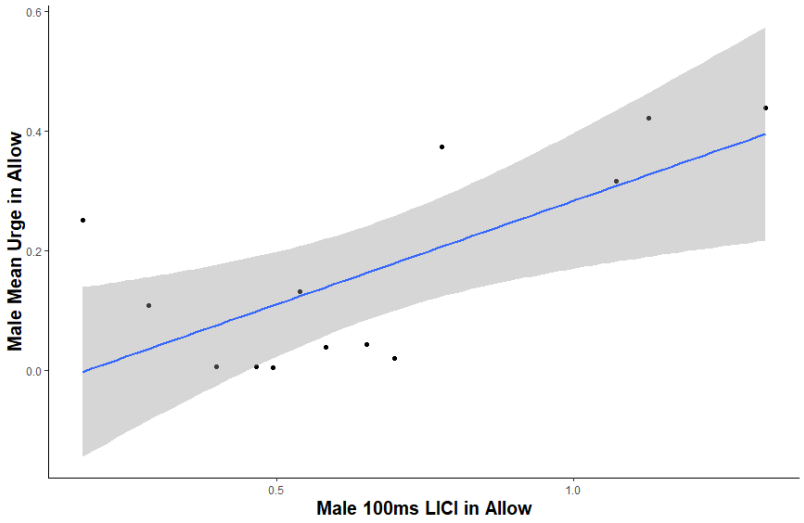


Figure 5-12: Scatter plot depicting the association between 100ms LICI in the resist yawning condition (x axis) and the number of full yawns in the free condition (y axis) for males.

Similarly, 100ms LICI in the free to yawn condition could significantly predict and account for 34% of the individual variability observed in the number of full yawns in the free to yawn condition for males (coefficient=0.31, t statistic=2.782; $F = 7.74$, $p < 0.01$, adjusted- $R^2 = 0.34$) (figure 5.13).

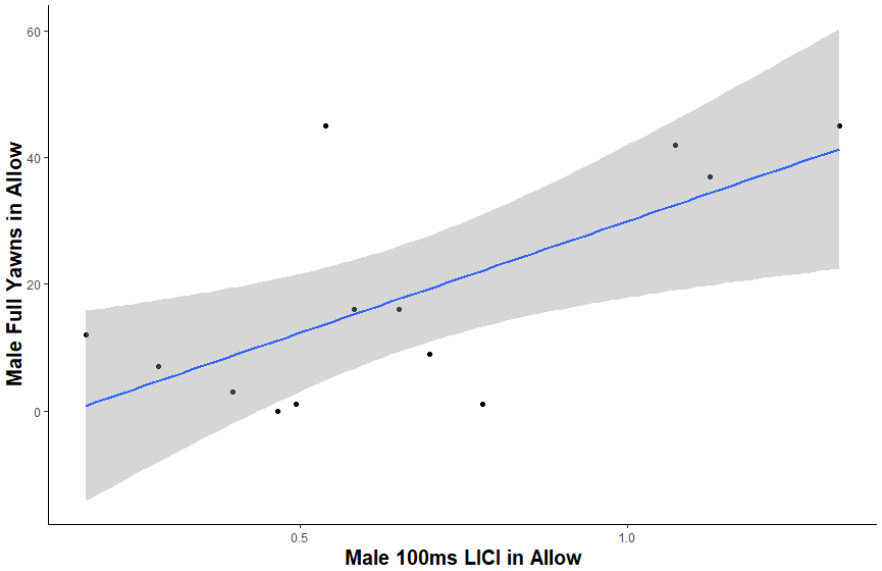


Figure 5-13: Scatter plot depicting the association between 100ms LICI in the free to yawn condition (x axis) and the mean urge-to-yawn ratings in the free condition (y axis) for males.

5.8.7 Resist Yawning Condition – Male Results

Stepwise regression results revealed that none of the online-TMS measures of cortical excitability and physiological inhibition could significantly predict the number of stifled yawns in the resist yawning condition for males. In contrast, further stepwise regression analysis for the mean urge-to-yawn ratings in the resist condition for males demonstrated that 1ms SICI in the resist condition could significantly predict and account for 34% of the individual variability in the mean urge-to-yawn ratings in the resist condition for males (coefficient =0.612, t-statistic = 2.78, $p < 0.01$; F=7.74, adjusted- R^2 =.34) (figure 5.14).

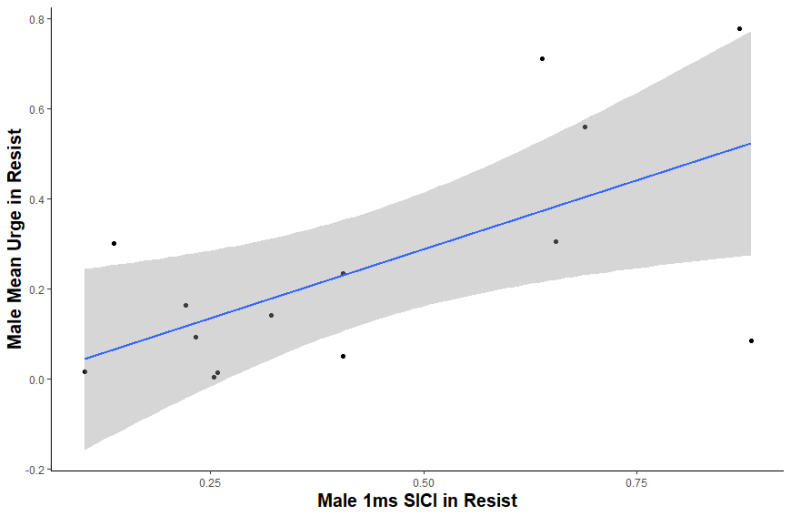


Figure 5-14: Scatter plot depicting the association between 1ms SICI in the resist yawning condition (x axis) and the mean urge-to-yawn ratings in the resist condition (y axis) for males. Note a ratio value of < 1 represents an inhibitory effect of the conditioning pulse (see text for more details).

5.8.8 Sex Differences in Autism Quotient (AQ) Scores

To determine if there were any sex differences in AQ scores an independent samples t-test was performed to compare AQ scores for females and males. There was a trend towards a significance difference in the AQ scores for females (M=14 SD=7.05) and AQ scores for males (M=19, SD=10.75)

conditions; t(26)=-1.38, p =0.09). To further establish if any of the online-TMS measures of cortical excitability and physiological inhibition could predict sex differences in AQ scores further stepwise regression analysis was performed. Results revealed none of the online-TMS measures of cortical excitability and physiological inhibition could significantly predict AQ scores for the groups' female and males.

5.9 *Discussion*

In the present study, the neural basis of contagious yawning was further explored via the use of online-TMS measures of motor cortex excitability and physiological inhibition. The online-TMS data was collected while participants simultaneously undertook the same behavioural contagious yawning task as in the previous chapter. In the previous work it was found that increased baseline motor excitability is associated with increases in the propensity for CY. Moreover, it was further discovered that the instruction to resist yawning significantly increased self-estimated urge-to-yawn ratings, and as such altered how stifled yawns might be expressed. However, it was further found that this change in yawn expression had no effect on an individual's propensity for contagious yawning. Unfortunately, how yawn instruction changed this behavioural expression at the neural level remained uncertain, and as a consequence it then informed the primary research focus of the current study. The effects that behavioural instruction might have on yawn expression was investigated via online-TMS measures, alongside self-estimated ratings of urge-to-yawn, and self-reported autism quotient (AQ) scores.

5.9.1 Effects of Instruction on Self-Reported Urge-to-Yawn Ratings

Results of the current research also suggests that instructions to resist yawning does not alter the propensity for contagious yawning but does change yawn expression. The result is a near perfect replication of the previous chapters findings, and those of Bartholomew & Cirulli, (2014), who found that an individual's propensity for contagious yawning remains stable over time. In contrast to the findings of the former chapter however, whole group analyses from the current research found no significant effects of yawn instruction on self-estimated urge-to-yawn ratings in either the 'free to yawn', or the 'resist yawning', behavioural conditions during online-TMS measures. This would suggest that instructions are possibly processed in a cortical region outside of the primary motor cortex, and as such not detectable by the current online-TMS protocol. Alternatively, and given that the previous study found significant predictors of instruction on self-estimated urge-to-yawn at a baseline level, it could be that instruction is processed far earlier in the behavioural task than currently known. Thus, it could be suggested that the lack of significant findings for the online version of the task is more to do with latency as opposed to cortical region per se. This finding suggests that further investigation is needed to precisely establish what is going on during instruction processing.

However, further whole group analyses did reveal that some of the online-TMS measures of motor cortex excitability, physiological inhibition, and AQ scores could significantly predict self-estimated mean urge-to-yawn ratings in the resist yawning condition. Similarly, it was discovered that the slope of the TMS induced recruitment curve (IO slope) could significantly predict self-estimated mean urge-to-yawn ratings in the 'free to yawn' condition. This discovery also

contrasts with the finding of the previous study. The former finding suggested that while motor cortical excitability was a significant predictor of the propensity for contagious yawning, it was not a significant driver of, or associated with, the urge-to-yawn.

As noted earlier, this finding would appear to be consistent with Jackson et al., (2012) previous acknowledgement regarding the urge-for-action being most likely associated with upstream brain areas such as the anterior insular cortex and/or the cingulate motor cortices. However, the current finding would suggest that there is some involvement of primary motor cortices at the neural level when recording self-estimated urge-to-yawn ratings. Nevertheless, it would be wise to remain cautious of this finding insofar as, participants were executing a motor action (moving slider mechanism) at the time the measures were being collected. It would be reasonable to assume that this motor cortical response could possibly reflect this action and may not be related to the urge-to-yawn more specifically. Therefore, additional research is required to further establish what is going on at a cortical level during self-estimated urge-to-yawn ratings.

5.9.2 Effects of motor excitability and physiological inhibition on propensity for contagious yawning

Results of the current study found that none of the online-TMS measures of motor cortex excitability and physiological inhibition could significantly predict the propensity for contagious yawning at the group level for either the ‘free to yawn’, or the ‘resist yawning conditions. While this result matches the former study for the resist yawning condition, it is in contrast to that for the ‘free to yawn’ condition, whereby three factors were found to predict yawn propensity in

this condition. This could suggest that something entirely separate is happening at the neural level during online TMS. For example, it is acknowledged that the unconscious intention to act could be occurring some time prior to online TMS data collection and at a neural level outside the scope of online TMS data collection. As noted earlier, it is also evident from the analyses that there are a greater number of yawns and stifled yawns elicited during the online TMS protocol. This would suggest that the administration of TMS to primary motor cortex (M1) increases the incidence of contagious yawning. This is an interesting finding and as such requires further exploration in order to ascertain why contagious yawning increases exponentially during online TMS when compared to offline baseline measures.

5.9.3 Between Group Analyses

Considering the observed sex differences seen among those with neurological conditions that present with echophenomena such as, Autism spectrum disorders or Gille's De La Tourette's syndrome, and given that we collected data from an equal number of males and females, further post hoc analyses were conducted. When the data was analysed, accounting for sex differences, it was found that several measures of cortical excitability and physiological inhibition in the primary motor cortex could account for and explain marked sex differences in the propensity for contagious yawning. There were also significant sex differences in both the cortical excitability and physiological inhibition observed during online-TMS. Moreover, both behavioural instruction and propensity for contagious yawning appeared to be predicted by different online-TMS measures both within and between the two sexes.

For instance, the current research found that RMT could predict the individual variability in the number of full yawns in the free to yawn condition for females but not males. Similarly, both IO slope and 12ms ICF significantly predicted individual mean urge-to-yawn ratings in the free to yawn condition for this group. Furthermore, IO slope and 3ms SICI could predict the individual mean urge-to-yawn ratings in the resist yawning condition for females. In contrast, results of the current study found that 100ms LICI could significantly predict both observed variability in the number of full yawns, and the mean urge-to-yawn ratings, in the free to yawn condition for males, while none predicted the number of stifled yawns in the resist condition for this group.

However, it was found that 1ms SICI could significantly predict mean urge-to-yawn ratings in the resist condition. Additional analyses also found that some measures of cortical excitability and physiological inhibition did indeed differ according to instruction between the sexes. Similar findings in observed sex differences for motor cortical excitability and inhibition have been found previously (Cheng et al., 2007; Kuo, Nitsche, & Paulus, 2006) . Moreover, sex differences in brain anatomy have also been observed and documented (Luders & Toga, 2010). However, the importance of sex difference in brain structure and function during episodes of echophenomena are significantly underrepresented in the literature.

This last point is highlighted in a recent systematic review paper on sex differences in unconscious social mimicry (Lehane, 2015). Lehane (2015) highlights that former research regarding unconscious mimicry assumes that females will more often mimic their communication partners when compared to males. While several research studies have explored the relationship between

mimicry, recognition of emotion, and empathic processing, there is an imbalance in the way participants are recruited. Lehane (2015) stresses that there is an unhealthy trend for research in this area to use same-sex samples. The result of this bias leads to researchers overlooking a vital debate relating to the role that sex difference, as a potential moderator of unconscious mimicry, might play. Indeed, the findings of Lehane (2015) indicates that unconscious mimicry may well be facilitated by sex depending upon, among other things, the choice of mimicry measures, the length of stimulus exposure, and social environments and/or contexts. However, as noted, very few research studies address potential sex differences in unconscious mimicking behaviours, and as such, many are mired by methodological limitations (Lehane, 2015).

This is an important consideration given that there is a higher ratio of males who present with neurological and neuropsychiatric conditions such as Tourettes's syndrome, ADHD, and Autism Spectrum Disorders (ASD) (Baron-Cohen et al., 2009; Ganos et al., 2012b). Similarly, it has been found that urge-for-action is also strongly related to the same neurophysiological conditions (Bechara, 2012; Bliss, 1980; Gullo & Dawe, 2008; Rasmussen & Eisen, 1992; Simons, 1974). Moreover, comorbidity across many of these conditions is reported to be high among males (Cafri, Olivardia, & Thompson, 2008; Lewin, Wood, Gunderson, Murphy, & Storch, 2011). Indeed, Baron-Cohen (2002) argued that there are distinct sex differences among those who present with ASD. Baron-Cohen (2002) suggested that male brains are defined psychometrically as individuals who can systemise considerably better than they can empathise.

Conversely, he argued that the female brains are better defined as opposing cognitive profiles to that of males. Baron-Cohen used these definitions to

describe ASD as an extreme of the typical male cognitive profile, and cited extensive psychological evidence for his extreme ‘male brain theory of autism’ (Baron-Cohen, 2002). While this controversial view of the human brain would appear somewhat simplistic, the occurrence of ASD, and similar conditions, being greater among males cannot be denied. The current study’s findings regarding sex differences in cortical excitability, physiological inhibition, self-estimated urge-to-yawn, and scores on the AQ questionnaire, would point towards some degree of disparity between the sexes, especially with regards to both their neural and subjective cognitive processing.

5.9.4 Conclusions

The current research expanded upon the previous chapter, whereby evidence supporting the suggestion that measures of cortical excitability and physiological inhibition could predict the propensity for contagious yawning; and that behavioural instructions could alter the subsequent yawn expression, was found. This work successfully replicated the contagious yawning behavioural task and yielded further support for the hypothesis that an individual’s propensity towards contagious yawning remains stable across time. In contrast, whole group analysis demonstrated mixed findings, when compared to the previous work. For example, the association between online-TMS measures of cortical excitability and inhibition and contagious yawning were significantly different to the offline TMS findings of the previous study. For example the current findings are in contrast to the findings of the previous chapter. Indeed, the current chapter failed to find any significant effects of yawn instruction on self-estimated urge-to-yawn ratings in either the ‘free to yawn’, or the ‘resist yawning’, behavioural conditions during the online-TMS protocol. It is thought

that this result suggests that instructions might be processed in a cortical region outside of the primary motor regions, and as such not detectable by the current online-TMS protocol. Alternatively, and given that the previous study found significant predictors of instruction on self-estimated urge-to-yawn at a baseline level, it could be that instruction is processed far earlier in the behavioural task than the current study was able to capture. Therefore, the lack of significant findings for the online version of this task could be as a result of latency and not to any specific motor cortical region per se.

However, within and between sex difference analyses demonstrated unexpected and striking relationships between motor cortex excitability, GABAergic inhibition, and the propensity towards contagious yawning, and self-estimated urge-to-yawn ratings. This finding is supported by previous research evidence that suggests males are most likely to present with neurological, or neuropsychiatric conditions, which involve a greater likelihood towards altered urge-for-action, such as Tourette's syndrome and/or ASD. The results are in line with the finding that individuals with these conditions also present with an altered propensity towards echophenomena. Lehane (2015) suggestion, that more research regarding sex differences is needed to understand more precisely the neural mechanisms that underly unconscious mimicry, is also bolstered by the current research findings.

In sum, the current research endeavour raises further questions regarding the study of echophenomena, and more precisely the neural basis of neurological conditions such as Tourette's and ASD. Moreover, and to the best of our knowledge, this is the first research study to demonstrate significant sex differences in the propensity towards contagious yawning, and potentially the

neural mechanisms underlying these and other automatic unconscious behaviours. In addition, and as discussed earlier, many of these conditions also present with altered impulse control, which is also said to be related to the urge-for-action. Therefore, the next two chapters will explore features of unconscious automatic impulsive action in order to ascertain how automatic impulsive action develops among children. Finally, the last study in this thesis will explore the neural basis for unconscious impulsive action using a similar paradigm to that used in chapter 4. The purpose of this is to establish whether automatic impulsive action is mediated by the same neural mechanisms as echophenomena.

Chapter 6 Drag-Racing 1: Investigating non-social inhibitory control in Children

6.1 *Introduction*

Impulsivity is frequently described as involving the propensity to display behaviours that are characterised by little to no forethought, reflection, or consideration of potential outcomes (Evenden, 1999). Prior to Dickman's (1990) research impulsivity had frequently been thought of as a negative trait that could lead to adverse consequences and potential difficulties in life. Dickman' (1990) suggested that impulsivity can be viewed as two separate dimensions, namely dysfunctional and functional impulsivity. Dickman (1990) posits that functional impulsivity is a specific type of impulsivity that could lead to optimal outcomes and subsequently considered a positive attribute.

Despite the suggested difference between functional and dysfunctional impulsivity, research that evaluates dysfunctional impulsivity, among adults and children, has received considerably more attention in recent years. Moreover, this interest appears to be related specifically to dysfunctional impulsivity's relationship with many behavioural disorders associated with lack of impulse control such as, attention deficit hyperactivity disorder (ADHD), TS, aggression, pathological gambling, substance misuse, schizophrenia, and dementia (Chamberlain & Sahakian, 2007). In contrast, so called 'functional impulsivity' appears to be significantly underrepresented in the literature, particularly among children.

However, as already noted impulsive action can also be elicited by either a situation or an event (Frijda, Ridderinkhof, & Rietveld, 2014) and as such cannot be measured by questionnaires' alone. Frijda et al (2014) posit impulsive action is activated by how the object or event is appraised. Moreover, Frijda and colleagues propose that impulsive action is induced by what the event or object might offer, or do, to the individual, or could withhold from them. They argue that an individual is directly faced with relevant information which is needed to guide their actions, and that they can do so without the need for explicit goal representation. In essence, they are faced with an object, or event, that they are appraising, which remains before their eyes, or before their mind's eye, until they have completed the action.

Dreyfus (2005) and Pacherie (2000, 2001) suggest this impulsive action relates to motor intention, while Searle (1983) refers to it as 'intention in action'. However, these suggestions could simply be referred to as an intent, produced by what objects or events seems to promise or spell out for the individual, in the way that relevant information obtained from the world around us does (Frijda et al., 2014). Put more simply, impulsive action is elicited by the motivation to alter a current state encountered in the world in order to estimate a more optimal state.

Searle (1983) used the term 'intention in action' in his analysis of action. For Searle (1983), an action represents *"a causal and Intentional transaction between mind and the world"* (1983, p. 88). Therefore, an action according to Searle's theory is comprised of two components; an intention to move, and the movement itself. Moreover, the intentional component is approximately related to the mental and causal component, which represents conditions of satisfaction

that are to be met by the appropriate movement. During instances of premeditated, or deliberative acts, action is caused by what Searle (1983) refers to as a prior intention, that is, an intention to initiate an action, which is formulated in advance of the action itself.

However, many, if not the majority of everyday acts are not entirely premeditated, and as such cannot always be credited to prior intention. Indeed, the intention in action is initiated in order for the mind to account for these actions. In contrast to the prior intention however, the intention in action is not formulated prior to the action, but rather generates the act by representing its conditions of satisfaction while in progress (Searle, 1983). Therefore, the basic intentional content of Searle's (1983) so named 'intention in action', is characterised by self-referential causality.

This suggests that action selection, when implementing a motivated state in response to events, does not result from either deliberate goal-directed action, or overlearned habits, but rather from non-reflective action priming by properties of an event or situation encountered and recognised (Frijda et. al., 2014). This priming is said to elicit anticipation of an action's effects, which subsequently imposes a prediction of its interoceptive and/or exteroceptive sensory outcome. This is achieved via efference copies or 'forward models' and leads to a state of action readiness.

Thus, this hypothesis suggests that the forward model affords the evaluation and fine-tuning of anticipated action effects, and measures this against what the action should accomplish, and in turn allows the impulsive action to have a purpose. Moreover, it could be argued that so called 'functional impulsivity' is

actually the action of forward model processing. Since forward models are thought to follow a developmental time course, the age dependent effects documented within the functional impulsivity literature could be evidence of such a phenomenon.

However, it is acknowledged that, while age-dependent effects in dysfunctional impulsivity has been widely investigated in childhood, adolescence, and early adulthood (Galvan, Hare, Voss, Glover, & Casey, 2007; Leshem & Glicksohn, 2007), studies on age-dependent effects regarding impulsive actions that result in an optimal outcome is limited. Heyes et al. (2012) did investigate the age-dependent effects in adults (age range 18-79 years) and showed that anticipatory behaviour, that did result in optimal outcomes, which Heyes and colleagues say might reflect functional impulsivity, reduced with age. However, to our knowledge, the age-dependent effects in young children have not yet been investigated.

The potential of the traffic light task employed by Heyes et al. (2012), in which the participants had to make rapid decisions while in search of time-sensitive risky rewards, was identified and adapted for the current study. In Heyes et al., (2012) task, participants could optimise their rewards by making some advance anticipatory responses as opposed to passively waiting for the cue to respond. This response was facilitated by the fact that the value of the rewards declined quickly with increasing reaction time. Heyes et al. (2012) conducted a two-horse linear rise-to-threshold model to dissociate anticipatory and reactive responses. Their study demonstrated that the index of anticipatory responses was correlated with one aspect of impulsivity, “lack of premeditation” as measured by the UPPS impulsivity questionnaire. It was advantageous for participants to

make some impulsive anticipatory responses in the task, in order to optimise their rewards. Thus, the subsequent anticipatory responses by the participants were then thought to reflect their individual level of functional impulsivity (Heyes et al., 2012).

The aim of the current study was to determine if this optimal anticipatory behaviour could be better understood as the action of internal modelling, and whether this behaviour follows a similar developmental time-course in young children. The conventional traffic light task was converted into a ‘drag racing’ game in order to test rapid decision making and the possible action of internal models among children. It was hypothesised that if the children’s performance on the drag-racing task improved with age then this could be attributed to a developmental trajectory and possibly the action of forward model processing.

Previous studies that adopted the traffic light task provided reward in the form of scores, or hypothetical money, according to an inverse exponential temporal discount function to encourage faster responses. A similar approach was adopted in the current task, insofar as the chance to win was also scaled by an inverse exponential function. However, our drag racing task provided feedback as win, lose, or false-start results. This form of feedback was expected to be far more straightforward for young children to understand.

This study was conducted as part of the University of Nottingham’s public engagement event known as Summer Scientist Week. The parent/carer of the child completed several questionnaires relating to the child during or prior to the event. The questionnaire of interest was, The Strengths and Weaknesses of ADHD Symptoms and Normal Behaviour Rating Scale (SWAN), (Swanson,

Shuck, Mann, Carlson, Hartman, Sergeant, & McCleary, 2006; Swanson et al., 2012). The SWAN Rating scale measures inattentive and hyperactive/impulsive symptoms among children. Pearson's correlation analysis was conducted to investigate the relationship between questionnaire-based impulsivity (i.e. subset scores 'hyperactive/impulsive symptoms' of SWAN) and behavioural measures of impulsivity from our drag racing task. However, it is understood that the SWAN measure mainly evaluates dysfunctional impulsivity only. Therefore, it was unlikely to be correlated to the behavioural measures employed in our task, or to questionnaire measures of so called 'functional impulsivity'. In addition, questionnaire-based measures of 'functional impulsivity' were not available from the event, nor are there any reliable measures of functional impulsivity available to measure this construct in children.

6.2 *Method*

6.2.1 Study design

A within and subjects' experimental design was employed. The study incorporated a psychophysics behavioural paradigm in order to investigate age dependent effects of impulsive action among children aged 4-12 years of age.

6.2.2 Ethics

Ethical approval for the study was sought and granted by the University of Nottingham ethics committee.

6.2.3 Participants

The sample consisted of 73 children (42 male) between 4 years 2 months and 12 years 7 months (mean age: 8 years 4 months) were recruited from the 2016

Summer Scientist Week event held at the University of Nottingham. The Summer Scientist Week 2016 event received ethical approval from the University of Nottingham ethics committee. Informed consent was received from the parents for all studies prior to the children's attendance at the event. Parents/care givers completed the SWAN questionnaire to evaluate the children's level of impulsivity.

6.2.4 Procedure

A modified version of Heyes et al., (2012) traffic light task was developed using Matlab version 2010b (Mathworks Inc). On each trial, two images of a racing car were presented at the bottom of the screen. On the bottom left was a red car (participants vehicle), and to the bottom right was a blue car (computer vehicle). An image of a traffic light was presented at the top of the screen. Three vertical white lines were positioned between the cars and the traffic light images to indicate car lanes. The traffic light changed its colour sequentially from red, amber, to green.

Participants were instructed to press the space bar as fast as they could when the green light turned on. The study was described as a car racing game in which the participant (i.e. the left red car) competes against the computer (i.e. the right blue car). They were told that there would be a greater chance to win if they made faster responses. Conversely, they were told that they would lose the trial if they responded before the green light. At the end of each trial feedback was presented showing the accumulated scores of the participant and the computer, along with text informing the participant on how they had

performed on each trial (e.g. you win, you lose, false start, or too slow) (figure 6.1).

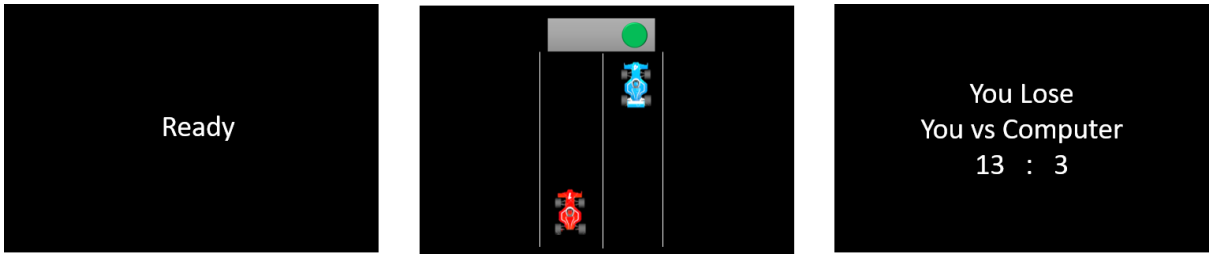


Figure 6-1: Image depicting a representative example of the drag-racing game.

The task parameters were chosen in a similar way to Heyes et al. (2012) as they demonstrated that their Traffic Light task could successfully encourage participants to make rapid anticipatory responses by providing time-sensitive rewards. The duration of the red-light presentation was 1 second. The duration of the amber-light was randomly decided on each trial via a Gaussian distribution, with a mean of 750 ms and SD 125 ms. While Heyes et al. (2012) provided the reward in hypothetical money, this study provided the feedback as binary results (e.g. win or lose). On each trial the chance for the participant to win was decided by an inverse exponential temporal discount function; chance to win = 1/exp(RT*2) (figure 6.2). If the participant responded within 1 second from the onset of the green light, the results (e.g win or lose) were decided according to the chance level at the reaction time (RT) of the trial. If the participant did not respond within 1 s from the onset of the green light he/she would lose that trial. There were 120 trials in total. The task was programmed and run using Matlab 2010b with Psychtoolbox on a 13-inch Macbook computer.

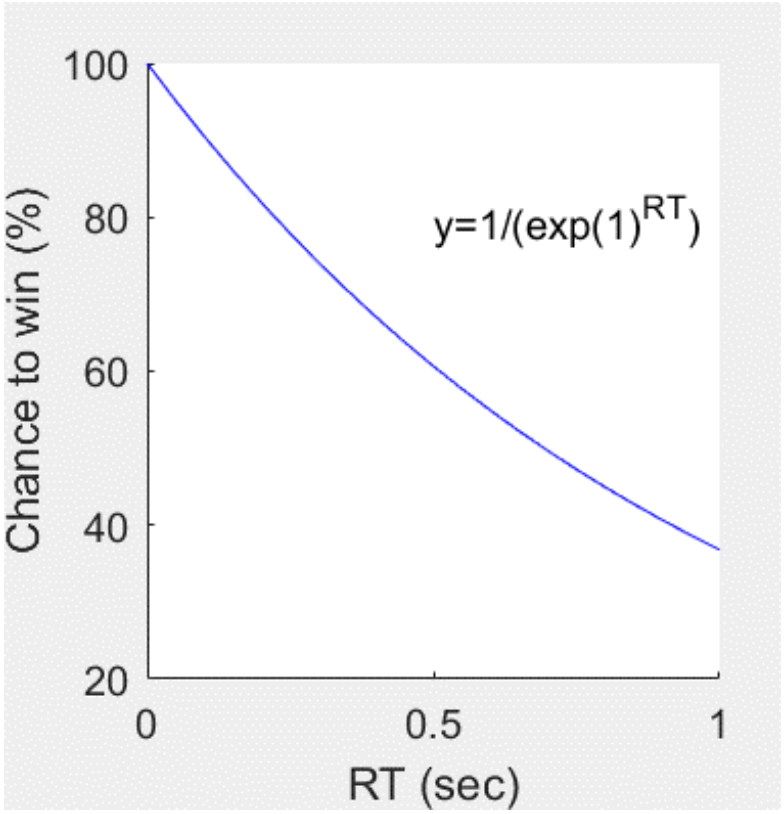


Figure 6-2: Graphical representation of the exponential temporal discount function used to determine the chance to win in the drag-racing game.

6.3 *Analysis*

Reaction time (RT) was measured from the onset of the green light. If the participant responded prior to the onset of the green light then the RT was measured as a negative value. The trials in which the participant did not respond within 1 s from the green onset (e.g. too slow), were excluded from the analysis. As a result, less than 2% of the total 120 trials were excluded for each participant on average. The ratio of the negative RT trials and the ratio of win trials were then calculated for each ot the participants.

In the traffic light task, including our drag-racing task, the responses can be triggered by two different processes. The first is the anticipatory response which

is initiated prior to the green light onset, and second, the reactive response which is triggered by the green light onset (Reddi & Carpenter, 2000). A two-horse linear rise-to-threshold model (Adam, Bays, & Husain, 2012; Heyes et al., 2012) was applied to RT distributions to model these two processes.

RT distributions were probabilistically assigned to populations elicited from an anticipatory and reactive decision making process according to the cumulative probability distribution equation from Heyes et al. (2012). Four parameters of mean and SD of the distribution of anticipatory responses (i.e. μ_a and σ_a) and reactive processes (i.e. μ_r and σ_r) were fitted to this model for each individual's RT distributions using maximum likelihood function (figure 6.3). All the data analyses were conducted using Matlab 2018a. Pearson's correlation analysis was performed to investigate the relationship between individuals' performances in the drag-racing task and age, or questionnaire-measured impulsivity (e.g. SWAN inattention, SWAN hyper activity, SWAN total score.

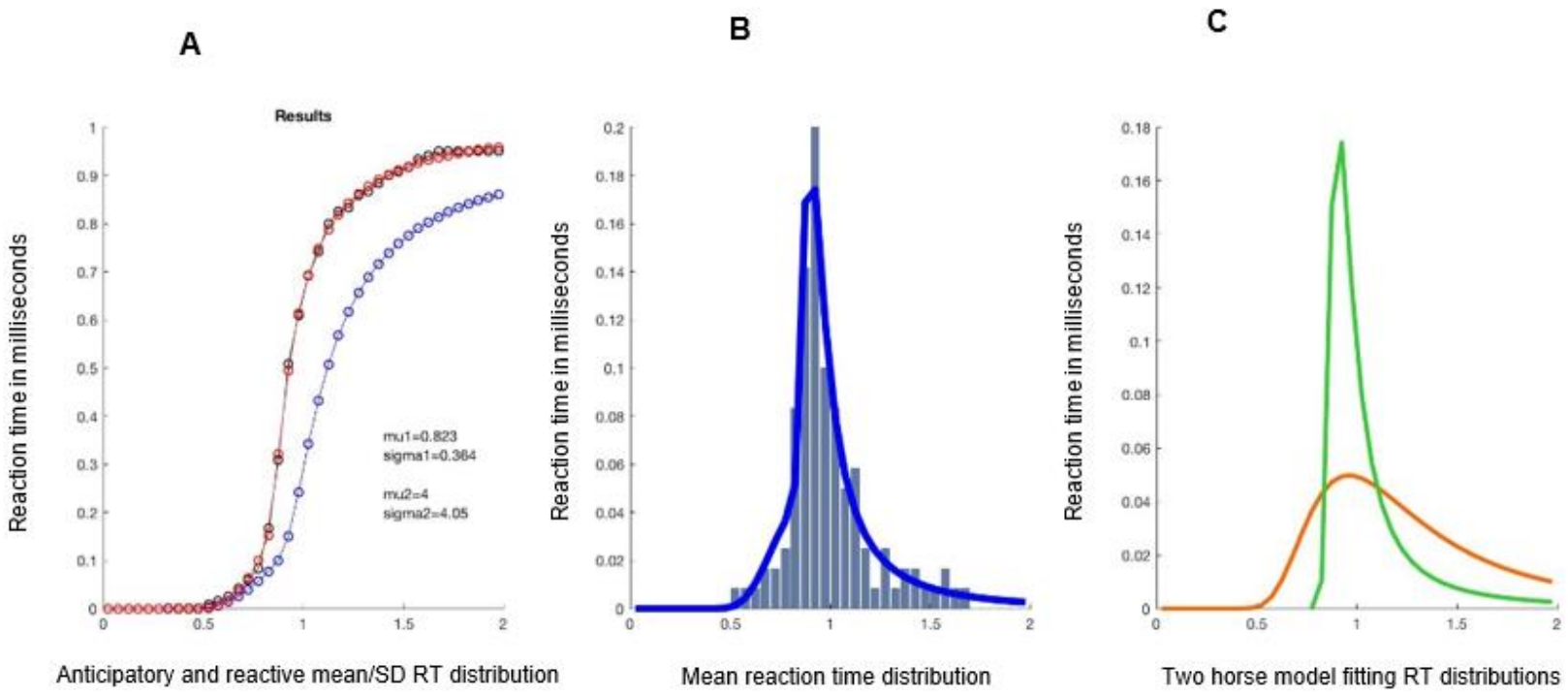


Figure 6-3: Graphical representations depicting one participants' reaction time distributions and results of the two-horse model fitting. A: shows mean and standard deviations for anticipatory (mu1, SD1) and reactive (mu2, SD2) responses. B: shows the RT distribution. C: shows the results of the two-horse model fitting – red line corresponds to anticipatory responses, while the green line corresponds to the reactive responses.

6.4 *Results*

The mean RT of the entire group of participants was 0.12 seconds. Individuals' mean RT was not correlated to age p>0.05 (figure 6.4).

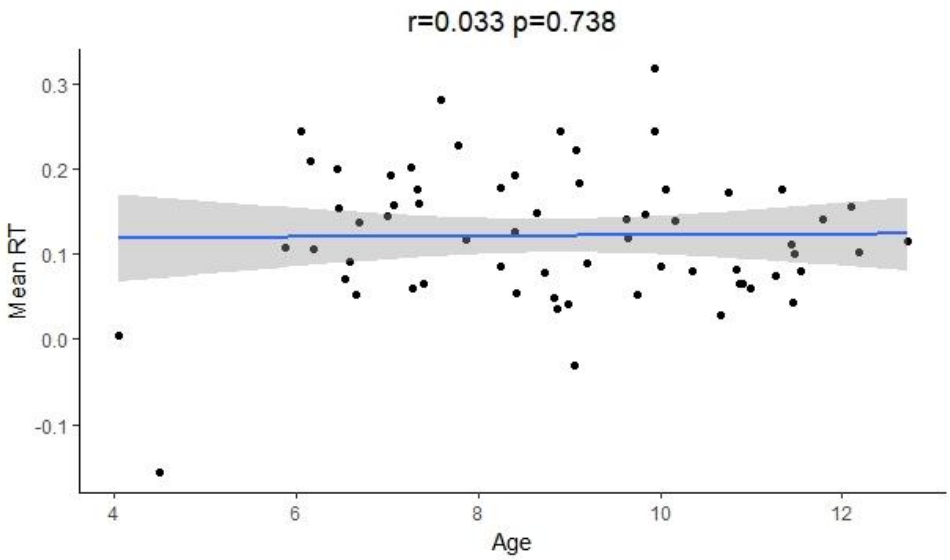


Figure 6-4: Relationship between group mean RT and age.

The participants responded prior to the onset of the green light (e.g. negative RT trials) in 47% of trials on average. The ratio of the negative RT trials was not correlated to age p>0.05. In contrast, the ratio of win trials was significantly correlated to age such that older participants showed a better performance in the drag racing task (r=0.549, p<.01), (figure 6.5).

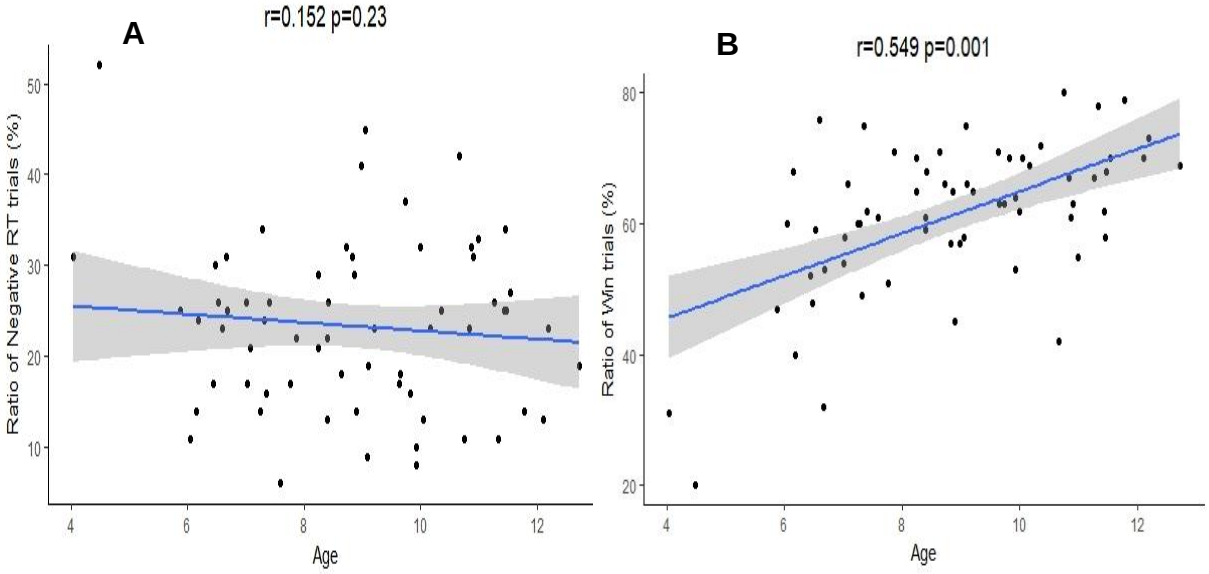


Figure 6-5: A. Relationship between the ratio of negative RT trials (%) and age. B. Relationship between the ratio of win trials (%) and age.

This finding suggests that most of the participants responded prior to the onset of the green light in a number of trials regardless of their age. However, the exectution of early responses during the task were advantageous for older children only. Modelling analysis also revealed results consistent with this finding. There was a significant positive correlation between anticipatory responses (e.g. μ_a) and age ($r=.421$, $p<.01$) However, there was no significant correlation between reactive responses (e.g. μ_r) and age $p>.05$, (figure 6.6).

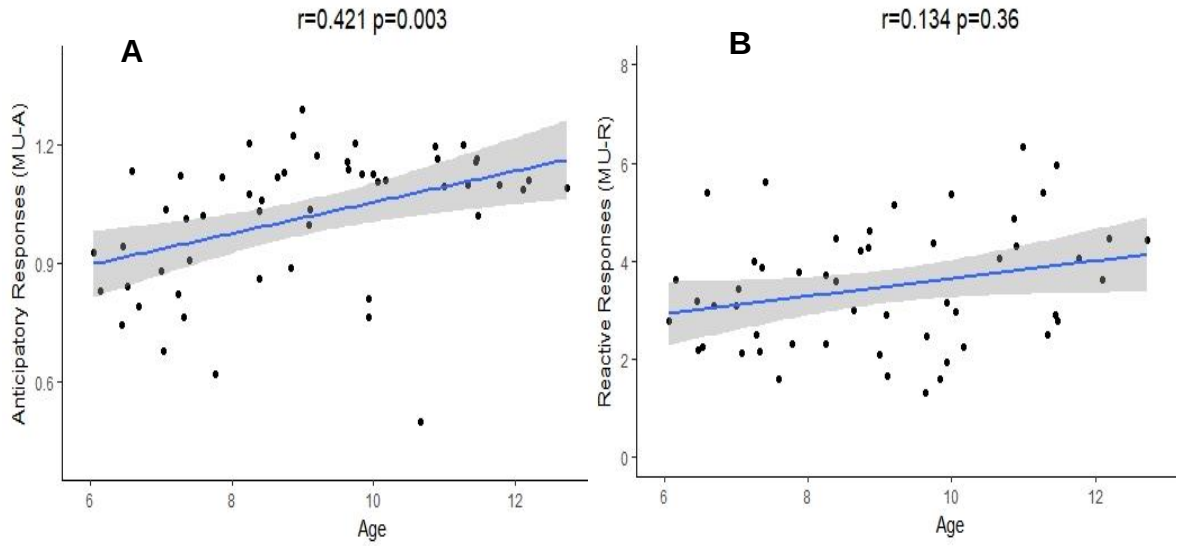


Figure 6-6: A. Relationship between anticipatory responses (μa) and age. B. Relationship between reactive responses (μr) and age.

In addition, whether levels of impulsivity as measured by SWAN can predict the performances in the drag racing task were investigated. However, there was no relationship between the individual participants' anticipatory responses (i.e. μ_a) and SWAN impulsivity, SWAN hyperactivity, or SWAN total score p>.05, (figure 6.7).

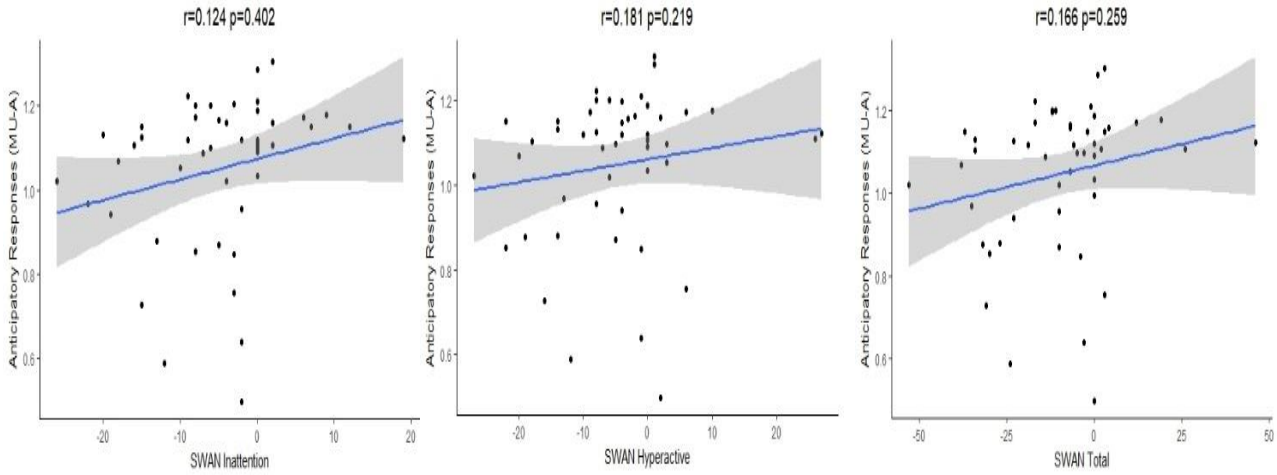


Figure 6-7: The relationship between individual participants' level of impulsivity measured by SWAN and the anticipatory response parameter of the modelling analysis (μa).

6.5 *Discussion*

The existing “Traffic Light” paradigm developed by Heyes et al., (2012), which was shown to test fucntional impulsivity, was adapted into a drag racing game. Results of this newly devised task demonstrated that there are age-dependent effects among young children in levels of functional impulsivity. In the current study, it was discovered that older children were more sucessful at responding in an anticipatory manner, and in doing so secured far more win trials on the drag racing task. Heyes et al., (2012) previous research also demonstrated that anticipatory responses were correlated with one construct of the UPPS questionnaire measure ‘lack of premeditation’(Whiteside & Lynam, 2001). Thus, and in line with this idea, the current findings would suggest that older children are able to keep a balance between rapid opportunistic responding and careful premeditation (Dickman, 1990, Heyes et al., 2012).

In addition, Brunas-Wagstaff et al. (1997) also reported a similar pattern of distinction among children and adolescents, which followed on from Dickman’ (1990) idea that there are two uncorrelated domains of impulsivity among adults. Brunas-Wagstaff and colleagues (1997) discovered that test-retest reliability of functional impulsivity was comparatively poorer than that of dysfunctional impulsivity. They postulated that it could indicate that the construct of ‘functional impulsivity’ might develop as a consistent trait only as children grow older. Another recent study conducted by Cosi et al. (2008), not only reported poor internal consistency in the measures of functional and dysfunctional impulsivity, but also questionned the existence of two-factor sturcture of impulsivity in children altogether. Both studies suggest that questionnaire based measures are not appropriate to meausre levels of

functional impulsivity in children. In support of this notion, and as discussed previously, impulsive action can also be elicited by either a situation or an event (Frijda, Ridderinkhof & Rietveld., 2014), and as such cannot be measured by questionnaires' alone.

According to Frijda and colleagues (2014) impulsive action is most likely activated by how an object or event is appraised. Moreover, they suggest that impulsive action is induced by what the event or object might offer, or do, to the individual, or could withhold from them. They argue that an individal is directly faced with relevant information which is needed to guide their actions, and that they can do so without the need for explicit goal representation. Impulsive action has also been argued to relate to motor intention (Dreyfus, 2005). This suggests that the intention to act is initiated by what objects or events might promise or spell out for the individual, in the way that relevant information obtained from the environment might (Frijda et al., 2014). Therefore, impulsive action is elicited by the motivation to alter a current state encountred in the world in order to estimate a more optimal state representation.

Frijda et. al., (2014) further suggests that action selection does not result from either deliberate goal-directed action, or overlearned habits, but rather from non-reflective action priming by properties of an event or situation encountered. This priming is said to elicit anticipation of an action's effects, which subsequently imposes a prediction of its interoceptive and/or exteroceptive sensory outcome. This is thought to be achieved via efference copies or 'forward models', which in turn leads to a state of action readiness. Forward models allow for the evaluation and fine-tuning of anticipated action effects, and measures this against what the action should accomplish., and affords the

impulsive action to have a purpose (Frijda et al., 2014). As noted previously, and given that forward models are thought to follow a developmental timecourse, it would be fair to argue that so called *'functional impulsivity'* is actually the action of forward model processing (Contreras-Vidal, 2006).

However, the lack of a significant relationship between levels of impulsivity, as measured by the SWAN questionnaire, and the anticipatory responses in the drag racing task are in line with Dickman (1990) who suggested that the level of the functional and dysfunctional impulsivity are not correlated across individuals. Morgan & Norris, (2010) were also able to demonstrate that individuals with ADHD displayed strong correlations with dysfunctional impulsivity only, and not with functional impulsivity. It is unfortunate that questionnaires measuring 'functional' impulsivity were not available in this study. Dickman Impulsivity Inventory for children (the DII-c; Brunas-Wagstaff et al., 1997), could be used alongside, or instead of the SWAN, to measure the functional impulsivity. However, and as noted previously, former studies have demonstrated poor internal consistency with the DII-c especially for functional impulsivity (Cosi et al., 2008). Thus, the DII-c may not be a suitable questionnaire to test functional impulsivity either.

6.6 *Concluding comments*

The drag racing task was developed in order to provide a useful measure of rapid decision-making while under risk. However, this paradigm provided much more straightforward feedback (e.g. win or lose). This task potentially measured levels of functional impulsivity in young children and as such revealed age-dependent effects. The current finding provides behavioural evidence that

functional impulsivity may develop according to the developmental time-course in children. This is evidenced in the older childrens success on the drag-racing task and could suggest support for forward model processing. This finding could potentially throw the existence of the construct of funcional impulsivity into question. The task also harnesses the potential to reveal how this process might differ in children when compared to adults, and later patient groups. Impulsive behaviour in pathological groups (Chamberlain & Sahakian, 2007) is frequently characterised by rapid and risky decision-making and very few tasks measure this directly.

However, a limitation of these findings might be that the older childrens' success on the drag-racing task may well be an increased ability to perceive the passge of time rather than functional impulsivity or forward model processing. Unfortunately the control task such as a temporal duration discrimination task (Bueti et al., 2008; Heyes et al., 2012) was not included in the current study due to procedural limitation and time constraints. As a result, this alternative interpretation cannot be ruled out completely. Despite this limitation the research question that was asked; are behavioural measures of impulsivity correlated with questionnaire-based measures of impulsivity? is important. However, due to the lack of a questionnaires available that measure levels of functional impulsivity reliably, this question cannot be studied effectively. The current findings and limitations prompted the need for next research study. The aim of the next study will be to investigate the neural basis for impulse control in adults and to determine whether impulsivity is an automatic behavior mediated by the primary motor cortex. The same non-invasive brain stimulation techniques utilised in our earlier projects will be employed.

Chapter 7 Drag racing 2: Investigating automatic impulsive action in adults

7.1 *Introduction*

Results of the newly devised drag-racing task, employed in the previous chapter, demonstrated that there are age-dependent effects among young children in levels of what is often referred to as 'functional impulsivity' (Dickman, 1990). However, the previous study does not provide knowledge regarding the underlying mechanisms related to the control of this behaviour beyond childhood. For example, despite impulsive action being linked to neurodevelopmental and neuropsychiatric disorders there still remains no definitive understanding regarding the role that the human motor cortices might play during automatic impulsive decision-making. This chapter hopes to build upon the previous study's findings and address this additional point.

The close examination of decision-making in the form of impulsive action has been the focus of intense research in the cognitive neuroscience community (Heyes et al., 2012). As a result of this research effort impulsive action is now typically characterised as abnormal or functional depending on both the situation and the natural behaviour of those involved (Dickman & Meyer, 1988; Dickman, 1990; Heyes et al., 2012). However, there are several limitations regarding both questionnaire and the naturalistic tasks currently used to evaluate abnormal decision-making.

As noted previously, impulsivity is frequently described as involving the propensity to display behaviours that are characterised by little to no forethought, reflection, or consideration of potential outcomes (Evenden, 1999).

In addition, this type of behaviour is typically thought of as badly conceived, overtly risky, expressed prematurely, or completely inappropriate to a given situation (Zermatten et al., 2005). Such impulsive action is also said to impair long term goals, strategies for success, and can ultimately lead to negative outcomes (Gregory Madden et al., 2010).

As can be seen from the literature review, this fundamentally maladaptive description of impulsivity, also known as dysfunctional impulsivity, is often cited as a clinically important feature of numerous neuropsychiatric and neurodevelopmental conditions such as; ADHD (Anholt et al., 2010), Tourette's Syndrome (Cavanna et al., 2011), Autism Spectrum Disorders (Aman., Farmer., Holoway., & Arnold, 2008) Bipolar Disorder, (Victor et al., 2011), and Schizophrenia (Chamberlain & Sahakian, 2007; Kaladjian et al., 2011). However, despite the link that impulsive behaviours among pathological groups are frequently characterised by rapid and risky decision-making, not many behavioural tasks measure this directly.

In addition, investigations regarding impulsive behaviour among the general population also lacks a definitive agreement among researchers. This lack of consensus appears to be primarily due to disagreements regarding its underlying theoretical assumptions (Miller et al., 2004). Indeed, it was Miller et al (2004) who suggested that such debates have led to confusion regarding how best to measure and define impulsive action. Early personality and behavioural theorists postulated that impulsive behaviour is typically related to an individuals' personality type (Barratt, 1959; Carver & White, 1994; Eysenck, 1952; Gray, 1970 & 1981; Patton, Stanford, & Barratt, 1995). These theorists

cite that certain personality types are also likely to exhibit impulsive behavioural traits and not just those with neuropsychiatric disorders.

However, others suggest that impulsivity is not just associated with personality traits but also encompasses a range of separate, albeit connected, constructs (Dawe & Loxton, 2004). Dawe and Loxton (2004) suggest that it is better to conceive impulsivity as comprising two main facets, which they characterised as rash impulsiveness and reward sensitivity, also known as 'reward drive'. However, evidence from converging psychometric studies has implied that two dimensions are far too inadequate to cover the numerous differences seen in impulsive actions (Logan et al., 1997; Poythress & Hall, 2011; Whiteside et al., 2005).

For example, Whiteside & Lynam (2001) factor analysis of a variety of frequently administered self-report instruments of impulsiveness derived four separate dimensions. These dimensions included sensation seeking, lack of perseverance, urgency, and lack of premeditation (Whiteside & Lynam, 2001). These four dimensions subsequently featured in their UPPS questionnaire of impulsive action. According to Whiteside & Lynam (2001) the UPPS model appears to be useful for clarifying any variations seen in behaviours characteristic of rash impulsiveness. However, while self-report measures are a popular and frequently used instrument for measuring impulsivity, they are only subjective measures of impulsive action from an individual perspective. More importantly, these measures tell us nothing about impulsive action from a behavioural perspective.

As discussed earlier, experimental cognitive paradigms such as; delay discounting (Mobini et al., 2007; Reynolds & Schiffbauer, 2004); probabilistic gambling (Upton et al., 2011); and information sampling tasks (Banca et al., 2016; Clark et al., 2006; Quiroga et al., 2011), do not measure how well participants respond to the task while faced with time sensitive constraints. Moreover, any rapid 'impulsive' decision making during these tasks is always considered suboptimal (Heyes et al., 2012). However, these tasks do offer some insight into the negative consequences of impulsive action.

It is worth noting again though that not all acts of impulsivity result in negative consequences or are necessarily deemed maladaptive in nature. For instance, as Dickman and Meyer (1988) suggest, some acts of impulsivity can be conceptualised as having adaptive qualities, and/or positive outcomes. Dickman and Meyer (1988) found that participants who were considered highly impulsive could on occasion outperform individuals with low trait impulsivity when completing a simple task under time pressure. This observation led Dickman (1990) to further conclude that there may well be two distinct forms of impulsivity namely, *'dysfunctional'* and '*functional impulsivity'.* Dickman (1990) emphasised that functional impulsivity, while still characterised by behaviours executed with little to no forethought, can often result in positive or optimal outcomes. Dickman (1990) also suggests that the ability to respond in a quick and skillful manner, particularly in the absence of significant deliberation, can be both adaptive and beneficial in some circumstances.

In support, Heyes et al., (2012) demonstrated that *'dysfunctional impulsivity'* is inversely related with the capacity for inhibitory action, while others found that *'functional impulsivity'* measures do not exhibit this same inverse relationship

(Colzato et al., 2010). Consequentially, Heyes et al (2012) suggest that this should be considered when developing new experimental paradigms, especially if we want to accurately measure these similar, but seemingly very different constructs of impulsive behaviour. It was this particular issue that prompted Heyes et al., (2012) to develop their manual *'traffic light'* behavioural paradigm.

Indeed, Heyes et al (2012) suggests that it is of benefit to respond in an *'impulsive,'* anticipatory manner, and further state that their task "captures *'functional impulsivity,'* (Heyes et al., 2012, pg. 3). In addition, subjects who obtained greater scores on a specific dimension of self-reported impulsivity (UPPS lack of premeditation) demonstrated greater levels of anticipatory behaviour and therefore accumulated higher rewards. This suggests that this type of task could be used to support the findings of self-report measures and subsequently applied in research investigating functional vs. dysfunctional impulsivity in healthy controls or clinical groups. Moreover, Heyes et al., (2012) findings demonstrate the usefulness of the *'Traffic Light paradigm'* for investigating automatic response behaviour, as well as separating out the possibility that there may well be two separate types of impulsive behaviour. However, in order to achieve optimal outcomes via unconscious automatic action, a degree of inhibition would most likely be required. Unfortunately, the traffic light task paradigm cannot secure evidence regarding the occurrence of neural inhibition alone.

Therefore, the purpose of this study was to extend the work of Heyes et al (2012), and that of the previous chapters, to determine if automatic decision-making among neurotypical adults is facilitated by the same neural networks as automatic imitation. In addition, impulsivity questionnaire measures were

incorporated into the design to determine if there is any relationship between automatic impulsive behaviour and subjective self-report measures of impulsivity. Measures on the Autism Quotient were also added to ascertain if there was any relationship between impulsivity and autistic traits among the general population.

7.2 *Method*

7.2.1 Study Design

A within and between subjects' mixed methods experimental design was employed. The first method in this study consisted of physiological TMS measures of resting motor thresholds (RMT), motor cortical excitability (MCE), and physiological inhibition and facilitation. Measures of cortical excitability for each subject were ascertained via single TMS induced input-output curve (IO) measurements of motor evoked potentials (MEP). Physiological inhibition was determined via paired pulse TMS, 1 and 3-millisecond short interval cortical inhibition (SICI), and 100-millisecond long interval cortical inhibition (LICI). Cortical facilitation was determined via 12-millisecond intracortical facilitation (ICF). The behavioural measures of impulsivity were determined via the same drag-racing task used in chapter 6. However, in this study the number of trials in the task was increased to 150, and the task was undertaken twice. Each participant completed 3 blocks of 50 trials in each drag-racing task session.

During the second session of the task anodal transcranial direct current [a-tDCS] and random noise [tRNS] electrical stimulation (relative to sham stimulation) was utilised to increase the cortical excitability of the supplementary motor area [SMA]. The primary aim of this part of the study was to examine

whether performance on the drag-racing task could be moderated by excitatory stimulation, and to ascertain whether the SMA is involved in the genesis of impulsive decision making. In addition to this, measures of participants' subjective ratings of impulsivity, and autism quotient scores were collected via the UPPS (Whiteside et al., 2005), AQ (Baron-Cohen et al., 2001), and BIS BAS (Carver & White, 1994), questionnaires.

7.2.2 Ethics

Ethical approval for this study was sought and granted by the University of Nottingham ethics committee.

7.2.3 Participants

Thirty-six young adults (9 male) aged 19-27 years (mean age=22 ± SD=3.52), were recruited via opportunity sampling from the University of Nottingham. Prior to the study commencing all participants were assessed through appropriate TMS and TES screening forms. Following successful application of the screening protocol informed consent was then sought and obtained. All participants were made aware of their right to withdraw at any time throughout the duration of the study and up until publication of the results. All participants were financially compensated for their time and contribution to the study.

7.3 *Procedure*

7.3.1 Questionnaire Measures

In order to establish participants subjective level of impulsive behaviours two impulsivity questionnaires, the UPPS (Whiteside & Lynam, 2001), and the BIS/BAS (Carver & White, 1994), were employed. Given that impulsive action

frequently occurs in those with neurodevelopmental disorders, such as Autism Spectrum Disorder (ASD), an additional questionnaire that measures autistic traits among the general population, the Autism Quotient (AQ) questionnaire (Baron-Cohen et al., 2001), was included. All questionnaire data was collected and scored prior to the behavourial task commencing.

7.3.2 TMS Procedure

A Magstim Bistim 2^{TM}, with a 70mm figure of eight coil, was used to administer TMS to the left M1 in an area corresponding to the first dorsal interosseous (FDI) muscle of the right hand. Motor hotspot was defined as the coil location that elicited maximal MEP responses in FDI by positioning the TMS coil over each subject' left motor cortex (M1) at approximately 45° (Pascual-Leone et al., 1994). The coil location was continuously tracked throughout the study, via BrainSightTM version 2.0 (Rogue Research Inc. ©, 2016). EMG responses were recorded using BrainVision Recording software at a sampling rate of 5000 Hz and band pass filtered (10-2000 Hz). Disposable Ag-AgCl surface electrodes were placed onto the FDI muscle in a standard 'belly-tendon' configuration.

7.3.3 RMT and IO curves

Following localisation of motor hotspot resting motor threshold (RMT) was then obtained. Each subjects RMT was determined as the minimum TMS intensity needed to elicit an FDI generated MEP of at least 150–200 μV in a minimum of 5 out of 10 trials. TMS intensities administered ranged from 100% - 150% of RMT and delivered in 10% increments resulting in 6 TMS intensities with an inter-trial interval (ITI) of 5s. The IO curve measurements were estimated by

calculating the median intra-individual MEP amplitudes for each of the TMS intensities (i.e., 100–150% of RMT). A linear fit was then applied to the resulting values. Median values were calculated as opposed to the mean to limit the effect of non-standard distribution of individual data.

7.3.4 Paired pulse TMS (SICI, LICI, & ICF)

Paired pulse TMS (ppTMS) was performed at four inters-stimulus intervals (ISIs); 1ms, 3ms (SICI), 12ms (ICF) and 100ms (LICI). For 1 and 3ms SICI the conditioning stimulus (CS) was set as 55% of RMT, ICF at 75%, and LICI at RMT. The test stimulus was set at SI 1mV for all conditions (20 trials per stimulus condition). There were 60 unconditioned stimuli (total 140 trials). All conditions were delivered in a pseudo-randomised order with an ITI of 6s. Paired pulse TMS measures were reported at a ratio to unconditioned responses (e.g. conditioned MEP/unconditioned MEP).

7.3.5 Drag-racing task procedure

The same modified version of Heyes et al., (2012) traffic light task that was used in chapter 6, was employed again in this study. However, directly following TMS procedures the participants completed the drag-racing task twice. Participants' completed 3 blocks of 50 trials (total 150 trials) each time. The study was described as a car racing game in which the participant (e.g. the red car on bottom left of screen) competes against the computer (e.g. the blue car on bottom right of screen). Participants were asked to follow the onscreen instructions. Following the completion of on screen demographic information (e.g. date of birth and gender), participants were instructed to press the space bar as fast as they could when the green light turned on. They were told that

there would be a greater chance to win if they made faster responses. However, they were told that they would lose the trial if they responded too soon (e.g. responding during red or amber onset).

At the end of each trial feedback was presented showing the accumulated scores of the participant and the computer, along with text informing the participant on how they had performed on each trial (e.g. you win, you lose, false start, or too slow). After each block of 50 trials participants were given the option to have a short break. They were instructed to continue when ready by pressing the space bar. The first session of the drag-racing task was played without the application of transcranial electrical stimulation. The second session was played with the application of TES or sham. The experimental setup for the drag-racing task is illustrated in Figure 7.1.

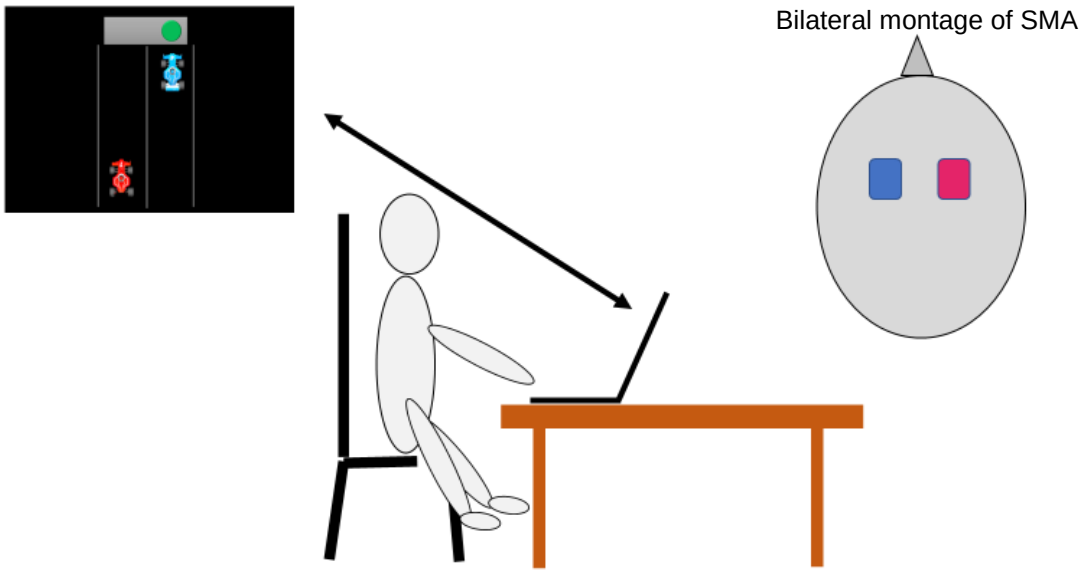


Figure 7-1: Drag-racing task experimental setup with illustrative representation of TES bilateral montage over supplementary motor area. Please note that TES stimulation was only administered during the second session of the drag-racing task.

The task parameters were again chosen in a similar way to Heyes et al. (2012) as they demonstrated that their ‘Traffic Light’ task could successfully encourage participants to make rapid anticipatory responses by providing time-sensitive rewards. The duration of the red-light presentation was 1 second, whereas the duration of the amber-light was randomly decided on each trial via a Gaussian distribution, with a mean of 750 ms and SD 125 ms. While Heyes et al. (2012) provided the reward in hypothetical money, the feedback in this study was calculated as binary results (e.g. win or lose).

On each trial the chance for the participant to win was decided by an inverse exponential temporal discount function; chance to win = 1/exp(RT*2) (figure 7.2). If the participant responded within 1 second from the onset of the green light, the results (e.g win or lose) were decided according to the chance level at the reaction time (RT) of the trial. If the participant did not respond within 1 s from the onset of the green light he/she would lose that trial. There were 150 trials in total for each session. The task was programmed and run using Matlab 2010b with Psychtoolbox on a 13-inch Macbook computer.

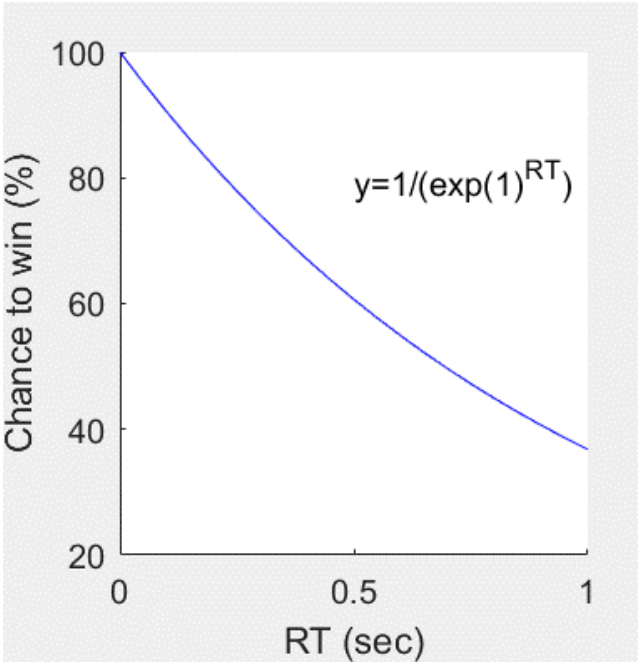


Figure 7-2: Graphical representation of the exponential temporal discount function used to determine the chance to win.

7.3.6 Transcranial Electrical Stimulation (TES)

The drag-racing study utilised three separate TES techniques, tDCS, tRNS and sham. Participants were randomly assigned to one of the three TES conditions. Stimulation was administered during the second session of the drag-racing task only. Counterbalancing was not possible due to the carry over effects of electrical stimulation. TES was administered via a NeuroConn DC-stimulator plus (GmbH, Ilmenau, Germany). Stimulation was administered via two rubber electrodes each measuring 35cm^2. Each electrode was contained within a sponge applicator, which was saturated in saline solution (concentration 0.9% sodium chloride (NaCI) to water)

The anodal and cathodal electrodes were positioned bilateral to the supplementary motor area (SMA) as determined by the electroencephalography

(EEG) 10-20 system (figure 7.1). The EEG 10-20 system locates SMA as 15% of the distance between nasion to inion, from preauricular to preauricular, anterior to Cz (Jurcak, Tsuzuki, & Dan, 2007). The decision to place the electrodes bilateral to SMA was determined by issues relating to the forward problem. The forward problem generally occurs as a result of standard bipolar electrode montage placement. This is because a standard bipolar placement montage typically induces widespread current flow fields, which subsequently results in the strongest field intensities being located in non-targeted brain regions (Wolters, 2017).

Therefore, the electrode placement used for chapter 4's study may not have been optimal. Specifically, the current placement may have been anterior to the SMA, or possibly even over the pre-SMA. In order to determine the best montage for optimal stimulation to the SMA a modelling algorithm known as COMETS was utilised. COMETS (Computation of Electric field due to Transcranial current Stimulation) was developed as a MATLAB-based toolbox by Jung, Kim, & Im, (2013). COMETS is a three-dimensional (3D) algorithm used for simulating local electric fields generated by tDCS (Jung et al., 2013). Jung et al (2013) states that the numerical computation of electric fields generated by tDCS has broadened understanding regarding the underlying mechanisms of electrical current conduction and as such, accelerated the development of novel electrode montages. It has also enabled researchers to facilitate far more accurate field concentrations to targeted brain regions (Jung et al., 2013; Kim et al., 2014).

According to Jung and colleagues COMETS incorporates a simple interactive graphical user interface, which allows its users to easily simulate various

electrode configurations, electrode sizes, and orientations. Moreover, COMETS does all of this without the need for additional MATLAB scripts (Jung et al., 2013). Jung et al., (2013) COMETS algorithm can evaluate 3D cortical current distributions and is primarily based upon the electrostatic finite element method (FEM). Thus, COMETS was used in the current study to run a simulation based on the previous TES parameters utilised in chapter 4. As suspected, the results of the simulation identified issues with the previous placement insofar as, while it located the anode over the SMA, the model suggests that the current distribution was located much further forward of SMA (figure 7.3).

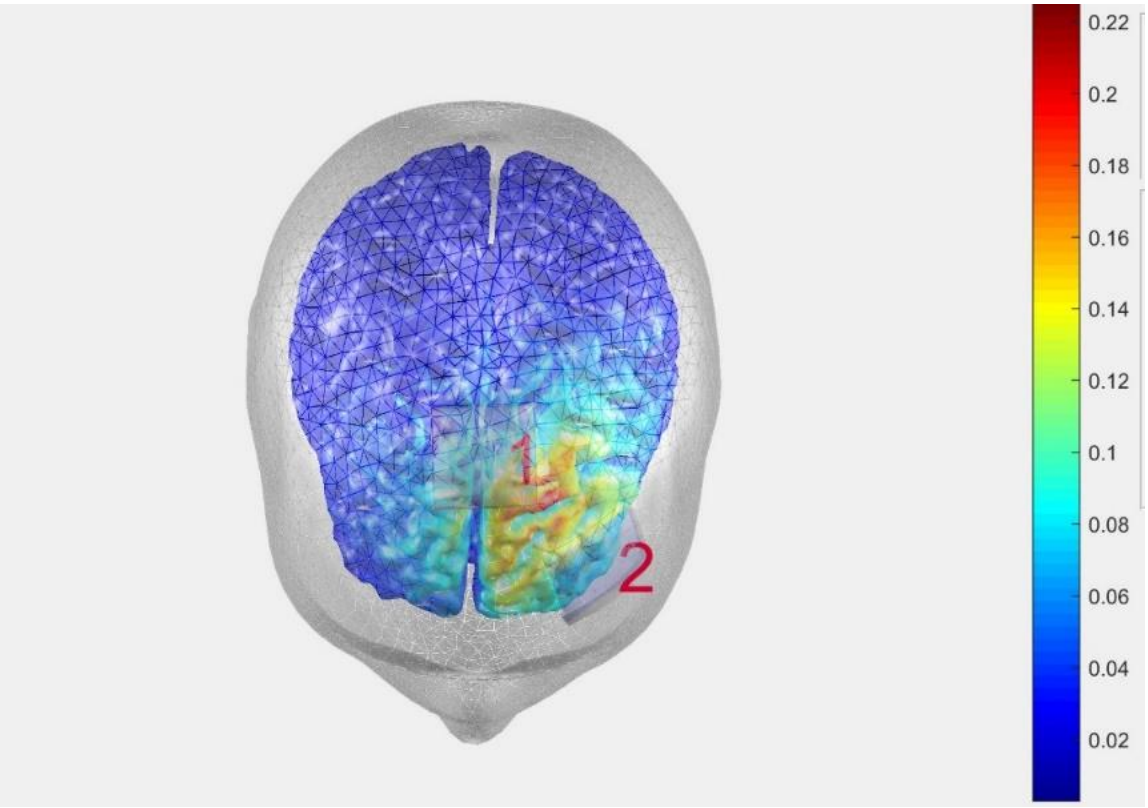


Figure 7-3: COMETS simulation of TES orbitofrontal montage showing optimal current flow forward of the SMA. Position 1 depicts anodal electrode positioned over SMA region. Position 2 depicts cathodal electrode positioned over orbitofrontal region according to the EEG 10,20 system.

Further modelling parameters were entered into the COMETS algorithm which suggested the optimal position of the electrodes would be bilateral to (e.g. either side of) the SMA. The model suggested that there would be no forward problem as the current would be maximal between the two electrodes (figure 7.4).

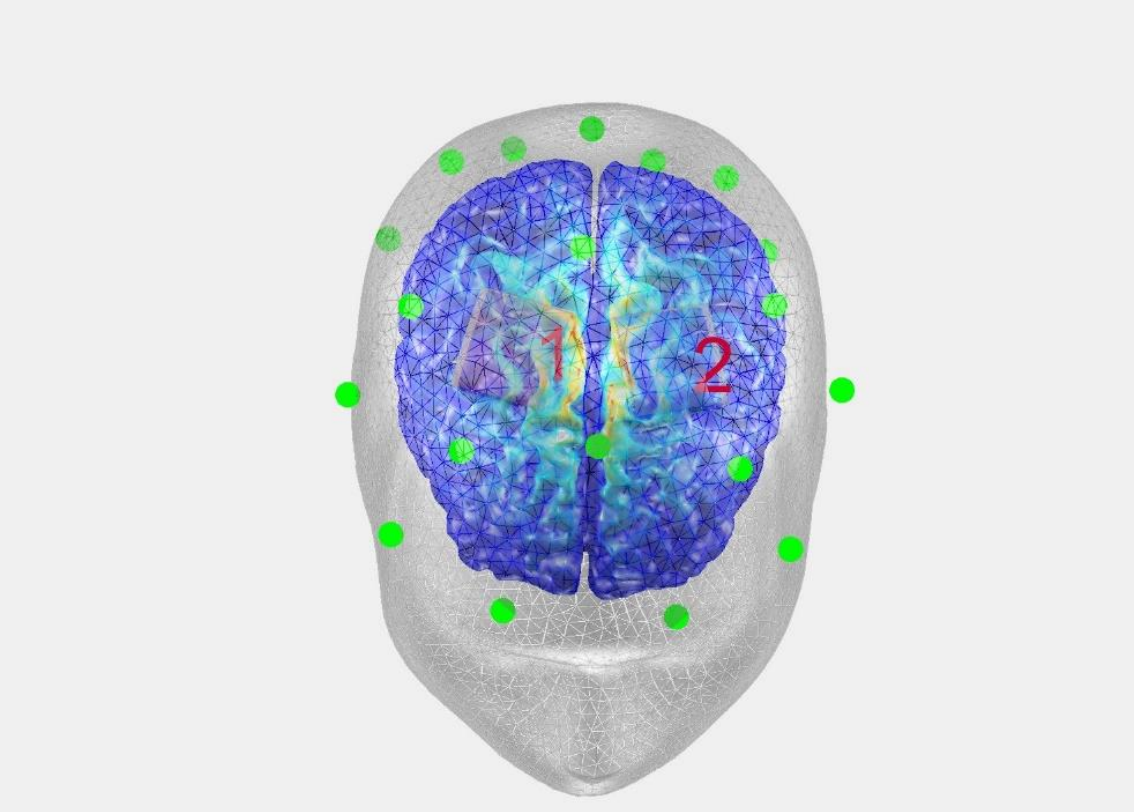


Figure 7-4: COMETS simulation of TES bilateral montage showing optimal current flow to the SMA. Position 1 depicts anodal electrode positioned rightwards of the SMA region. Position 2 depicts cathodal electrode positioned leftwards of the SMA region. The EEG 10/20 system was used to map the area corresponding to the SMA region (e.g. green dots).

The position of each electrode was maintained by using cobalt self-adhering bandage. Anodal tDCS was delivered at a constant stimulation output of 2mA for 20 minutes with a ramp up & ramp down of 15 seconds. The tRNS stimulation was administered at a HF noise mode at 2mA, with the offset set to zero. For sham an identical set-up to that used for tDCS was used but the current was applied for 15 seconds with a ramp up & down of 15 seconds.

7.4 *Analysis*

Reaction time (RT) was measured from the onset of the green light in the same way as in the previous chapter. If the participant responded prior to the onset of the green light then the RT was measured as a negative value. The trials in which the participant did not respond within 1 s from the green onset (e.g. too slow), were excluded from the analysis. As a result, less than 1% of the total 150 trials were excluded for each participant on average. The ratio of the negative RT trials and the ratio of win trials were then calculated for each ot the participants.

As discussed earlier, responses in the drag-racing task can be triggered by two different cognitive processes. The first process is the anticipatory response which is initiated prior to the green light onset, and secondly, the reactive response which is triggered by the green light onset (Reddi & Carpenter, 2000). Again a two-horse linear rise-to-threshold model (Adam et al., 2012; Heyes et al., 2012) was applied to RT distributions to model these two processes. RT distributions were probabilistically assigned to populations elicited from an anticipatory and reactive decision making process according to the cumulative probability distribution equation from Heyes et al. (2012). Four parameters of mean and SD of the distribution of anticipatory responses (i.e. μ_a and σ_a) and reactive processes (i.e. μ_r and σ_r) were fitted to this model for each individual's RT distributions using maximum likelihood function (figure 7.5).

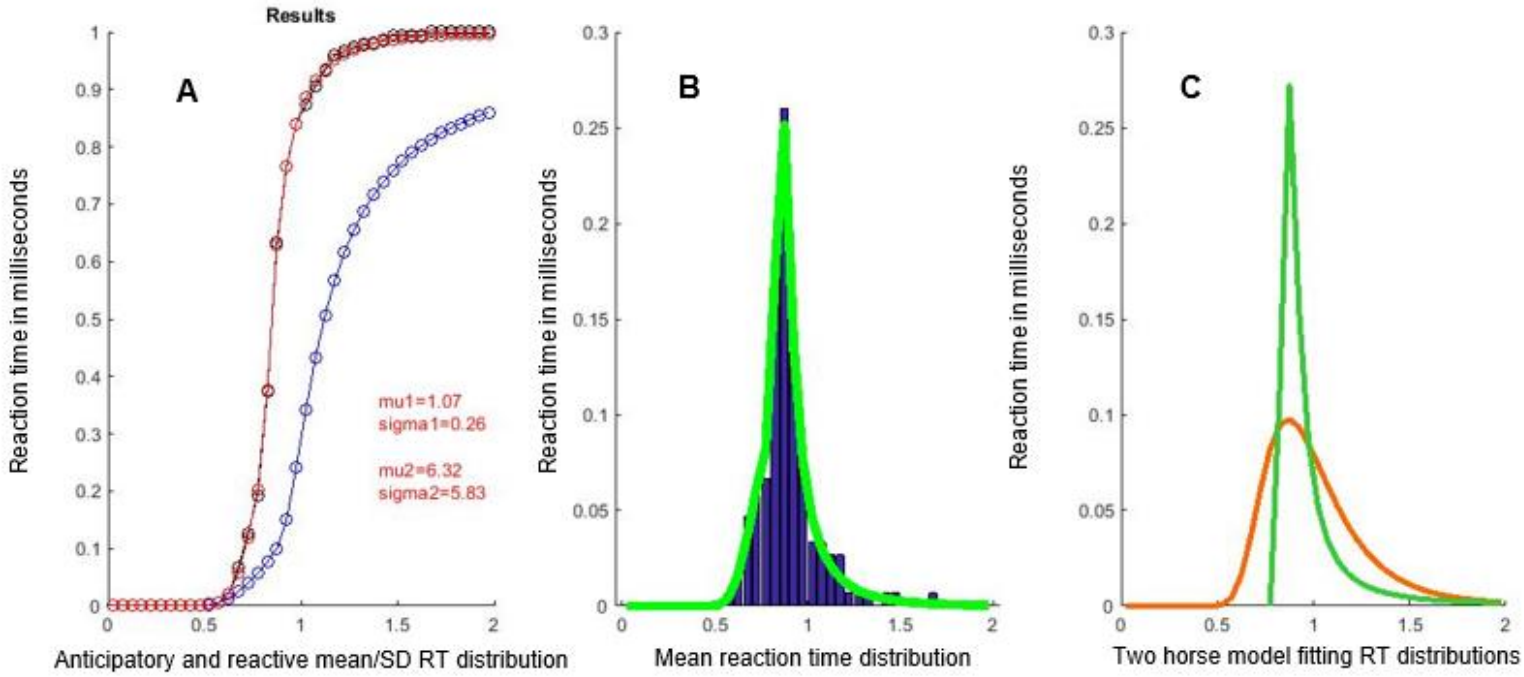


Figure 7-5: Graphical representations depicting one adult participant's reaction time distributions and results of the two-horse model fitting. A: shows mean and standard deviations for anticipatory (mu1, SD1) and reactive (mu2, SD2) responses. B: shows the RT distribution. C: shows the results of the two-horse model fitting – red line corresponds to anticipatory responses, while the green line corresponds to the reactive responses.

All the data analyses were conducted using Matlab 2018a. Various within subject statistical analyses were performed to investigate the relationship between individuals' performances in the drag-racing task, their physiological measures of excitability and inhibtion, scores on the autism quotient, and the result from the questionnaire measures of impulsivity (e.g. BIS-BAS, and UPPS). Futher between groups analyses were conducted to determine if performance on the drag-racing task could be altered via transcranial electrical stimulation (TES) to the supplementary motor area (SMA).

7.4.1 EMG pre-processing

All EMG signals recorded during the single and paired pulse TMS procedures were analysed using EEGLAB via MATLAB. Peak-to-peak amplitudes of the MEPs were measured for each individual trial. Data for each of these trials was also inspected visually to check for contaminated electrical activity, all contaminated trials were excluded from analysis. Less than 5% of trials were excluded in any given individual dataset.

7.5 *Results*

7.5.1 TMS corticospinal excitability IO Data

MEP amplitudes for each individual subject were mapped to show his or her individual CSE IO curves. These were then combined to show the overall spread of the MEP data for all 36 subjects (see figure 7.6). Both RMT and input/output (IO) slopes were found to be normally distributed (RMT: Mean=45.03, SD=9.36; & IO: Mean=59.72, SD=56.48). Finally, a repeated measures ANOVA, of MEPs at each TMS intensity level, was then conducted in

IBM SPSS version 22. Results revealed a significant effect of TMS intensity on MEP response f (5, 216) = 13.27, p<.001.

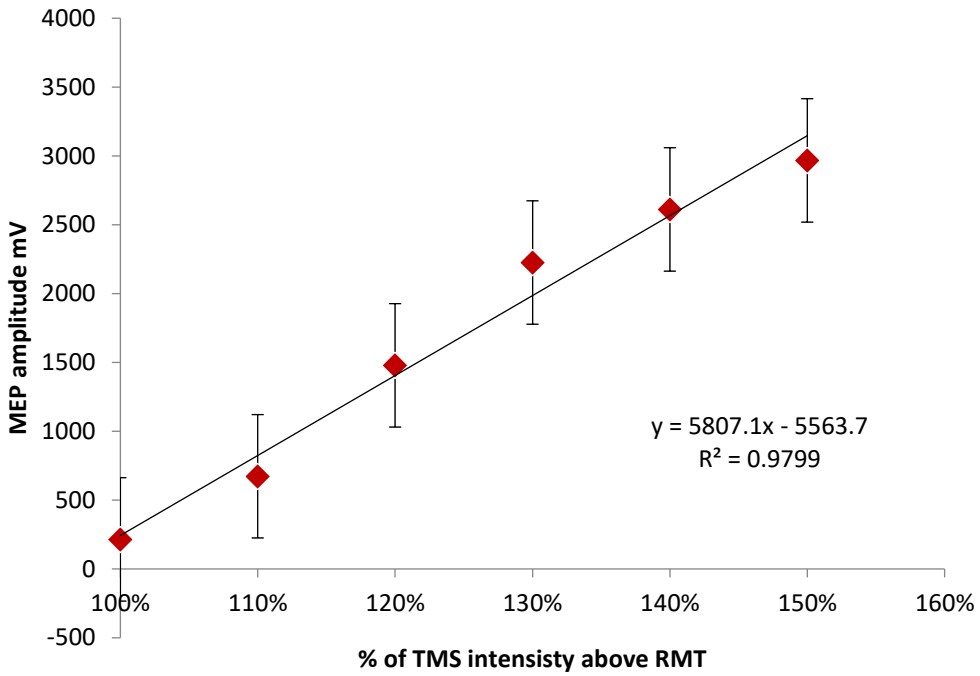


Figure 7-6: Graph showing data (N=36) of TMS recruitment curves (means of individuals' median MEP values, measured in microvolts) for each TMS stimulated output intensity, as a % of each individuals' RMT.

7.6 *Behavioural Learning Effects*

In order to establish if there were any learning effects across testing sessions the datafile was split across TES groups, sham, tDCS, and tRNS and examined. Given that tDCS and tRNS have the capacity to influence the behavioural outcomes of the task, only the sham group was explored for potential learning effects. Paired samples t-tests, whereby both model free and two-horse modelled performance on the drag-racing task were compared for both session one and session two, were conducted. Results demonstrated that there was a significant difference in the model free ratio number of lose trials for

session one (M=.63, SD=.024), and the ratio number of lose trials for session two (M=.60, SD=.037) t(-2.45), df=11, p=0.03. There were no significant differences between the model free ratio number of win or false-start trials between session one and two, all p=>0.05. Similarly, there were no significant differences between the modelled anticipatory or reactive responses between session one and two of the drag-racing task, all p=>0.05.

7.7 *Model Free Analyses: Pre-stimulation session 1 - Relationship between physiological and questionnaire measures on model free performance in the drag-racing task*

7.7.1.1 Ratio Number of Win trials

In order to establish whether individual differences in measures of cortical motor excitability and/or physiological inhibition, along with questionnaire measures of impulsivity and autism traits, were related to individual variability, prior to stimulation or modelling analysis, on the performance on the drag-racing task, a number of stepwise regression analyses were performed. Firstly, stepwise regression analysis of the ratio number of win trials accumulated during session one of the drag-racing task yielded no significant results.

7.7.1.2 Ratio Number of Lose trials

Further stepwise regression analysis of the ratio number of lose trials accumulated during session one of the drag-racing task demonstrated that a model based on two factors; the impulsivity construct ‘lack of premeditation’ from the UPPS impulsivity questionnaire and 3ms SICI could significantly

predict and account for 38% of the variability observed (p=<0.001, adjusted-R^2=0.38). The order of entry into the model for these factors was as follows; UPPS lack of premeditation (coefficient=0.003, t-statistic=-4.82, p=<0.001, F=11.80, adjusted-R^2=0.32); and 3ms SICI (coefficient=0.003, t-statistic=2.159, F=11.80, adjusted-R^2=0.38).

7.7.1.3 Ratio Number of False-Start trials

Final stepwise regression analysis of the ratio number of false-start trials accumulated during session one of the drag-racing task demonstrated that a model based on four factors; Slope, BAS Drive, UPPS lack of perseverance, and negative urgency, could significantly predict and account for 47% of the individual variability observed (p=<0.001, adjusted-R^2=0.52). The order of entry into the model for these factors was as follows; Slope (coefficient=0.0005, t-statistic=3.91, p=<0.001, F=15.32, adjusted-R^2=0.29); BAS drive (coefficient=-0.01, t-statistic=-2.60, p=0.01; F=12.35, adjusted-R^2=0.39); UPPS lack of perseverance (coefficient=-0.003, t-statistic=2.33, p=0.002; F=11.15, adjusted-R^2=0.47) and finally UPPS negative urgency score (coefficient=-0.002, t-statistic=-2.10, p=<0.04; F=10.37, adjusted-R^2=0.52).

7.7.2 IO slope

To further establish what influence cortical excitability, as measured by the TMS recruitment curve (IO slope), on pre-modelled early response performance during session one (no-stimulation condition) of the drag-racing task, further Bayesian statistical analysis was conducted. Results of this further analysis suggests that higher cortical excitability, as measured by the TMS recruitment curve (IO slope), very strongly predicts the probability of a greater number of

false starts in the baseline no stimulation condition BF_{10} 75.136, (H0 is the null hypothesis) (figure 7.7).

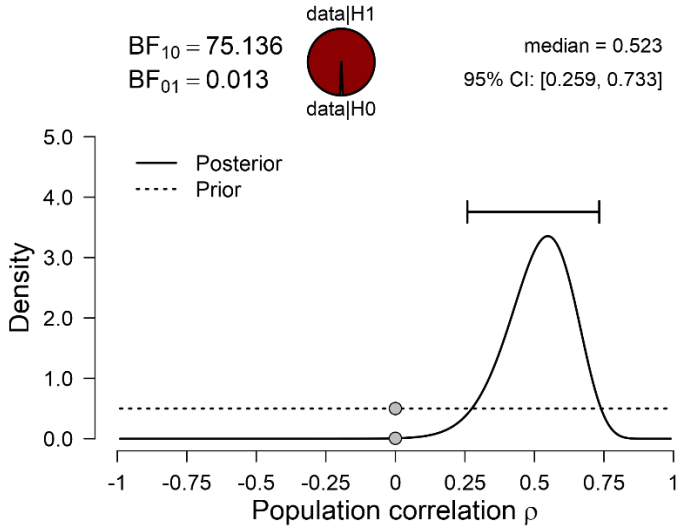


Figure 7-7: Bayesian analysis depicting the influence of the cortical excitability (IO slope) on the occurrence of false starts in the pre-stimulation session of the drag-racing task. Please note the red shaded area represents support for the alternative hypothesis.

7.7.3 Pre-stimulation: Correlation analyses of TMS physiological measures and questionnaire scores

In order to determine whether there are any significant relationships between questionnaire measures of impulsivity, autistic traits, and physiological measures of cortical excitability and inhibition further Pearson's correlation analyses were performed.

7.7.3.1 RMT

Pearson's correlation analyses demonstrated a significant positive correlation between RMT and scores on the autism quotient questionnaire only t=2.473, df (34), r =.39, p = $\leq$ .001 (figure 7.8).

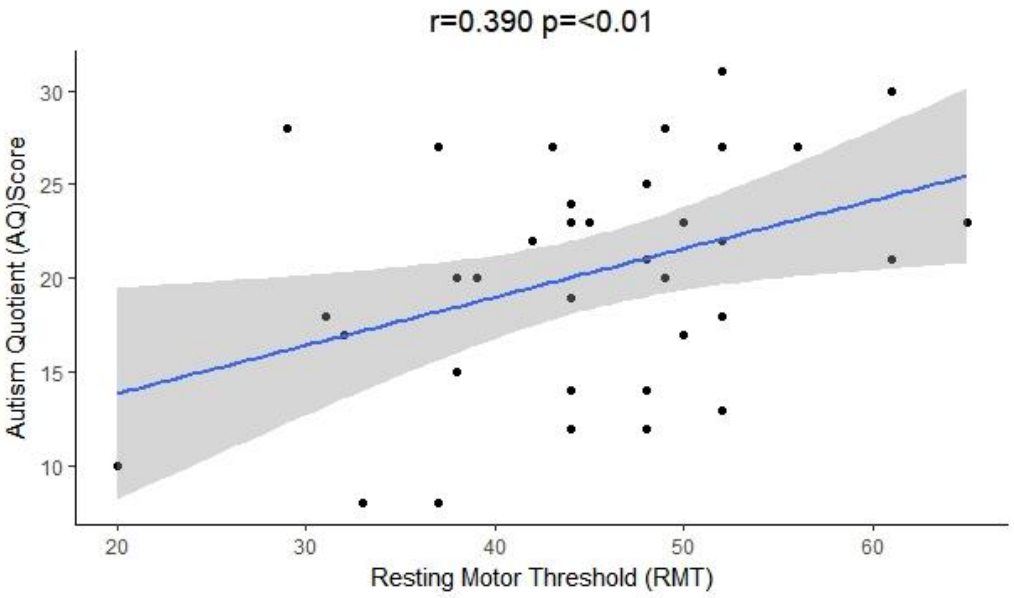


Figure 7-8: Relationship between RMT and scores on the Autism quotient questionnaire.

Further Bayesian statistical analysis was conducted to test the strength of this effect. Results suggests that higher resting motor thresholds (RMT) moderately predict the probability of higher scores on the autism quotient questionnaire BF_{10} 2.981, (H0 is the null hypothesis) (figure 7.9).

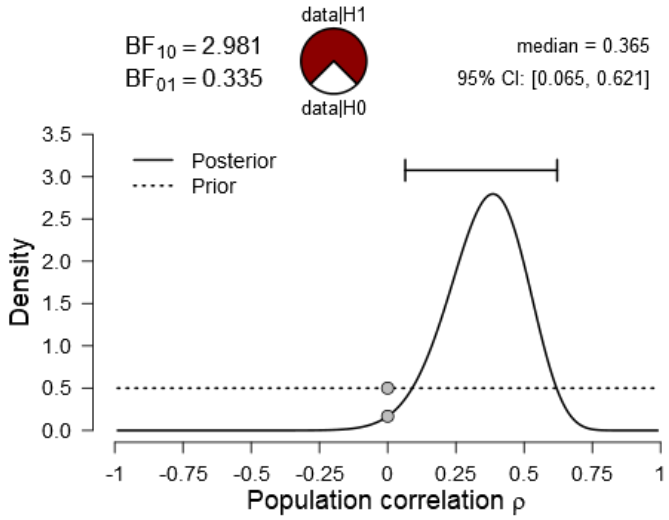


Figure 7-9: Bayesian analysis depicting the strength of the relationship between RMT and scores on the Autism Quotient (AQ) questionnaire. Please note the red shaded area represents support for the alternative hypothesis, and white the null hypothesis.

There were no significant correlations between RMT and any of the questionnaire measures of impulsivity, all p=>0.05.

7.7.3.2 Slope

There were no significant correlations between the slope of the TMS recruitment curve (IO slope) and any of the questionnaire measures of impulsivity, all p=>0.05. However, a relationship between IO slope and scores on the autism quotient (AQ) questionnaire was approaching significance p=0.06.

7.7.3.3 1 millisecond SICI

Pearson's correlation analyses demonstrated significant positive correlations between 1ms SICI and the BAS Drive construct from the BIS-BAS impulsivity questionnaire t(2.807), df=34, r=.43, p=0.008, and 1ms SICI and BIS-BAS total scores t(2.966), df=34, r=.45, p=0.005 (figure 7.10).

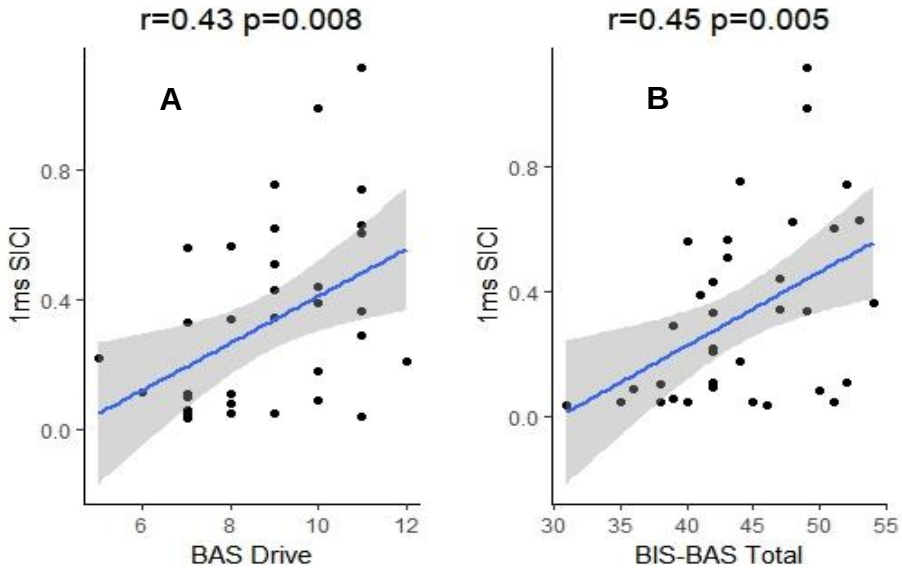


Figure 7-10: A. Positive relationship between 1ms SICI and BAS drive score on the BIS-BAS questionnaire of impulsivity. B. Relationship between 1ms SICI and BIS-BAS questionnaire total scores.

Further Bayesian statistical analysis was conducted to test the strength of these effects. Results suggests that 1ms SICI moderately predicts the probability of higher scores on the BAS drive construct of the BIS-BAS impulsivity questionnaire BF_{10} 2.981. In addition, 1ms SICI strongly predicts the probability of higher total scores on the BIS-BAS impulsivity questionnaire (figure 7.11).

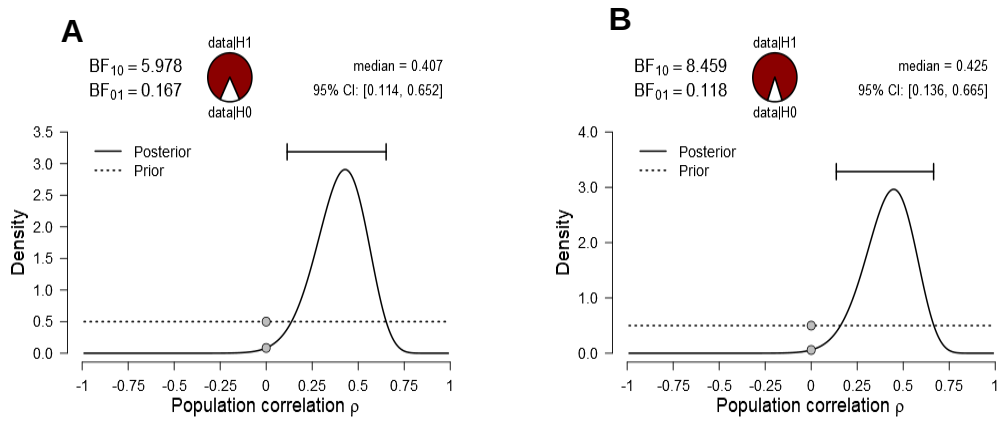


Figure 7-11: A. Bayesian analysis depicting the strength of the relationship between 1ms SICI and BAS Drive scores on the BIS-BAS impulsivity questionnaire. B. Bayesian analysis depicting the strength of the relationship between 1ms SICI and BIS-BAS Total scores on the BIS-BAS impulsivity questionnaire. Please note the red shaded area represents support for the alternative hypothesis, and white the null hypothesis.

7.7.3.4 3 millisecond SICI

Pearson's correlation analyses also demonstrated significant positive correlations between 3ms SICI and two separate constructs from the BIS-BAS impulsivity questionnaire as follows; 3ms SICI and BAS fun seeking scores t(3.582), df=34, r=52, p=0.001, and 3ms SICI and BAS Drive scores t(2.507),the BAS Drive df=34, r=.40, p=0.01. There was also a significant positive correlation between 3ms SICI and the lack of premeditation construct of the UPPS impulsivity questionnaire t(2.0961), df=34, r=34, p=0.04. Conversely,

there was a significant negative correlation between 3ms SICI and scores on the AQ t(-2.495), df=34, r=-.39, p=0.01 (figure 7.12).

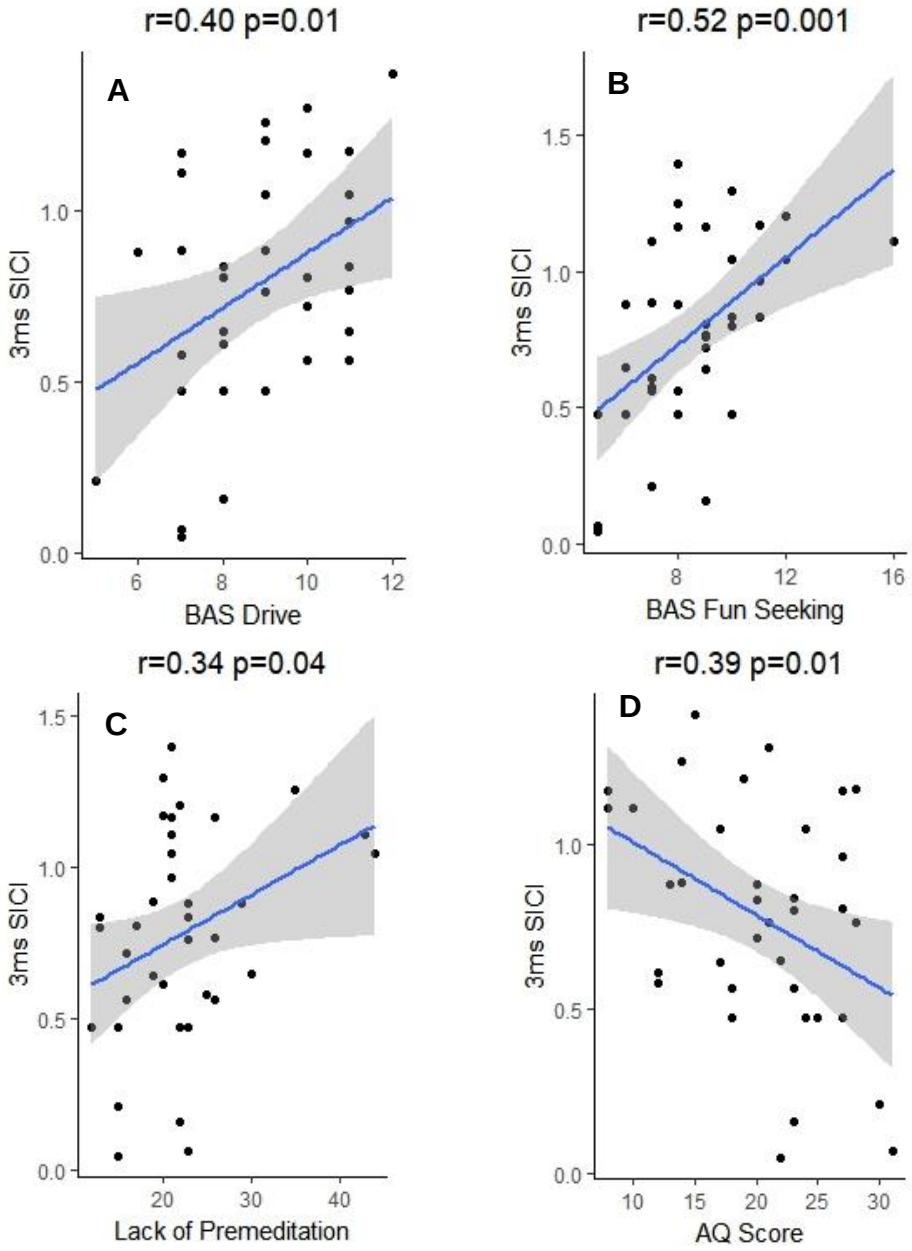


Figure 7-12: A. Positive relationship between 3ms SICI and BAS drive score on the BIS-BAS questionnaire of impulsivity. B. Positive Relationship between 3ms SICI and BAS Fun Seeking element of the BIS-BAS impulsivity questionnaire. C. Positive Relationship between 3ms SICI and the Lack of premeditation element of the UPPS impulsivity questionnaire. D. Negative Relationship between 3ms SICI and scores on the Autism Quotient (AQ) questionnaire.

Further Bayesian statistical analysis was conducted to test the strength of these effects. Results suggests that 3ms SICI only moderately predicts the probability of higher scores on the BAS Drive construct of the BIS-BAS impulsivity questionnaire BF_{10} 3.194 (figure 7:13A). Bayesian analysis suggests that 3ms SICI very strongly predicts scores on the Fun Seeking construct of the BIS-BAS impulsivity questionnaire BF_{10}=36.054 (7:13B). In contrast, Bayesian analysis suggests only anecdotal evidence for a relationship between the lack of premeditation construct on the UPPS impulsivity questionnaire BF_{10}=1.470 (figure 7:13C). Finally, Bayesian analysis suggests that 3ms SICI moderately predicts scores on the AQ questionnaire BF_{10}=3.199 (figure 7:13D).

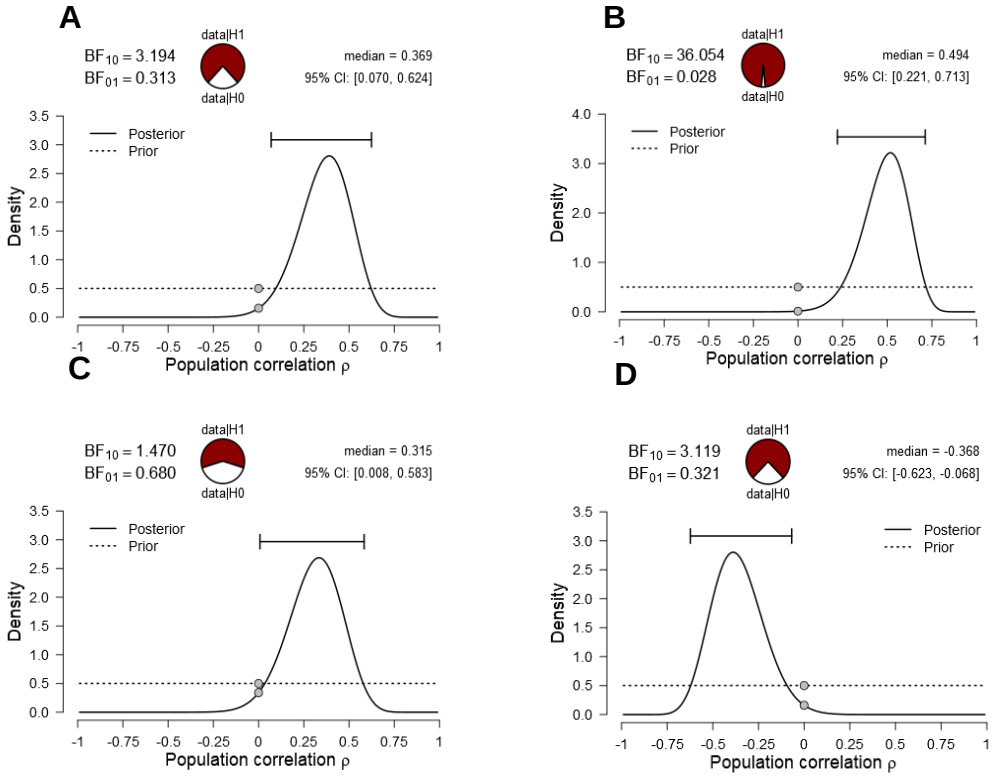


Figure 7-13: A. Bayesian analysis depicting the strength of the relationship between 3ms SICI and BAS Drive scores on the BIS-BAS impulsivity questionnaire. B. Bayesian analysis depicting the strength of the relationship between 3ms SICI and BAS Fun Seeking scores on the BIS-BAS impulsivity questionnaire. C. Bayesian analysis depicting the strength of the relationship between 3ms SICI and the Lack of Premeditation scores on the UPPS impulsivity questionnaire. D. Bayesian analysis depicting the strength of the relationship between 3ms SICI and scores on the Autism Quotient (AQ) questionnaire. Please note the red shaded area represents support for the alternative hypothesis, and white the null hypothesis.

7.7.3.5 12ms ICF & 100ms LICI

There were no significant correlations between 12ms ICF, nor between 100ms LICI, and any of the questionnaire measures of impulsivity or Autism Quotient questionnaires, all p=>0.05.

7.8 *Model Free performance with non-invasive electrical stimulation*

7.8.1 Stimulation: Effects of excitatory non-invasive brain electrical stimulation on performance on the drag-racing task

Students' t-tests were conducted in order to examine the effects of non-invasive brain stimulation (TES) on the pre-modelled performances on the drag racing task.

7.8.1.1 Sham Stimulation effects on pre-modelled performance

Analyses revealed significant differences between the ratio number of lose trials for session one (no stimulation condition) M=.63, SD=.024, and session two (stimulation condition) M=.60, SD=.037, t=(2.454), df(11), p=0.03, for the sham condition. In contrast, there were no significant differences between the ratio number of win trials for session one M=.28, SD=.033, and session two M=.32, SD=.060, t=(-1.955) df(11), p=0.07, nor between the ratio number of false starts for session one M=.08, SD=.073, and session two M=.07, SD=.064, t(.976), df(11), p=0.35, for the sham condition.

7.8.1.2 tDCS Stimulation effects on pre-modelled performance

Analyses revealed no significant differences between the ratio number of win, lose, or false-start trials, for performances achieved during session one and two of the tDCS condition all p=>0.05.

7.8.1.3 tRNS Stimulation effects on pre-modelled performance.

Similarly, analyses revealed no significant differences between the ratio number of win, lose, or false-start trials, for performances achieved during session one and two of the tRNS condition all p=>0.05.

7.9 *Two-horse Model Analyses*

7.9.1 Pre-Stimulation: Effects of motor cortex excitability and inhibition on modelled performance in the drag-racing task

In order to establish whether individual differences in measures of cortical motor excitability and/or physiological inhibition could predict individual variability on the two-horse modelled performance on the drag-racing task, separate stepwise regression analyses of the number of anticipatory and reactive responses during session one (no stimulation condition) were conducted.

Stepwise regression analyses demonstrated that none of the TMS physiological measures of excitation or inhibition could predict anticipatory responses in the pre-stimulation session of the drag-racing task. Similarly, stepwise regression analyses again demonstrated that none of the TMS physiological measures of excitation or inhibition could predict reactive responses during session one (pre-stimulation) of the drag-racing task.

7.9.2 Pre-stimulation: Two-horse model correlation analyses of performance on drag-racing task and questionnaire measures

7.9.2.1 Questionnaire measures of Impulsivity

Pearson's correlation analyses demonstrated no significant correlations between anticipatory performance on the drag-racing task and questionnaire measures of impulsivity. Similarly, there were no significant correlations between reactive performance on the drag-racing task and questionnaire measures of impulsivity.

7.9.2.2 Autism Quotient (AQ) Scores

Pearson's correlation analyses demonstrated no significant correlations between anticipatory performance on the drag-racing task and scores on the Autism Quotient (AQ) questionnaire. Similarly, there were no significant correlations between reactive performance on the drag-racing task and scores on the AQ questionnaire.

7.10 *Stimulation: Effects of excitatory non-invasive brain electrical stimulation on modelled performance on the drag-racing task*

Students' t.tests were conducted in order to examine the effects of non-invasive brain stimulation (TES) on the modelled performances during the drag racing task.

7.10.1.1 Sham Stimulation effects on modelled performance

Analyses revealed no significant differences between mean reaction times for anticipatory responses for session one (no stimulation condition) M=1.06, SD=.086, and session two (stimulation condition) M=1.07, SD=.037, t=(-.149), df(11), p=0.88, for the sham condition. There was also no significant difference between mean reaction times for reactive responses for session one M=3.22, SD=.657, and session two M=3.11, SD=.840, t=(.561) df(11), p=0.58, in the sham condition.

7.10.1.2 tDCS Stimulation effects on modelled performance

Analyses revealed significant differences between mean reaction times for anticipatory responses during session one (no stimulation condition) M=1.04, SD=.095, and session two (stimulation condition) M=1.08, SD=.037, t=(-2.697), df(11), p=0.02, for the tDCS condition. In contrast, there was no significant difference between mean reaction times for reactive responses for session one M=-10.6, SD=34.17, and session two M=3.39, SD=1.31, t=(.561) df(11), p=0.18, in the tDCS condition.

7.10.1.3 tRNS Stimulation effects on pre-modelled performance.

Analyses revealed no significant differences between mean reaction times for anticipatory responses for session one (no stimulation condition) M=1.07, SD=.077, and session two (stimulation condition) M=1.06, SD=.090, t=(.180), df(11), p=0.86, for the tRNS condition. There was also no significant difference between mean reaction times for reactive responses for session one M=2.72, SD=.609, and session two M=3.09, SD=.1.68, t=(-.718) df(11), p=0.48, in the tRNS condition.

7.11 *Discussion*

The neural correlates of impulsive decision-making, while under time constraints, was investigated using a mixed methods design. A combination of non-invasive brain stimulation techniques, questionnaire measures, and our modified version of the drag-racing task were used in this study. The primary aim of this chapter was to examine whether automatic impulsive action could be accurately predicted by any of the measures employed. In the current study, the hypothesis that automatic impulsive action might be associated with motor excitability and inhibition was investigated. The administration and effects of excitatory non-invasive brain stimulation (A-tDCS and tRNS v Sham) to the supplementary motor area (SMA) was also examined. The SMA is a cortical brain area thought to be associated with the volitional control of action (Bonini et al., 2014; Cunnington, Windischberger, & Moser, 2005; Tanji, 1994), and effector-specific control of motor outputs at a subconscious level (Sumner et al., 2007). Therefore, it seemed feasible that active stimulation to the SMA could possibly alter performance on the drag-racing task.

In addition, further evidence was sought for this proposal via two TMS protocols, namely single- and paired pulse-TMS respectively. This protocol was administered in order to ascertain whether individual differences in baseline measurements of motor cortical excitability and physiological inhibition were associated with automatic impulsive action while under time pressure. Prior to the commencement of the drag-racing experiment, TMS measurements of cortical excitability and physiological inhibition were recorded from the left primary motor cortex (M1) of each participant. Subsequently, these measurements were used to predict participants' impulsive action on the drag-

racing task. However, please note that it is not currently possible to measure cortical excitability and physiological inhibition from the SMA directly (further discussion on this point is highlighted in chapter 4).

7.11.1 Physiological task results

The physiological sp-TMS paradigm yielded significant results, which demonstrates that the method was highly effective. This protocol clearly showed that as TMS intensity increased, there was a significant increase in the MEP amplitudes observed. This result indicates a corresponding rise in neuronal recruitment. This finding was consistently seen across all participants in the study regardless of their starting RMT level (RMT range 20-65).

7.11.2 Learning effects

Learning effects across model free and two-horse model performance during drag-racing testing sessions were explored. Results of this analysis demonstrated that only the ratio number of lost trials were significantly reduced across testing sessions. This finding would suggest that participants showed some degree of learning, which subsequently enabled them to reduce the number of lost trials in the second testing session. However, there were no significant differences in the ratio number or win, or false-start trials, across testing sessions. This would suggest that learning only occurred in one domain of the model free performance on the drag-racing task, namely the ratio number of lost trials. Similarly, there were no significant differences in the two-horse modelled mean reaction times for anticipatory and reactive responses across testing sessions. This could indicate that modelled performance, and as such impulsive action, on the drag-racing task remains consistent across time.

Similar results were yielded by Heyes et al (2012) in their traffic light task. Heye's and colleagues (2012) argued that this reflects stable individual differences in strategy, which is present from the outset (e.g. participants inclination to take risks and anticipate the green-light onset).

7.11.3 Relationship between physiological and questionnaire measures of impulsivity on model-free performance in the drag-racing task

To further explore the idea that automatic impulsive action might be associated with individual variability in motor cortex excitability, several single and paired-pulse TMS protocols were employed. This allowed measures of cortical excitability and physiological inhibition within the primary motor cortex (M1) of the left hemisphere (contralateral to the dominant right hand) for each participant to be obtained. Additional physiological measures in this study were, 1 & 3ms SICI, 12ms ICF, and 100ms LICI (see methods). Questionnaire measures of participants' subjective ratings on both impulsivity and autistic traits were also measured. Significant associations between model-free performance on the drag-racing task and several physiological effects of cortical excitability and inhibition, and questionnaire measures of impulsivity and autistic traits, were observed.

7.11.3.1 Ratio Number of Win Trials

Firstly, no measures were found to significantly predict the ratio number of win trials, accumulated during session one of the drag-racing task.

7.11.3.2 Ratio Number of Lose Trials

However, there were two measures that predicted the ratio number of lost trials in the drag-racing task, namely the UPPS lack of premeditation construct and 3ms SICI. The UPPS lack of premeditation could predict and account for 29% of the variance observed. Lack of premeditation is said to reflect an individual's inability to think and reflect on the consequences of an act before engaging in that act (Whiteside & Lynam, 2001). Further analysis revealed a significant negative correlation between the number of lost trials and lack of premeditation scores. Those who scored lower on this construct incurred far more lost trials. This is not unexpected given that a large proportion of the lost trials in this study reflect a tendency towards longer reaction times. Similar results were found in a study by Torres et al., (2013). Torres and colleagues (2013) found that those who scored higher on the lack of premeditation construct had slower responses in their Go/No-go task. Although this result, and those of the current study, appear counterintuitive, previous research has demonstrated that, in speeded decision-making tasks, impulsive behaviour typically interferes with response selection. For instance, earlier research also found that highly impulsive individuals are affected far more by stimulus-response incompatibility, and as a consequence present higher response latencies (Expósito & Andrés-Pueyo, 1997).

The next predictor in the model was 3ms SICI which along with the UPPS lack of premeditation could predict and account for 38% of the variance observed. SICI is a paired-pulse TMS protocol whereby two TMS pulses are delivered in rapid succession (1-5ms ISI) through a single coil. SICI protocols involve a standard supra-threshold TMS pulse preceded by the delivery of a sub-

threshold conditioning pulse. SICI typically leads to a reduction in MEP amplitudes, and as discussed in earlier chapters this is thought to reflect the operation of $GABA_A$ mediated inhibitory interneurons acting upon corticospinal neurons (Ziemann, 2013).

The relationship between 3ms SICI, and the ratio number of lost trials in this research suggests that physiological inhibition is associated with a corresponding increase in the number of lost trials observed. Lost trials in this study reflect longer reaction times and as such a corresponding reduction in impulsive action. This result is consistent with the key role that $GABA_A$ receptor activity, whereby inhibitory mediated pathways are proactively recruited during response certainty, plays in controlling behaviour (Cirillo, Cowie, MacDonald, & Byblow, 2018). Moreover, it is arguably advantageous in many situations to inhibit certain behaviours in order to optimise goal-directed behaviours (Logan et al., 1997).

Logan et al., (1997) state that those deficient in inhibitory processes are profoundly affected in their everyday life. Such deficits are then thought to lead to problems with impulse control, and as such, typically considered detrimental to the individual. As noted earlier, impulsive action has been consistently linked to many types of addiction, neurodevelopmental disorders, and neuropsychiatric conditions (Bari & Robbins, 2013). It would seem therefore that the result from the current study would support the suggestion that greater physiological inhibition helps to facilitate optimal choices and appropriate less risky decision-making.

7.11.3.3 Ratio Number of False-Start Trials

Finally, the measures that were found to significantly predict the ratio number of false-start trials, accumulated during session one of the drag-racing task, were IO slope, BAS drive, UPPS lack of perseverance and negative urgency. These measures could significantly predict and account for 52% of the individual variability observed. The key aim of the drag-racing task is to make rapid impulsive decisions while under time pressure. The false-start trials in this study occurred as a result of responding too early (e.g. responding during the amber phase of the task), and as such are indicative of greater impulsive action that results in a negative outcome. This would suggest that some individuals with higher levels of impulsivity demonstrate faster, non-optimal performance when compared to less impulsive individuals, particularly in instances where only a short time is available for decision-making.

Furthermore, the present study found that TMS measures of motor cortical excitability, specifically the slope of each individual's TMS recruitment curve measure prior to electrical stimulation, was a significant predictor of the number of false-start trials. Further Bayesian analysis demonstrated the robustness of this finding with a Bayes factor in the very strong to extreme range. Given that false-starts are the fastest, and as such the most impulsive, of the overall responses it would seem reasonable to suggest that suboptimal impulsive action is related to individual motor cortex excitability. In support, and as discussed in chapter 4, individual differences in motor cortex excitability are significantly associated with the execution of automatic behaviours, and impulsive action, and are frequently seen in those with neuropsychiatric,

neurodevelopmental, and impulse control disorders (Ganos et al., 2012b; Heyes, 2011).

Moreover, Perdeci, Ozmenler, Dogruer, Ozdag, & Turkbay, (2009) suggest that those with an imbalance in motor cortex excitability typically present with behavioural issues such as impulsive action, reactive aggression, and an inability to control behaviour. In contrast, Jentsch & Taylor, (1999) suggest that in higher mammals who have the ability to exert inhibitory control over conditioned response and automatic reflexes have evolved the ability to also slow down cognitive processes. Moreover, this slowing of cognition is thought to guide behaviours in specific circumstances (Jentsch & Taylor, 1999). Thus, it seems that behavioural expression of impulsive action is more likely to occur in those with an imbalance in their cortical excitability and inhibitory pathways.

In addition to the physiological measure, three separate self-report measures of impulsivity were also found to significantly predict the number of false-start trials, namely BAS drive, UPPS lack of perseverance and negative urgency. BAS drive typically measures an individual's impulsive tendency towards actively pursuing rewards (Carver & White, 1994). In addition, the UPPS lack of perseverance reflects an individual’s inability to remain focused on a task, while negative urgency refers to the tendency to experience strong impulses under conditions of negative affect (Whiteside & Lynam, 2001). Higher scores on these subscales indicate a higher level of self-reported impulsivity. In order to obtain a greater ratio of win trials on the drag-racing task participants had to make automatic risky decisions while under time pressure. Therefore, a higher number of false-starts would appear to suggest that BAS drive, UPPS lack of perseverance, and negative urgency, coupled with physiological measures of

excitability, accurately reflect a general tendency toward non-optimal risk-taking behaviours.

7.11.4 Pre-stimulation: Analyses of TMS physiological measures and self-report measures of Impulsivity and Autism quotient scores

In order to determine whether there were any significant relationships between questionnaire measures of impulsivity, autistic traits, and physiological measures of cortical excitability and inhibition further Pearson's correlation and Bayesian analyses were performed. Results of this analysis demonstrated that higher resting motor thresholds (RMT) moderately predicted higher scores on the autism quotient questionnaire. In addition, it was found that the relationship between the slope of the TMS recruitment curve (IO slope) and scores on the Autism Quotient (AQ) questionnaire was approaching significance. In contrast, there was a significant negative correlation between 3ms SICI and scores on AQ. These findings appear to be in line with Rubenstein and Merzenich (2003) leading biological theory of autism spectrum disorder (ASD). Rubenstein and Merzenich (2003) proposed a model whereby those with this condition are typically said to present with cortical hyperexcitability and altered inhibitory processing, which in turn impacts on multiple neural processes (Rubenstein & Merzenich, 2003).

Moreover, increasing robust evidence, which supports the notion of increased levels of cortical excitability and altered inhibition among those with ASD, are now well documented in the literature (see Takarae & Sweeney, 2017 for a comprehensive review). On reviewing this evidence, it appears the current findings are in line with previous research in this area.

In contrast, no significant correlations were found between RMT and any of the questionnaire measures of impulsivity. Similarly, there were no significant correlations between IO slope and any of the questionnaire measures of impulsivity. There were however significant positive correlations between 3ms SICI and several constructs contained within the BIS/BAS and UPPS impulsivity questionnaires, namely, BAS drive, BAS fun seeking, and UPPS lack of premeditation.

This would suggest that a relationship between some elements of self-reported impulsivity and individual differences in some levels of neural inhibitory processing are at work. In support, SICI has also been reported as a neurophysiological indicator of hyperactivity in attention-deficit/hyperactivity disorder (ADHD) (Hoegl et al., 2012). Hoegl et al (2012) time course analysis was able to identify different patterns of excitability for three separate cohorts and found particular inhibitory patterns for children with different levels of hyperactivity and impulsivity symptoms.

Similarly, Buchmann et al., (2006) own neurophysiological theory proposed that motor hyperexcitability could primarily arise as a consequence of insufficient motor facilitation or insufficient motor inhibition. The authors further suggest that it could also arise as a result of “dysfunctional interactions between both phenomena within cortico-striatal-thalamo-cortical motor circuits in the context of deficits in behavioural inhibition” (Buchmann et al., 2006). As discussed earlier in this chapter, it was noted that there are circumstances when action needs to be inhibited in order to allow the emergence of goal directed behaviours (Bari & Robbins, 2013). According to Bari and Robbins (2013) inhibitory processing is a cognitive function that is fundamental to the successful

control of planned and unplanned action behaviours. In contrast however, no significant correlations between 12ms ICF, nor between 100ms LICI, and any of the questionnaire measures of impulsivity or Autism Quotient questionnaire were found.

7.11.5 Effects of excitatory non-invasive brain electrical stimulation on model free performance on the drag-racing task

The effects of non-invasive brain stimulation (TES) on model free performance on the drag-racing task was explored. As discussed earlier there was a significant difference in the ratio number of lose trials in the sham condition insofar as the number of losses significantly dropped in the second session. It was established that this could be evidence of learning effects across testing sessions. Conversely, there were no significant differences in ratio number of wins, nor false-start trials across the two testing sessions for the sham condition. Which would suggest learning effects could only facilitate a reduction in the number of times participants lost a trial and not overall performance on the task.

Similarly, analyses revealed no significant differences between the ratio number of wins, lose, or false-start trials, for performances achieved during session one and two of the tDCS condition. Likewise, results also revealed no significant differences between the ratio number of wins, lose, or false-start trials, for model free performance achieved during session one and two of the tRNS condition. This finding suggests that any potential learning effect, evidenced by a significant reduction in the number of lost trials for those in the sham

condition, could effectively be extinguished by both tRNS and tDCS stimulation to the SMA.

It is well established that the SMA is significantly involved in the preparation and execution of simple and complex motor tasks (Hupfeld, Ketcham, & Schneider, 2017; Nachev, Wydell, O'Neill, Husain, & Kennard, 2007). Moreover, Hupfeld et al (2017) specifically argue that the application of anodal TES to the SMA can modulate neural activity in this region and in turn increase SMA related performance on a variety of tasks including, reaction time, balance, and pegboard tasks. Given that the lost trials in this study are indicative of the slowest reaction times it would suggest that anodal TES to the supplementary motor area had the opposite effect in this instance.

However, this contrast in findings could be wholly related to individual differences in the response to excitatory non-invasive electrical stimulation (Dyke et al., 2016). Dyke and colleagues (2016) examined intra-subject responses to anodal stimulation across four separate testing sessions and found that the amount of change in excitability across these four sessions was only weakly associated. Dyke et al., (2016) also found relatively poor reliability across the same testing sessions yielding an intraclass correlation coefficient of a mere 0.276. They conclude that although 2 mA anodal tDCS can effectively increase cortical excitability at a group level, the effects are unreliable within individual participants, which is particularly evident when testing individuals across repeated stimulation sessions (Dyke et al., (2016).

7.12 *Two-horse Model Analyses*

7.12.1 Pre-Stimulation: Effects of motor cortex excitability and inhibition on modelled performance in the drag-racing task

In order to establish whether individual differences in measures of cortical motor excitability and/or physiological inhibition could predict individual variability on the two-horse modelled performance on the drag-racing task, separate stepwise regression analyses on the mean anticipatory and mean reactive response times during session one (no stimulation condition) were conducted. The result of this analyses demonstrated that none of the TMS physiological measures of excitation or inhibition could predict anticipatory responses in the pre-stimulation session of the drag-racing task. Similarly, stepwise regression analyses again demonstrated that none of the TMS physiological measures of excitation or inhibition could predict reactive responses during session one (pre-stimulation) of the drag-racing task. This result is surprising given the significant and robust results demonstrated in the model free performance on the drag-racing task. This would suggest that, while general performance on the traffic-light task and self-report measures of impulsivity and autism quotient scores are significantly predicted by physiological measures of excitability and inhibition, opportunistic and passive decision-making are not.

One explanation of this finding could be that two different decision processes are at work which are facilitated by different cortical regions. For example, 1) the decision on when to initiate movement (e.g. pressing of the space bar in response to traffic lights) could be facilitated by primary motor cortex, and 2) the outcome of whether risky or passive responses are made could be facilitated by

another brain region not currently tested (e.g. frontal and/or subcortical regions). Indeed, recent animal research conducted by Ledbetter, Chen, & Monosov, (2016) found evidence for two relatively distinct mechanisms, which process uncertainty regarding rewards, within distinct sub-regions of the primate basal forebrain. Ledbetter and Colleagues (2016) also discovered that when primates were faced with uncertainty they suppressed the representation of sure (or safe) reward values via neuronal activation in the dorsal-lateral basal forebrain, specifically in regions containing the ventral pallidum. This uncertainty-related suppression activation was apparent when the primates made risky choices. It appears that further understanding regarding the neural basis of risky decision making among humans is therefore warranted.

7.13 *Pre-stimulation: Two-horse model correlation analyses of performance on drag-racing task and questionnaire measures*

Further analyses on modelled performance on the drag-racing task demonstrated no significant correlations between anticipatory, nor reactive performance on the drag-racing task and questionnaire measures of impulsivity. Similarly, Pearson's correlation analyses demonstrated no significant correlations between anticipatory performance, nor reactive responses, on the drag-racing task and scores on the Autism Quotient (AQ) questionnaire. While it has been determined that self-reported questionnaire measures, along with several measures of physiological excitability and inhibition are highly related to model free performance on the drag-racing task, they do not explain what is at work during anticipatory, nor reactive, decision making. This counter to the

finding of Heyes et al., (2012) who found the UPPS lack of premeditation could significantly predict participants' modelled performance on the drag-racing task.

However, one explanation for this difference could be that, since the drag-racing task in this study did not offer monetary rewards, but rather only win, lose, or false-start written feedback, that different motivational processes could be at work. For example, external events can engage motivational circuits that can either, engage sensory systems which facilitate attention and perceptual processing, or create reflex responses which mobilise an organism and prompt it into action (Frijda, Ridderinkhof & Rietveld., 2014). Frijda et al., (2014) posit that this form of motivation is driven by event-induced states of short duration and wholly dependent on whether or not the individual or organism is interested in acting or not. Moreover, they state that the traditional view of motivation is that it is greater when we encounter situations or opportunities that result in more satisfying outcomes (Frijda, Ridderinkhof & Rietveld., 2014). Based on this theory alone, it could be that the traffic light task, and/or drag-racing task, are measuring motivational processing and impulsive action simultaneously.

7.14 *Stimulation: Effects of excitatory non-invasive brain electrical stimulation on modelled performance on the drag-racing task*

Analyses regarding the potential effects that excitatory non-invasive brain stimulation has on modelled performance in the drag-racing task revealed no significant differences between mean reaction times for anticipatory nor reactive responses for session one (no stimulation condition) and session two (stimulation condition) among those in the sham condition. Similarly, results

also revealed no significant differences between mean reaction times for anticipatory and reactive responses for session one, nor session two for those in the tRNS condition. There was also no significant difference between mean reaction times for reactive responses for session one and session two for those in the tDCS condition.

However, results did demonstrate significant differences between mean reaction times for anticipatory responses during session one and session two for those in the tDCS condition. It appears that bilateral application of tDCS to the SMA influenced response selection and significantly increased anticipatory reaction times during the excitatory tDCS session for this group. A similar finding was seen in research conducted by Marshall, Molle, Siebner, & Born, (2005). Marshall et al., (2005) discovered that bilateral tDCS to frontal brain area linearly increased reaction times during a working memory task. Marshall et al., (2005) concluded that the observed decrease in performance was as a result of an interference in the temporal dynamics of cortical processing. In contrast, Jacobson, Javitt, and Lavidor (2011) found that anodal stimulation led to a significant reduction in stop signal response times (SSRT). These researchers attribute this finding to a disturbance in endogenous task-related cortical oscillatory action which in turn affected the time locked selection, and/or generation of participant response latencies (Jacobson, Javitt, & Lavidor, 2011).

7.15 *Concluding comments*

Many of the behavioural measures of impulsivity, which are currently in use, typically favour a more cautious, albeit deliberate, response strategy (Bechara et al.,1994; Kirby and Herrnstein,1995; Clark et al.,2006), and as such are

incapable of measuring rapid, potentially functional aspects of impulsive action. However, the Stop Signal task is a potential exception to this, as it can index rapid motor responses, and their subsequent suppression, following a stop-signal (Chamberlain and Sahakian, 2007; Liddle et al.,2009). However, there is currently very little evidence regarding the neural basis for this type of automatic rapid responding.

The results of the current study provide potential evidence for the role that motor cortex excitability and inhibition have on model free performance on the drag-racing task. In addition, physiological measures of cortical excitation and inhibition were highly correlated with both self-report measures of impulsivity and autism quotient scores. Similarly, several self-report measures of impulsivity were significantly related to model free performance on the drag-racing task. However, the same physiological measures did not predict modelled performance on the same task. This finding could suggest that more cognitive processes are initiated during this type of task and as such would require additional investigation. Moreover, the link between modelled performance on the drag-racing task and motor cortex involvement was not found.

This would suggest that automatic rapid decision-making while under time pressure is not mediated in the same way as automatic imitation. However, it was found that excitatory stimulation to the SMA does alter anticipatory response times, which could suggest some involvement of motor cortex processing in rapid-decision making. Impairments in impulse control are frequently observed in a number of neurodevelopmental conditions such as ADHD, ASD, TS; and neuropsychiatric disorders including schizophrenia, and

dementia, this knowledge along with the current findings would suggest further exploration is needed into the neural basis for such behaviours

Chapter 8 General Discussion

Through a sequence of multi-modal experiments, the primary aim of this thesis was to ascertain the neural and behavioural basis for automatic behaviours, in the form of echophenomena and impulsivity. In addition, how this could further our understanding regarding the atypical presentation of these behaviours, which is often seen in neurodevelopmental disorders such as autism spectrum disorders (ASD) and Tourette's syndrome, was explored. The first three research studies (chapters 3, 4, & 5) were designed to investigate the neural and behavoural basis of echophenomena. Echophenomena, in the form of contagious yawning, was investigated among neurologically typical developed individuals. TMS physiological measures of cortical excitability, inhibition, and facilitation, and direct current electrical stimulation techniques, were utlilised to determine if the genesis of echophenomena is mediated by primary motor regions. The work in this thesis also sought to establish, and identify, individual subjective self-estimated ratings of the urge for action in these paradigms.

In the fourth study (chapter 6) positive and negative impulsive action in a group of neurotypical children aged between 4-12 years was investigated. This study was conducted to ascertain whether there are age dependent effects of automatic impulsive behaviours. This paradigm was then expanded to include an adult cohort during experiment five (Chapter 7). However, this study included the same TMS physiological measures of cortical excitability, inhibition, and facilitation as chapter four. This protocol was employed in order to ascertain whether the same neural networks mediate automatic impulsive decision making as automatic imitation and mimicry. The application of electrical

stimulation to the SMA was also used in order to explore whether or not this could alter decision-making during a time-sensitive impulsivity task. However, this chapter incorporated an improved electrical stimulation protocol to that used in experiments 1 & 2. Thus, within this thesis the following research questions were addressed;

1. What is the role of motor cortex excitability on the occurrence of echophenomena (e.g. contagious yawning)?
2. Does increasing excitability using electrical stimulation to motor cortical areas modulate contagious yawning?
3. Do subjective measures of urge for action correlate with subsequent behavioural expressions of echophenomena?
4. Do instructions to inhibit echophenomena alter perceived urge for action?
5. What is the role, if any, of the motor cortex during automatic non-social impulsive behaviours?
6. Are there two separate features of impulsive behaviour, namely dysfunctional and functional?
7. Can the application of electrical stimulation to SMA alter decision-making during a time sensitive impulsivity task?
8. How does knowledge regarding the neural and behavioural correlates of automatic social and non-social behavour inform our understanding of echophenoma in atypical development?

8.1.1 Chapter 3 – Echophenomena 1

Within Chapter 3 of this thesis echophenomena, in the form of contagious yawning was explored. In this study a mixed physiological single-pulse TMS

and behavioural task paradigm was employed. The initial aim of this chapter was to explore whether contagious yawning could be predicted by either resting motor threshold (RMT) and/or corticospinal excitability (CSE) IO slopes. This was considered a particularly important research area for generating further understanding regarding human behavioural and social communication mechanisms.

It was considered important to establish a more thorough understanding regarding the neural foundations of echophenomena as this could help elucidate why some populations develop absent or unusual forms of social mimicry (Arnott et al., 2009; Rogers et al., 2003). Earlier research discovered that differences in RMT and motor cortex excitability might well mediate the occurrence of echophenomena (Finis et al., 2012). However, Finis et al., (2012) did not pursue this avenue of discovery further, and as such left a gap in the research literature regarding this issue. Therefore, it seemed reasonable to assume that RMT, and/or motor cortex excitability, might also mediate the occurrence of contagious yawning and subsequently prompted this initial research project.

Firstly, the results of the single-pulse TMS paradigm yielded significant results, demonstrating that this chosen method was highly effective. The initial analysis in this study clearly showed that as the TMS intensity increased, there was a simultaneous, and equally significant, increase in motor evoked potential (MEP) amplitudes. This finding provided evidence of a corresponding rise in neuronal recruitment at the site of TMS, which was consistent across all participants recruited into the study regardless of their starting resting motor thresholds (RMT range 26-46).

Similarly, results for the behavioural task in this chapter were found to be equally effective. A significant effect of yawn condition on yawn response was found. In addition to this, results discovered a significant interaction between yawn condition and response. For instance, there were significantly more *'full yawns'* in the *'free to yawn'* condition than in the *'resist the urge to yawn'* condition, and considerably more *'stifled yawns'* than '*full yawns'* in the *'resist the yawning'* condition. In addition, the non-significant results for the, *'stifled yawns'* in the '*free to yawn'* versus the *'full yawns'* in the *'resist yawning'* condition, revealed that the task instructions were followed correctly.

8.1.2 RMT and the occurrence of contagious yawning

Initial findings for the role that RMT might play on the occurrence of contagious yawning were somewhat mixed. It was discovered that RMT could not significantly predict the number of *'stifled yawns'* observed in the '*free to yawn'* condition, or for *'full yawns'* in the *'free to yawn'* condition, nor for *'full yawns'* in the *'resist the urge to yawn'* condition. Conversely, significant effects of RMT were found regarding the occurrence of stifled yawns in the resist the urge to yawn condition. It is proposed that this result suggests that lower motor thresholds are associated with reduced ability to stifle yawns in the resist the urge to yawn condition. It would appear that the instruction to inhibit yawning behaviour had a profound effect on how this behaviour was expressed.

8.1.3 Corticospinal excitability and the occurrence of contagious yawning

It was observed that lower CSE IO curves significantly predicted the number of full yawns in the *'free to yawn'* condition. While a near significant trend for the

'full yawns' in the *'resist the urge to yawn'* was found, it was thought that this may have occurred as a result of a lack of statistical power, or because of the five participants who did not yawn in any of the four conditions. Nevertheless, the findings did appear to suggest that lower motor cortex excitability results in a reduction in the ability to stifle yawns in the *'resist the urge to yawn'* condition. Also, the trend observed in the full yawn in resist condition demonstrates that there is at least some influence of CSE on the direction of contagious yawning expression

8.1.4 Limitations

The study within this chapter was the first, to our knowledge, to investigate the role the motor cortex might play during the occurrence of echophenomena, particularly in the form of contagious yawning. Several methodological issues were inevitably encountered during this initial investigation. For example, a control condition was not included, and as such left it open to criticism. It could be argued that this study is unable to differentiate between spontaneous and contagious yawns without a control condition. This criticism would be intensified by the fact that each participant was sat alone in a dark room following a lengthy period of TMS measures. It is entirely possible that the participants were also spontaneously yawning during the behavioural task.

Another issue found was related to inter-rater reliability outcomes. While the counting of full yawns did yield a high degree of agreement, the counting of stifled yawns did not. The moderate level of reliability for stifled yawns was reported by the raters to be caused by the difficulty in determining whether the participants had stifled a yawn or were simply covering their mouth with their

hand. This issue did help with adapting the subsequent tasks insofar as including a means of measuring each participant' self-estimated urge to yawn as opposed to simply relying on the video data alone.

8.1.5 Chapter 4 – Echophenomena 2

The limitations from the previous chapter helped inform the design of chapters 4 and 5. It was hoped that by including a measure of self-estimated urge-to-yawn ratings, cross-validation of the number of stifled yawns counted by our raters, and the number of urges reported by our participants, could be achieved. This additional measure also allowed for further exploration regarding the relationship between the number of urges reported and measures of CSE. Finally, given that the previous study involved elements of inhibitory processing (e.g. 'resist yawning condition'), it was deemed important to include additional physiological TMS measures of inhibition. The results of chapter 3 also provided some initial evidence regarding the role that motor cortex excitability might have on the occurrence of contagious yawning, and appeared to go some way towards supporting the hypothesis that the human motor system, and possibly the human mirror neuron system (hMNS), might be primary mediators of both echophenomena (Ganos et al., 2012a), and contagious yawning (Platek et al., 2005).

Therefore, the primary aim of chapter 4 was to further examine the role that motor cortex excitability, along with self-estimated urge-to-yawn ratings and physiological inhibition, might have upon the occurrence of contagious yawning. The neural basis for CY was also investigated via the use of non-invasive brain stimulation [NIBS]. This research technique was applied in an attempt to

modulate contagious yawning behaviour via the supplementary motor area (SMA). The SMA is a cortical region previously associated with the genesis and occurrence of Echophenomena (Bohlhalter et al., 2006; Finis et al., 2013).

Results for chapter 4 supported the hypothesis that contagious yawning propensity is significantly associated with the balance of cortical excitability and physiological inhibition within the primary and secondary motor cortex regions. Specifically, this study found that baseline TMS measures of cortical excitability and physiological inhibition were found to significantly predict behavioural expression in the form of CY. In addition, NIBS (anodal-tDCS and tRNS) were found to significantly increase the cortical excitability of the SMA, a brain area previously associated with the occurrence of echophenomena, and the occurrence of contagious yawning. This finding was evidenced through subsequent changes in the propensity for CY post-stimulation when compared to the change observed following a sham stimulation control condition. These results are entirely consistent with Ganos et, (2012) and Finis, et al., (2013) earlier findings regarding CSE and the origins of echophenomena.

Thus, the overall findings for chapter 4 suggested that increased baseline motor excitability is significantly associated with increases in the propensity for CY. Furthermore, it was found that the instruction to resist yawning significantly increases self-estimated urge-to-yawn ratings, and as such alters how the stifled yawns might be expressed. However, this change in yawn expression was found to not change an individual's propensity for contagious yawning. However, how yawn instructions changed behavioural expression at the neural level remained uncertain, and as such formed the focus of the next research chapter.

8.1.6 Chapter 5 – Echophenomena 3

The purpose of Chapter 5 was to further establish how cortical excitability and physiological inhibition relate to the propensity towards contagious yawning and self-estimated urge-to-yawn ratings. However, a novel online-TMS paradigm was employed in order to measure these specific neural correlates whilst simultaneously measuring contagious yawning behaviourally. Additionally, given that echophenomena frequently occurs among those with the neurological condition ASD, a self-report measure, the Autism Quotient, was included in this study in order to ascertain whether there exists a relationship between the TMS measures, contagious yawning, and AQ scores. It was hypothesised that the findings of this further research might provide additional knowledge regarding the association between motor excitability and the occurrence of echophenomena more generally.

Moreover, employing online-TMS provided the opportunity to establish what might be happening at the neural level at the precise time the contagious yawning behaviour was occurring. To our knowledge, examination of contagious yawning in this way had not been attempted previously. As a consequence of this new approach methodological issues were expected. However, the paradigm worked surprisingly well and yielded some expected, but equally, surprising results. Indeed, initial results demonstrated that online-TMS measures of cortical excitability yielded a near perfect replication of the behavioural task results between yawn condition (Resist v Free) and yawn response (Full v Stifle) and the mean yawn frequency across conditions seen in both chapter 3 and 4. For example, the instruction to resist contagious yawning was again found to be only partially successful and as such led to a significant

decrease in full yawns, but an increase in the number of stifled yawns observed in the resist yawning condition. Furthermore, the instruction to resist yawning again influenced yawning behavioural expression. However, exploration of the combined total of full and stifled yawns, observed during each instruction condition, revealed that the means were not significantly different from one another. This finding further supports the notion that yawn instructions, whether they are ‘freely yawn’ or ‘resist yawning’, does not alter an individual’s propensity for contagious yawning.

In contrast to the findings of chapter 4, the current chapter failed to find any significant effects of yawn instruction on self-estimated urge-to-yawn ratings in either the ‘free to yawn’, or the ‘resist yawning’, behavioural conditions during the online-TMS protocol. It is thought that this result suggests that instructions might be processed in a cortical region outside of the primary motor regions, and as such not detectable by the current online-TMS protocol. Alternatively, and given that chapter 4 found significant predictors of instruction on self-estimated urge-to-yawn at a baseline level, it could be that instruction is processed far earlier in the behavioural task than the current study was able to capture. Therefore, the lack of significant findings for the online version of this task could be as a result of latency and not to any specific motor cortical area.

However, chapter 5 did reveal that several variables including, online-TMS measures of motor cortex excitability, physiological inhibition, and AQ scores, did significantly predict self-estimated mean urge-to-yawn ratings in the resist yawning condition. This contrasts with the finding of chapter 4 where none of the TMS measures of motor cortex excitability and physiological inhibition could predict urge-to-yawn ratings in either the free to yawn or the resist yawning

conditions. Similarly, it was discovered that in this chapter the slope of the TMS induced recruitment curve (IO slope) could also significantly predict self-estimated mean urge-to-yawn ratings in the ‘free to yawn’ condition. While the finding of chapter 4 appears consistent with Jackson et al., (2012) previous acknowledgement regarding the urge-for-action being most likely associated within upstream brain areas such as the anterior insular cortex and/or the cingulate motor cortices, the finding of chapter 5 would suggest that there may be some involvement of primary motor cortices at the neural level when recording self-estimated urge-to-yawn ratings.

However, a degree of caution was advised regarding this new finding. This caution was raised given the fact that participants were executing a motor action (moving slider mechanism) when these measures were being collected. Results of chapter 5 also found that none of the online-TMS measures of motor cortex excitability and physiological inhibition significantly predicted the propensity for contagious yawning at the group level for either yawn instruction. This result runs counter to that chapter 3 for the ‘free to yawn’ condition. Chapter 3 discovered that three factors could predict yawn propensity in this condition. Such a contrast could suggest that something different might be occurring at the neural level during online TMS.

However, the most surprising finding from chapter 5 was the observed sex differences observed in contagious yawning. Results revealed that several measures of cortical excitability and physiological inhibition accounted for significant sex differences in the propensity for contagious yawning. Significant sex differences in both the cortical excitability and physiological inhibition observed during online-TMS were also found. Moreover, both behavioural

instruction and propensity for contagious yawning appeared to be predicted by very different online-TMS measures both within and between the sexes. Sex differences regarding the occurrence of echophenoma are important to consider given the fact that there is a much higher ratio of males who present with neurological and neuropsychiatric conditions where echophenomena is a symptom (Baron-Cohen et al., 2009; Ganos et al., 2012b). Similarly, previous research found that urge-for-action is significantly associated with these same neurological and neuropsychiatric conditions (Bechara, 2012; Bliss, 1980; Gullo & Dawe, 2008; Rasmussen & Eisen, 1992; Simons, 1974). This surprising, but not entirely unexpected, result requires further investigation in order to establish the precise role sex differences have on the occurrence of echophenomena in both neurotypical groups, and those who present with neurodevelopmental and neuropsychiatric conditions.

8.1.7 Chapter 6 – Drag-Racing 1

The primary aim of chapter 6 was to explore positive and negative impulsive action in a group of neurotypical children aged 4-12 years. This study was conducted to ascertain whether there are age dependent effects of automatic impulsive behaviours. This was considered an important extension of this thesis as many neurological and neuropsychiatric conditions incorporate altered impulse control. Moreover, there are impulse control disorders where an urge-for-action typically precedes the expression of an action; an example of such would be premonitory urges followed by tic expression in Gilles de la Tourette's Syndrome (GTS). Thus, it would seem from the literature that the impulse, or urge to act out a behavour, maybe highly related. However, that said, not all

impulsive behaviours can be considered along the same axis as urges for action, nor can they be considered as conscious social acts.

That said, impulsive actions are oftentimes cited as automatic acts that also occur without explicit awareness or forethought (Evenden, 1999). Impulsivity, is also frequently cited as a clinically important facet of many other neuropsychiatric and neurodevelopmental conditions such as; ADHD (Anholt et al., 2010), Autism Spectrum Disorders (ASD) (Aman., Farmer., Holoway., & Arnold, 2008) Bipolar Disorder, (Victor et al., 2011), and Schizophrenia (Chamberlain & Sahakian, 2007; Kaladjian et al., 2011), to name a few. Moreover, many of these conditions that present with impulsivity as a symptom, also present with a high degree of comorbidity for multiple conditions. This point is particularly true for male populations (Moeller et al., 2001). Moreover, many of these conditions appear to begin in early childhood and/or adolescence. With these points in mind this chapter was specifically designed to explore whether there are age dependent effects of impulsive action.

Results of this study demonstrated that older children were more sucessful at responding in an anticipatory manner, and in doing so secured far more win trials on the drag racing task. Heyes et al., (2012) previous research also demonstrated that anticipatory responses were correlated with one construct of the UPPS questionnaire measure ‘lack of premeditation’(Whiteside & Lynam, 2001). Thus, and in line with this idea, the current findings would suggest that older children are able to keep a balance between rapid opportunistic responding and careful premeditation (Dickman, 1990, Heyes et al., 2012).

The drag racing task for this chapter was developed in order to provide a useful measure of rapid decision-making while under risk. However, this paradiem provided much more straightforward feedback (e.g. win or lose). The current finding appears to evoke behavioural evidence that functional impulsivity may develop according to a developmental time-course in children. This is evidenced in the older childrens success on the drag-racing task and could potentially provide support for forward model processing. This result could also throw the existence of the construct of funcional impulsivity into question. This new task also harnessed the potential to demonstrate how this process might differ in children when compared to adults, and later patient groups. Indeed, impulsive behaviour in pathological groups (Chamberlain & Sahakian, 2007) is frequently characterised by rapid and risky decision-making and very few tasks measure this directly.

8.1.8 Chapter 7 – Drag-Racing 2

Results of the newly devised drag-racing task, used in the chapter 6, revealed that there are age-dependent effects among young children in levels of what is often referred to as ‘functional impulsivity’ (Dickman, 1990). However, the findings of chapter 6 were unable to provide knowledge regarding the underlying mechanisms related to the control of this behaviour beyond childhood. For instance, despite impulsive action being linked to neurodevelopmental and neuropsychiatric disorders there still remains no definitive understanding regarding the role that the human motor cortices could play during automatic impulsive decision-making. The question was raised with regards to the suggestion that there are two separate features of impulsive behaviour, namely dysfunctional and functional impulsivity?

Chapter 7 was designed to build upon the previous study's findings and address these additional points. Measures of self-reported impulsive action along with measures of cortical excitability and physiological inhibition were also employed. Further still, a TES protocol similar to that used in chapter 4 was utilised in order to explore whether impulse action could be facilitated via stimulation of the SMA. The overall aim was to determine if automatic unconscious impulsive action is mediated by the same neural systems as automatic imitation, in the form of contagious yawning, and the urge-for-action.

Results of chapter 7 provided some evidence for the potential role that motor cortex excitability and physiological inhibition might have on model free performance on the drag-racing task. Moreover, physiological measures of cortical excitation and inhibition were found to be highly correlated with both self-report measures of impulsivity and autism quotient scores. In addition, several of the self-report measures of impulsivity were also found to be significantly related to the participants' model free performance during execution of this task.

Conversely, the same physiological measures could not significantly predict the modelled performance on this same task. Such a finding might suggest that more cognitive processes are initiated during this type of task that were not measured via this protocol. Interestingly, the link between modelled performance on the drag-racing task and potential involvement of the motor cortex was not found. This would suggest that automatic rapid decision-making while under time pressure is not mediated in the same way as automatic imitation. Nevertheless, it was found that excitatory stimulation to the SMA does significantly alter participants' anticipatory response times, which might be an

indication of some involvement of the motor cortex in rapid-decision making processes.

8.2 *Concluding comments and future directions*

Within this thesis it was found that several measures of motor cortex excitability and physiological inhibition could significantly predict individual propensity towards contagious yawning. It was also discovered that the instruction to resist yawning proved to be only partially successful indicating that while contagious yawning remains consistent over time, yawn expression was not. Results also found that electrical stimulation to motor cortical areas could modulate the occurrence of echophenomena in the form of contagious yawning. Further exploration regarding subjective measures of urge for action found significant differences between participants self-estimated urge-to-yawn ratings and their subsequent behavioural expressions of echophenomena. Notably, instructions to inhibit contagious yawning significantly altered yawn expression and perceived urge for action in this condition. Finally, there were marked sex differences in the neural basis for contagious yawning. This finding is one that requires further examination, especially given the fact that there is a clear disparity in the presentation of neurological and neuropsychiatric conditions, whereby echophenomena is an issue, among the sexes.

Similarly, the role of the motor cortex during automatic non-social impulsive behaviours yielded mixed, yet intriguing results. Findings suggest that anticipatory impulse action is most likely mediated in regions outside of the primary motor cortices and as such cannot be considered in the same vein as urge-for-action. However, the application of electrical stimulation to SMA did

prove to be partially successful in modulating non-modelled decision-making during the time sensitive impulsivity paradigm. In addition, the findings raised questions regarding the validity of impulsive action being considered as two separate constructs, namely dysfunctional and functional impulsivity, and as such would require additional exploration.

Overall the work in this thesis helped provide some knowledge towards understanding the neural and behavioural mechanisms that may be mediating automatic social and non-social behavours. However, the findings were only able to inform understanding of echophenoma and impulsive action in neurotypically developed individuals. Given the extensive reports in the scientific literature, which state that impairments in echophenomena, and impulse control, are frequently observed in several neurodevelopmental and neuropsychiatric conditions, it remains important to extend this work further. Further examination would help elucidate further knowledge regarding altered imitative and impulsive action in those with these conditions.

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Chapter 1

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Appendices

Table of outcome measures

	Echophenomena (Contagious Yawning)					
	Free condition			*Resist condition*		
	μ Full Yawn (fy)	***μ Stifles (sy)***	***μ Urge (Hz)***	***μ Full Yawn***	***μ Stifles***	***μ Urge***
Experiment 1	7.86 (fy)	0.98 (sy)	X	1.05 (fy)	2.43 (sy)	X
Exp 2 pre TES	5.11 (fy)	0.22 (sy)	0.15 (Hz)	0.19 (fy)	3.75 (sy)	0.17 (Hz)
Exp 2 post TES	5.58 (fy)	0.19 (sy)	0.15 (Hz)	0.38 (fy)	4.27 (sy)	0.16 (Hz)
Exp 3 Female	18.14 (fy)	0.85 (sy)	0.30 (Hz)	3.14 (fy)	17.14 (sy)	0.26 (Hz)
Exp 3 Male	**17.29** (fy)	0.14 (sy)	0.15 (Hz)	1.57 (fy)	15.14 (sy)	0.24 (Hz)
Exp 3 Group	18.50 (fy)	0.54 (sy)	0.24 (Hz)	1.65 (fy)	16.54 (sy)	0.27 (Hz)

	Resting state motor threshold (RMT) in μV			
	Experiment (Exp) 1	**Experiment 2**	**Experiment 3**	**Exp 4 Drag-Racing**
Female	X	X	41 μV	X
Male	X	X	43 μV	X
Group Total	39 μV	48 μV	41 μV	45 μV

	Cortical spinal excitability input/output curves (IO slope)				
	Exp 1	**Exp 2**	**Exp 3 Free**	**Exp 3 Resist**	**Exp 4 Drag-Racing**
Female	X	X	8.67 mV	9.50 mV	X
Male	X	X	9.82 mV	9.41 mV	X
Group Total	65.08 mV	62.09 mV	9.23 mV	9.43 mV	64.14 mV

	TMS physiological measures of facilitation/inhibition			
Offline TMS	**Exp 1**	**Exp 2**	**Exp 3**	**Exp 4 Drag-Racing**
1ms SICI	**X**	0.40 mV	**X**	**0.33** mV
3ms SICI	**X**	0.83 mV	**X**	**0.78** mV
12ms ICF	**X**	1.70 mV	**X**	**1.58** mV
100ms LICI	**X**	0.89 mV	**X**	**0.70** mV
Online TMS Exp 3 only	**1ms SICI Free**	**3ms SICI Free**	**12ms ICF Free**	**100ms LICI Free**
Male	**0.51** mV	**0.78** mV	**0.89** mV	**0.68** mV
Female	0.32 mV	0.80 mV	1.61 mV	1.26 mV
Group	0.41 mV	0.80 mV	1.27 mV	0.96 mV
Online TMS Exp 3 only	**1ms SICI Resist**	**3ms SICI Resist**	**12ms ICF Resist**	**100ms LICI Resist**
Male	0.43 mV	0.91 mV	1.13 mV	0.86 mV
Female	**0.34** mV	**0.73** mV	**1.30** mV	**1.12** mV
Group	0.40 mV	0.83 mV	1.24 mV	0.99 mV

Contagious Yawning Protocol

- Screen participants to ensure suitability for TMS
- Collect consent, demographic information and questionnaire data
- Book TMS lab for approximately one hour to collect motor threshold, followed by input/output curves of 1st dorsal interosseous (FDI) muscle in order to ascertain cortical excitability for each participant.
- Take participant to video lab and give them information on what to expect ***but not that they are being videoed*** (debrief to follow).
- Videos will be presented randomly using an '**ABBA' ''BAAB' (A = *'free to yawn'* and B = *' suppress yawn')*** block design. There will be …… blocks in total with each block lasting for approximately 6 minutes.
- The yawning videos include both female and male faces. Participants will be asked to concentrate on the faces and told that there will be some questions to follow their viewing time (to see if they were attending to the faces).
- At the end of the contagious yawing task participants will be debriefed fully before leaving!!
- Video recordings to be rated by two individual raters in order to count the number of yawns in the ***'free to yawn'*** condition and the ***'suppress yawn'*** condition. Count data to be compared and a final number for each condition agreed upon.
- The I/O data will be analysed to obtain median results for each participant, and this data, along with the questionnaire and yawn data, will be collated into an excel file.
- All data relevant to each researcher will be run through the most appropriate statistical analyses for their research.

TMS screening form

School of Psychology

TMS Safety Questionnaire

VOLUNTEERS PARTICIPATING IN TRANSCRANIAL MAGNETIC STIMULATION STUDIES

NAME: .....DATE OF BIRTH: .....

1. Did you ever undergo TMS in the past?
   Y/N

   If yes, have you ever had an adverse reaction to TMS?

   Y/N

2. Have you ever experienced any faintness, fainting spells, or blackouts?
   Y/N

   If yes, please describe on which occasion(s).

3. Have you ever had a seizure?
   Y/N
4. Do you or anyone in your family have epilepsy?
   Y/N
5. Do you suffer from frequent headaches or migraines?
   Y/N
6. Do you have any hearing problems or have ever suffered from hearing loss?
   Y/N
7. Have you ever had a stroke?
   Y/N

   Have you ever been told that your blood pressure was abnormal?
   Y/N
8. Have you ever had a head injury?
   Y/N
9. Have you ever had neurosurgery or any other major operations/surgical procedures?
   Y/N

   If yes, please specify.

10. Do you suffer from a medical condition (such as diabetes, asthma or a heart disease)
    Y/N
11. Are you currently taking any medication?
    Y/N

If yes, please specify.

13. Do you have any implanted (electronic, mechanical, metallic, or magnetic) devices such as cardiac pacemaker, medical pump, surgical clips, cochlear implants, or any other?
Y/N

14. Have you ever been injured by metallic fragments or worked in a machine tool shop

without eye protection?
Y/N

15. If you are female, is there a chance you are pregnant?
Y/N

16. Is there anything else you think we should know?
Y/N

17. Do you need further explanation of TMS and its associated risks?
Y/N

Thousands of healthy subjects and patients have undergone TMS allowing an assessment of relative risks. The occurrence of seizures (i.e., the most serious TMS-related acute adverse effect) has been extremely rare, with most of the few cases receiving TMS exceeding previous guidelines, often in patients under treatment with drugs which potentially lower the seizure threshold.

I have read and understood all the questions, and I certify that the above information is correct

to the best of my knowledge.

Signature of the participant: Date:
Verified by researcher: Date:

TMS follow-up questionnaire

Transcranial Magnetic Stimulation

(TMS) Follow-Up

Questionnaire

As part of our research programme, we routinely monitor the health of participants following TMS. We would be grateful if you could answer the questions listed below. Completing this form is entirely voluntary. The information you provide will be treated as confidential and will be held in secure conditions. Group results of this survey may be published, but no information will be disclosed that can identify any individual person.

If you are unsure how to answer any of the questions, please ask the researcher who gave you this form.

Name:
Date:

Please tell us if you experienced any of the following symptoms in the 24 hours following your most recent TMS session. If the answer is YES to any of these questions, we would be grateful for additional details

Seizure
Yes No **Details:**

Fainting or Collapse
Yes No **Details:**

Dizziness
Yes No **Details:**

Nausea or vomiting
Yes No **Details:**

Headache
Yes No **Details:**

Muscular aches
Yes No **Details:**

Muscle spasm or twitch
Yes No **Details:**

Insomnia
Yes No **Details:**

Sensory Problems
Yes No **Details:**

Difficulties speaking or understanding speech
Yes No **Details:**

Lack of coordination
Yes No **Details:**

Slowness or impairment of thought
Yes No **Details:**

Other (please specify
Yes No **Details:**

Any other comments:

Echophenomena 1 Information Sheet

School of Psychology

Information Sheet

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

Title of Project: **Assessing the role of motor cortex excitability on contagious yawning**

Researcher: Beverley Brown lpxbjbr@nottingham.ac.uk

Supervisors: Prof. Georgina Jackson & Prof. Stephen Jackson

This is an invitation to take part in a research study on whether motor cortex excitability affects the rate of contagious yawning. Before you decide if you wish to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully.

If you participate, you will be taking part in two separate investigations. During one of these you will undergo TMS (transcranial magnetic stimulation) which will take approximately one hour. TMS is known to have the ability to temporarily alter neural activity in a safe and reversible way. This technique makes it possible to measure neural activity. The study will also involve having electrodes attached to your hand/wrist, and the motor area of your brain stimulated to produce a twitch in your hand muscle.

To elicit this twitch in your muscle a TMS coil will be placed on the head to deliver magnetic pulses to the brain. This is a safe and painless procedure as used in the School of Psychology and has no long-term effects. The most serious known risk is epileptic seizures but these have not been reported in healthy adults at normal levels of stimulation. As a precaution you will be asked to complete a safety screening questionnaire and a follow-up questionnaire to report any unexpected after-effects.

The second part of the study will comprise of watching a set of videos on which you will be asked questions post viewing. Instructions will be giving prior to watching the videos on any conditions to be met during the procedure. This will take roughly 30 minutes. Whether these two parts are conducted at the same time depends on your availability and room/lab availability. You will also be asked to complete two questionnaires before or after the experiment.

Participation in this study is voluntary and you are under no obligation to take part. You are free to withdraw at any point before or during the study. All data collected will be kept confidential and used for research purposes only. It will be stored in compliance with the Data Protection Act.
If you have any questions or concerns please don't hesitate to ask now. We can also be contacted after your participation at the above address.

If you have any complaints about the study, please contact: Stephen Jackson (Chair of Ethics Committee) stephen.jackson@nottingham.ac.uk

<u>References:</u>

Echophenomena 2 Information Sheet

School of Psychology

Information Sheet

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

Investigating the role of motor cortex excitability on contagious yawning: A TMS and Transcranial Electrical Stimulation (TES) study.

Ethical Approval Number: 219

Researchers: Beverley Brown & Hannah Saunders

Supervisors: Professor Stephen Jackson

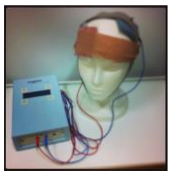
Contact Details lpxbjbr@nottingham.ac.uk

Thank you for your interest in our study. Before you decide if you would like to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully.

The study involves investigating the role of motor cortex excitability and effects of low intensity Transcranial Electrical Stimulation (TES) on the propensity for contagious yawning. TES is known to have the ability to temporarily alter neural activity in a safe and reversible way. TES is known to modulate cognitive functions in healthy individuals, but the potentials of TES have not been fully understood. The current study aims to investigate the behavioural effects of TES in healthy individuals using both physiological and behavioural measures.

If you participate, you will be taking part in a study that has two separate investigations. The first part of the study you will undergo TMS (transcranial magnetic stimulation), which will take approximately one hour. TMS is known to have the ability to temporarily alter neural activity in a safe and reversible way. This technique makes it possible to measure neural activity. The study will also involve having electrodes attached to your hand/wrist, and the motor area of your brain stimulated to produce a twitch in your hand muscle. To elicit this twitch in your muscle a TMS coil will be placed on the head to deliver magnetic pulses to the brain. This is a safe and painless procedure as used in the School of Psychology and has no long-term effects. The most serious known risk is epileptic seizures but these have not been reported in healthy adults at normal levels of stimulation. As a precaution you will be asked to complete a safety screening questionnaire and a follow-up questionnaire to report any unexpected after-effects.

The second part of the study will involve watching a set of videos on which you will be asked questions post viewing. Instructions will be giving prior to watching the videos on any conditions to be met during the procedure. This will take roughly 40 minutes. You will also be asked to record your urges to yawn using a sliding mechanism (please see the additional information sheet on this). You will also be asked to complete screening questionnaires before and after the experiment.
During the last 20 minutes of this part of the study you will receive TES stimulation (Max: 20 minutes), which has a temporary effect of changing brain activity. The application of TES involves attaching electrodes in thin saline-soaked sponges to your head. During TES stimulation, a weak current will pass through the electrodes. While stimulated, you may experience an itching, tingling, or mild burning sensation (will not actually burn you). TES has been used widely in research for over a decade and no serious adverse effects have been reported. Currently, the only known risks are skin irritation for participants with sensitive skin or open head wounds. In the unlikely event of you noticing any adverse effects after the stimulation you should inform the researcher. This study aims to test healthy participants who are at minimal risk of experiencing any side effects of the stimulations used. Therefore, it is important that you read and answer the screening forms carefully. If you meet any of the criteria that would put you at elevated risk of side effects you will not be able to participate.



Example of TES.

If you have any questions or concerns please do not hesitate to ask now. We can also be contacted using the above email addresses. If you have any further concerns or complaints, please contact; Stephen Jackson (Chair of Ethics Committee, stephen.jackson@nottingham.ac.uk)

Echophenomena 2 Video Recording Information Sheet

EXPERIMENTAL RECORDING INFORMATION
School of Psychology
University of Nottingham

Name of Experimenters:
Beverley Brown
Katie Fitzgerald
Ellie Raven

Email of Experimenters:
lpxbjbr@nottingham.ac.uk
lpykf1@nottingham.ac.uk
lpyer2@nottingham.ac.uk

Name of Supervisors:
Prof. Georgina M. Jackson
Prof. Stephen R. Jackson

Email of Supervisors:
Georgina.jackson@nottingham.ac.uk
Stephen.Jackson@nottingham.ac.uk

Firstly thank you for participating in our study.
Ethics approval number: 219
Title of Experiment:
Assessing the role of motor cortex excitability on contagious yawning

Background/Hypothesis:
This study is designed to investigate the relationship between cortical excitability and the relationship, if any with contagious yawning, and/or certain personality traits such as empathy. The use of TMS helps us to measure your particular level of cortical excitability. The type of TMS/TES used in the study is not associated with any long term effect or changes to neurological activity (Rossi et al., 2009).

The purpose of this study is to better define how certain factors affect someone's susceptibility to contagious yawning. In order to determine your susceptibility we will videotape you during the second part of the study via a webcam. We do so in order to capture your spontaneous yawning episodes in response to the actors in the videos you will view. These videotaped sessions also allow us to count the episodes of yawning. Please be assured that the videos of you are simply for the purpose of collecting count data (how man times you yawned or were able to suppress your yawns) while viewing the videos.

** If you are interested in participating in other TMS studies, please contact Hilmar or Beverley since we are constantly running TMS studies in our lab.*

Thank you for your participation.

Consent for video data

- Have you read and understood the Information provided regarding the video recording? YES/NO
- Have you had the opportunity to ask questions about this? YES/NO
- Have all your questions been answered satisfactorily? YES/NO
- Do you understand that you are free to withdraw from the study? YES/NO (at any time and without giving a reason)

- I give permission for my data from this entire study (including video data) to be shared with other researchers provided that my anonymity is completely protected. YES/NO

If you are unhappy at any point we will destroy the video data.

- Do you agree to us analysing your video data? YES/NO
- **If yes please sign at point 1 or if no sign at point 2**

Signature of the Participant for keeping data:
Date:
Name (in block capitals)

2) Signature to indicate that you are happy with everything
Signature of researcher: Date:

Signature of Participant Date:

Transcranial Direct Current Stimulation (tDCS) Screening Questionnaire

Echophenomena and motor cortex excitability (phase 2 research)

Nottingham School of Psychology Ethics reference: 219

It is important that you answer all of the following questions truthfully.
If any of the questions/terms on this form are unclear, or if you are unsure how to answer them, please do not hesitate to ask the Primary Investigator of the study.

	Yes	No
Have you ever had a seizure?		No
Have you ever had a head injury resulting in a loss of consciousness that has required further investigation (including neurosurgery)?		No
Do you suffer from Migraines?		No
Do you currently have a medical diagnosis of a psychological or neurological condition which requires medication?		No
Do you have any metal in your head (outside of the mouth) such as shrapnel or surgical clips?		No
Do you have any implanted devices (e.g. cardiac pacemaker, brain stimulator)?		No
Do you have a skin condition on your scalp? (e.g. psoriasis)		No
Do you have a head wound that has not completely healed?		No
Have you ever had an adverse reaction to tDCS?		No
For female participants: Is there the possibility that you might be pregnant?		No
Are you currently taking any prescribed medications, other than the contraceptive pill?		No

The possible hazards of tDCS have been explained to me, and I understand that I can withdraw at any point for any reason, and that I do not have to disclose the reason(s) to the experimenter. By signing below I acknowledge that I understand this screening form and attest to its accuracy

Participant's signature	Researcher's signature	Date

Echophenomena 3 Information Sheet

School of Psychology

Information Sheet

The University of Nottingham

UNITED KINGDOM · CHINA · MALAYSIA

A functional transcranial magnetic stimulation (fTMS) study investigating the neural basis for instruction processing during episodes of contagious yawning.

Ethical Approval Number:

Researchers: Beverley Brown

Supervisors: Professor Stephen Jackson

Dr Danielle Ropar

Professor Georgina Jackson

Contact Details lpxbjbr@nottingham.ac.uk

Thank you for your interest in our study. Before you decide if you would like to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully.

The study involves investigating the role of motor cortex excitability/inhibition, and certain psychometric measures, on how individuals' process instructions during episodes of contagious yawning. TMS is known to have the ability to temporarily alter neural activity in a safe and reversible way. TMS is known to measure cognitive functions in healthy individuals. The current study aims to investigate the neural basis of instruction processing during contagious yawning in healthy individuals using both physiological and behavioural measures. An inconvenience allowance is also paid.

If you participate, you will be taking part in a study that investigates contagious yawning while undergoing online TMS. The task involves viewing four blocks of actors yawning on a computer screen and you will be asked to follow two specific instructions relating to these stimuli. For two of the yawning blocks you will be asked to yawn freely, while for the other two blocks the instruction will be, 'please stop yourself from yawning' (stifle the yawns). We will also like you to record your urge to yawn using a sliding mechanism. There will be a practice session on the use of the slider prior to undertaking the study to allow you to familiarise yourself with this part of the task. During the study you will undergo TMS (transcranial magnetic stimulation), while carrying out the above tasks. Your yawn/stifled yawn responses will be videoed throughout the duration of the study for counting offline. TMS is known to have the ability to temporarily alter neural activity in a safe and reversible way. This technique makes it possible to measure your particular level of cortical excitability and/or inhibition. The study will also involve having electrodes attached to your hand/wrist, and the motor area of your brain stimulated to produce a twitch in your hand muscles. To elicit this twitch in your muscle a TMS coil will be placed on the head to deliver magnetic pulses to the brain. This is a safe and painless procedure as used in the School of Psychology and has no long-term effects. The most serious known risk is epileptic seizures (older style TMS not occurred in our lab) but these have not been reported in healthy adults at normal levels of stimulation. As a precaution you will be asked to complete a safety screening questionnaire and a follow-up questionnaire to report any unexpected after-effects.

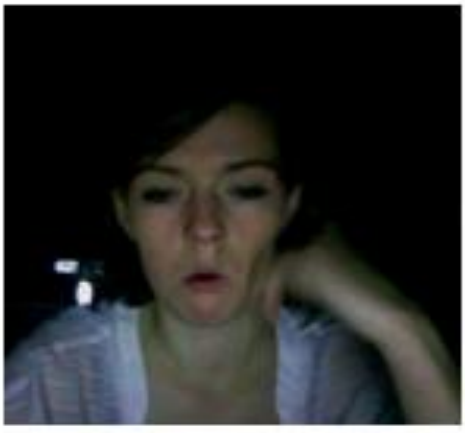
This study aims to test healthy participants who are at minimal risk of experiencing any side effects of the stimulation used. Therefore, it is important that you read and answer the screening forms carefully. If you meet any of the criteria that would put you at elevated risk of side effects you will not be able to participate. Please be assured that your safety is our primary concern.

If you have any questions or concerns please do not hesitate to ask now. We can also be contacted using the above email addresses. If you have any further concerns or complaints, please contact; Stephen Jackson (Chair of Ethics Committee, stephen.jackson@nottingham.ac.uk)

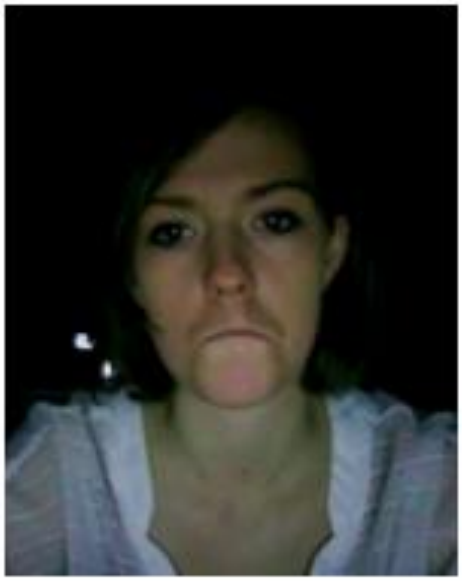
TMS yawn rater protocol

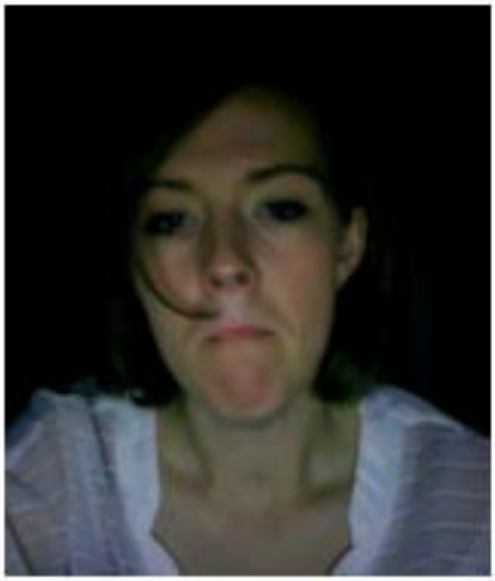
Contagious Yawning Rater Protocol

After the first set of instructions has been presented the first block of yawning videos will appear. Please count the number of yawns in the first block and make a note of the number. The images below count as possible yawns. However if you see something that you feel constitutes a yawn please count this in your number. There is more than one rater and an average of your counts will be agreed upon at the end of the counting sessions.



After the first block the screen will go black for a minute while the subject is answering the questions they were set. This also indicates that the first block is finished. The next block will start as soon as one minute elapses. Please count the next block of yawns and make a note of the number. In each block of yawning please look out for indications that the subject is supressing yawns. The next few images also show incidences that may count as yawning.
Tension in the jaw is indicative of a yawn, as is pursing or biting ~~one's~~ lip;

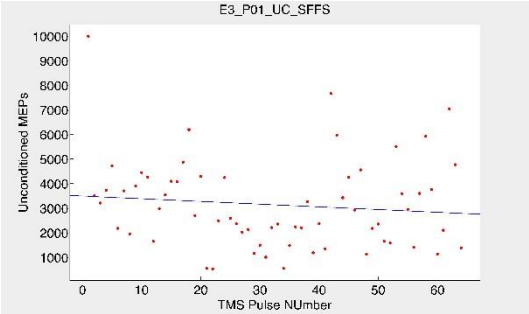


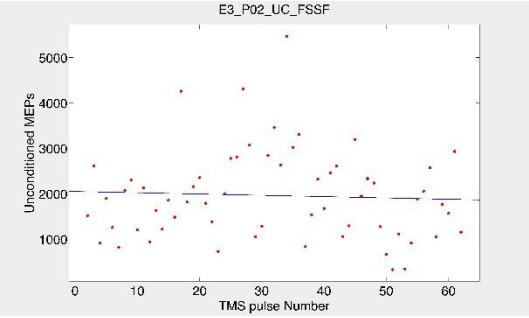


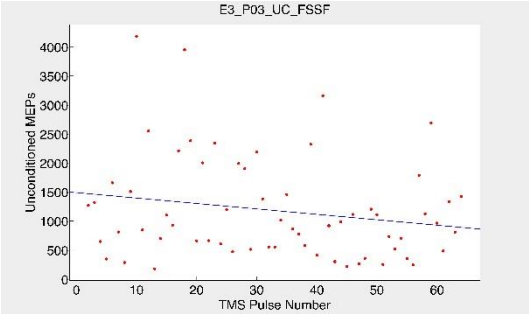
Other indicators that the subject is about to yawn is hiding their face behind their hands, ducking out the way of the screen, or obscuring their mouth somehow see the following;

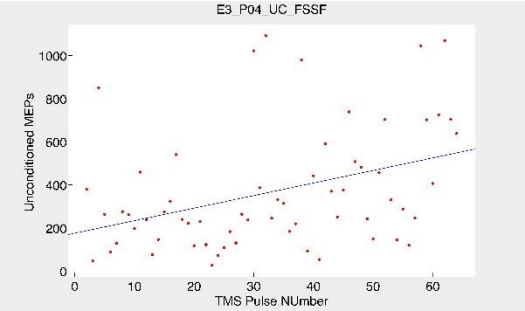
Count all the yawns for each block. There will be four blocks in total, please count the yawns for each block separately and make a note of the number eg. block 1 = 5 yawns. Your count data will be will compared with another independent rater in order to ascertain the number of yawns per block. Thank you.

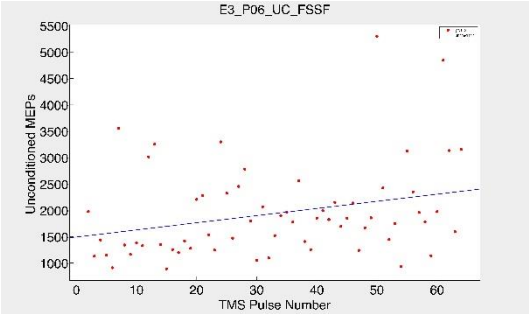
Echophenomena 3 unconditioned MEP's

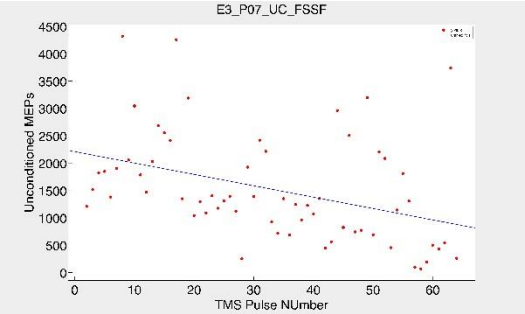


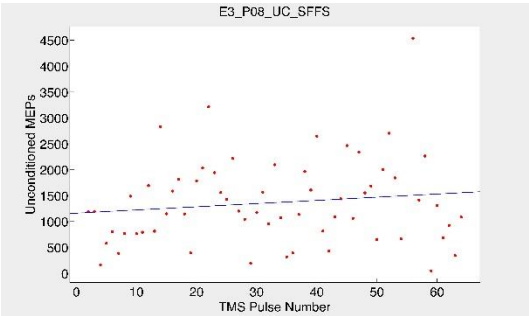


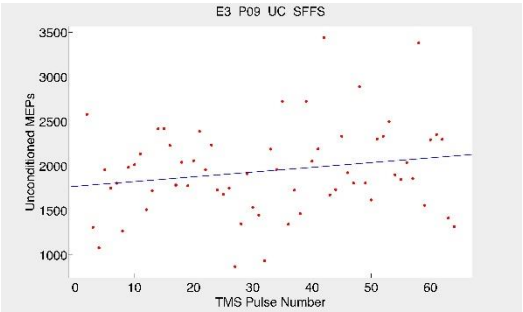


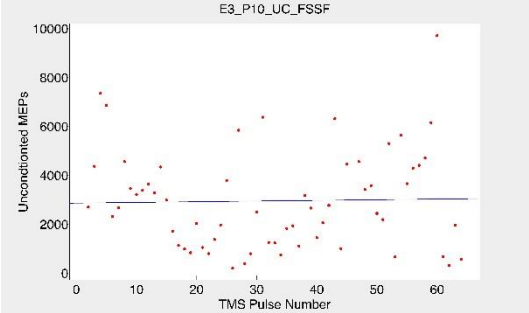








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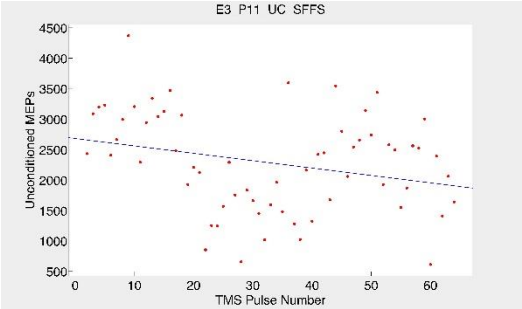
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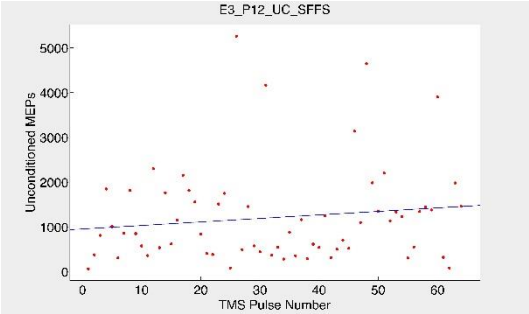
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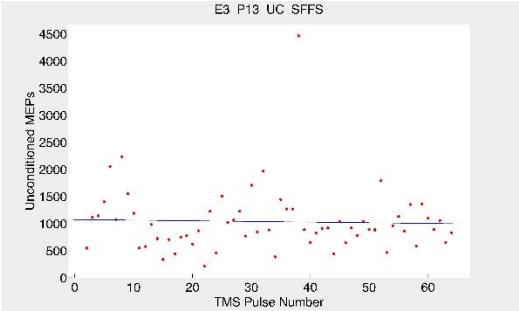
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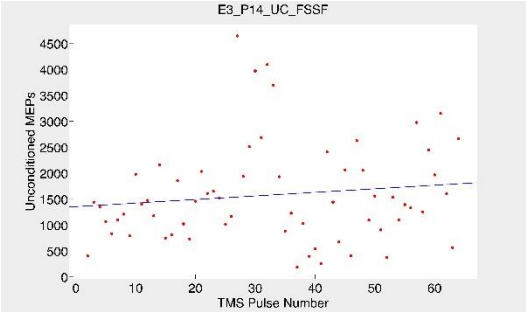
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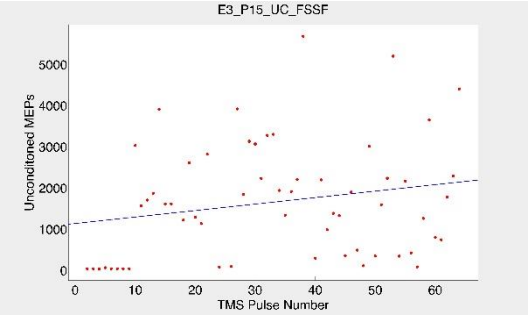
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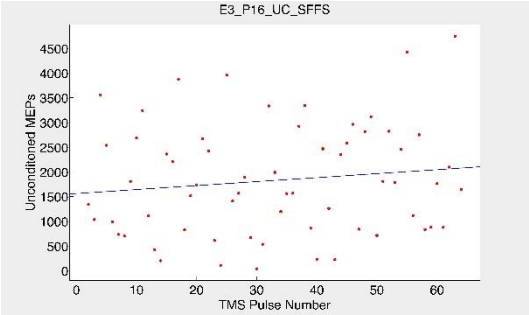
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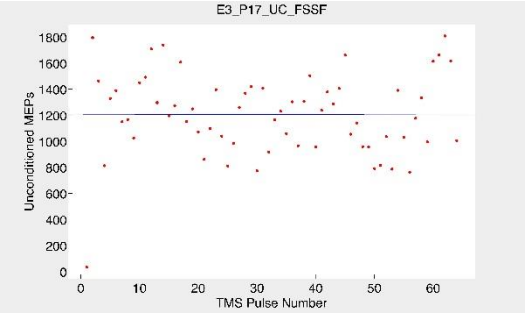
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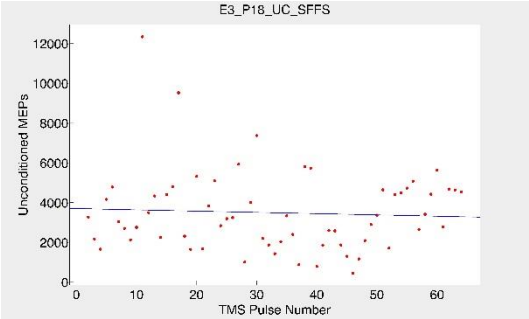
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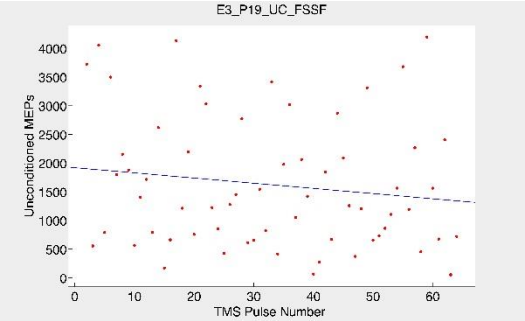
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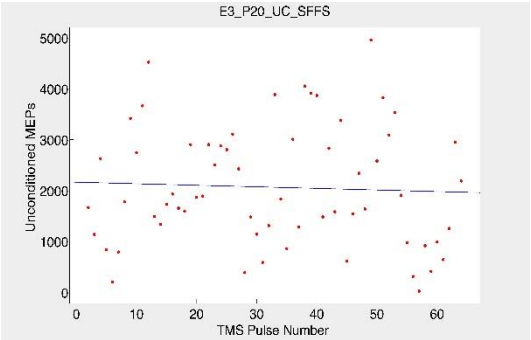
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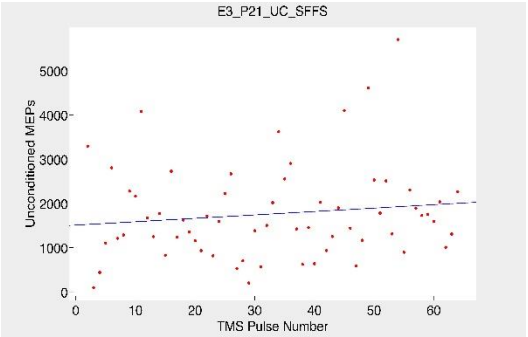
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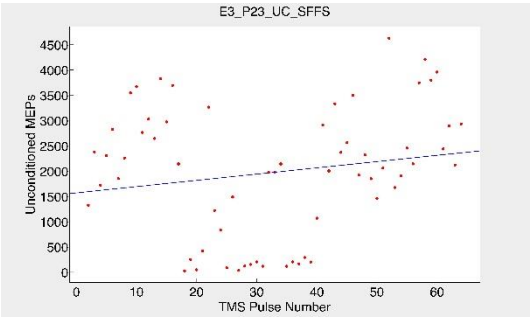
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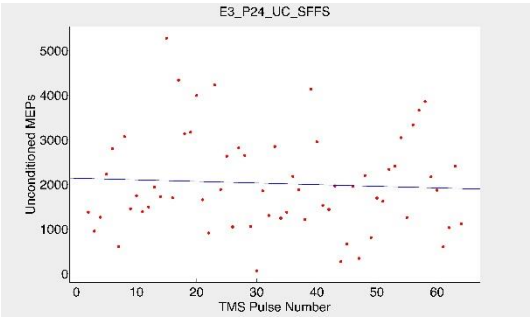
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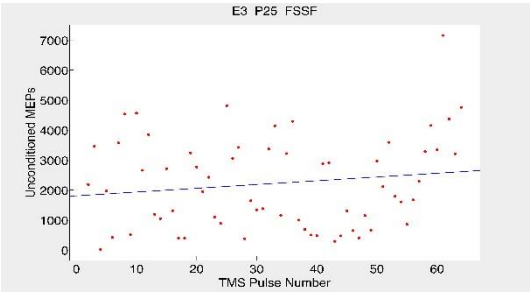
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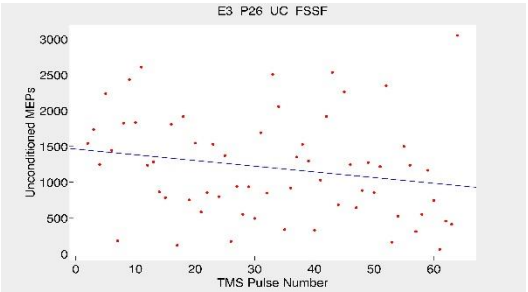
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Autism Quotient Questionnaire

The Adult Autism Spectrum Quotient (AQ)

Ages 16+

SPECIMEN, FOR RESEARCH USE ONLY.

For full details, please see:

S. Baron-Cohen, S. Wheelwright, R. Skinner, J. Martin and E. Clubley, (2001)
The Autism Spectrum Quotient (AQ) : Evidence from Asperger Syndrome/High Functioning Autism, Males and Females, Scientists and Mathematicians
Journal of Autism and Developmental Disorders 31:5-17

Name:..... Sex:.....

Date of birth:..... Today's Date.....

How to fill out the questionnaire

Below are a list of statements. Please read each statement very carefully and rate how strongly you agree or disagree with it by circling your answer.

DO NOT MISS ANY STATEMENT OUT.

Examples

E1. I am willing to take risks.	definitely agree	slightly agree	slightly disagree	definitely disagree
E2. I like playing board games.	definitely agree	slightly agree	slightly disagree	definitely disagree
E3. I find learning to play musical instruments easy.	definitely agree	slightly agree	slightly disagree	definitely disagree
E4. I am fascinated by other cultures.	definitely agree	slightly agree	slightly disagree	definitely disagree

1. I prefer to do things with others rather than on my own.	definitely agree	slightly agree	slightly disagree	definitely disagree
2. I prefer to do things the same way over and over again.	definitely agree	slightly agree	slightly disagree	definitely disagree
3. If I try to imagine something, I find it very easy to create a picture in my mind.	definitely agree	slightly agree	slightly disagree	definitely disagree
4. I frequently get so strongly absorbed in one thing that I lose sight of other things.	definitely agree	slightly agree	slightly disagree	definitely disagree
5. I often notice small sounds when others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree
6. I usually notice car number plates or similar strings of information.	definitely agree	slightly agree	slightly disagree	definitely disagree
7. Other people frequently tell me that what I've said is impolite, even though I think it is polite.	definitely agree	slightly agree	slightly disagree	definitely disagree
8. When I'm reading a story, I can easily imagine what the characters might look like.	definitely agree	slightly agree	slightly disagree	definitely disagree
9. I am fascinated by dates.	definitely agree	slightly agree	slightly disagree	definitely disagree
10. In a social group, I can easily keep track of several different people's conversations.	definitely agree	slightly agree	slightly disagree	definitely disagree
11. I find social situations easy.	definitely agree	slightly agree	slightly disagree	definitely disagree
12. I tend to notice details that others do not.	definitely agree	slightly agree	slightly disagree	definitely disagree
13. I would rather go to a library than a party.	definitely agree	slightly agree	slightly disagree	definitely disagree
14. I find making up stories easy.	definitely agree	slightly agree	slightly disagree	definitely disagree
15. I find myself drawn more strongly to people than to things.	definitely agree	slightly agree	slightly disagree	definitely disagree
16. I tend to have very strong interests which I get upset about if I can't pursue.	definitely agree	slightly agree	slightly disagree	definitely disagree
17. I enjoy social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree
18. When I talk, it isn't always easy for others to get a word in edgeways.	definitely agree	slightly agree	slightly disagree	definitely disagree
19. I am fascinated by numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree

20. When I'm reading a story, I find it difficult to work out the characters' intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
21. I don't particularly enjoy reading fiction.	definitely agree	slightly agree	slightly disagree	definitely disagree
22. I find it hard to make new friends.	definitely agree	slightly agree	slightly disagree	definitely disagree
23. I notice patterns in things all the time.	definitely agree	slightly agree	slightly disagree	definitely disagree
24. I would rather go to the theatre than a museum.	definitely agree	slightly agree	slightly disagree	definitely disagree
25. It does not upset me if my daily routine is disturbed.	definitely agree	slightly agree	slightly disagree	definitely disagree
26. I frequently find that I don't know how to keep a conversation going.	definitely agree	slightly agree	slightly disagree	definitely disagree
27. I find it easy to "read between the lines" when someone is talking to me.	definitely agree	slightly agree	slightly disagree	definitely disagree
28. I usually concentrate more on the whole picture, rather than the small details.	definitely agree	slightly agree	slightly disagree	definitely disagree
29. I am not very good at remembering phone numbers.	definitely agree	slightly agree	slightly disagree	definitely disagree
30. I don't usually notice small changes in a situation, or a person's appearance.	definitely agree	slightly agree	slightly disagree	definitely disagree
31. I know how to tell if someone listening to me is getting bored.	definitely agree	slightly agree	slightly disagree	definitely disagree
32. I find it easy to do more than one thing at once.	definitely agree	slightly agree	slightly disagree	definitely disagree
33. When I talk on the phone, I'm not sure when it's my turn to speak.	definitely agree	slightly agree	slightly disagree	definitely disagree
34. I enjoy doing things spontaneously.	definitely agree	slightly agree	slightly disagree	definitely disagree
35. I am often the last to understand the point of a joke.	definitely agree	slightly agree	slightly disagree	definitely disagree
36. I find it easy to work out what someone is thinking or feeling just by looking at their face.	definitely agree	slightly agree	slightly disagree	definitely disagree
37. If there is an interruption, I can switch back to what I was doing very quickly.	definitely agree	slightly agree	slightly disagree	definitely disagree
38. I am good at social chit-chat.	definitely agree	slightly agree	slightly disagree	definitely disagree

39. People often tell me that I keep going on and on about the same thing.	definitely agree	slightly agree	slightly disagree	definitely disagree
40. When I was young, I used to enjoy playing games involving pretending with other children.	definitely agree	slightly agree	slightly disagree	definitely disagree
41. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plant, etc.).	definitely agree	slightly agree	slightly disagree	definitely disagree
42. I find it difficult to imagine what it would be like to be someone else.	definitely agree	slightly agree	slightly disagree	definitely disagree
43. I like to plan any activities I participate in carefully.	definitely agree	slightly agree	slightly disagree	definitely disagree
44. I enjoy social occasions.	definitely agree	slightly agree	slightly disagree	definitely disagree
45. I find it difficult to work out people's intentions.	definitely agree	slightly agree	slightly disagree	definitely disagree
46. New situations make me anxious.	definitely agree	slightly agree	slightly disagree	definitely disagree
47. I enjoy meeting new people.	definitely agree	slightly agree	slightly disagree	definitely disagree
48. I am a good diplomat.	definitely agree	slightly agree	slightly disagree	definitely disagree
49. I am not very good at remembering people's date of birth.	definitely agree	slightly agree	slightly disagree	definitely disagree
50. I find it very easy to play games with children that involve pretending.	definitely agree	slightly agree	slightly disagree	definitely disagree

Developed by:
The Autism Research Centre
University of Cambridge

Drag Racing Information sheet

School of Psychology

Information Sheet

The University of Nottingham
UNITED KINGDOM · CHINA · MALAYSIA

Assessing the role of motor cortex excitability on levels of functional impulsivity: A TMS and Transcranial Electrical Stimulation (TES) study.

Ethical Approval Number: 219
Researchers: Beverley Brown
Supervisors: Professor Stephen Jackson
Dr Danielle Ropar
Professor Georgina Jackson
Contact Details lpxbjbr@nottingham.ac.uk

Thank you for your interest in our study. Before you decide if you would like to take part, it is important for you to understand why the research is being conducted and what it will involve. Please take time to read the following information carefully.

The study involves investigating the role of motor cortex excitability and effects of low intensity Transcranial Electrical Stimulation (TES), and certain psychometric measures, on individuals' levels of functional impulsivity. TES is known to have the ability to temporarily alter neural activity in a safe and reversible way. TES is known to modulate cognitive functions in healthy individuals, but the potentials of TES have not been fully understood. The current study aims to investigate the behavioural effects of TES in healthy individuals using both physiological and behavioural measures.

If you participate, you will be taking part in a study that has two separate investigations. An inconvenience allowance is paid. During the first part of the study you will undergo TMS (transcranial magnetic stimulation), which will take approximately one hour. TMS is also known to have the ability to temporarily alter neural activity in a safe and reversible way. This technique makes it possible to measure your particular level of cortical excitability. The study will also involve having electrodes attached to your hand/wrist, and the motor area of your brain stimulated to produce a twitch in your hand muscle. To elicit this twitch in your muscle a TMS coil will be placed on the head to deliver magnetic pulses to the brain. This is a safe and painless procedure as used in the School of Psychology and has no long-term effects. The most serious known risk is epileptic seizures but these have not been reported in healthy adults at normal levels of stimulation. As a precaution you will be asked to complete a safety screening questionnaire and a follow-up questionnaire to report any unexpected after-effects.

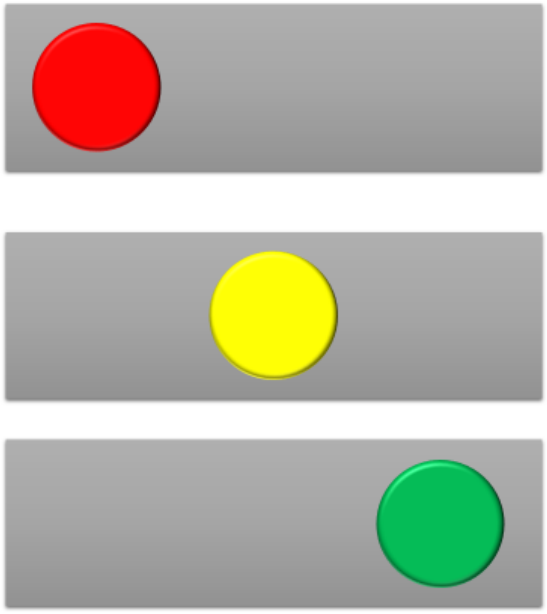
The second part of the study will involve playing a drag racing computer game. Instructions will be given on how to play the game. You will be asked to play the game twice and this will take roughly 30 minutes. You will also be asked to complete screening questionnaires and psychometric questionnaire before the experiment begins.

During the second drag racing game you will receive TES stimulation (Max: 15 minutes), which has a temporary effect of changing brain activity. The application of TES involves attaching electrodes in thin saline-soaked sponges to your head. During TES stimulation, a weak current will pass through the electrodes. While stimulated, you may experience an itching, tingling, or mild burning sensation (will not actually burn you). TES has been used widely in research for over a decade and no serious adverse effects have been reported. Currently, the only known risks are skin irritation for participants with sensitive skin or open head wounds. In the unlikely event of you noticing any adverse effects after the stimulation you should inform the researcher. This study aims to test healthy participants who are at minimal risk of experiencing any side effects of the stimulations used. Therefore, it is important that you read and answer the screening forms carefully. If you meet any of the criteria that would put you at elevated risk of side effects you will not be able to participate.

Example of TES.

If you have any questions or concerns please do not hesitate to ask now. We can also be contacted using the above email addresses. If you have any further concerns or complaints, please contact; Stephen Jackson (Chair of Ethics Committee, stephen.jackson@nottingham.ac.uk)

Drag Racing Stimuli



UPPS questionnaire

Participant Name	Age:	Gender:	Todays date:			
Below are a number of statements that describe ways in which people act and think. For each statement, please indicate how much you agree or disagree with the statement. If you **Agree Strongly** place an **X** in this box**,** if you **Agree Somewhat** circle **2**, if you **Disagree somewhat** circle **3**, and if you **Disagree Strongly** place an **X** in this box and so on. Please only choose one box per question and do not leave any boxes blank. Be sure to indicate your agreement or disagreement for every statement below. Also, there are questions on the following pages, please complete all 59 questions.			Strongly agree (1)	Somewhat agree (2)	Somewhat disagree (3)	Strongly disagree (4)
1. I have a reserved and cautious attitude toward life.						
2. I have trouble controlling my impulses.						
3. I generally seek new and exciting experiences and sensations.						
4. I generally like to see things through to the end.						
5. When I am very happy, I can't seem to stop myself from doing things that can have bad consequences.						
6. My thinking is usually careful and purposeful.						
7. I have trouble resisting my cravings (for food, cigarettes, etc.).						
8. I'll try anything once.						
9. I tend to give up easily.						
10. When I am in great mood, I tend to get into situations that could cause me problems.						
11. I am not one of those people who blurt out things without thinking.						
12. I often get involved in things I later wish I could get out of.						
13. I like sports and games in which you have to choose your next move very quickly.						
14. Unfinished tasks really bother me.						
15. When I am very happy, I tend to do things that may cause problems in my life.						
16. I like to stop and think things over before I do them.						
17. When I feel bad, I will often do things I later regret in order to make myself feel better now.						
18. I would enjoy water skiing.						
19. Once I get going on something I hate to stop.						
20. I tend to lose control when I am in a great mood.						

BIS/BAS questionnaire

BIS/BAS

Participant Name	Age:	Gender:	Todays date:			
Each item of this questionnaire is a statement that a person may either agree with or disagree with. For each item, indicate how much you agree or disagree with what the item says. Please respond to all the items; do not leave any blank. Choose only one response to each statement. Please be as accurate and honest as you can be. Respond to each item as if it were the only item. That is, don't worry about being "consistent" in your responses.			Very true for me (1)	Somewhat true for me (2)	Somewhat false for me (3)	Very false for me (4)
1. A person's family is the most important thing in life.						
2. Even if something bad is about to happen to me, I rarely experience fear or nervousness.						
3. I go out of my way to get things I want.						
4. When I'm doing well at something I love to keep at it.						
5. I'm always willing to try something new if I think it will be fun.						
6. How I dress is important to me.						
7. When I get something I want, I feel excited and energized.						
8. Criticism or scolding hurts me quite a bit.						
9. When I want something I usually go all-out to get it.						
10. I will often do things for no other reason than that they might be fun.						
11. It's hard for me to find the time to do things such as get a haircut.						
12. If I see a chance to get something I want I move on it right away.						
13. I feel pretty worried or upset when I think or know somebody is angry with me.						
14. When I see an opportunity for something I like I get excited right away.						
15. I often act on the spur of the moment.						
16. If I think something unpleasant is going to happen I usually get pretty "worked up."						
17. I often wonder why people act the way they do.						
18. When good things happen to me, it affects me strongly.						
19. I feel worried when I think I have done poorly at something important.						
20. I crave excitement and new sensations.						
21. When I go after something I use a "no holds barred" approach.						
22. I have very few fears compared to my friends.						
23. It would excite me to win a contest.						
24. I worry about making mistakes.						

Davis IRI questionnaire

INTERPERSONAL REACTIVITY INDEX

The following statements inquire about your thoughts and feelings in a variety of situations. For each item, indicate how well it describes you by choosing the appropriate letter on the scale at the top of the page: A, B, C, D, or E. When you have decided on your answer, fill in the letter next to the item number. READ EACH ITEM CAREFULLY BEFORE RESPONDING. Answer as honestly as you can. Thank you.

ANSWER SCALE:

A	B	C	D	E
DOES NOT DESCRIBE ME ME WELL				DESCRIBES VERY WELL

1. I daydream and fantasize, with some regularity, about things that might happen to me. (FS)
2. I often have tender, concerned feelings for people less fortunate than me. (EC)
3. I sometimes find it difficult to see things from the "other guy's" point of view. (PT) (-)
4. Sometimes I don't feel very sorry for other people when they are having problems. (EC) (-)
5. I really get involved with the feelings of the characters in a novel. (FS)
6. In emergency situations, I feel apprehensive and ill-at-ease. (PD)
7. I am usually objective when I watch a movie or play, and I don't often get completely caught up in it. (FS) (-)
8. I try to look at everybody's side of a disagreement before I make a decision. (PT)
9. When I see someone being taken advantage of, I feel kind of protective towards them. (EC)
10. I sometimes feel helpless when I am in the middle of a very emotional situation. (PD)
11. I sometimes try to understand my friends better by imagining how things look from their perspective. (PT)
12. Becoming extremely involved in a good book or movie is somewhat rare for me. (FS) (-)
13. When I see someone get hurt, I tend to remain calm. (PD) (-)
14. Other people's misfortunes do not usually disturb me a great deal. (EC) (-)
15. If I'm sure I'm right about something, I don't waste much time listening to other people's arguments. (PT) (-)
16. After seeing a play or movie, I have felt as though I were one of the characters. (FS)
17. Being in a tense emotional situation scares me. (PD)
18. When I see someone being treated unfairly, I sometimes don't feel very much pity for them. (EC) (-)
19. I am usually pretty effective in dealing with emergencies. (PD) (-)