INDIVIDUAL DIFFERENCES IN THE INHIBITION OF STIMULUS-STIMULUS AND STIMULUS-RESPONSE ASSOCIATIONS AND MEDICATION EFFECTS ON ASSOCIATIVE LEARNING IN TOURETTE SYNDROME AND ADHD

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ABSTRACT

Inhibition deficits have been the subject of intensive investigation in the context of 'impulsivity', both in relation to normal variation and clinical disorder. Until now the focus has been on inhibition of stimulus-response (S-R) associations, using tasks such as the Go/NoGo. However, a chain of antecedent stimuli may be important in the triggering of any particular response, which can thus depend on other aspects of the context beyond the immediately preceding stimulus. The present thesis therefore examines the inhibition of stimulus-stimulus (S-S) associations in both normal participants and participants with Attention Deficit Hyperactivity Disorder (ADHD) or Tourette syndrome (TS).

Two novel conditioned inhibition procedures with engaging storylines (a serially presented 'Mission to Mars' version and a simultaneously presented comic book based Wolverine/Weapon X task) were developed to be age appropriate in the level of understanding, and ease of use for younger participants. The tasks were first validated in a series of experiments conducted with undergraduate populations, assessing variation in performance in relation to individual differences and comparing performance with established tests of response inhibition, measured using Go/NoGo, colour-word Stroop and Simon tasks. The studies with undergraduates used the Craver and White's (1994) BIS/BAS (behavioural inhibition system/behavioural activation system) questionnaire, as well as questionnaire measures of ADHD and TS. The results showed that in general, TS and ADHD-like individual difference behaviours had no effect on either S-S, or S-R inhibition in the normal population. There were similarly no differences in inhibition in relation to the BIS/BAS scores.

However, inhibition deficits were expected to be more extreme in cases of clinically diagnosed ADHD and TS. These disorders have been attributed to inhibitory deficits resulting from dysfunction of the dopamine system and the basal ganglia. At face value, 'prediction error' models of learning generate the same prediction of impaired conditioned inhibition in cases of dopaminergic disorder (Schultz, Dayan, & Montague, 1997; Schultz & Dickinson, 2000). Counter to prediction, both the TS and ADHD groups showed overall normal conditioned inhibition compared to matched controls. However, unplanned comparisons revealed significant effects of medication in both ADHD and TS groups. In both tasks, there was a reduction in the expression of conditioned inhibition in TS participants medicated with clonidine, with no effect of medication on excitatory learning. In the ADHD clinical group, there was an overall improved performance of the Weapon X test discrimination by the participants on the higher dosage (or longer treatment time) of methylphenidate. Thus, it appears that the medications used for TS and ADHD had distinguishable effects on the excitatory (methylphenidate) versus inhibitory (clonidine) learning demonstrated in the conditioned inhibition tasks.

The results of the current investigation demonstrate that the inhibition of S-S associations is unaffected by TS and ADHD. This provides a possible avenue for behavioural modification treatments of ADHD and TS, which modify S-S associations that are believed to bring about the unwanted behaviours observed in the clinical populations. The present results also suggest that the effectiveness of such behavioural treatments will be influenced by medication for these disorders.

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CHAPTER 1: GENERAL INTRODUCTION

Inhibition is an important aspect of behaviour control that prevents an individual from committing certain behaviours deemed inappropriate in certain environments or situations. For example, in social situations, individuals often censure thoughts and behaviours (such as speaking ill of someone whom they dislike in their presence or shouting obscenities in a formal public setting upon hearing bad news) that would be considered inappropriate and abnormal to all those in attendance, or bring about psychological and social discomfort for the individual him/herself. However, there are certain psychological disorders in which such this level of behavioural inhibition broken down. Two well-known examples of disorders of inhibition are Attention Deficit/Hyperactivity Disorder (ADHD) and Tourette Syndrome.

Previous research has implicated that these disorders may result from an inhibitory deficit (Barkley, 1998; Gilbert, et al., 2004). Research has shown that while response inhibition (the inhibition of stimulus-response (S-R) associations) deficits in ADHD have been demonstrated by a number of studies (Berwid, et al., 2005; Bitsakou, Psychogiou, Thompson, & Sonuga-Barke, 2008; Klein, Wendling, Huettner, Ruder, & Peper, 2006; Seidman, Biederman, Faraone, Wever, & Ouellette, 1997; Trommer, Hoeppner, Lorber, & Armstrong, 1988; Young, Bramham, Tyson, & Morris, 2006), research has shown little evidence for response inhibition deficits in TS (Channon, et al., 2009; Marsh, Zhu, Wang, Skudlarski, & Peterson, 2007; Ozonoff, Strayer, McMahon, & Filloux, 1994; Roessner, Albrecht, Dechent, Baudewig, & Rothenberger, 2008; Stebbins, et al., 1995). However, despite the majority of research having focused on possible behavioural inhibition deficits (i.e. response inhibition deficit), little or no research has investigated deficits in the more cognitive aspects of inhibition. With regards to TS, the formation of stimulus-stimulus (S-S)

associations have been implied as a possible cause of tics, in that, for example, the sound of a cough heard on a bus may result in the onset of a premonitory sensation that results in a tic (James F. Leckman, 2003; Verdellen, Keijsers, Cath, & Hoogduin, 2004). Moreover, preventative measures such as habit reversal (HR) and exposure and response prevention (ER) therapies that act to interrupt S-S associations that have formed through classical conditioning that lead to the onset of tics have proven to be successful (Verdellen, et al., 2008; Verdellen, et al., 2004).

The current investigation was set up to examine the possibility of a deficit in the inhibition of S-S associations in TS and ADHD populations. S-S associations form the basis of classical conditioning, and as such, conditioned inhibition provides means to investigate the inhibition of S-S associations (Pavlov, 1927; Rescorla, 1969). The term inhibition has been used in the literature in a variety of different ways and to refer to different underlying psychological processes. Thus, the general introduction will first consider what is meant by inhibition and how the term will be used in the present thesis. In particular, the inhibition of S-S associations will be measured using procedures developed for the animal learning literature. The individual measures used in the thesis will be described next. I will then go on to outline our current understanding of the neural and psychological bases of (1) ADHD and (2) TS as the results obtained testing participants with these disorders will be presented in Chapters 4 and 5.

1.1: INHIBITION

There are various aspects to the phenomenon of inhibition. With numerous meanings attributed to the term 'inhibition', how can one find a common connection between the various definitions used in psychopathology? Nigg (2001) categorized inhibition (as related to theories of ADHD) in terms of executive and motivational inhibition. According to Nigg, *executive inhibition* involves the suppression of a cognition or response directed at achieving an internally represented goal at a later time. Executive inhibition is measured by such tasks as the Stroop (where the individual inhibits a competing stimulus represented by a colour word such as the word “red” from interfering with naming the colour of the ink in which the word is printed; for example, the word “red” written in blue ink). Nigg defined *motivational inhibition* as the cessation of actions and behaviours that are driven by fears or anxieties resulting from signals of danger, punishment, or unexpected stimuli. Motivational inhibition is derived from Gray's (1982) Behavioural Inhibition System (BIS) theory. According to Gray (1982; 1994), behaviour is mediated by the activation of distinct systems: (1) The behavioural activation system (BAS) which activates a behaviour in response to cues that may signal probable non-punishment or reward, and (2) the behavioural inhibition system (BIS) which inhibits a behaviour in response to cues that may signal probable punishment or non-reward. Gray further stated that it is the relative strength of the BIS or the BAS system (which are antagonistic to one another) that dictate the individual differences in personality (i.e. people with a stronger BAS system or a weaker BIS system tend to be impulsive, whereas people with a stronger BIS system or a weaker BAS system tend to be anxious). As will be described later on, Gray’s BIS/BAS model has been used as a model of ADHD (Quay, 1988a, 1988b, 1997).

The majority of the researches for the presence of an inhibitory deficit in TS and ADHD have involved the search for deficits in behavioural inhibition involving S-R associations (as measured by such tasks as the Go/NoGo, The Stoop and the stop signal task among others). However, few investigations have involved cognitive inhibition deficits involving S-S associations. With regards to TS, S-S associations provide a mechanism through which the environment may act as triggers for the onset of tics (James F. Leckman, 2003) such as the sound of a cough initiating a tic in a TS patient.

A method through which S-S associations can be investigated is through classical conditioning (Pavlov, 1927). Although relatively sparse in numbers, a number of investigators have used classical conditioning to study S-S associations in TS and ADHD. Pliszka, et al. (1993) investigated punishment sensitivity in ADHD children using an aversive classical conditioning paradigm (which used a loud noise as the aversive stimulus). The authors found no significant difference between the ADHD and the normal children in the level of aversive conditioning demonstrated. Moreover, Oades and Müller (1997) investigated the development of conditioned blocking with in ADHD, TS and normal children. Blocking occurs when the S-S associative learning between a stimulus (CS_b) and an unconditioned stimulus (UCS) is blocked by the pairing the stimulus in question another stimulus (CS_a) that had been previously associated with the UCS. The authors found that while the ADHD group showed impaired conditioned blocking in later development (ages 11-14) compared to the matched controls, conditioned blocking was completely absent in the TS group regardless of age. Also, in a study of 'latent inhibition' (in which stimulus pre-exposure should reduce S-S associative learning) in TS population, Swerdlow, Magulac, Filion, & Zinner (1996) found this effect to be normal in TS participants. However to date,

no research has examined the inhibition of an S-S association in either the TS or ADHD population. Neither conditioned blocking nor latent inhibition are true measures inhibitory S-S learning. Although pre-exposure to a stimulus can retard later S-S associations with the previously exposed stimulus in latent inhibition, the stimulus does not become inhibitory. Similarly, in blocking, the previous CS_1-UCS association only retards later S-S association when a new stimulus (CS_2) is introduced in a CS-UCS association in compound with CS_1 (CS_1CS_2-UCS). The true measure of an inhibition of an S-S association is achieved through conditioned inhibition.

1.2: CLASSICAL CONDITIONING AND CONDITIONED INHIBITION

The concept of conditioned inhibition was first introduced by Pavlov (1927). In a conditioned inhibition paradigm, the presence of a stimulus (CS_2) during an excitatory association (CS_1-UCS) signals the absence of the otherwise expected event (CS_2, CS_1-No UCS), thereby becoming a conditioned inhibitor ([CS_2]-). Rescorla (1969) stated that although the properties of conditioned inhibition are not well specified, there are a few points of agreement listed in psychological literature: (1) The past experience of the organism dictates the power of conditioned inhibition to produce changes in behaviour, and (2) based on those past experiences, the outcome would be that of a stimulus becoming capable of reducing a behavioural change attributed to excitation. According to Rescorla, conditioned excitation is defined by satisfying two conditions that he defined as "an operation relating the conditioned stimulus (CS) and the unconditioned stimulus (UCS), such as a pairing of the two or the arrangement of a positive contingency between them, and a change in behaviour resulting from this operation". Rescorla noted that several

conditions must be met when identifying a conditioned inhibitor. He stated that the conditioned inhibitor must be described in relation to the same UCS as that was used in identifying the conditioned excitor. Moreover, the tendency that is assumed to be under the control of the conditioned inhibitor must be directly opposite to that of the conditioned excitor (i.e. if the excitor increases the level of responding, the inhibitor must reduce it). Conditioned inhibition can be appetitive or aversive; the only limiting factor is that it has to act in direct opposition to the conditioned excitor. Rescorla stated that to be identified as a conditioned inhibitor, a stimulus must obtain its inhibitory power through some relation it has with the UCS based on the subject's past experience.

The Rescorla-Wagner model (Rescorla & Wagner, 1972) describes Pavlovian conditioning in terms of changes in associative strength (V) between a signal (CS) and the unconditioned stimulus (UCS) that ensues. According to the model, on a learning presentation where a compound stimulus AX is followed by a UCS (UCS_1): $\Delta V_A = [\alpha_A \beta_1] (\lambda_1 - V_{AX})$ and $\Delta V_X = [\alpha_X \beta_1] (\lambda_1 - V_{AX})$, where $V_{AX} = V_A + V_X$. In this model, λ_1 represents the associative strength required to successfully predict the occurrence of the reinforcer UCS_1, and α and β represent learning rate parameters that have fixed values based on the physical properties of the CS and UCS respectively. The Rescorla-Wagner model describes a conditioned inhibitor is as a stimulus with a negative V, which reduced the total positive strength on a given presentation in a paradigm where A is followed by a UCS (thereby V_A is close to λ) and AX is followed by no UCS. When X is initially added to A, it has a V value of 0 (because initially it is neutral, thus $V_X = 0$). However since AX is continuously followed by non reinforcement, V_{AX} has a value of 0, and since V_A has a positive value and the sum of V_A and V_X has a value of zero, V_X decrements from an initial zero value to a negative value. It was

from The Rescorla-Wagner model of learning that the prediction-error learning model was derived.

1.2.1: DOPAMINE PREDICTION ERROR MODEL OF LEARNING

According to the prediction error model of learning (Schultz, 2007; Schultz, et al., 1997; Schultz & Dickinson, 2000), learning is dependent on the unpredictability of the reward by the sensory stimulus, and the proposition that no learning will take place if reward is fully predicted by the sensory stimulus in question. This model is best described with reference to the observation of learning in a conditioned blocking paradigm (Kamin, 1968) shown in Table 1-1.

	Stage 1	**Stage 2**	**Test**
Experimental:	A → Reinforcer	AX → Reinforcer	X
Control:	B → Nothing	BY → Reinforcer	Y

Table 1-1: A model of conditioned blocking (Kamin, 1968)

According to Schultz and Dickinson (2000), The degree of the unpredictability of a reinforcer can be summarized in terms of $(\lambda - \sum V)$ where λ is the associative strength required to successfully predicted the occurrence of a reinforcer and $\sum V$ is the sum of the associative strength of all the stimuli present during a learning episode. Thus $(\lambda - \sum V)$ represents the prediction error. Because X and Y have been presented an equal amount of times with the reinforcer, one would expect that the associative strength of X and Y be equal. However, as a result of stage 1 where unlike A, B was never paired with the reinforcer, the $\sum V$ in the start of stage 2 of the control group equals to zero (since neither B nor Y was previously paired with the reinforcer). Thus, the prediction error equals λ, which represents the fact that in this case, the reinforcer is completely unexpected. For the

experimental group however, in stage 2, since A completely predicts the reinforcer (due to its association with the reinforcer in stage 1), the $\sum V$ in the start of stage 2 of the experimental group equals to λ and thus the prediction error equals zero, which represents the fact that in this case, the reinforcer is completely expected.

According to Schultz and Dickinson (2000), dopamine neurons show homogeneous short latency response to two classes of stimuli; attention-inducing stimuli (such as a novel or intense stimulus) and reward-related stimuli (which also includes auditory/visual stimuli that predict such rewards). According to the authors, when presented with attention-inducing stimuli, such presentations result in an activation-depression sequence of activity in the dopamine neurons. Moreover, the presentation of reward-related stimuli (as well as auditory/visual stimuli that predict such rewards) results in the pure activation of the dopamine neurons. Dopamine neurons code errors in the prediction of reward in that primary rewards that are unpredicted during the initial behavioural reaction elicit activation of the dopamine neurons. This activation decreases with continuing experience as the reward becomes predicted by the conditioned stimuli. Over time, the conditioned reward-predicting stimulus induces pure activations similar to the reward itself. However, if the predicted reward fails to occur resulting in an error in responding, a depression in the dopamine neurons is observed at the time when the reward would have been presented. This in turn shows that dopamine neurons not only code for the expected reward but also for the specific time of the reward as well (Schultz, 2007; Schultz, et al., 1997; Schultz & Dickinson, 2000; Tobler, Dickinson, & Schultz, 2003; Waelti, Dickinson, & Schultz, 2001). As such, the dopamine neurons code for the S-S associations acquired during classical conditioning.

In a test of the dopamine prediction error hypothesis, Waelti, Dickinson and Schultz (2001) found that the deactivation of the dopamine neurons corresponded to the behavioural results of the conditioned blocking paradigm. Moreover, an investigation into whether dopamine neurons can differentiate between the prediction of reward (conditioned excitor) and non-reward (conditioned inhibitor) using a conditioned inhibition paradigm was undertaken by Tobler, Dickenson and Schultz (2003). The authors found that while the conditioned excitor led to the activation of all the analyzed dopamine neurons (242% above baseline), the conditioned inhibitor produced a depression of approximately 70% of the neurons tested (median level of 35% below baseline), while producing minor activation in the remaining 30% (median level of 69% above baseline). These results indicated that dopamine neurons distinguish between a conditioned excitor and a conditioned inhibitor. Moreover the authors noted that phasic activation of the dopamine neurons occurred in response to reward-predicting stimuli, in that the presentation of reward-omitting stimuli (i.e. conditioned inhibitor) results in a minor activation, followed by notable depression of the dopamine neurons. Further support is also provided by Harmer and Phillips (1999) who investigated whether enhanced conditioning occurred in sensitized animals (whom had prior exposure to intraperitoneal (IP) d-amphetamine treatments) using a conditioned inhibition paradigm. The authors found that prior treatment with the dopamine releasing agent d-amphetamine enhanced the acquisition of both conditioned excitation as well as conditioned inhibition in sensitized animals compared to vehicle controls.

With regards to neuroanatomical structures, previous research has shown support for the involvement of the basal ganglia in the acquisition of S-S associations (Brown, Bullock, &

Grossberg, 1999; Rhodes & Killcross, 2007; Winstanley, Baunez, Theobald, & Robbins, 2005). In a model of the involvement of the basal ganglia in the learning of excitatory and inhibitory associations, Brown, Bullock, and Grossberg (1999) suggest that the reward signal originates in the lateral hypothalamus, which in turn directly stimulates the pedunculopontine tegmental nucleus (PPTN). The PPTN in turn fires a brief burst that excites the substantia nigra pars compacta (SNc) (via cholinergic and/or glutaminergic projections) prior to habituating, which leads a phasic dopamine burst in the striatum at the time of the primary reward. It is supposed that at some time prior to the actual reward, the CS is received and stored in the in the prefrontal cortex as a working memory. The CS trace generates output signals along the striosomes and well as the ventral striatum, in that, the occurrence of the reward results in a dopamine burst which facilitates long term potentiation (LTP) in the limbic cortical-ventral striatal path. The limbic cortical-striosomal projections, through metabotropic glutamate receptors, activate a variety of Ca2+ spikes in the striosomal cells. Thus, the CS-activated limbic-cortical connections to any spiking components of the striosomal timing spectrum is strengthened by the arriving dopamine burst from the SNc, which leads to the striosomal cells learning to inhibit the dopamine burst through the inhibitory striosomal-SNc path. Thus according to this model, when CS is received at the expected time prior to the reward during later trials, the trace memory of the CS activates the ventral striatal cells which cause the excitation of the PPTN. This excitation leads to an immediate dopamine burst in the SNc that in turn cause an adaptively timed inhibition of the SNc by their striosomal cells. As such, the absence of a reward signal in a particular trial leads to a phasic dip in the dopamine signal due to striosomal inhibition.

Based on this model, it can be postulated that abnormalities in the dopamine system can be investigated through the examination of S-S associations.

1.2.2: TRANSLATIONAL MODEL OF CONDITIONED INHIBITION

While the study of conditioned inhibition has occurred predominantly under animal learning, several studies have attempted to create a translational model animal learning conditioned inhibition paradigm to be used on human subjects (Karazinov & Boakes, 2004; Migo, et al., 2006; Neumann, Lipp, & Siddle, 1997; O'Boyle & Bouton, 1996; Williams, 1995; Williams, Sagness, & McPhee, 1994). Karazinov and Boakes (2004) investigated a translational model of conditioned inhibition using a food-migraine association scenario (where the presence or combinations of foods were related to the occurrence of a migraine) on a normal population. The authors found that the conditioned inhibitor reduced the predictive ratings of a transfer stimulus to a greater level than when the transfer stimulus was paired with a negative control cue (a stimulus that was presented alone throughout the training phase followed by the absence of the UCS). According to the authors, the results indicated that a conditioned inhibitor provides a positive training cue with greater level of inhibitory strength greater than any that would be produce by a negative contingency presented alone.

Moreover, O'Boyle and Bouton (1996) investigated conditioned inhibition in human subjects in a multiple category-learning paradigm. Their task involved a game called "Clues and Culprits" where subjects were asked to judge the predictive strength of the clues paired with culprits in a series of hypothetical burglaries, where one clue was paired with

one culprit when presented on its own, yet, when presented with a second clue, it was paired with a second culprit (A→culprit 1, AX→culprit 2). According to the authors, X should acquire inhibitory status for the first culprit (A+, AX-) in this feature negative procedure, as it should acquire greater inhibitory strength than a differential cue merely associated with a second culprit (A→culprit 1, X→culprit 2). However, O'Boyle and Bouton reported that inhibition occurred in both the feature-negative as well as the differential procedures and that the level of inhibition did not differ between procedures. Thus, the association of the conditioned inhibitor (i.e. negative feature) and the differential cue with culprit 2 was sufficient to inhibit culprit 1. The authors state that both feature-negative and differential cues act as negative predictors of the expected event (or the culprits with which they were contrasted with). Moreover, O'Boyle and Bouton also state that both humans and animals treat the omission of an event as an event itself.

Previously, Migo et al. (2006) created a test of conditioned inhibition as a means of developing a more direct method of assessing cognitive inhibition to evaluate inhibitory processes in associative learning as well as identified individual differences to which it relates (based on findings that many of the dysfunctional processes found in schizophrenics are also observed in individuals who score high on schizotypal personality scales). In their task, a visual stimulus (an exploding rocket) was presented following the conditioned inhibitor to signify the absence of a UCS (an intact rocket). The authors reported that conditioned inhibition was successfully demonstrated and confirmed by the summation tests. Moreover, their results also showed that the level of conditioned inhibition was negatively associated with schizotypy.

Thus, translational models of conditioned inhibition have been successfully applied to human participants. The current sets of investigations discussed in the following chapters involve conditioned inhibition paradigms adapted from the task developed by Migo et al.

1.3: ATTENTION DEFICIT/HYPERACTIVITY DISORDER (ADHD)

ADHD is a prevalent childhood psychiatric disorder defined by impaired and inappropriate levels of impulsivity, inattentiveness, and hyperactivity (American Psychiatric Association, 2000; Kytja & Voeller, 2004; Sheppard, Bradshaw, Purcell, & Pantelis, 1999) affecting approximately anywhere between 5-18% of school-aged children (Barkley, 1997, 1998; Faraone, Sergeant, Gillberg, & Biederman, 2003; Kytja & Voeller, 2004; Pliszka, et al., 1993; Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007) with males being diagnosed notably more frequently than females (Barkley, 1997, 1998; Pliszka, et al., 1993).

The diagnosis of ADHD is based on a list of nine hyperactivity-impulsivity behavioural characteristics (which includes such items as: 'Often fidgets with hands or feet or squirms in seat', and 'Often has trouble waiting one's turn' among others) and a list of nine inattention behavioural characteristics (which includes such items as 'Is often easily distracted, and 'Often does not seem to listen when spoken to directly' among others) outlined in the DSM-IV (American Psychiatric Association, 2000). According to the DSM-IV at least six items from each category must be met as criteria to be diagnosed with ADHD (Kytja & Voeller, 2004). However, the diagnosis of ADHD has not been without controversy. While many view ADHD as a distinct psychological disorder, there are others who do not share this view. Furman (2005) has proposed that ADHD may not be a discrete disease

entity but perhaps a collection of symptoms from other disorders that represent a common behavioural pathway of learning, emotional and psychological problems. According to Furman, support for this notion comes from the findings that ADHD rarely occurs alone and is often comorbid with other psychological disorders such as TS. Further support comes from the lack of the discovery of unique aetiology or genetic markers for ADHD (Furman, 2005; Sheppard, et al., 1999). However, the majority of research tends to discuss ADHD as a distinct psychological disorder (Barkley, 1997; Castellanos, et al., 1996; Castellanos, et al., 2001; De Quiros & Kinsbourne, 2001; Giedd, Blumenthal, Molloy, & Castellanos, 2001; Kytja & Voeller, 2004; Quay, 1988a, 1997; Schachar, Mota, Logan, Tannock, & Klim, 2000; Sheppard, et al., 1999).

Neurophysiologically, the involvement of the basal ganglia, the frontal lobes, the corpus callosum, and the cerebellum in ADHD have been found (Giedd, et al., 2001). Previous researchers have noted that ADHD patients appear to possess smaller frontal lobe, cerebellum, and regions of the basal ganglia such as the caudate nucleus compared to controls (Aylward, et al., 1996; Castellanos, et al., 1996; Kytja & Voeller, 2004). Casey et al. (1997) investigated the relationship between specific frontostriatal structures such as the basal ganglia and the prefrontal cortex and the response inhibition deficits observed in ADHD, as demonstrated by three tasks measuring the three stages of attentional processing. The tasks in question were a sensory task (forced choice discrimination task), a response selection task, and a response execution task (an auditory Go/NoGo task) which assessed proponent response inhibition. The results of the investigation showed a significant correlation between task performance and volumetric measures of the prefrontal cortex, the caudate nucleus and globus pallidus (but not the putamen). More

specifically, correlation between the prefrontal and caudate volumes and task performance were predominantly observed in the right hemisphere. The authors found that the right prefrontal and right caudate measures correlated with the sensory task performance, while the globus pallidus measure and the caudate symmetry correlated with the performance of response selection and response execution. The results further showed that while the caudate and globus pallidus measures correlated with performance on both the control and the inhibition trials, only the prefrontal measures correlated with performance on the inhibitory conditions of the tasks. Thus, Casey et al. concluded that while the right prefrontal cortex functions in suppressing attentional and behavioural responses to irrelevant but salient stimuli, the basal ganglia functions in the execution of the behavioural responses.

Stemming from the neurophysiology of ADHD, several researches have implicated the involvement of dopamine and the dopamine system in ADHD (Cook, et al., 1995; Kytja & Voeller, 2004; Solanto, 2002). A number of studies have reported an association between ADHD and the dopamine transporter gene, where an association between ADHD and the 480-bp DAT1 allele of the dopamine transporter gene using family-based association studies (Cook, et al., 1995; Gill, Daly, Heron, Hawi, & Fitzgerald, 1997). This may explain the efficacy of methylphenidate, a dopamine agonist purported to act by blocking the dopamine transporter (Cook, et al., 1995; Krause, Dresel, Krause, Kung, & Tatsch, 2000; Nora D. Volkow, Wang, Fowler, & Ding, 2005; N. D. Volkow, et al., 1998) in the treatment of ADHD (Lopez, Silva, Pestreich, & Muniz, 2003; Pelham, et al., 2001; Swanson, Kinsbourne, Roberts, & Zucker, 1978). Indeed, in a PET study of the pharmacokinetics of methylphenidate hydrochloride (Ritalin), Volkow et al. (1995) observed that the maximal

concentration occurred in the striatum. Thus, based on research evidence, the involvement of the basal ganglia and the dopamine system in ADHD is quite apparent.

1.3.1: ADHD AND INHIBITION

It is widely believed that the psychological symptoms of ADHD arrive from deficient inhibitory control (Barkley, 1997; Ozonoff, Strayer, McMahon, & Filloux, 1998; Pliszka, et al., 1993; Quay, 1988a, 1997; Schachar & Logan, 1990; Schachar, et al., 2000). In the Hybrid Model of ADHD (Figure 1-1) proposed by Barkley (1997), Barkley specifies poor behavioural inhibition as the core deficiency of the disorder, linking behavioural inhibition with four executive functions, which depends upon such inhibition.

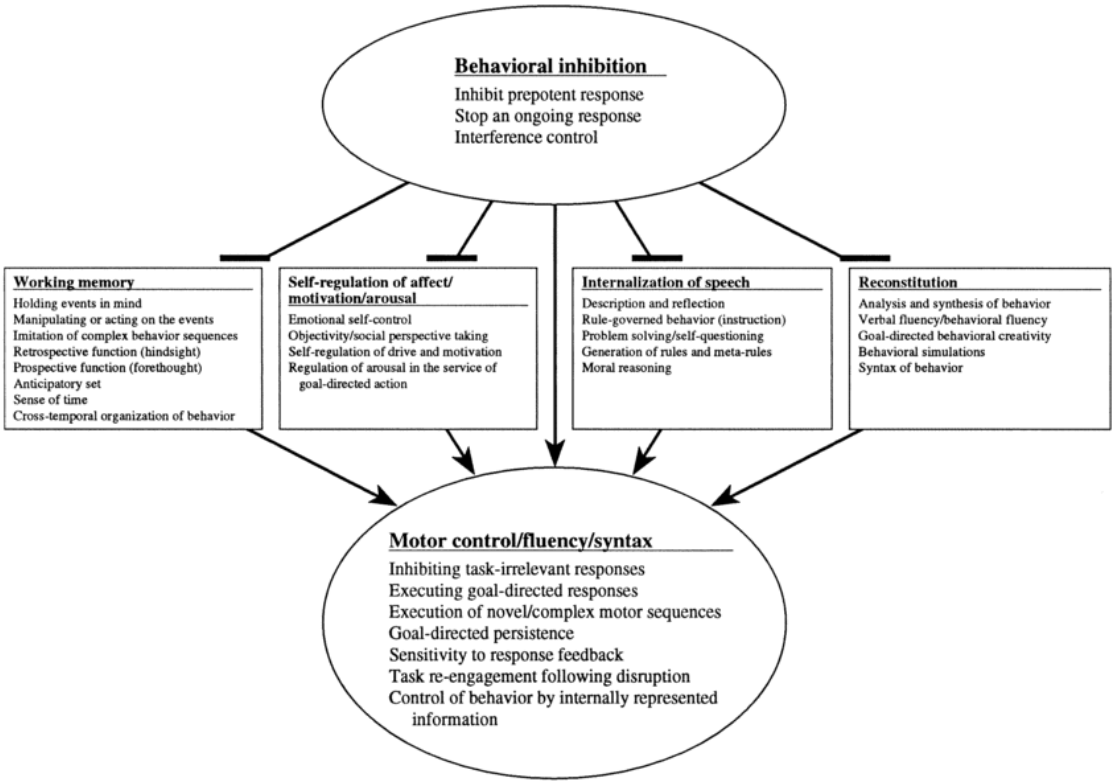

Figure 1-1: Barkley's Hybrid Model of executive functions. Figure obtained from Barkley (1997).

Barkley's model describes behavioural inhibition as a product of two processes: (1) Response inhibition - the capacity to inhibit prepotent responses that have been initiated (thereby creating a delay in responding to an event) and (2) interference control - The protection of the delay in responding created as a result of response inhibition, the self directed action and the resulting goal directed behaviour from disruption by competing events and their prepotent responses (Barkley, 1997, 1998). Barkley states that as a result of the postponement of the prepotent response and the resulting delay that it creates, the occasion is set for four executive functions to act and modify the behaviour of the individual to achieve a greater, yet temporally distant reward/consequence as opposed to a more immediate one. The four executive functions are (1) Working memory – defined as the ability to maintain mental information on mind that can be stored and recalled to guide later motor responses; (2) self-regulation of affect/motivation/arousal (i.e. emotional self control) - described as the control of the initial emotional response that may have been elicited (which at times may be inappropriate); (3) internalization of speech - which according to the author allows one to reflect upon and thus create new rules for behaviour as well as provide instruction to control motor responses that lead to the behaviour, or the inhibition of it; and (4) Reconstitution –described as the use of private visual memory that during the delay can be used to disassemble the event in order to extract more information from it and recombine to create new ideas and new responses prior to the preparation of the response to the event in question. The creation of these rules for controlling behaviours allows the reduction in the control of behaviours by the surrounding context greater transfer of control to internally represented information or rules. Barkley states that the behavioural inhibitory deficit indirectly disturbs the operation of the noted four executive

functions that subserve goal directed behaviour and self control, thereby allowing immediate context and its impending consequences to control the behaviour of individuals with ADHD. Barkley's model is one of several models that attempt to define ADHD with respect to inhibitory deficits.

Based on Gray's BIS/BAS model of behaviour, Quay (1988; 1997) proposed a model of ADHD that suggested that ADHD in children is as a result of an underactive BIS. According to Quay's model, children with ADHD should be less responsive to punishment compared to controls. Working under a hypothesis based on Quay's model of ADHD, Oosterlaan and Sergeant (1996) compared the performance of ADHD children, anxious children and aggressive children on the Stop Signal task. The stop-signal paradigm involved engaging the subjects in a primary task (such as forced-choice letter discrimination) where on several occasions, they are presented with a stop-signal stimulus (which in their experiment was represented by a tone), which required the subjects to immediately inhibit their response. Oosterlaan and Sergeant found that the ADHD and the aggressive group demonstrated the poorest performance on the task, which the authors attributed to deficient inhibitory control.

The findings by Oosterlaan and Sergeant lend credence to the second type of inhibition mentioned by Nigg (2001) as noted above, namely that of motivational inhibition. According to Gray (1982; 1994), underactivity in the BIS system results in impulsive behaviours whereas BIS overactivity results in anxiety. As such, in accordance to the Gray's BIS theory, the level of inhibition demonstrated by individuals with a high level of anxiety should be greater than those demonstrated by individuals with ADHD (Jeffrey Alan Gray,

1982; Jeffrey Allan Gray, 1994), as observed in the investigation by Oosterlaan and Sergeant (1998). Moreover, according to a model of ADHD proposed by Quay (1988; 1997), which is based on Gray's BIS/BAS model, children with ADHD should be less responsive to punishment compared to controls.

Based on the notion that the activation of the behavioural activation system (BAS) can be measured physiologically via the heart rate and the behavioural inhibition system (BIS) via skin conductance, Iaboni, Douglas and Ditto (1997) investigated BIS and BAS activity using a motor response paradigm. In their investigation children were expected to perform a repetitive motor task (during which they had to turn off a light by pressing the adjacent button to the light) for which they won a reward except during extinction trials where no reward was presented. The authors found that while the heart rate of normal children rose in presence of a reward and their skin conductance rose when the reward was taken away, ADHD children failed to show the increase in skin conductance, which the authors attributed to a weak BIS. However, despite the findings of Iaboni, Douglas and Ditto, there has not been much experimental support for Quay's theory. In an investigation of how the levels of behavioural activation (BAS) and inhibition (BIS) relate to the lifetime diagnosis of a variety of psychological disorders including ADHD, Johnson, Turner, & Iwata (2003) failed to find a link between the BIS/BAS and ADHD.

Based on the works of Gray (1982; 1994) as well as Quay's model (1988a, 1997), which suggested that with respect to the Gray's BIS/BAS model, children with ADHD should be less responsive to punishment compared to controls to lower than optimum level of activity in the BIS system in children with ADHD, Pliszka, Hatch, Borcherding, & Rogeness

(1993) set out to test aforementioned hypothesis using an aversive classical conditioning paradigm. The authors used a loud white noise as the aversive unconditioned stimulus (the responses produced were measured as changes in heart rate and skin conductance of the participant). However, their findings failed to support Quay's hypothesis, in that no difference between the ADHD group, the ADHD-Anxiety comorbidity group, and the control group was observed with respect to responding to a conditioned stimulus signalling the occurrence of an aversive unconditioned stimulus.

The majority of the evidence for inhibitory deficits in ADHD results from studies investigating executive function deficits in ADHD. Working under the hypothesis that ADHD is a disorder of inhibitory control deficiency, Schachar and Logan, (1990) investigated the development and pathology of inhibitory control through the task they identified as *the stop-signal paradigm*. The results showed that the ADHD group demonstrated deficient inhibitory control compared to all other comparison groups (normal controls, learning disorder, emotional disorder, conduct disorder and comorbid ADHD-conduct disorder). Moreover, in an investigation of inhibitory control in ADHD children using three inhibitory tasks (the Stop signal, the Go/NoGo and a modified version of the Stroop task), Bitsakou, Psychogiou, Thompson, & Sonuga-Barke (2008) found that ADHD children demonstrated significant deficits compared to the controls on all of the inhibitory tasks, reinforcing the presence of inhibitory deficits in ADHD. Similar finding of significant inhibitory deficits (predominantly response inhibition) in ADHD have been reported by a number of other investigators as well (Engelhardt, Nigg, Carr, & Ferreira, 2008; Goldberg, et al., 2005; Iaboni, Douglas, & Baker, 1995; Oosterlaan & Sergeant, 1998; Young, et al., 2006).

Similar to ADHD, disorders that are often comorbid with ADHD are also attributed to deficits in behavioural inhibition. Among these is a disorder that has the highest comorbidity rate with ADHD, namely TS.

1.4: TOURETTE SYNDROME (TS)

TS has been identified as a disorder of inhibitory deficit (Brand, et al., 2002; Comings & Comings, 1987; Georgiou, Bradshaw, Phillips, Bradshaw, & Chiu, 1995; Gilbert, et al., 2004; Sheppard, et al., 1999; Swerdlow, et al., 1996). TS is a developmental disorder characterized by involuntary, repetitive, stereotypic tics, both motor and vocal (Albin & Mink, 2006; Chowdhury, 2008; Jankovic, 2001; James F. Leckman, 2003; Robertson, 2000, 2006; Sheppard, et al., 1999; Spencer, et al., 1998; Swerdlow, 2001; The Tourette Syndrome Classification Study Group, 1993). Developmentally, the onset of tics typically occurs between the ages of 3 and 8 years, peaks in the early teens, and reduces by the age of 19 or 20 years (Chang, Tu, & Wang, 2004; Chowdhury, 2008; Dooley, Brna, & Gordon, 1999; James F. Leckman, 2003; James F. Leckman, et al., 1998). Clinical features of TS include motor & vocal tics lasting more one year that manifest during childhood, which fluctuate in type, frequency and anatomical distribution. The occurrences of tics in general tend to ebb and flow, persisting for lengths of time as little as weeks and as much as years, which suddenly cease. The tics may be simple motor (eye blinks, nose twitches, etc…), simple vocal (grunts, throat clearing, etc…), complex motor (touching, hitting, scratching, etc…), or complex vocal (coprolalia, uttering phrases, etc…). Moreover, the tics may be initiated by an urge or a sensation, and may increase during periods of stress. It has been noted that motor

and phonetic tics are often preceded by premonitory sensations (such as burning sensation of the eye before a eye blink tic, or a sore throat sensation before grunting), which are alleviated by the performance of the tic (Jankovic, 2001; James F. Leckman, 2003; J. F. Leckman, Walker, & Cohen, 1993). As noted above, the comorbidity of TS and ADHD is quite prevalent (Kurlan, et al., 2002; Nigg, 2001; Ozonoff, et al., 1998; Robertson, 2006). In an analysis of 6805 cases obtained from the Tourette syndrome International database Consortium (TIC), Freeman (2007) reported a TS-ADHD comorbidity rate of 55.6%. (OCD was reported in 22.3% of the TS cases).

The diagnosis of TS can often is difficult, as for some individuals, the tics may go unnoticed, or be diagnosed as somatic tics. The Tourette Syndrome Classification Study Group (1993) has outlined a set of criteria for the definite diagnosis of TS. According to the group, for the diagnosis of TS, both multiple motor and one or more vocal tics must be present at some time during the illness, although not necessarily concurrently. Moreover, tics may occur many times a day (usually in bouts), nearly every day, or intermittently throughout a period of more than a year. In addition, the anatomic location, number, frequency, complexity, or severity of tics changes over time. The onset of the tics must occur before the age of 21. In addition, to be diagnosed with TS, involuntary movements and noises cannot be explained by other medical conditions.

With respect to neural and structural factors, ADHD and TS share some commonalities. A number of studies have noted abnormalities in the basal ganglia and the dopaminergic functions in TS (Albin & Mink, 2006; Baym, Corbett, Wright, & Bunge, 2008; Minzer, Lee, Hong, & Singer, 2004; Sheppard, et al., 1999; Singer, et al., 1993; Stern, et al., 2000).

Neuroanatomical abnormalities such as a reduction in size of the corpus callosum and the reduced volume of the caudate nuclei and globus pallidus have been noted in TS (Banaschewski, et al., 2006).

Casey, Durston, and Fossella (2001) hypothesized that the basal ganglia (whose output consists predominantly of inhibitory GABA projections) are involved in the inhibition of inappropriate behaviours; the disruption of which results in abnormalities in behavioural control. Moreover, the frontal cortex (whose output consists primarily of excitatory glutamate projections) is involved in the maintenance of relevant information for action, whereby disruptions in this region result in deficits in performing relevant actions. Peterson et al. (1998) conducted an investigation in the neuroanatomical structures involved in tic suppression in patients with TS using fMRI. The authors found significant increased activity in the right frontal cortex, which was associated with increased activity in the right caudate nucleus that in turn was associated with reduced activity in the globus pallidus, the putamen and the thalamus. Also, in an MRI study on ten monozygotic twins with concordant tic disorder but discordant symptom severity, Hyde et al. (1995) found that the anterior right caudate volume and the left lateral ventricle in the twin with the more severe symptoms were reduced compared to the other twin. The authors noted that due to the identical genetic makeup of monozygotic twins, the discordance in symptom severity indicates the involvement of other factors besides genetics in the development of TS. Moreover, in a PET neuroimaging investigation of the functional neuroanatomy of tics by Stern et al. (2000), significant activity in the motor, dorsolateral prefrontal as well as the anterior cingulate circuits of the cortico-striato-pallido-thalamo-cortical circuit (where

within such circuit the direct and indirect basal ganglia pathways provide a balance of inhibition and excitation) was observed when the TS participants experienced tics.

According to Casey et al (2001), dopamine acts as a neuromodulator (believed to play an important role in the maintenance of the internal representations of contextual information against possible interference) in the basal ganglia-thalamocortical circuitry, especially in the striatum and the prefrontal regions. Using post mortem analysis of brain tissue from three TS patients and aged matched controls; Yoon, Gause, Leckman, and Singer (2007) set out to evaluate a possible underlying neurochemical abnormality in the frontal cortex, by measuring the relative densities of various neurochemical markers such as Dopamine (D1 and D2), Serotonin, alpha adrenergic receptors (α-2A), and the dopamine transporter (DAT). The authors found consistent increase in the D2 receptor and DAT density in five of the 6 frontal regions in all of the TS patients, as well as in increase in the D1 and the α-2A receptors in few of the regions of the frontal lobe. Moreover, Cheon et al. (2004) reported increased Dopamine Transporter (DAT) density in the Basal Ganglia (irrespective of laterality) in drug naive TS children compared to age and sex matched controls in a SPECT imaging study.

1.4.1: TS AND INHIBITION

It has been hypothesized that similar to ADHD; TS may be as a result of an inhibitory dysfunction (Gilbert, et al., 2004; Ozonoff, et al., 1998; Sheppard, et al., 1999). However, the reports of an inhibitory deficit (primarily measured by tasks of response inhibition such as the Stroop or the Go/NoGo) in the TS population have been quite mixed. While a number of

studies have found evidence of an inhibitory deficit in TS (Crawford, Channon, & Robertson, 2005; Georgiou, et al., 1995; Marsh, et al., 2004), a large number of investigations report no significant difference between TS and matched controls. In a study investigating inhibitory performance in TS adults (Mean age = 29.48), Channon et al. (2009) found that TS group showed no deficit compared to the matched controls in the colour-word Stroop. However, the TS participants did demonstrate S–R deficits in tasks with greater inhibitory demands such as the Flanker-Stroop task as well as the continuous performance task. In another investigation, using a Go/NoGo paradigm as a measure of response inhibition, Roessner, Albrecht, Dechent, Baudewig, and Rothenberger (2008) did not find a significant difference in performance on the task between medication naive uncomplicated TS participants and matched controls. Similar results were also reported by Serrien, Orth, Evans, Lees, and Brown (2005) as well as by Ozonoff, Strayer, McMahon, and Filloux (1994).

An fMRI investigation of possible disturbances in the maturation of neural systems that mediate self-regulatory processes (that would contribute to motor and vocal tics) in children and adults with TS matched controls while performing a word-colour Stroop task was conducted by Marsh, Zhu, Wang, Skudlarski, and Peterson (2007). The authors found that while poorer performance on the Stroop task correlated with the activation of the frontostriatal region in the TS group, no significant main effect of diagnosis or diagnosis by age interaction on word-colour Stroop task performance or correlation between symptom severity and task performance was found.

Some investigators have attributed the inhibition deficits observed in TS on comorbid conditions such as ADHD (Brand, et al., 2002; Gilbert, et al., 2004). Evidence for this was found by Channon, Pratt and Robertson (2003) investigating the performance of TS, TS-ADHD, TS-OCD comorbids and matched controls on executive measures such as inhibition and strategy management (word-colour Stroop task, Hayling test, and Letter Fluency Test). The authors found that while the TS-ADHD comorbid group demonstrated significant inhibitory deficits on inhibitory measures, no significant difference between the matched controls and the pure TS was found. Further evidence is provided by Ozonoff et al. (1998) in a study examining central inhibitory function in children with TS using a negative priming task (which involved the subjects responding to the target stimuli while simultaneously ignoring distractor stimuli). The results showed that that while subjects did not differ from the controls, when the large group was segregated into two groups, one with TS patients with no comorbidity, and the second group with TS and ADHD and/or OCD comorbidity, the TS only group responses were analogous to those of the controls while the comorbidity groups performed significantly worse than the controls.

Thus, while evidence of an inhibitory deficit may be observed in the ADHD population, such deficits may not be seen in the TS population. However, if both ADHD and TS are as a result of dysfunctions in the dopamine system, disruption in the performance on a dopamine sensitive paradigm as conditioned inhibition may be observed.

1.5: CURRENT INVESTIGATION

The current investigation attempts to explore the deficient inhibitory control theory of ADHD and TS, using a translational model of conditioned inhibition. It is hypothesized that as a result of the dysfunction of the dopamine system and the basal ganglia in TS and ADHD, a deficit in the level of conditioned inhibition demonstrated will be observed in the clinical groups compared to matched controls. Prior to the investigation of conditioned inhibition in clinical TS and ADHD populations, the conditioned inhibition tasks adapted by Migo et al (2006) were adapted to be used on younger populations by reducing the number of training and testing trials as well as the addition of a storyline to make the tasks more engaging. The newly developed conditioned inhibition tasks were then tested on a normal population to see whether the changes had affected the integrity of the original task created by Migo et al, prior to being applied to the clinical populations.

1.5.1: INDIVIDUAL DIFFERENCE BEHAVIOURS

Based on the negative association between schizotypy (measured in a normal population) and conditioned inhibition observed by Migo et al. (2006), the current investigation also looked at possible associations between conditioned inhibition and TS/ADHD behaviours in the normal population as measured by TS and ADHD individual difference behavioural measures. Moreover, in order to assess Gray's BIS/BAS model of behaviour and its possible involvement in ADHD and TS behaviours, as well as the possible effects of dominant BIS/BAS personalities on the inhibition of S-S associations, the level of BIS and BAS were measured in each participant using the BIS/BAS scale developed by Carver and White (1994). Finally, several studies have implicated excessive yawning as a possible complex tic exhibited in Tourette's syndrome (Dalsgaard, Damm, & Thomsen, 2001; Greco &

Baenninger, 1993; Sandyk, 1996; Walusinski, 2006, 2009). Working on the theory Tourette's syndrome results from increased dopamine activity caused by postsynaptic dopamine receptor sensitivity, Sandyk (1996) found that administration of small doses of apomorphine, which is a dopamine D2 autoreceptor agonist, produced yawning in both animals as well as humans. Moreover, the exposure to brief extracranial applications of picotesla flux electromagnetic fields produced yawning followed by increased motor tic activity in two Tourette's patients. Thus, in order to investigate the possible association between excessive yawning and TS/ADHD a measure of yawning was obtained using a yawning scale developed by Greco and Baenninger (1993).

CHAPTER 2: CONDITIONED INHIBITION PARADIGMS

2.1: INTRODUCTION

To date, investigations of inhibitory deficits in TS and ADHD have mainly looked at response-inhibition as measured by such tasks as the Stroop (Albrecht, et al., 2008; Lansbergen, Kenemans, & van Engeland, 2007; Schwartz & Verhaeghen, 2008; Young, et al., 2006) and the Go/NoGo (Serrien, et al., 2005; Trommer, et al., 1988). Tasks such as the Stop signal, the Go/NoGo and the Stroop focus on the level of response inhibition demonstrated by the particular individuals investigated (such as ADHD or TS participants), in that they measure the ability of the individuals under investigation in the inhibition of an inappropriate response when required (such as when a NoGo signal is presented). However, few investigations have focused on the possible S-S associations by way of which environmental events through an action on the associative chain may act to initiate an unwanted behaviour (via an S-R). For example, a sound of a cough may result in a premonitory urge (tickling in the throat) that may initiate a tic in a TS patient (James F. Leckman, 2003; James F. Leckman & Peterson, 1993). Thus, aside from the degree of behavioural inhibition demonstrated, it is also important to investigate the degree which TS and ADHD are capable in inhibiting S-S associations that can lead to unwanted behaviours.

A method in which the inhibition of S-S association can be investigated is through the study of conditioned inhibition. A thorough explanation and examination of conditioned inhibition is provided in Chapter 1. The inhibition of S-S associations through conditioned inhibition has been demonstrated by number of animal-learning investigations (Baker & Mackintosh, 1977; Cole, Barnet, & Miller, 1997; Harmer & Phillips, 1999; Rescorla &

Holland, 1977). For example, in an evaluation of Rescorla's (1969) two-test strategy (summation and retardation test) of conditioned inhibition, Cole, Barnet and Miller (1997) reported that inhibition was successfully evaluated by both the summation as well as the retardation test when each test was evaluated in the absence of the other using rats. Also, Rescorla and Holland (1977) in an investigation of the underlying elements involved in conditioned inhibition, reported that a conditioned inhibitor acts on the representation of the UCS, as it successfully inhibited a transfer stimulus signalling the same UCS as the original CS even when the CS-UCS association of the original CS was extinguished prior to test. However, no such inhibition was observed when the transfer CS signalled for a different UCS than the original CS.

While conditioned inhibition has been predominantly investigated through animal studies, a number of investigators have successfully demonstrated conditioned inhibition in humans using human analogues of the animal conditioned inhibition paradigms (Chapman, 1991; Grillon & Ameli, 2001; Neumann, et al., 1997; Williams & Docking, 1995). Karazinov & Boakes (2004) successfully demonstrated conditioned inhibition in human participants using a food-migraine paradigm where the presence or combination of foods (CS) was related to the occurrence of a migraine (UCS). Their task entailed that the subjects make a decision on whether the combination of particular foods consumed by patients on certain days led to a migraine. The participants made their made their decision using a slider bar marked "Migraine certain to occur", "Don't know" and "Migraine certain not to occur" presented below the image of the food combinations. Following their selection, the participants were presented with a message informing them whether the food combination did indeed lead to a migraine or no migraine occurred. Moreover, using an aversive

conditioned inhibition paradigm, Neumann et al. (1997) studied conditioning of autonomic responses in human subjects, where they presented subjects with four geometric shapes (CSs) labelled A, B, C and D, and used a mild electric shock as the UCS. Conditioned responses were recorded using a measure of skin conductance, respiration and self-reported UCS expectancy. During training, the subjects received presentations of A-UCS, C-UCS, AB-NoUS, and presentations of AC-UCS, B-NoUS. Conditioned inhibition was measured using summation tests, where the subjects received three presentations of C-UCS, CB-No UCS and CD-No UCS (whereby C served as the transfer stimulus, and the CD served as a neutral compound stimulus). The authors reported that conditioning was evident based on self-reported UCS expectancy as well as the electrodermal responses.

Based on the review of the literature cited in this thesis, it has been observed that while Rescorla's two-test strategy has been predominantly employed in animal learning paradigms, human conditioned inhibition paradigms notably employ the summation test in absence of a retardation test (Grillon & Ameli, 2001; Karazinov & Boakes, 2004; Migo, et al., 2006; Neumann, et al., 1997).

The focus of the current investigation was to develop tasks that would reliably measure the level of conditioned inhibition in human populations for use in ADHD and TS patient populations in later investigations. The tasks in question are based on the previously developed computer based conditioned inhibition paradigm by Migo et al. (2006) that successfully measured conditioned inhibition in the normal population. As outlined in this chapter, three distinct tasks were developed based on the original Migo et al. conditioned inhibition task. While the conditioned inhibition task by Migo et al. was found to be more

than suitable to be used on a younger population, the length of the original task was likely to be too taxing on the maintenance of the attention of the children, particularly for the clinical ADHD population. As such, the number of training and testing trials was reduced to a level that made the tasks less taxing as well as providing an appropriate number of trials as to leave the acquisition of conditioned inhibition unaffected.

The tasks were also modified to be more engaging with the inclusion of storylines suitable for young participants. The storylines were selected to be more tailored towards a male audience, as ADHD and TS clinical populations are predominantly male (Faraone, et al., 2003; Robertson, 2000, 2006). One of the tasks, identified as the Mission to Mars task, involved participants imagining themselves as starship commander on a Mission to Mars with their fleet of spaceships, while another task was based on the story of the comic book character "The Incredible Hulk", and the third task was based on the story of the comic book character "The Wolverine" from the popular X-Men comic books and films. With the exception of the storyline and the reduced number of training/testing trials, the Mission to Mars task was quite similar to the original Migo et al. task.

Aside from their storylines, the tasks also differed with regards to the implicit or explicitness of the instructions provided. Using a non-aversive "conditioned suppression" procedure involving a Martian invasion scenario (in which the subjects were required to press the spacebar to activate a gun upon seeing the Martian spacecraft on screen), Arcediano, Ortega, & Matute (1996) reported that while the participants successfully demonstrated the acquisition of the CS-UCS association in their first experiment (which was presented with implicit instructions), the results of their second experiment (which

was presented with more explicit instructions) were more pronounced. As such, the tasks used in this thesis differed with the level of instructions provided; with the instructions provided in the entitled "Weapon X" as well as the "Incredible Hulk" tasks being explicit and those of the "Mission to Mars" task being implicit.

In the experiment by Migo et al. (2006), the conditioned inhibition task was set up as a serial presentation conditioned inhibition paradigm, where the presentation of the conditioned inhibitor (CI) preceded the presentation of the CS. In a series of experiments by Holland (Holland, 1984; Holland & Lamarre, 1984), it was reported that while the conditioned inhibitor from a simultaneous paradigm (A+, AX-) would readily inhibit the transfer stimulus in the summation test, no such inhibition of the transfer stimulus was noted in the serial (A+, X→A-) conditioned inhibition paradigm. Moreover, in a serial versus simultaneous test of feature negative discrimination learning in humans, Baeyens et al (2004) found that the transfer of an inhibition by a conditioned inhibitor (A+/AX- where X is the conditioned inhibitor) to a transfer stimulus was perfect in a simultaneous presentation paradigm, irrespective of the learning history of the transfer stimulus (B+/YB- vs. B+ only group). However, in a sequential presentation paradigm, the authors found that the transfer of inhibition by the conditioned inhibitor (X) to the transfer stimulus was successful only if the transfer stimulus had been involved in another sequential feature negative training (B+/YB-) but not if the transfer stimulus had been consistently reinforced (B+ only group). However, Migo et al. reported successful demonstration of conditioned inhibition in a serial presentation conditioned inhibition task using a transfer stimulus that had never been presented in a feature negative training. Thus, in order to test for the level

of conditioned inhibition demonstrated in a serially or simultaneously presented conditioned inhibition paradigms, the serially presented "Mission to Mars" conditioned inhibition task was tested against the simultaneously presented "Weapon X" task.

Finally, Migo et al. (2006) reported a negative association between the level of conditioned inhibition demonstrated and the level of schizotypy measured in a normal population. As such, the current investigation also looked at possible associations between conditioned inhibition and TS/ADHD-like behaviours in the normal population as measured by TS and ADHD individual difference behavioural measures. The ADHD individual difference was adapted from a diagnostic ADHD scale developed by Kessler et al (2005). The TS individual difference behavioural measure was a novel scale based on the Kessler et al. ADHD scale and was developed by Dr. Helen Cassaday and myself. Moreover, in order to assess Gray's BIS/BAS model of behaviour and its possible involvement in ADHD and TS-like behaviours, as well as the possible effects of dominant BIS/BAS personalities on the inhibition of S-S associations, the level of BIS and BAS were measured in each participant using the BIS/BAS scale developed by Carver and White (1994). Finally, several studies have implicated yawning as a possible complex tic exhibited in Tourette's syndrome (Dalsgaard, et al., 2001; Greco & Baenninger, 1993; Sandyk, 1996; Walusinski, 2006, 2009). Thus, in order to investigate the possible association between excessive yawning and TS/ADHD a measure of yawning were obtained using a yawning scale developed by Greco and Baenninger (1993).

2.2: EXPERIMENT 1A - THE ANALYSIS OF THE INCREDIBLE HULK AND THE MISSION TO MARS CONDITIONED INHIBITION PARADIGM ON A SAMPLE POPULATION FROM THE SCHOOL OF PSYCHOLOGY

2.2.1: METHODS AND MATERIALS

2.2.1.1: PARTICIPANTS

The participants in the current investigation consisted of twenty-six postgraduate and undergraduate volunteers from the School of Psychology in the University of Nottingham (male: n = 5, female: n = 22, mean age = 23 years; range = 20-32 years). The participants were paid a £5 inconvenience allowance for their participation in their study. The procedures conformed to the guidelines set by the School of Psychology, University of Nottingham Ethics Committee.

2.2.1.2: MATERIALS

All of the programs were produced in E-studio and utilized E-prime (Psychology Software Tools Inc., Pittsburgh, USA) to present the material to the participants. The programs were run on personal computer with 17" monitor. Participants made their responses using the computer mouse. The stimuli presented in each of the two tasks are shown in figure 2-1.

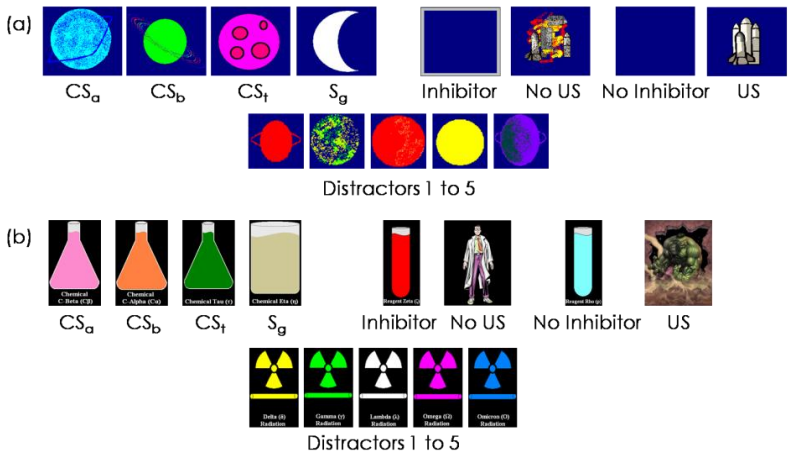

Figure 2-1: The stimuli presented during (a) Mission to Mars, and (b) The Incredible Hulk task variants.

2.2.1.3: PROCEDURES

The participants completed two conditioned inhibition task variants followed by four sets of individual difference behavioural measures. The full description each task variant and individual difference behaviour measure is outlined below. The order of presentation of the two conditioned inhibition tasks was counterbalanced between participants.

2.2.1.3.1: THE MISSION TO MARS TASK

The task scenario was based on a hypothetical Mission to Mars. Participants were informed that they were to play the role of a commander of a fleet of starships travelling on an exploration Mission to Mars. However, trouble arises as, during the course of the mission, spaceships in the fleet keep mysteriously exploding. The training phase consisted of 45 learning trials of the types shown in Table 2-1.

Training Phase	Testing Phase
CS_a+	CS_t+
[CI, CS_a]-	[CI, CS_t]-
CS_b+	S_g+
[CI, CS_b]-	[CI, S_g]-
CS_t+	

Table 2-1: The stimulus combinations presented during the training and testing phase of the two tasks (example stimuli are shown in Figure 1). A '+' indicates the presentation of the UCS (i.e. an intact rocket for the Mission to Mars and a picture of Wolverine for the Weapon X task, or the Hulk in the Incredible Hulk task). A '-' indicates the absence of the UCS (i.e. an exploded rocket for the Mission to Mars and a picture of Feral Logan for the Weapon X task, or the Dr. Bruce Banner in the Incredible Hulk task).

There were nine cycles of five stimulus sequences: CS_a+, [CI, CS_a]-, CS_b+, [CI, CS_b]-, and CS_t+, where "+" signified a normal excitatory association (i.e. rocket UCS presentation), and "-" signified inhibition (i.e. no rocket UCS presentation, represented as an exploded rocket). The five stimulus sequences were presented in a random order. As the masking task, participants were required to keep track of the number of surviving spaceships, so that the associations to be learned were less obvious. On inhibited trials, a 1-second gray frame surrounding a blue screen was presented, which represented the CI. On excitatory trials, there was a 1-second presentation of an empty blue screen (at the equivalent point in the stimulus sequence). Following this, the CS (a large planet) was followed by 3 distractors (smaller planets) appearing and disappearing on the same screen, for a combined total of 4 seconds, followed by the presentation of the UCS (i.e. rocket presentation) on excitatory trials or absence of the UCS (i.e. exploded rocket presentation) on inhibited trials. Participants were required to click any of the keys on the mouse to continue on to the next presentation**.**

The testing phase followed on immediately from the training phase and consisted of twenty trials. There were five cycles of four stimulus sequences: S_g+, [CI, S_g]-, CS_t+, and [CI, CS_t]-, in which S_g was a generalized stimulus not previously introduced during the training phase. The four stimulus sequences were presented in a random order. The procedure for test trials was identical to that used in training, except that prior to the presentation of the UCS or its absence, participants were presented with an on-screen rating, scaled from 1 to 9. At this point, the participants were required to estimate the likelihood of the spaceship surviving versus exploding, with a rating of "9" to represent the highest likelihood of survival, and a rating of "1" to represent the highest likelihood of rocket explosion. An intermediate rating of "5" represented complete uncertainty in the outcome. The ratings were made by clicking in the appropriate on screen box using the mouse as shown in figure 2-2.

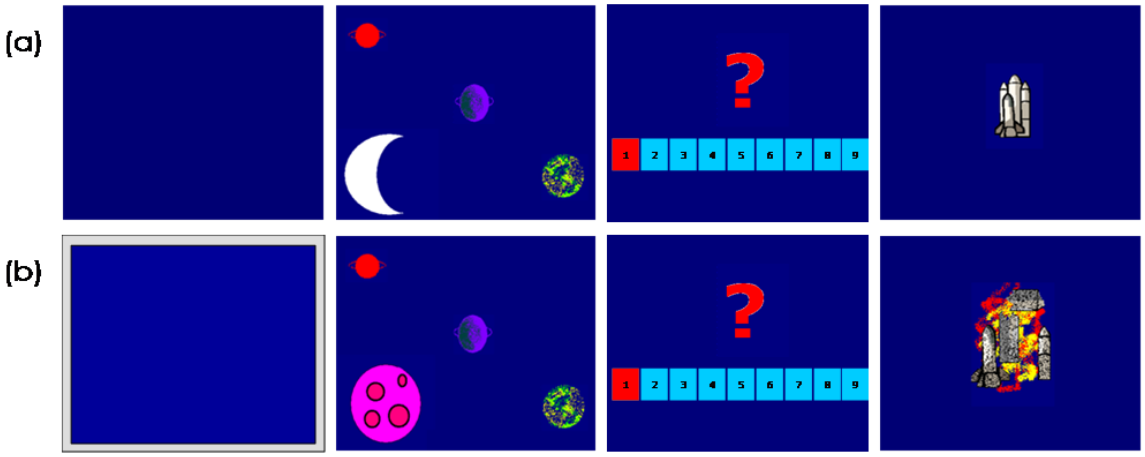

Figure 2-2: The images in row (a) depict the presentation of a non-inhibited generalized stimulus during the testing phase, and the images in row (b) depict the presentation of an inhibited transfer stimulus during the testing phase during the Mission to Mars task variant.

This was a summation test of conditioned inhibition. Participants' ratings provided a measure of the inhibitory properties of the CI using two kinds of test stimuli: (1) generalized (a stimulus that was from the same category but had not been explicitly pre-

trained); and (2) transfer (a stimulus familiar from training but that had not previously been preceded by the CI).

2.2.1.3.2: THE INCREDIBLE HULK TASK

The task was presented with a background story suitable for use with younger participants, here with a scenario based on the comic book story of The Incredible Hulk (Figure 2-3). In this experiment, participants were informed that they were to play the role of a rival of Dr. Bruce Banner, who had discovered the technique to turn from a mild mannered biophysicist to the Incredible Hulk. Participants were further informed that in order to learn Dr. Banner's secret, they were to carefully observe his experiments and discover what procedure led to success and what resulted in failure.

Similar to the previous task, the training phase consisted of forty-five learning trials, presented as nine cycles of the five stimulus sequences shown in Table 2-1. The stimuli were different in that in this task variant, participants were asked to observe a computer simulation of the Incredible Hulk transformation. This consisted of three stimuli appearing simultaneously: the CI or its absence (represented by a test tube), the CS (a flask), and a distractor (presented as a type of radiation), for a total of 4 seconds on screen. These images were followed by a 1-second presentation of an image of a molecular explosion, followed the presentation of the UCS or its absence. The success or failure of the transformation was represented by an image of Incredible Hulk as the UCS, or a picture of Dr. Banner representing the absence of the UCS. Participants were required to click any key of the mouse to continue.

Again the testing phase consisted of twenty trials (as per Table 2) with the generalized (S_g) and transfer stimuli (CS_t) for the summation test of conditioned inhibition. Similar to the Mission to Mars task, an on-screen scale of 1 to 9 was used to rate the likelihood of a success. All choices were made via clicking on the appropriate box on screen by the mouse.

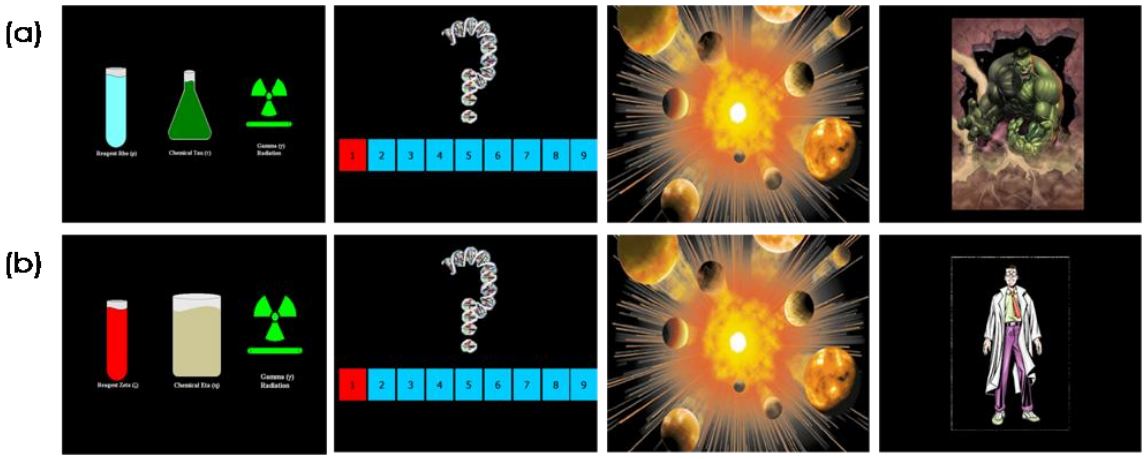

Figure 2-3: The images in row (a) depict the presentation of a non-inhibited generalized stimulus during the testing phase, and the images in row (b) depict the presentation of an inhibited transfer stimulus during the testing phase during the Incredible Hulk variant.

2.2.1.3.3: INDIVIDUAL DIFFERENCE MEASURES

Following the conclusion of the computerized tasks, the participants were asked to fill out four individual difference measures. The first measure was an adapted version of an 18-item ADHD scale with all reference to ADHD diagnostics removed. The items of this questionnaire were from the Adult ADHD Self-Report Scale (ASRS-v1.1) obtained from Kessler et al. (2005) shown in table 2-2. The items were suitable for use with normal participants. Some example items include "How often do you make careless mistakes when you have to work on a boring or difficult project?" and "How often are you distracted by activity or noise around you?" among others. The second personality measure was an in-

house 18-item TS personality questionnaire shown in table 2-3 developed by myself with the assistance of Dr. Helen Cassaday, based on the format of the aforementioned ADHD personality questionnaire. Some example items include “How often do you grunt without particular reason?” and “How often do you experience rapid blinking of one or both eyes?” among others. The third personality measure was the BIS-BAS questionnaire developed by Carver and White (1994). The BIS-BAS personality measure possesses four subscales: The BIS (behavioural inhibition system), The BAS (behavioural approach system) Drive (BAS-D), BAS Fun Seeking (BAS-FS), and the BAS Reward Responsiveness (BAS-RR). The final personality measure was a 24-item Yawing Scale developed by Greco & Baenninger (Greco & Baenninger, 1993) shown in table 2-4.

PARTICIPANT #: GENDER: M / F AGE:	DATE:				
Please answer the questions below; rating yourself on each item by placing an X in the box that best describes you.	Never	Rarely	Sometimes	Often	Very Often
How often do you have trouble wrapping up the final details of a project, once the challenging parts have been done?					
How often do you have difficulty getting things in order when you have to do a task that requires organization?					
How often do you have problems remembering appointments or obligations?					
When you have a task that requires a lot of thought, how often do you avoid or delay getting started?					
How often do you fidget or squirm with your hands or feet when you have to sit down for a long time?					
How often do you feel overly active and compelled to do things, like you were driven by a motor?					
How often do you make careless mistakes when you have to work on a boring or difficult project?					
How often do you have difficulty keeping your attention when you are doing boring or repetitive work?					
How often do you have difficulty concentrating on what people say to you, even when they are speaking to you directly?					
How often do you misplace or have difficulty finding things at home or at work?					
How often are you distracted by activity or noise around you?					
How often do you leave your seat in meetings or other situations in which you are expected to remain seated?					
How often do you feel restless or fidgety?					
How often do you have difficulty unwinding and relaxing when you have time to yourself?					
How often do you find yourself talking too much when you are in social situations?					
When you're in a conversation, how often do you find yourself finishing the sentences of the people you are talking to, before they can finish them themselves?					
How often do you have difficulty waiting your turn in situations when turn taking is required?					
How often do you interrupt others when they are busy?					

Table 2-2: ADHD individual difference behavioural measure (Kessler, et al., 2005)

PARTICIPANT #: GENDER: M / F AGE:	DATE:				
Please answer the questions below; rating yourself on each item by placing an X in the box that best describes you.	Never	Rarely	Sometimes	Often	Very Often
Not counting those times when you may feel particularly tired, how often do you find yourself yawning?					
How often do you find yourself biting your lips or cheeks?					
How often do you tidy your personal or household things in a fixed order or arrangement?					
How often do you shrug your shoulders without particular reason?					
How often does your head move in a way that you had not intended?					
How often do you typically find yourself checking and re-checking whether electrical items, taps, gas ovens or fires have been switched off?					
How often do you often swear without provocation?					
How often do you grunt without particular reason?					
Not counting those times when you may have a cold or flu, how often do you find yourself coughing?					
How often do you experience rapid blinking of one or both eyes?					
How often do you find that your mouth or some other part of your face twitches uncontrollably?					
Not counting those times when you may have a cold or flu, how often do you find yourself sniffing?					
How often do you repeatedly clear your throat for no particular reason?					
How often do you make movements that you do not really intend?					
How often are you bothered by unpleasant thoughts or images that repeatedly enter your mind, such as worries about dirt or infection?					
How often do you make sounds that you did not really intend?					
How often do you say things that you wish you had not?					
How often do you shout for no particular reason?					

Table 2-3: TS individual difference behavioural measure

Date:

Participant: **Age:** **Gender: M/F**

Yawning Scale						
Please indicate the choice that corresponds to your yawning behaviour in each situation:	**Not at all**	**Just a little**	**Somewhat**	**Moderately**	**Quite a lot**	**Very much**
Listening to speech or lecture						
Sitting in a traffic jam						
Waiting for a train or bus						
Driving at night on lonely highway						
Driving on a sunny day (no traffic)						
While giving a speech or lecture						
Waiting to begin a competitive event						
Being interviewed for a job						
Lying in bed before falling asleep						
Getting out of bed in the morning						
Morning						
Afternoon						
Evening						
On a date						
Tired						
Lecture/Class						
Lack of sleep						
Stress						
After a meal						
See others yawn						
Working						
Study at night						
In Church						
While taking this survey						

Table 2-4: Yawning individual difference behavioural measure (Greco & Baenninger, 1993)

2.2.1.4: DESIGN AND ANALYSIS

Analysis of variance (ANOVA) was run in a mixed design with up to four within-subjects factors to assess the development of conditioned inhibition: inhibition (the presence or absence of the CI); task (Mission to Mars versus the Incredible Hulk); stimulus type (summation test with the generalized stimulus versus the previously trained transfer stimulus); presentation (of which there were five levels). Analyses were collapsed across task, stimulus type and presentation where these factors did not affect the development of

conditioned inhibition. The F ratios were checked for sphericity via Mauchly's test of sphericity and adjusted accordingly (by Greenhouse-Geisser correction when the value of epsilon was between the values of 0.5 to 0.75 and via Huynh-Feldt correction when epsilon was greater than 0.75).

The dependent variable was the participants' expectancy scores (for appearances of an intact rocket in task 1 or the successful transformation of Dr. Bruce Banner into the Incredible Hulk in task 2). Planned comparisons (*t*-tests at $p \leq 0.05$) were conducted further to examine effects of a priori interest.

To test the relationship between conditioned inhibition and individual difference scores in use, a conditioned inhibition ratio that was calculated by dividing the average expectancy score for inhibited stimulus presentations by the average expectancy score for non-inhibited stimulus presentations for each task variant. As such, conditioned inhibition is indicated by a ratio less than one and the absence of conditioned inhibition by a ratio greater than or equal to one. The interrelationship between the level of conditioned inhibition summarized by the ratio and the rating scores on each of the four individual difference behaviour measures and (including the BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness subscales of the BIS/BAS measure) was explored by 2-tailed Pearson's r correlation.

Also, in order to analyze the effects of the behaviours as measured by the four individual difference questionnaires on the level of conditioned inhibition demonstrated, a median split was performed on individual difference scores and analyzed as a between subjects factor with the data from the conditioned inhibition task on a repeated measures ANOVA.

Median split analysis were performed for the overall BAS and the BIS scores only (the BAS Reward Responsiveness, BAS fun Seeking, and BAS Drive sub scales were analysed only in the correlational analysis).

2.2.2: RESULTS

The results showed a significant main effect of inhibition ($F_{1, 25} = 61.968$, $p < 0.001$), as seen in Figure 2-4a. Moreover, a significant interaction between Task and Inhibition was found ($F_{1, 25} = 16.781$, $p < 0.001$). As seen in Figure 2-4b, the level of inhibitory responding ($t_{25} = 3.974$, $p = 0.001$) and excitatory responding ($t_{25} = 3.986$, $p = 0.001$) was significantly diminished in the Mission to Mars task compared to the Incredible Hulk task variant. However, despite the observed differences, conditioned inhibition was successfully demonstrated in both task variants (Incredible Hulk: $t_{25} = 9.22$, $p = 0.001$, Mission to Mars: $t_{25} = 3.65$, $p = 0.001$). No significant interaction between inhibition and Stimulus ($F_{1, 25} = 3.263$) or inhibition and presentation ($F_{4, 100} = 1.07$) was found. Thus, subsequent analyses were collapse across stimulus and presentation.

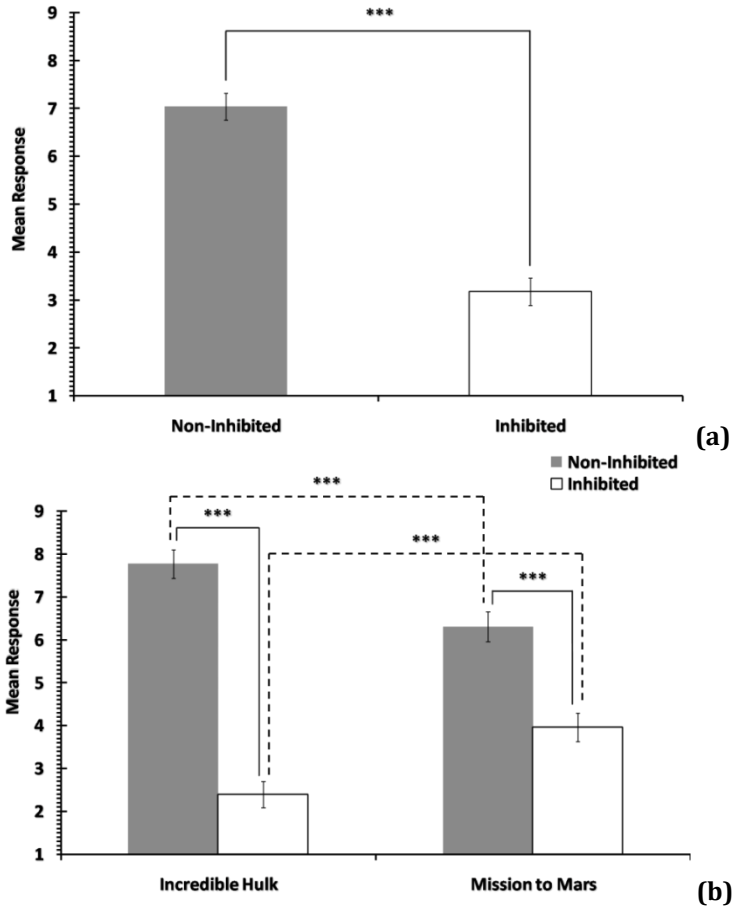

Figure 2-4: The results showed (a) a significant main effect of inhibition as well as (b) a significant interaction between task and inhibition for the psychology population sample. While significant level of conditioned inhibition was demonstrated in both task variants, the level of level of excitatory and inhibitory responding measured was significantly lower in the Mission to Mars task compared to the Incredible Hulk task variant (* = p<0.05, ** = p<0.01, *** = p<0.001)

The results of the median split analysis of the four individual difference behavioural measures showed no interaction between inhibition and the ADHD behavioural measure ($F_{1, 24} = 0.047$). However, a significant interaction between ADHD and task by inhibition was found ($F_{1, 24} = 13.105$, p = 001). As shown in Figure 2-5, while conditioned inhibition was successfully demonstrated in the Incredible Hulk task by the participants in both the below or equal ($t_{14} = 4.928$, $p < 0.001$) and above the median ($t_{10} = 15.827$, $p < 0.001$), only the participants in the below or equal group successfully demonstrated conditioned inhibition for the Mission to Mars task ($t_{14} = 3.65$, $p < 0.01$).

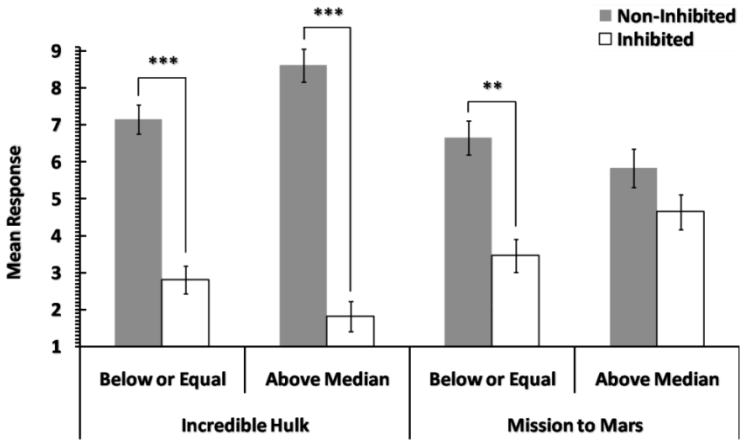

Figure 2-5: Task by inhibition interaction for participants who scored below or equal to or above the median in the ADHD individual differences behavioural measure. As shown, participants who scored above the median for the ADHD behavioural measure failed to demonstrate conditioned inhibition in the Mission to Mars task variant. (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$)

No other significant interaction between inhibition or inhibition-by-task and the remaining individual difference behavioural measures was observed (max $F_{1, 24} = 1.866$).

2.2.2.2: CORRELATIONAL ANALYSIS

There were no correlations between any of the individual difference behavioural measures and performance on either of the conditioned inhibition tasks summarized by the conditioned inhibition ratios (Maximum $r_{26} = 0.39$).

A significant positive correlation between the TS and the yawning behavioural measure was found ($r_{26} = 0.59$, $p < 0.01$). To ensure that the correlation obtained was not due to the yawning item found on the TS scale, the correlation was reanalyzed with the item removed, where it was found that the correlation still remained ($r_{26} = 0.545$, $p < 0.01$).

A significant positive correlation was found between the BIS and the TS behaviour measure ($r_{26} = 0.40$, $p < 0.05$). Moreover, a significant positive correlation between scores on the TS and the ADHD behaviour measure was also found ($r_{26} = 0.425$, $p < 0.05$). Finally, a

significant correlation was observed between the yawning and the BIS behavioural measure ($r_{26} = 0.62$, $p = 0.001$). No other significant correlations were noted (max $r_{26} = 0.351$).

2.2.3: DISCUSSION

The participants successfully demonstrated a significant conditioned inhibition in both the Mission to Mars as well as the Incredible Hulk tasks. Also, summation test was passed by both the transfer (that had never been paired with the CI during training) as well as the generalized stimuli (a stimulus which had never been introduced during training) in both task variants. Thus, conditioned inhibition was successfully measured by both task variants (Rescorla, 1969). The results observed were similar to those previously obtained by Migo et al. (2006).

Although conditioned inhibition was obtained in both task variants, the effect was more pronounced in the Incredible Hulk task compared to the Mission to Mars task. This may have been due to the more explicit instructions provided for the Incredible Hulk task in that the participants were told to look for the stimuli that would inform them whether Dr. Banners transformation to the Incredible Hulk would occur or not. However, the instructions provided for the Mission to Mars task during the training presentations were implicit (the participants were not explicitly told to look for the case of the explosion, just to count the number of surviving rockets). A similar effect was obtained by Arcediano et al. (1996), who found that while conditioned suppression did occur during both of their experiments; the degree of conditioned suppression demonstrated was stronger for the

task with explicit instructions on the significance of the CSs compared to their earlier experiment which did not have explicit instructions. On the other hand, this effect may have been as a result of the fact that although serially presented, the CI in the Incredible Hulk task remained on screen for a total of 4 seconds, starting from the time of the presentation of the CI/non-CI to the presentation of the distractor. This was unlike the Mission to Mars task where the CI was presented and removed prior to the presentation of the CS and the distractors. As such, the prolonged presentation of the stimuli (particularly the CI) may have made the CI presented during the Incredible Hulk task more salient.

With regards to the individual differences measures, the absence of a correlation between the conditioned inhibition ratios and the individual differences measures suggests that conditioned inhibition was unaffected by ADHD and TS-like behaviours in normals. This was also true with impulsive or anxious behaviours (as measured by the BIS/BAS). However, because the participants were all normal individuals with no reported ADHD or TS diagnosis, the results may not have shown a great deal of variability in the individual difference scores to register a significant correlation with performance on the conditioned inhibition task variants. That being said, median split analysis of the ADHD individual difference behaviour measure did reveal that at least with respect to the Mission to Mars task variant, individuals who reported higher than the median ADHD behaviours failed to demonstrate conditioned inhibition. Thus, it may be that predisposition to ADHD behaviours could reduce the level of conditioned inhibition demonstrated. This result however is contrary to what has been previously found, where previous research, using aversive conditioning paradigms have failed to show a significant difference between

ADHD and normal participants (Coffin, Baroody, Schneider, & O'Neill, 2005; Pliszka, et al., 1993).

The well acknowledged TS-ADHD comorbidity in clinical groups (Comings & Comings, 1987; Gilbert, et al., 2004; Sheppard, et al., 1999; Spencer, et al., 1998) supports the finding of a strong positive correlation between the scores obtained on the TS and the ADHD behaviour measures, which helps lend credibility to the newly created TS scale used in the current investigation. Moreover, the strong positive correlation found between the yawning behaviour measure with both the TS and the ADHD behaviour measures and lends support to the view that excessive yawning may be as a result of an underlying predisposition TS and/or ADHD (Dalsgaard, et al., 2001; Greco & Baenninger, 1993; Sandyk, 1996; Walusinski, 2006, 2009). However, due to the fact that none of the participants reported being diagnosed with ADHD or TS, such findings cannot be considered conclusive until such findings are noted in clinically diagnosed TS and/or ADHD participants. As previously stated, the TS and ADHD scales employed during the current analysis were not used as diagnostic tools, and thus high ratings in the noted scales cannot be inferred as the presence of TS and/or ADHD in the subject.

The absence of a correlation between the BIS/BAS component with respect to the TS and the ADHD behaviour measures, as well as performance on either of the conditioned inhibition tasks summarized by the conditioned inhibition ratios do not support Gray's BIS/BAS model of behavioural inhibition (Fowles, 1987; Jeffrey Alan Gray, 1982; Jeffrey Allan Gray, 1994) or Quay's model of childhood mental disorders' (Quay, 1988a, 1997). However, it may have been that while some individuals may have scored somewhat low in

the BIS components, their scores may not have been significantly different from average. As noted above, since none of the participants reported being diagnosed with ADHD and/or TS, such findings cannot be considered conclusive unless the populations tested have been clinically diagnosed TS and/or ADHD. Furthermore, such results may have arisen as a consequence of an anomaly due to the small population sample size used in the current pilot studies.

While conditioned inhibition was significantly demonstrated in both tasks by the participants, one cannot deny that possible knowledge of the theories behind the current investigation may have influenced the results obtained as the set of participants in the current experiments were students from the School of Psychology, and thus may not have been truly naïve with regards to the purpose of the experiment. As such, the results may not be a true representation of the population. Thus, as outlined in experiment 1B, a replication of the current task was performed using student volunteers from outside of the School of Psychology in order to assess whether the current results could be replicated.

2.3: EXPERIMENT 1B - THE ANALYSIS OF THE INCREDIBLE HULK AND THE MISSION TO MARS CONDITIONED INHIBITION PARADIGM ON A NON-PSYCHOLOGY STUDENT SAMPLE POPULATION

2.3.1: METHODS AND MATERIALS

2.3.1.1: PARTICIPANTS

The participants in this investigation consisted of twenty three non-psychology postgraduate and undergraduate students from the from all other departments with the exception of the School of Psychology at the University of Nottingham and one final year A-level student visitor (males; n = 10, females: n = 13, mean age = 24 years; range = 17-32 years). A £5 inconvenience allowance was compensated to each participant for his or her participation in the study. The procedures conformed to the guidelines set by the School of Psychology, University of Nottingham Ethics Committee.

2.3.1.2: MATERIALS

The stimuli and materials are outlined in experiment 1A.

2.3.1.3: PROCEDURES

The procedures are a replication of those outlined in experiment 1A.

2.3.1.4: DESIGN AND ANALYSIS

The design and analysis were identical to those used in experiment 1A.

2.3.2: *RESULTS*

A significant main effect of inhibition was found ($F_{1, 21} = 32.315$, $p < 0.001$) as shown in Figure 2-6a. Moreover, similar to the previous investigation, a significant interaction between task and inhibition was noted ($F_{1, 21} = 19.283$, $p < 0.001$). As Show in Figure 2-6b, while conditioned inhibition was successfully demonstrated in both the Incredible Hulk ($t_{22} = 6.527$, $p < 0.001$) as well as the Mission to Mars ($t_{22} = 2.48$, $p < 0.05$) task variants, the level of both excitatory ($t_{22} = 4.202$, $p < 0.001$) and inhibitory learning ($t_{22} = 3.684$, $p = 0.001$) was much reduced in the Mission to Mars task variant compared to the Incredible Hulk Task.

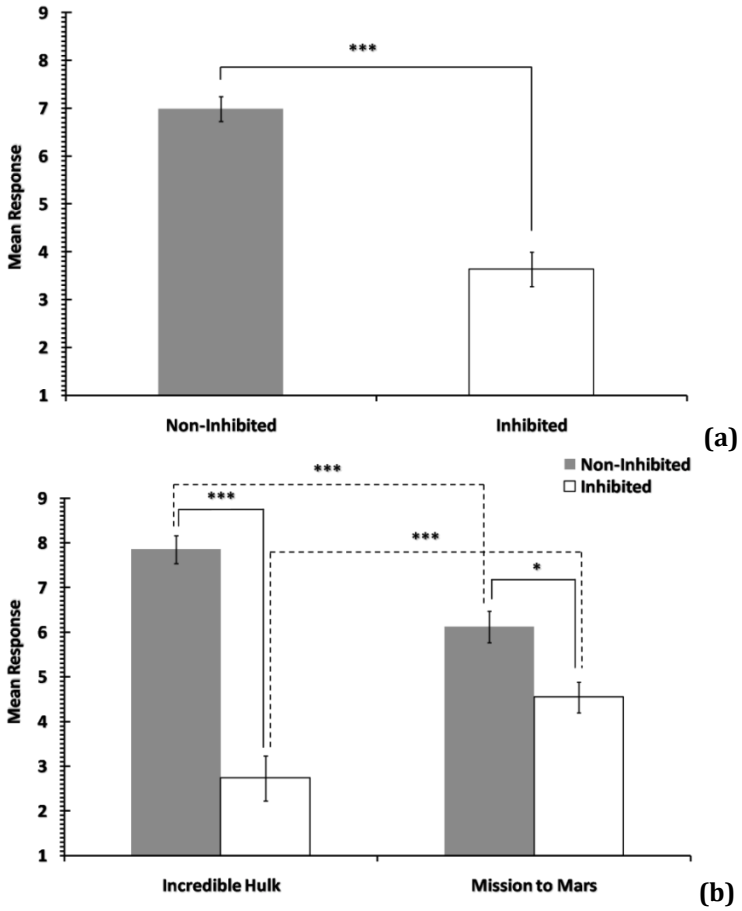

Figure 2-6: The results showed (a) a significant main effect of Inhibition and (b) a significant interaction between task and inhibition. Although conditioned inhibition was demonstrated in both task variants, the level of excitatory and inhibitory was significantly diminished in the Mission to Mars task compared to the Incredible Hulk task variant. (* = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$)

No significant interaction between inhibition and stimulus ($F_{1, 24} = 0.534$), or inhibition and presentation ($F_{4, 84} = 2.264$) was found. Thus, subsequent analyses were collapsed across the two factors.

With respect to the median split analysis of the individual difference behavioural measures, no significant interaction was found between inhibition and ADHD (max $F_{1, 21} = 0.346$), TS (max $F_{1, 21} = 0.377$), BAS (max $F_{1, 21} = 3.077$), BIS (max $F_{1, 21} = 0.903$), or the yawning (max $F_{1, 21} = 0.669$) behavioural measures.

2.3.2.1: CORRELATIONAL ANALYSIS

Correlational analysis showed a significant negative correlation between the conditioned inhibition ratio for the Incredible Hulk task and the BAS ($r_{23} = -0.608$, $p < 0.01$), the BAS fun seeking ($r_{23} = -0.61$, $p < 0.01$), and the BAS drive behavioural measures ($r_{23} = -0.426$, $p < 0.05$). No significant correlations between the BAS reward responsiveness and the Incredible Hulk task conditioned inhibition ratio was observed (max $r_{23} = -0.281$). Moreover, no significant correlations between conditioned inhibition ratio of the Mission to Mars task and any of the individual difference behavioural measures were found (max $r_{23} = -0.396$).

A significant positive correlation was found between the yawning and the TS ($r_{23} = 0.84$, $p < 0.001$) as well with the ADHD behaviour measure ($r_{23} = 0.70$, $p < 0.001$). A reanalysis with the yawning item on the TS scale removed showed that the significant correlation still

remained ($r_{23} = 0.82$, $p < 0.001$). Moreover, similar to experiment 1A, the TS behaviour measure was positively correlated the ADHD behaviour measure ($r_{23} = 0.734$, $p < 0.001$).

The results also showed that the BIS scores were positively correlated with the TS ($r_{23} = 0.56$, $p < 0.01$), the ADHD ($r_{23} = 0.69$, $p = 0.001$) as well as the yawning ($r_{23} = 0.476$, $p < 0.025$) behavioural measures. No other significant correlations were found (max $r_{23} = -0.361$).

2.3.3: DISCUSSION

Similar to experiment 1A, the participants successfully demonstrated conditioned inhibition in both task variants. While the expression of conditioned inhibition was significantly more pronounced in the Incredible Hulk task, conditioned inhibition was expressed significantly in both task variants, where both the transfer as well as the generalized stimuli successfully passed summation test (Rescorla, 1969).

The existence of a negative correlation between the conditioned inhibition ratio of the Incredible Hulk task and the BAS Fun seeking, BAS drive, and the overall BAS score seems to indicate that, at least with respect to this task variant, individuals that are more impulsive demonstrate a higher degree of conditioned inhibition (a higher conditioned inhibition ratio shows a reduction in the level of conditioned inhibition demonstrated). One reason for this may be the rewarding nature of the task itself (in that the tasks are designed as a game, and specifically for the incredible Hulk task, the participant is actively searching for a solution to the conundrum posed by the task) may act on the BAS system itself, which has been suggested to be involved in reward motivational system (Fowles, 1987; Jeffrey

Alan Gray, 1982). Previously, Berkman, Lieberman, and Gable (2009), using novel task that crossed rewarding/aversive unconditioned stimuli with approach/avoidance conditioned responses, had shown that high BAS (especially BAS Drive) individuals produced faster correct responses to all trial types regardless of whether the stimulus was hedonistically aversive or rewarding. Based on their result, the authors stated that such a finding reinforces the hypothesis that the BAS is sensitive to reward learning and is distinct from impulsivity. Based on this conclusion, perhaps the storyline of the Incredible Hulk task was seen as more engaging and rewarding which in turn led to a better performance on the task itself by those individuals whom have greater desire for seeking out new rewards and pursuit goals (which in this task was the recognition of under what circumstances the experiment undertaken by Dr. Banner was successful).

Once more, similar to the findings in experiment 1A, a strong positive correlation was observed between the scores obtained on the TS and the ADHD individual difference behavioural measures, reaffirming the link between TS and ADHD even in normals. This is supported by the findings that both disorders are often comorbid in clinical groups (Comings & Comings, 1987; Ozonoff, et al., 1998; Robertson, 2000, 2006; Sheppard, et al., 1999; Spencer, et al., 1998).

The positive correlation between the BIS score and the ADHD as well as the TS behavioural measures would imply that individuals who demonstrate greater levels of TS and/or ADHD-like behaviours would also demonstrate higher levels of behavioural inhibition. This contradicts the hypothesis that TS and ADHD may be because of deficits in behavioural inhibition, (Barkley, 1997; Crawford, et al., 2005; Gilbert, et al., 2004; Ozonoff, et al., 1998;

Quay, 1988a, 1997; Schachar & Logan, 1990; Schachar, et al., 2000; Sheppard, et al., 1999). As such, contrary to the results obtained, one would expect a negative correlation to exist between the BIS component as ratings on the TS and ADHD scales. However, as previously noted, since none of the participants reported being diagnosed with ADHD or TS, one cannot necessarily extrapolate the results obtained to represent TS and ADHD in clinical populations.

In conclusion, conditioned inhibition was successfully demonstrated by a population who would have little or no knowledge of the field of psychology and the theories of conditioning in particular which may affect the outcomes of the current investigation. However, what overall effect familiarity with psychology and the theories of conditioning may have on the current investigation is not known. As such, the following section will investigate whether such an effect does exist, and if so, in what manner does it affect the results obtained.

2.4: COMBINED ANALYSIS OF THE DATA FROM EXPERIMENT 1A AND EXPERIMENT 1B

A combined analysis of experiments 1A and 1B were conducted in order to observe whether a difference in the level of conditioned inhibition exhibited existed between the two population samples.

2.4.1.1: DESIGN AND ANALYSIS

The analysis conducted in the current investigation is in large a repetition of the analysis outlined in Experiment 1A, with the exception that the variable *population groups* (Psychology or Non-psychology population from experiments 1A and 1B) was included as a between-subject variable.

2.4.2: RESULTS

No significant interaction between inhibition and two population groups was found ($F < 1$) as shown in Figure 2-7.

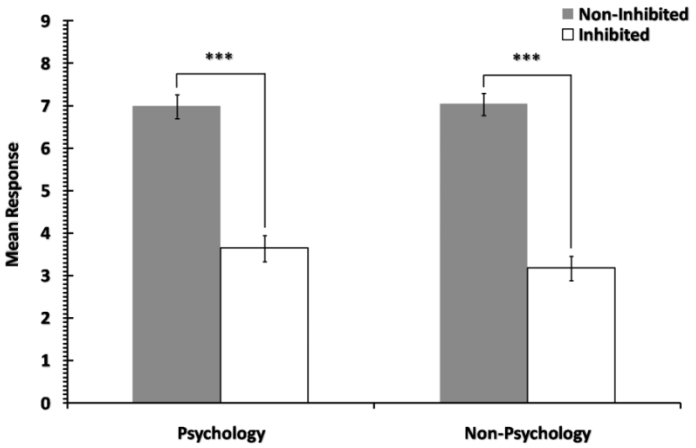

Figure 2-7: The combined analysis of the participants from experiments 1A and 1B showed no significant interaction between population sample and Inhibition. The analysis was collapsed over tasks, stimuli and presentations. (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$)

Also, no significant interaction between the two population groups and inhibition-by task, inhibition-by-stimulus, and inhibition by presentation was found (max $F_{4, 188} = 1.602$). Thus, based on the results obtained, the results from the two populations were combined for the correlational analysis with the individual difference behavioural measures.

2.4.2.2: CORRELATIONAL ANALYSIS

No significant correlation was found between any of the individual difference behavioural measures and performance on either of the conditioned inhibition tasks summarized by the conditioned inhibition ratios was found (max $r_{49} = -0.25$).

A significant positive correlation between the ADHD and the TS scales ($r_{49} = 0.599$, $p < 0.001$). A significant positive correlation was also observed between the yawning and the ADHD behaviour measure ($r_{49} = 0.527$, $p < 0.001$). Moreover, the yawning behaviour measure had also a significant positive correlation with the TS behavioural measure ($r_{49} = 0.726$, $p < 0.001$). This significant correlation still remained even when the yawing item on the TS scale was removed ($r_{49} = 0.696$, $p < 0.001$).

Significant positive correlations were found between the BIS and the TS behaviour measure ($r = 0.425$, $p < 0.01$) as well as with the ADHD behaviour measure ($r_{49} = 0.458$, $p = 0.001$). Also, a significant positive correlation was found between the yawing and the BIS behaviour measure ($r_{49} = 0.534$, $p < 0.001$). Lastly, a significant negative correlation between the BAS fun seeking and the yawing behaviour measure was found ($r_{49} = -0.282$, $p = 0.05$). No other significant correlations were noted (max $r_{49} = -236$).

2.4.3: DISCUSSION

The absence of a significant difference between the psychology and the non-psychology groups demonstrated that possible familiarity with the research background by the psychology student population had no bearing on the performance demonstrated in the investigation. Moreover, the presence of a significant main effect of inhibition showed that conditioned inhibition was successfully demonstrated in both task variants. The current results provide further support for the successful demonstration of conditioned inhibition by human participants using a translational model from the animal learning paradigms (Arcediano, et al., 1996; Karazinov & Boakes, 2004; Migo, et al., 2006; Neumann, et al., 1997; O'Boyle & Bouton, 1996; Williams, 1995; Williams, et al., 1994). Moreover, the results of the summation test indicate that in both task variants, the participants demonstrated significant level of conditioned inhibition when the conditioned inhibitor was presented in combination with the either transfer or the generalized stimuli. As such both the generalized as well as the transfer stimulus passed summation test (Rescorla, 1969).

With respect to the individual difference behavioural measures, the absence of a correlation between the TS or ADHD individual difference behavioural measures and the expression of ADHD (as expressed by the conditioned inhibition ratio) suggests that the inhibition of S-S associations are not affected by TS and ADHD-like behaviours (as measured in the normal population). Looking at the individual difference measures themselves, the strong positive correlation found between the yawning scale with both the

TS as well the ADHD behaviour measures and lends support to the view that excessive yawning may be a possible marker of TS and/or ADHD (Greco and Baenninger, 1993, Dalsgaard et al., 2001, Sandyk, 1996, Walusinski, 2006). However, such finding cannot be considered conclusive due to the fact that none of the participants in the current investigation reported being diagnosed with either ADHD and/or TS. Nonetheless, although it would be rather presumptuous to draw any solid conclusions without observing similar results in TS or ADHD clinical groups, these findings regarding the relationship between yawning and TS as well as ADHD and are nonetheless quite interesting.

Moreover, similar to the results seen in the previous investigation, a positive correlation was found between the BIS and the TS as well as the ADHD behavioural measures, revealing that individuals demonstrating greater levels of TS and/or ADHD behaviours also tend to show higher levels of behavioural inhibition. This finding is contrary to the hypothesis that ADHD and/or TS may be as a result of a breakdown in the individual's behavioural inhibition (Barkley, 1997; Iaboni, et al., 1997; Quay, 1997). It also does not support previous findings that have failed to find a link between behavioural inhibition and TS/ADHD (Channon, Gunning, Frankl, & Robertson, 2006; Johnson, et al., 2003; Pliszka, et al., 1993). With regards to the TS population, this may be due to compensation as a result of practice in controlling tics. Previously, Mueller, Jackson, Dhalla, Datsopoulos, and Hollis (2006) found that in a switching task paradigm, the TS group produced significantly fewer errors on the switch trials compared to the controls. Further analysis demonstrated that this effect was not due to switching saccades independent of the switching-task or the result of a speed-accuracy trade-off. The authors hypothesised that such a result may be due to the compensatory change in which the chronic suppression of tics by TS patients

result in a generalized suppression of reflexive behaviour and as such, increased cognitive control. However, due to the fact that none of the participants reported having ADHD/TS, the measured scores even the individuals demonstrating a high rate of TS/ADHD behaviours were 'normal', and as such any reported correlation may not be representative of the clinical population.

Looking at the tasks themselves, while conditioned inhibition was successfully demonstrated in both task variants, the level of excitatory and inhibitory responding shown the Incredible Hulk task was significantly greater than those of the Mission to Mars task as observed in both experiment 1A and 1B. This could be as a result of the Mission to Mars task proving to be to be more difficult than the Incredible Hulk task, perhaps as a result of the implicit (Mission to Mars) versus the explicit (the Incredible Hulk) nature of the instructions provided. Another possible reason may be as a result of the structure of the tasks themselves. While the stimuli in both tasks were shown in a serial presentation, unlike the incredible Hulk task, the CI was presented and removed prior to the presentation of the CS and the distractors for the Mission to Mars task. Also, the presentations of the CS and the distractors was always randomised on screen during each trial in the Mission to Mars task, unlike the Incredible Hulk task, for which the CI, CS and the distractors were always shown in the same location during each presentation. Taken together, performance on the Incredible Hulk task may have been more pronounced as a result of the task being much easier to decipher. Support for this hypothesis is also provided by the participants themselves, when, following informal observations at the end of each experiment, each was asked about the task variants, such as which experiment they found more difficult or more enjoyable, in order to assess the quality of each task and

modify it if need be. Overall, informal observations of the participants suggested that while they found the Incredible Hulk task to be more engaging due to the storyline, they also found it to be notably less difficult than the Mission to Mars task.

Due to the issues raised above regarding the Incredible Hulk task, a new task was created using the same comic book element as the Incredible Hulk task with an increase in the level of challenge similar to that of the Mission to Mars task. As noted in the procedures, the elements of the Incredible Hulk task were presented serially, with the CI presented first, followed by the CS and finally the distractor stimulus, with each element appearing in the same position on screen as the preceding presentations. The elements in the Mission to Mars task were also presented in a serial presentation, the CI presented first, followed by the CS and finally the distractor stimulus. However, with the exception of the CI (which was presented as a gray border around the screen), the CS and the distractor stimuli appeared in random positions on screen during each presentation. As such, the new conditioned inhibition task (The Weapon X task, based on the popular X-Men Wolverine comic book storyline) employed the same random presentation element of the Mission to Mars task, as well as the story element of the Incredible Hulk task. However, unlike the previous task variants, the stimuli in the new Weapon X task were shown in a simultaneous presentation. This was based on the Holland's conditioned inhibition experiments (Holland, 1984, Holland and Lamarre, 1984) who had previously found that while the conditioned inhibitor from a simultaneous paradigm (A+, AX-) readily inhibit the transfer stimulus in the summation test, no such inhibition of the transfer stimulus was noted in the serial (A+, X→A-) conditioned inhibition paradigm. It may be that while the inhibitor established in a serial conditioned inhibition paradigm acts on a particular CS-UCS association, inhibiting

only the particular CS it had been associated with during training in animal learning paradigms, this effect seems to be lost in humans, who seem to form an inhibitory association between the feature and the reinforcer, which according to the summation rule, inhibits the responding induced by another stimulus that possesses similar features to the CS (namely the transfer and the generalized stimuli) even in a serial presentation.

The final investigation of this chapter (experiment 1C) looks at performance by a normal population on the serial presentation Mission to Mars and the simultaneous presentation Weapon X conditioned inhibition task variants, whereby the performance of the new Weapon X task variant is compared again the more established Mission to Mars task.

2.5: EXPERIMENT 1C - THE MISSION TO MARS AND THE WEAPON X CONDITIONED INHIBITION PARADIGMS

2.5.1: METHODS AND MATERIALS

2.5.1.1: PARTICIPANTS

Thirty three participants (male: n = 12, female: n =21, Mean age = 23 years, Range = 17-40 years) took part in the study. The participants consisted of post-graduate and undergraduate students from the University of Nottingham, as well as a visiting student (17 years of age). The participants were screened for prior knowledge of the experimental theories (Pavlovian conditioning and conditioned inhibition) at the end of the experiment (so that inquiries about Pavlovian conditioning would not provide any clues to the nature of the tasks). However, no exclusions were made as none of the participants revealed any prior knowledge of Pavlovian conditioning. The procedures conformed to the guidelines set by the School of Psychology, University of Nottingham Ethics Committee.

2.5.1.2: MATERIALS

The task programs were produced in E-studio and utilized E-prime (Psychology Software Tools Inc., Pittsburgh, USA) to present the material to the participants. The programs were run on personal computers with 17" monitors. Participants' responses were made using a mouse. The stimuli presented during each of the two tasks are shown in Figure 2-8.

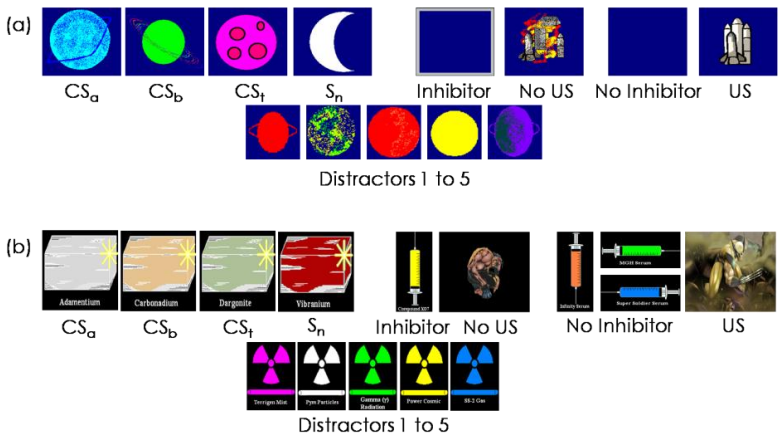

Figure 2-8: The stimuli presented during (a) Mission to Mars and (b) Weapon X task.

2.5.1.3: PROCEDURES

2.5.1.3.1: THE MISSION TO MARS TASK

The procedure for the Mission to Mars task follow those outlined in experiment 1A.

2.5.1.3.2: THE WEAPON X TASK

This task was presented with a scenario based on the Weapon X comic book story. Participants were informed that they were to play the role of Professor Thorton, Director of the Weapon X project, with the job to create the ultimate living weapon, using metallurgic skeletal bonding to convert Logan into Wolverine. Failure results in the feral mutation of Logan. Participants were further informed that in order to learn Thorton's secret, they were to carefully observe his work in order to work out the causes of success (Wolverine) versus failure (the feral mutation).

As for the previous task, the training phase consisted of forty-five learning trials, presented as nine cycles of the five stimulus sequences shown in Table 2. The stimuli were different in

that in this task variant, participants were asked to observe a computer simulation of the Weapon X transformation. This consisted of three stimuli appearing simultaneously: the CI or its absence (represented by an injector syringe), the CS (a block of a certain fictitious alloy), and a distractor (presented as a type of radiation), for a total of 4 seconds on screen. These images were followed by a 1 second presentation of an image of Logan in the midst of the attempted transformation, then the presentation of the UCS or its absence. The success or failure of the metallurgical bonding was represented by an image of Wolverine as the UCS, or a picture of feral Logan representing the absence of the UCS. Participants were required to click any key of the mouse to continue.

Again the testing phase consisted of twenty trials (as per Table 2-1) with the key generalized (S_g) and transfer stimuli (CS_t) for the summation test of conditioned inhibition. Similar to the previous tasks, an on-screen scale of 1 to 9 was used to rate the likelihood of a success. All choices were made via clicking on the appropriate box on screen by the mouse as shown in figure 2-9. The order of the presentations of the two tasks was counterbalanced across the two tasks.

Figure 2-9: The sequence of presentations during the Weapon X test phase. Row (a) illustrates the presentation of a non-inhibited generalized stimulus (shown as a silver block in the middle of the first image). Row (b) illustrates the presentation of an inhibited transfer stimulus (shown as an orange block at the top of the first image). The inhibitor was provided by a yellow syringe (shown in the left corner of the first image in the bottom row). The second image in each row is the rating screen. The third image in each row is Logan mid-transformation. The fourth image in each row is the UCS (top) or its absence following presentation of the inhibitory stimulus (bottom).

2.5.1.3.3: INDIVIDUAL DIFFERENCE MEASURES

The description and procedures of the individual difference measures are outlined in experiment 1A.

2.5.1.4: DESIGN AND ANALYSIS

Analysis of variance (ANOVA) was run in a mixed design with up to four within-participants factors to assess the development of conditioned inhibition: inhibition (the presence or absence of the CI); task (Mission to Mars versus Weapon X); stimulus type (summation test with the generalized stimulus versus the previously trained transfer stimulus); presentation, of which there were five levels.

The dependent variable to assess conditioned inhibition was the participants' expectancy scores (for appearances of an intact rocket in task 1 or the successful transformation of Logan into Wolverine in task 2). The F ratios were checked for sphericity via Mauchly's test

of sphericity and adjusted accordingly (by Greenhouse-Geisser correction when the value of epsilon was between the values of 0.5 to 0.75 and via Huynh-Feldt correction when epsilon was greater than 0.75).

In addition, a conditioned inhibition ratio that was calculated by dividing the average expectancy score for inhibited stimulus presentations by the average expectancy score for non-inhibited stimulus presentations. Thus conditioned inhibition is indicated by a ratio less than one and the absence of conditioned inhibition by a ratio greater than or equal to one. The interrelationship between the level of conditioned inhibition summarized by the scores on each of the four individual differences measures listed above was explored by 2-tailed Pearson's r correlation.

2.5.2: RESULTS

As shown in figure 2-10a, an overall significant effect of inhibition was observed ($F_{1, 32} = 33.401$, $p < 0.001$). Analysis showed no significant interaction between inhibition and task ($F_{1, 32} = 2.481$), as conditioned inhibition was successfully demonstrated across the two task variants (figure 2-10b). Moreover, the results further showed that both the transfer and the generalized stimuli passed summation test, as no significant interaction between inhibition and stimulus was found ($F < 1$).

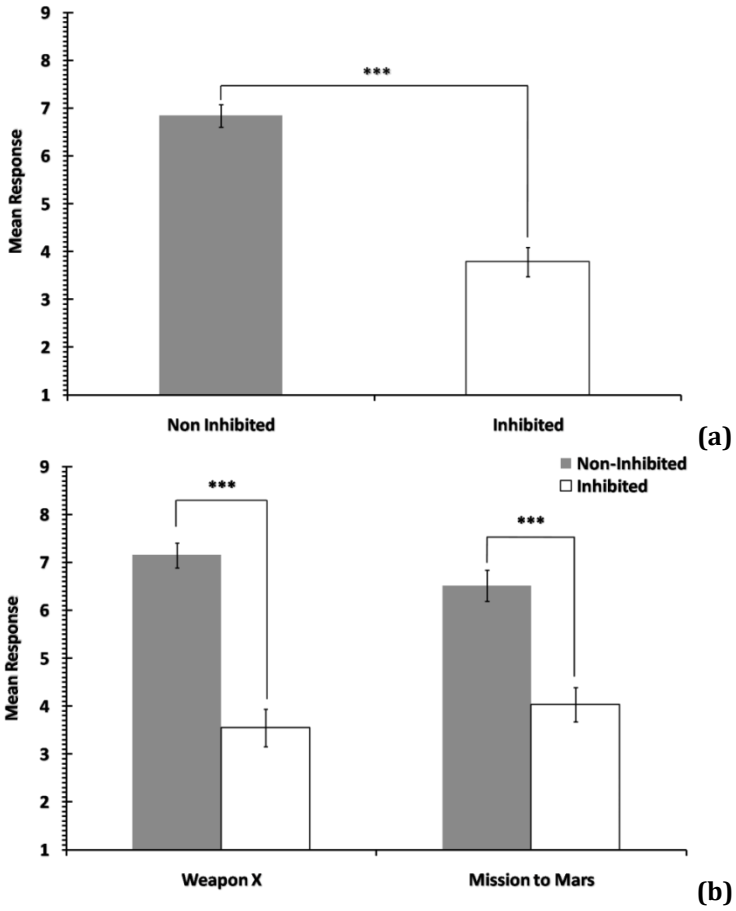

Figure 2-10: Significant main effect of (a) inhibition ($F_{1, 32} = 33.4$, $p = 0$) and (b) the interaction between task and inhibition. Conditioned inhibition was successfully demonstrated in both task variants. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

A significant interaction between inhibition and presentation ($F_{3.48, 111.29} = 3.031$, $p < 0.05$) was found. As seen in figure 2-11, post hoc analysis showed that while conditioned inhibition was seen in each of the five stimulus presentations (min $t_{32} = 4.191$, $p < 0.001$, max $t_{32} = 6.092$, $p < 0.001$), inhibitory responding improved progressively as inhibitory responding was significantly higher during the first presentation of the inhibitor compared to the third ($t_{32} = 2.116$, $p < 0.05$), the fourth ($t_{32} = 2.089$, $p < 0.05$), and the fifth ($t_{32} = 4.569$, $p < 0.001$) inhibitory presentations. A difference in excitatory responding was noted only between the second and fourth stimulus presentations ($t_{32} = 2.919$, $p < 0.01$). The following median split analyses were collapsed across the task and stimulus variables.

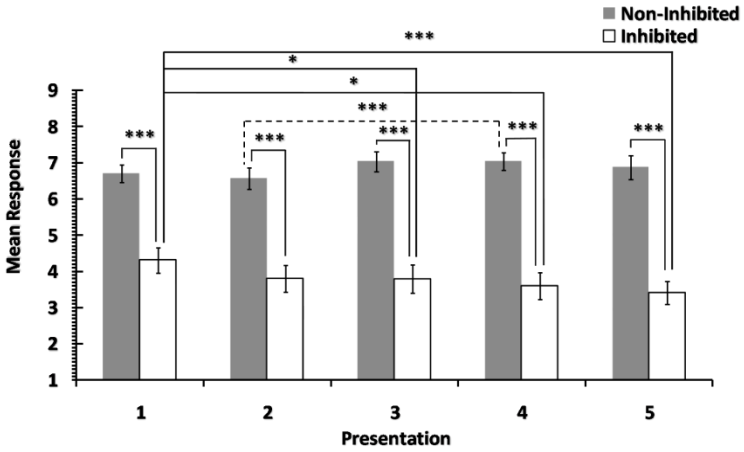

Figure 2-11: Significant interaction of inhibition and presentation ($F_{3.5, 111.3} = 3.03$, $p < 0.03$). (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

Median split analysis of the individual difference behaviour measured revealed a significant interaction between inhibition-presentation and the yawning behaviour measure ($F_{4, 124} = 2.572$, $p < 0.05$) (Figure 1-12). However, Post hoc analyses failed to show a significant difference between the individuals scoring above and the individuals scoring below or equal the yawning behaviour measure median (max $t_{31} = 1.4587$).

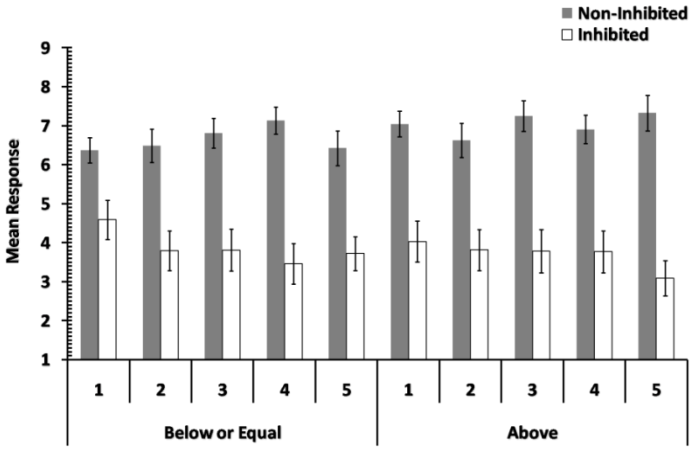

Figure 2-12: While a significant interaction between inhibition-presentation the yawning behaviour median split was found, no significant difference in responding between individuals in the above and the below or equal the yawning median groups was observed. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

No other significant interaction between the expression of conditioned inhibition and the remaining individual difference behavioural measures was found (max $F_{1, 31} = 2.492$).

2.5.2.1: CORRELATIONAL ANALYSIS

A significant positive correlation was noted between the Weapon X conditioned inhibition ratio and the ADHD behavioural measure ($r_{33} = 0.475$, $p = 0.008$). However, no such correlation between the ADHD behaviour measure and the Mission to Mars conditioned inhibition ratio was observed ($r_{33} = 0.02$). Moreover, a significant positive correlation was noted between the Weapon X conditioned inhibition ratio and BAS reward responsiveness measure ($r_{33} = 0.378$, $p < 0.05$). No other correlations between the individual difference behavioural measures and performance on either of the conditioned inhibition tasks summarized by the conditioned inhibition ratios were found (max $r_{33} = 0.294$).

A significant positive correlation was found between the TS and ADHD behavioural measures ($r_{33} = 0.412$, $p < 0.05$). Moreover, a significant correlation was found concerning the TS and the BIS behaviour measure ($r_{33} = 0.423$, $p < 0.05$) as well as the yawning ($r_{33} = 0.558$, $p = 0.001$) behavioural measure.

Furthermore, a significant positive correlation was noted between the yawning behaviour measure and BAS behaviour measure ($r_{33} = 0.346$, $p < 0.05$) as well as the BAS fun seeking measure ($r_{33} = 0.347$, $p < 0.05$). No other significant correlations were observed (max $r_{33} = 0.322$).

2.5.3: DISCUSSION

Conditioned inhibition was clearly demonstrated in the present study by both task variants. Conditioned inhibition was confirmed by the summation test, where the transfer

of inhibition to a CS not previously presented with the CI during training (CSt) and to a novel stimulus from the same category, to which participants would generalized their excitatory responding (Sg) was successfully demonstrated (Rescorla, 1969). Statistically, there was no difference in the level of conditioned inhibition shown by stimulus type. Moreover, unlike the previous investigations, no significant effect was task was found in the current investigation. The similarity of results across the two stimulus types and the two task variants provides strong evidence that the inhibitory properties of the CIs transferred both to a stimulus with which it had never previously been experienced and to a new stimulus with which they had no explicit prior training of any kind. While the two tasks were identical with respect to design and procedure, the tasks were quite different with regards to the task instructions, the serial versus stimulus presentation of the stimuli, as well as the content. Thus, the absence of a difference in performance by task also suggests that explicit learning instructions are not necessary to show conditioned inhibition. However, most importantly, the absence of a task difference also shows that the issues raised by the previous Incredible Hulk task has been successfully addressed by the new Weapon X task in that conditioned inhibition was clearly demonstrated by both tasks, while no difference in responding between the two tasks remained.

While a significant interaction between inhibition and presentation was observed, conditioned inhibition was significantly demonstrated in each of the five presentations. However, while excitatory responding remained the same, inhibitory responding improved over time, more than likely due to increased familiarity and confidence. This result demonstrated that no new learning took place during the testing phase.

Previously, Holland and Lamarre (1984) had found that in a feature discrimination procedure, the conditioned inhibitor failed to pass the summation test in a serial presentation paradigm, whereas the transfer of inhibition to a transfer stimulus was successfully demonstrated in a stimultanious presentation paradigm. Also, in a series of feature negative conditioned suppression experiments on human subjects using a space invasion task, Baeyens et al (2004) found that the transfer of inhibition by a conditioned inhibitor (A+/AX- where X is the CI) to a transfer stimulus was successful in a simultaneous presentation paradigm, irrespective of the learning history of the transfer stimulus (B+/YB- vs. B+ only group). However, in a sequential presentation paradigm, the authors found that the transfer of inhibition by the conditioned inhibitor (X) to the transfer stimulus was successful only if the transfer stimulus had been involved in another sequential feature negative training (B+/YB-) but not if the transfer stimulus had been consistently reinforced (B+). However, as noted, the conditioned inhibitor successfully passes summation test in both the serially presented Mission to Mars as well as the stimultaniously presented Weapon X task. In both the serially (sequentially) presented Mission to Mars task as well as the simultaneously presented Weapon X task, the transfer of inhibition by the CI to the transfer stimulus was successfully demonstrated. Thus, the effectiveness of the stimulus to act as an inhibitor did not depend on the temporal arrangement of the stimuli during the current investigation.

Looking at the individual difference behavioural measures, the results showed the level of conditioned inhibition demonstrated in the Weapon X task decreased with increasing levels of ADHD-like behaviours. However, no such effect was found for the Mission to Mars task despite the absence of a task difference as explained above. In addition, similar to the

previous investigations, none of the present sample of participants was from a clinical TS or ADHD populations, and as such, the ADHD and TS-like behaviours demonstrated by these participants may fall within a narrow normal range. Therefore, it would be rather presumptuous to conclude that conditioned inhibition deficits would occur as a result of ADHD-like behaviours. The level of conditioned inhibition demonstrated in the Weapon X task also showed a significant correlation with the BAS Reward Responsiveness, in that the level of conditioned inhibition diminished with increasing reward responsiveness. This result was the opposite of those found by Migo et al. (2006) who used an earlier version of the Mission to Mars task (which also lacked a the use of a background story) used in the current investigation.

Moreover, this result also differs from the Incredible Hulk task variant where no correlation between the conditioned inhibition ratio of that task and BAS Reward Responsiveness was found. Once more, no such correlation was observed with the Mission to Mars task. Since the design and the procedures of the two tasks were identical, such correlation may be as a result of the task content.

Similar to the previous investigation, a significant correlation between the ADHD and the TS behaviour measures was observed. Due to the high level of comorbidity between ADHD and TS (Banaschewski, Neale, Rothenberger, & Roessner, 2007; Barkley, 1998; Comings & Comings, 1987; Robertson, 2006), the current finding helps in the possible establishment of the novel TS measure used in the current set of investigations as a viable tool for the investigation of TS-like behaviours.

Individuals showing higher levels of TS-like behaviours also scored higher on the BIS behaviour measure, indicating that individuals demonstrating greater levels of TS behaviours showed greater degrees of behavioural inhibition, which is contrary to the hypothesis of TS being as a result of a deficit in behavioural inhibition (Casey, et al., 2001; Crawford, et al., 2005). However, as previously stated, since none of the participants was clinically diagnosed with TS, the current findings cannot be inferred to the TS clinical population.

Moreover, a significant correlation between the yawning and the BAS behaviours was observed. However, the positive correlation between the yawning and the BAS behaviours may be as a result of the more impulsive individuals becoming more fatigued readily compared to the less impulsive individuals (Fishbein, Lozovsky, & Jaffe, 1989).

In conclusion, the Weapon X task appears to be a more solid companion to the more established Mission to Mars task than the previous Incredible Hulk task. Moreover, while the serial versus simultaneous stimuli presentations was confounded with task instructions, conditioned inhibition was clearly demonstrated by both task variants. As such, the serial versus the simultaneous presentations of the two paradigms allows one to investigate two distinct routes of conditioned inhibition testing in the clinical population in order to investigate whether a deficit in conditioned inhibition is observed as a result of ADHD and TS symptoms in the clinical population.

CHAPTER 3: INDIVIDUAL DIFFERENCES IN THE INHIBITION OF S-R AND S-S ASSOCIATIONS IN THE NORMAL POPULATION

3.1: INTRODUCTION

Previously, it was reported by Migo et al. (2006) that the level of conditioned inhibition demonstrated in a novel conditioned inhibition paradigm was negatively associated with the level of schizotypy measured in a normal population. Based on this finding, the studies outlined in chapter 2 investigated whether the associative learning measured using similar conditioned inhibition paradigms as Migo et al. was affected by the individual differences in ADHD and TS-like behaviours in a normal population. However, the results showed no associations between the level of conditioned inhibition demonstrated and the individual difference in ADHD and TS behaviours.

The present chapter investigates the existence of such association with respect to behavioural inhibition as measured by the inhibition of S-R associations demonstrated by tasks such as the Go/NoGo, the colour-word Stroop, and the Simon task. According to Nigg (2000), the active inhibition of cognitive or motor responses involves: (1) interference control – defined as the prevention of influence by competing distractors, measured by such tasks as the Stroop; (2) behavioural inhibition – defined as the suppression of automatic or cued but inappropriate responses, measured by such tasks as the Go-NoGo or the stop signal; (3) cognitive inhibition - defined as the protection of working memory and attention from intrusive, unimportant thoughts, measured by such tasks as negative priming tasks, and (4) oculomotor inhibition - defined as the active suppression of ocular saccades, as measured by such tasks as the antisaccade tasks.

The Go/NoGo task is a widely used response inhibition paradigm that has been employed to successfully demonstrate deficits in response inhibition within the ADHD clinical

population (Berwid, et al., 2005; Bitsakou, et al., 2008; Iaboni, et al., 1995; Klein, et al., 2006; Trommer, et al., 1988). The Go/NoGo is a task that measures the level of response inhibition, evaluated by the number commission errors committed, and sustained attention, assessed by the number omission errors made by participants. Omission errors occur when a response is withheld at a time where a response is required by the presentation of a Go stimulus, predominantly as a result of inattention (Berwid, et al., 2005; Trommer, et al., 1988). Commission errors occur when a response is produced at a time when responding is required to be withheld as a result of the presentation of the NoGo stimulus, by reason of failing to inhibit a prepotent response.

A basic non-motivational Go/NoGo task provides a measure of executive inhibition, in that the Go response is set up as the dominant response by the greater presentation of the Go stimuli compared to the rarer NoGo stimulus presentations (Nigg, 2001). Through the use of the Go/NoGo task, deficits in executive function and attention have been observed in ADHD, where in general, ADHD participants demonstrate greater number of commission as well as omission errors compared to matched controls (Bitsakou, et al., 2008; Casey, et al., 1997; Klein, et al., 2006; Tamm, Menon, Ringel, & Reiss, 2004; Trommer, et al., 1988). The same deficits were observed in normal children who were viewed as high risk or low risk for ADHD, as a greater number omission as well as commission errors were observed in high risk children compared to low risk children (Berwid, et al., 2005). With regards to TS however, inhibitory deficit as measured by the Go/NoGo task is rarely observed (Ozonoff, et al., 1994; Roessner, et al., 2008; Serrien, et al., 2005).

The Stroop test is another popular test of response inhibition. Developed by John Ridley Stroop (Stroop, 1935), the Stroop effect is a test of response inhibition based on the notion that it takes individuals longer to name the ink colour of a colour word printed in a contrasting colour, such as naming the colour blue when the word "Red" is written in blue (incongruent stimuli) than of a neutral or congruent stimuli (where both the ink colour and the colour word are the same). With regards to TS, the results are similar to those of the Go/NoGo task, in that the studies generally fail to show response inhibition deficit as measured by the Stroop task in the TS population (Channon, et al., 2009; Channon, et al., 2003; Marsh, et al., 2007; Stebbins, et al., 1995).

Unlike the Go/NoGo task however, while some investigations have demonstrated response inhibition deficits in ADHD participants when tested with the Stroop task (Berwid, et al., 2005; Bitsakou, et al., 2008; Goldberg, et al., 2005; Lansbergen, et al., 2007; Seidman, et al., 1997; Young, et al., 2006) others have failed to find such response inhibition deficits (Channon, et al., 2003; Gaultney, Kipp, Weinstein, & McNeill, 1999; Schwartz & Verhaeghen, 2008). According to Nigg (2000) the Stroop task is a test of the measure of cognitive inhibition employing the concept of interference control (interference arising from stimulus competition), measuring motor interference. Nigg argues that Stroop has limitations in that it requires the participant to extract features of a *single* target rather than specific targets from a stimulus, which may reflect different features of interference control than those found in everyday activity (Nigg, 2000; Treisman, 1969). Nigg further states that interference control tasks such as the Stroop measure inhibition during effortful attention. However, the varying results observed in the ADHD population may not be due to the supposed inability of the Stroop to correctly measure response inhibition in a

population. Banaschewski et al. (2006) found that compared to matched controls, ADHD participants demonstrated a greater level of impairment in the blue-yellow axis of the colour spectrum, indicating that the impairment demonstrated by the ADHD participants in the colour-word Stroop task may not be due to (or partially due to) loss of inhibition but as a result of selective colour-blindness. They noted that while the ADHD participants did not differ in speed for naming words, they were however impaired in the colour naming and in the colour-word conditions compared to matched controls. Thus according to the authors, the deficiencies demonstrated by the ADHD population on the classic Stroop are due to selective colour blindness resulting from altered dopaminergic mechanisms (resulting in changes in the retinal dopaminergic mechanisms) in the ADHD population. Similar results were also reported by Albrecht, et al. (2008).

Similar to the Stroop and the Go/No tasks, the Simon task has also been a popular task for the measurement of response inhibition. The Simon effect is the influence on performance by an irrelevant spatial feature, which results from the interactions between two independent yet parallel processing paths that connect perception to action (Simon, 1969; Simon & Rudell, 1967). According to Simon, the two paths are defined as a direct conditional path based on task-defined associations (i.e. responding to colours) and an indirect unconditional path that activates responses based on the spatial location of the stimulus through pre-existing S-R associations that are independent of the task instructions. For example, the participants are required to respond to the red/green coloured boxes shown on screen (which may be shown on either the left or right side of a focal point on screen) using a keyboard/response pad (which has the button corresponding to each of the colours on opposing sides) while ignoring the spatial locations of the boxes.

The Simon effect occurs when the responses arising from the conditional and unconditional paths differ (i.e. the red box is shown on the left side of the screen while its corresponding response button is located on the right side of the response pad), which requires the incorrect response to be aborted that in turn causes an increase in the response time (Iani, Rubichi, Gherri, & Nicoletti, 2009; Simon & Rudell, 1967). In an investigation of cognitive inhibition under increasingly difficult task demands using a semantic Simon task with increasing levels of difficulty, Rankins, Bradshaw, & Georgiou-Karistianis (2006) reported inhibitory deficits in TS patients during the higher difficulty levels of the task. Moreover, inhibitory deficits measured by the classic Simon effect in TS participants were also reported by Georgiou et al. (1995).

The purpose of the investigation was to analyze whether the level of response inhibition as measured by the Go/NoGo, the colour-word Stroop and the Simon task were modulated by individual differences in ADHD and TS behaviours measured a normal population. Moreover, the current study also investigated whether individual differences in the level of behavioural activation (BAS) and inhibition (BIS) demonstrated (as measured by Carver & White's (1994) BIS/BAS individual difference behavioural measure) affected the degree of response inhibition demonstrated on the three tasks in question. According to Gray's model (Jeffrey Alan Gray, 1982, 1987) individuals that rate lower on the BIS and higher on the BAS scales would show a tendency to be more impulsive. Thus, would such impulsivity reflect as deficits in response inhibition as measured by the tasks in question? Finally, the task most resembling Migo et al. (2006) original conditioned inhibition task (i.e. the Mission to Mars task) was also tested along with the three response inhibition tasks. The purpose of this was to compare interrelationships with individual difference behavioural

measures. Moreover, the inclusion of this task also allowed for the analysis of the effect of individual difference in ADHD and TS behaviours (as well as the individual difference in BIS and BAS behaviours) within the normal population on the level of conditioned inhibition demonstrated using a large population sample (as a result of the combination of the results from the individual difference behavioural measures and the Mission to Mars conditioned inhibition results from the previous chapter as well as those from the current investigation).

3.2: EXPERIMENT 2A - THE INVESTIGATION OF RESPONSE INHIBITION IN THE NORMAL POPULATION USING THE KEYBOARD AS THE RESPONSE INPUT DEVICE

3.2.1: METHODS AND MATERIALS

3.2.1.1: PARTICIPANTS

Twenty-five participants (Male: n = 4, Female: n = 21) were recruited from the University of Nottingham student population (Mean age = 21.44 years). The participants were paid a £5 inconvenience allowance for their participation in their study. The procedures conformed to the guidelines set by the School of Psychology, University of Nottingham Ethics Committee.

3.2.1.2: MATERIALS

All of the programs were produced in E-studio and utilized E-prime (Psychology Software Tools Inc., Pittsburgh, USA) to present the material to the participants. The programs were run on personal computers with 17" monitors. Participants' responses were made using the computer's mouse (used for responding during the conditioned inhibition tasks) and the keyboard (used for responding during the response inhibition task). The order of presentation of the four tasks was counterbalanced across subjects.

3.2.1.3: PROCEDURES

3.2.1.3.1: THE GO/NOGO TASK

The task was obtained from The Sackler Institute (The Sackler Institute for Developmental Psychobiology, 2008). The task was introduced as a game of wack-a-mole where the participant was asked to "wack" a mole (which in this task represents the go signal) that has been invading the vegetable garden using a variety of disguises by pressing the spacebar as quickly as possible once the image of the mole disguised or otherwise appeared on screen. The participant was also informed that they must avoid "wacking" the vegetables in the garden (seen onscreen as a picture of an eggplant). The vegetable represented the NoGo signal. If the participant successfully "wacks" the mole, an image stating "WHACK!!" appears on screen immediately following the spacebar press. However, erroneous spacebar presses are met with an image stating "Oops!"

Figure 3-1: The Go/NoGo signals in the Wack-a-mole task: (a) i to v the Go signals, (b) the NoGo signals.

The task was broken down into four distinct blocks preceded by a short training block (7 Go and 3 NoGo trials). There were 41 Go and 13 NoGo trials in block 1, 42 Go and 14 NoGo trials in block 2, and 41 Go and 14 NoGo trials in both blocks 3 and 4, presented in random order in each block. Between each block, the participants observed a message stating "remember to whack the mole as fast as you can, but don't whack the eggplant!" and to press the spacebar when ready to start the next level. The Go and the NoGo signals were

presented for 2000 ms on screen prior to the presentation of the next trial. Failure to respond to a Go resulted in an omission error, whereas responding to the NoGo signal resulted in a commission error.

At the end of the task, the participants observed a message stating that they did a great job saving the garden and to press the spacebar to end the session.

3.2.1.3.2: THE SIMON TASK

The Simon task was based on a task created by J.R. Simon (Simon, 1969; Simon & Rudell, 1967) and developed in its current format and obtained from Dr. Roger Newport (University of Nottingham). As shown in figure 3-2, the task required participants place a left hand finger on the letter “c” and a right hand finger on the letter “m” and to stare at a central focus point (a cross) on screen, soon after which a red or green box was shown on either side of the central point. Once they were given the Go signal (seen as a box around the focus point) the participants were to make the specified response to the colour shown as quickly as possible, whereby they were to Press "c" for green on the keyboard when the colour green was shown on screen or Press "m" for red on the keyboard when the colour red was shown on the screen. The participants were instructed to try to ignore the location of the box and respond only to the colour shown. The colour signals were either presented congruently to the location of the response key and the responding hand (i.e. green on left side, red on right side of the focus point) or incongruently (i.e. green on left side, red on right side of the focus point). Moreover, the Go signal was presented either following a 100ms delay or a 900ms delay following the presentation of the colour signals.

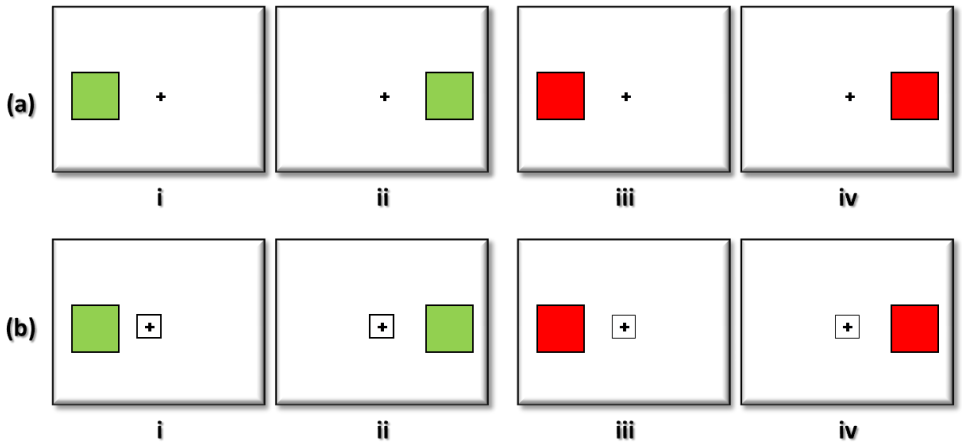

Figure 3-2: The stimuli used in the Simon task whereby the stimuli were presented congruently (i and iv) where the colour boxes fell on the same side as the corresponding response key or incongruently (ii and iii) where the colour boxes fell on the opposite side as the corresponding response key. The subjects were to respond when the Go signal (b) was presented either 100 or 900ms following the presentation of the coloured box (a). The colour of the stimuli shown in (i) and (ii) are green and in (iii) and (iv) are red.

The task was divided into two parts; a practice session followed immediately by the testing session. The practice session consisted of eight trials: two trials of congruent-short delay presentations, two trials of congruent-long delay presentations, two trials of congruent-short delay presentations, and two trials of congruent-long delays. The testing session was composed of 160 trials with forty congruent-short delay presentations, forty congruent-long delay presentations, forty incongruent-short delay presentations, and forty incongruent-long delay presentations. Responses were made using the left hand index finger for the "c" button presses using the right hand index finger for the "m" button presses. Each trial continued until the participant produced the correct response, and as such, the participant response times served as an indirect measure of response accuracy.

3.2.1.3.3: THE COLOUR-WORD STROOP TASK

This task was a computerized version of the task developed by Stroop (1935). The colour-word Stroop task used in the current investigation was developed and obtained from by Dr. Jonathan Stirk (University of Nottingham). In this task, the participant was shown name of a colour (blue, red or green) on the monitor printed in red, green or blue colours, as shown in figure 3-3.

The participants were asked to respond only to the colour ink the words have been printed in and as quickly as possible. Thus, if the word was written in red press they were to press the key '4' on the keyboard, if blue to press '5', and if green to press '6'. The colour word presentations were either congruent (the word and the colour were the same, i.e. the word "Red" written in red, etc…) or incongruent (the word and the colour were different, i.e. the word "Red" written in blue, etc…). The words were presented from 1000 ms or until such time a response were made, whichever came first.

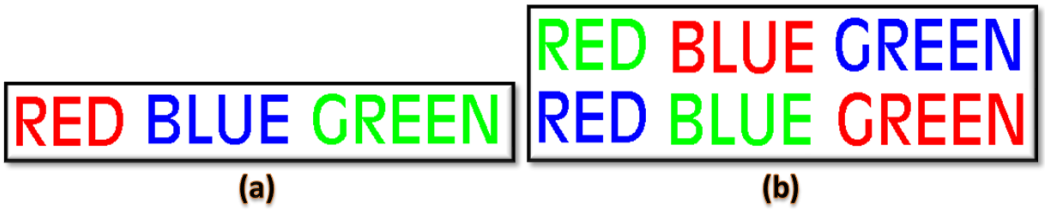

Figure 3-3: The stimuli presented in the Stroop task: (a) congruent stimuli, where the colour name written matches the ink it is written in (b) incongruent stimuli, where the colour name written is different than the ink it is written in (The lighter shade of gray shown represents the colour green). When the stimulus was written in the colour green the participants responded by pressing the number '4' key on the keyboard, when written in red they pressed the number '5' key and when written in blue they pressed the number '6' key.

The task was divided into two parts; a practice session followed immediately by the testing session. The practice session was composed of twelve trials with six congruent and six incongruent presentations. The testing session was composed of 48 randomly presented

trials with 24 congruent and 24 incongruent presentations. The participants received feedback regarding the accuracy of their response during the practice session. However, they received no such feedback during the testing session.

3.2.1.3.4: THE MISSION TO MARS TASK

The procedure of this task followed those outlined in chapter 2.

3.2.1.3.5: INDIVIDUAL DIFFERENCE MEASURES

Following the conclusion of the computerized tasks, the participants were asked to fill out four personality measures. A complete description of the individual difference behavioural measures is provided in chapter 2.

3.2.1.4: DESIGN AND ANALYSIS

3.2.1.4.1: THE GO/NOGO TASK

With regards to the analysis of response inhibition, analysis of variance (ANOVA) was run in a mixed repeated measure design with up to two within-subjects factors to assess the development of response inhibition: Stimulus type (the presentation of either a Go or a NoGo stimulus); and block, of which there were four levels. Each block was composed of a number of Go and NoGo trials whose average was calculated prior to the analysis of variance. As previously stated, there were 41 Go and 13 NoGo trials in block 1, 42 Go and 14 NoGo trials in block 2, and 41 Go and 14 NoGo trials in both blocks 3 and 4. The F ratios were checked for sphericity via Mauchly's test of sphericity and adjusted accordingly (by

Greenhouse-Geisser correction when the value of epsilon was between the values of 0.5 to 0.75 and via Huynh-Feldt correction when epsilon was greater than 0.75).

The dependent variable was the number of errors produced (for failure to respond to the Go stimulus or to inhibit responding to the NoGo stimulus). Planned comparisons (*t*-tests at $p \leq 0.05$) were conducted further to examine effects of a priori interest.

To test the relationship between response inhibition and individual difference scores in use, the mean total for the number of omission errors (on the Go trials) and Commission errors (on the NoGo trials) was calculated. As such, level of response inhibition demonstrated was measured by the combined number of commission errors compared to the combined number of omission errors produced. The level commission errors produced provided a measure of response inhibition demonstrated and the level of omission errors provided a measure of attention during the task. A two-tailed Pearson's r correlation analysis was performed to explore interrelationship the rating scores on each of the four individual difference behaviour measures (The ADHD, The TS, The BIS/BAS; including the BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness subscales of the BIS/BAS measure, and the Yawing individual difference behavioural measure) and the level of response inhibition (as measured by the mean of the number of commission errors) as well as the degree of attention (measured via the mean number of omission errors) demonstrated.

Also, in order to analyze the effects of the behaviours as measured by the four individual difference questionnaires on the level of response inhibition demonstrated, a median split

was performed on individual difference scores and analyzed as a between subjects factor with the data from the response inhibition measure on a repeated measures ANOVA. With regards to the BIS/BAS measure, median split analysis of the overall BAS and the BIS scores were performed only (the sub scores of the BAS were analyzed only for the correlational analysis).

With regards to the response time, the analysis was confined to responding to the Go trials only. The analysis of variance (ANOVA) was run in a mixed design with only one within-subjects factor to assess the development of response inhibition: block, of which there were four levels. The calculation of each of the four blocks is as described above. The dependent variable was the measured response time produced when presented with the Go stimulus. Planned comparisons (*t*-tests at $p \leq 0.05$) were conducted further to examine effects of a priori interest.

To test the relationship between response time and individual difference scores in use, the mean response time on the Go trials was obtained where the interrelationship between the level response time and the rating scores was explored by 2-tailed Pearson's r correlation.

Also, in order to analyze the effects of the behaviours as measured by the four individual difference questionnaires on the response time, a median split was performed on individual difference scores and analyzed as a between subjects factor with the data from response inhibition measure on a repeated measures ANOVA. With regards to the BIS/BAS measure, median split analysis of the overall BAS and the BIS scores were performed.

3.2.1.4.2: THE SIMON TASK

With regards to the analysis of response inhibition, analysis of variance (ANOVA) was run in a mixed design with up to three within-subjects factors to assess the development of response inhibition: congruence; delay (100ms or 500ms) and block, of which there were ten levels. Each block was composed four trials. The F ratios were checked for sphericity via Mauchly's test of sphericity and adjusted accordingly (by Greenhouse-Geisser correction when the value of epsilon was between the values of 0.5 to 0.75 and via Huynh-Feldt correction when epsilon was greater than 0.75).

The dependent variable was the time to respond. Planned comparisons (*t*-tests at $p \leq 0.05$) were conducted further to examine effects of a priori interest.

To test the relationship between response inhibition and individual difference scores in use, the overall mean response times in the congruent and the overall mean response times in the incongruent presentations were calculated. The interrelationship between the level of response inhibition and the rating scores on each of the four individual difference behaviour measures (including the BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness subscales of the BIS/BAS measure) were explored by 2-tailed Pearson's r correlation.

Also, in order to analyze the effects of the behaviours as measured by the four individual difference questionnaires on the level of response inhibition demonstrated, a median split was performed on individual difference scores and analyzed as a between subjects factor with the data from the response inhibition measure on a repeated measures ANOVA. With

regards to the BIS/BAS measure, median split analysis of the overall BAS and the BIS scores were performed.

3.2.1.4.3: THE COLOUR-WORD STROOP TASK

The analysis of response inhibition, analysis of variance (ANOVA) was run in a mixed design with up to two within-subjects factors to assess the development of response inhibition: congruence; and block, of which there were three levels. Each block was composed eight trials. The F ratios were checked for sphericity via Mauchly's test of sphericity and adjusted accordingly (by Greenhouse-Geisser correction when the value of epsilon was between the values of 0.5 to 0.75 and via Huynh-Feldt correction when epsilon was greater than 0.75).

The dependent variable was the correct responses produced (responding with the correct colour to the congruent/incongruent word). Planned comparisons (*t*-tests at $p \leq 0.05$) were as above.

To test the relationship between response inhibition and individual difference scores in use, the overall mean for the number of correct responses produced in the congruent and incongruent presentations were calculated. The interrelationship between the level of response inhibition (correct response on the congruent and incongruent presentations) and the rating scores on each of the four individual difference behaviour measure (including the BAS Drive, BAS Fun Seeking, and BAS Reward Responsiveness subscales of the BIS/BAS measure) were explored by 2-tailed Pearson's r correlation.

Also, in order to analyze the effects of the behaviours as measured by the four individual difference questionnaires on the level of response inhibition demonstrated, a median split was performed on individual difference scores and analyzed as a between subjects factor with the data from the response inhibition measure on a repeated measures ANOVA. With regards to the BIS/BAS measure, median split analysis of the overall BAS and the BIS scores were performed.

A repeat of the above design was conducted using the response time data (ms) obtained on the congruent and incongruent trials.

3.2.1.4.4: THE MISSION TO MARS TASK

Analysis of variance (ANOVA) was run in a mixed design with up to three within-subjects factors to assess the development of conditioned inhibition: inhibition (the presence or absence of the CI); stimulus type (summation test with the generalized stimulus versus the previously trained transfer stimulus); presentation, of which there were five levels. Analyses were collapsed across stimulus type and presentation where these factors did not affect the development of conditioned inhibition. The F ratios were checked for sphericity via Mauchly's test of sphericity and adjusted accordingly (by Greenhouse-Geisser correction when the value of epsilon was between the values of 0.5 to 0.75 and via Huynh-Feldt correction when epsilon was greater than 0.75).

The dependent variable was the participants' expectancy scores (for appearances of an intact rocket in the task). Statistical analysis of the Mission to Mars task and comparisons with the individual difference behavioural scores followed the procedures detailed in chapter 2.

3.2.2: RESULTS

3.2.2.1: THE GO/NOGO TASK

A significant difference between the number of omission and commission errors were found ($F_{1, 24} = 45.54$, $p < 0.001$), whereby the participants made significantly greater number of commission errors compared to omission errors (of which none was made, showing that attention was maintained throughout the task) as shown in Figure 3-4. No significant effect of block or response inhibition by block was found (max F <1). All further response inhibition analysis was collapsed across blocks.

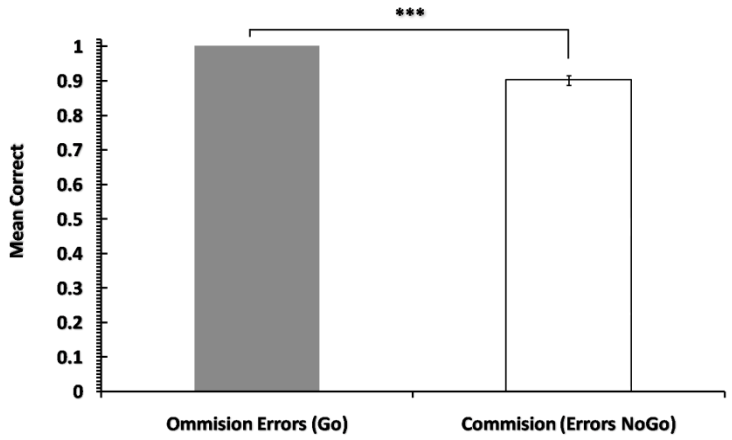

Figure 3-4: The proportion of correct responses on the Go and the NoGo trails in the Go/NoGo Task. The participants produced a greater number of commission errors. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

With respect to median split analysis of the individual difference behavioural measures (performed separately for each measure), the median split of the individual difference

behavioural measure (the between subject factor in a repeated measure analysis) did not reveal a significant interaction between the ADHD, TS, BIS, BAS, or the yawning individual difference behavioural measure (max $F_{1, 23} = 3.171$) and omission/commission errors.

Analysis of the response time during the presentation of the Go signal revealed an overall significant effect of blocks ($F_{3, 72} = 5.802$, $P = 0.001$) as shown in Figure 3-5. Post hoc analysis revealed that the participant's response time increased in the later blocks (blocks 3 and 4) compared to block 1 (Blocks 1 & 3: $t_{24} = 2.87$, $p < 0.01$; Blocks 1 & 4: $t_{24} = 3.10$, $p < 0.01$) and block 2 (Blocks 2 & 3: $t_{24} = 2.64$, $p < 0.05$, Blocks 2 & 4: $t_{24} = 2.66$, $p < 0.05$). There was no significant difference between the response times of blocks 1 and 2 or blocks 3 and 4 (max $t < 1$).

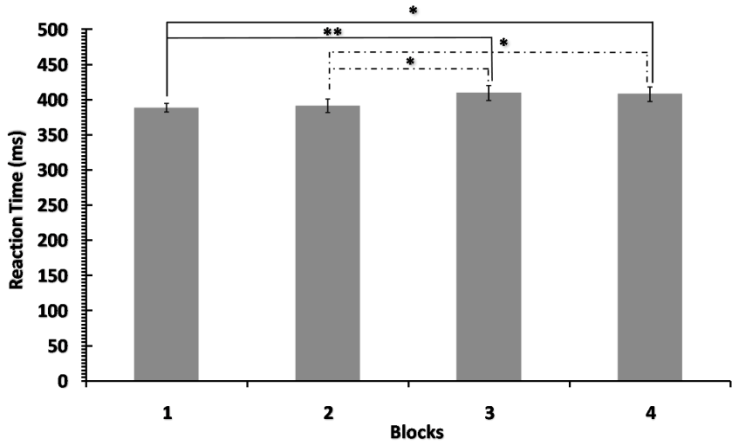

Figure 3-5: Overall response time following the presentation of the Go signal. The participants responded with slower response times in the later blocks or presented Go stimuli compared to the earlier blocks. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

The analysis of the effect of individual difference behavioural measures on response times did not reveal a significant interaction between response times measured during each block and the ADHD ($F < 1$), TS ($F < 1$), BIS ($F_{3, 69} = 1.023$), BAS ($F_{3, 69} = 1.394$), or the yawning individual difference behavioural measure ($F < 1$).

3.2.2.1.1: CORRELATIONAL ANALYSIS

Correlational analysis revealed a significant positive correlation between the response inhibition (commission errors) and the ADHD behavioural scale ($r_{25} = 0.504$, $p = 0.01$). No other significant correlation between the individual difference behavioural measures and the measure of response inhibition (mean commission errors committed), the measure of attention (mean omission errors committed) or the response times produced and the different individual difference behavioural measures were found (max $r_{25} = 0.334$).

3.2.2.2: THE SIMON TASK

The results showed a significant effect of delay ($F_{1, 24} = 208.87$, $p < 0.001$), where as shown in Figure 3-6a, the response times produced were slower following a 100ms response request delay compared to a 900ms delay. No significant effect of spatial correspondence (Figure 3-6b) or blocks was noted (max $F < 1$). Moreover, no significant interactions between spatial correspondence, delay and/or blocks was obtained (max $F_{1, 24} = 3.876$). As such, all further analysis was collapsed across spatial correspondence and blocks.

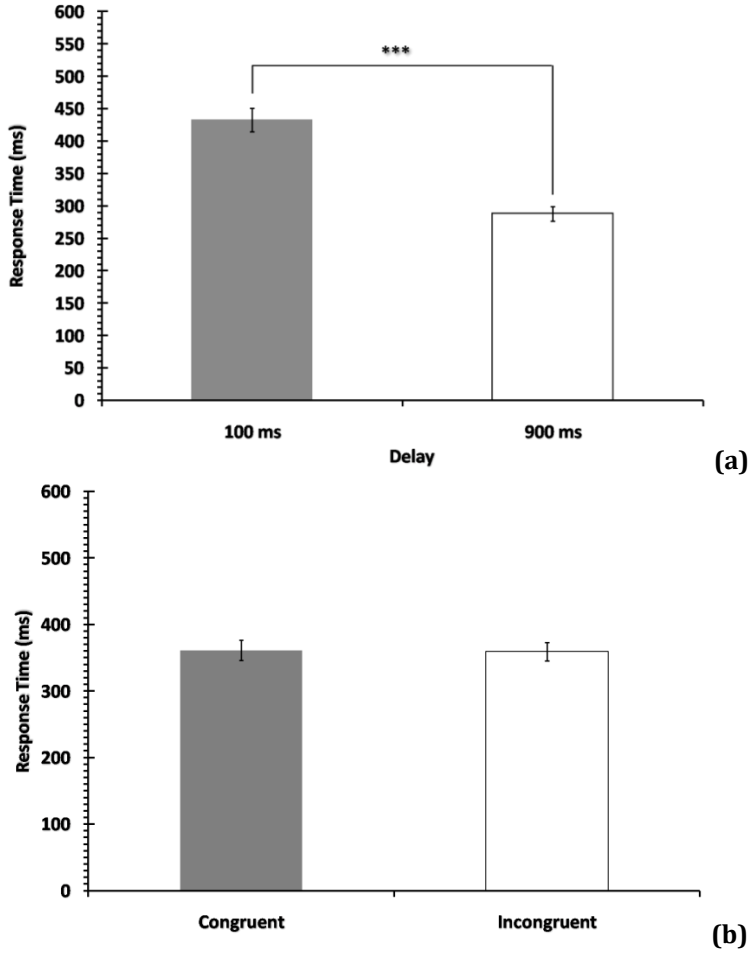

Figure 3-6: The effects of (a) response request delay in the Simon task, where a shorter delay between stimulus presentation and response request appears to cause longer response times. Analysis of Spatial correspondence (b) revealed no demonstration of Simon effect by participants. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

With regards to the effects of the individual difference behavioural measures and the performance on the Simon task, median split analysis revealed no significant interaction between delay or spatial congruence and the ADHD, TS, BAS, BIS, or the yawning behavioural measure ($F_{1, 23} = 1.961$).

3.2.2.2.1: CORRELATIONAL ANALYSIS

Correlational analysis revealed no significant correlation between the measures of the Simon task (spatial correspondence and delay) and the different individual difference behavioural measures (max $r_{25} = 0.314$).

3.2.2.3: THE COLOUR-WORD STROOP TASK

The analysis of response inhibition in the colour-word Stroop task revealed a significant effect of congruency ($F_{1, 24} = 13.019$, $p = 0.001$) where, as shown in Figure 3-7, the participants produced fewer errors during the congruent presentations as compared to the incongruent presentations.

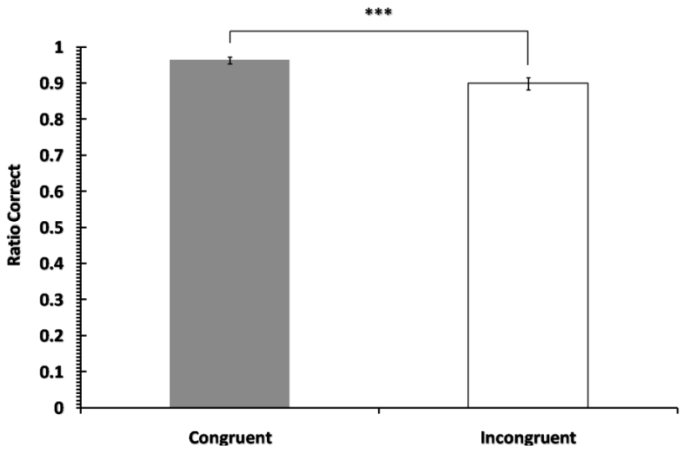

Figure 3-7: The effects of congruence on response inhibition during the colour-word Stroop task. The value for ratio correct for the congruent presentations was calculated by dividing the number of correct responses during the congruent presentation by the total number of congruent stimulus presentations. Similarly, the value for ratio correct for the incongruent presentation was calculated by dividing the number of correct responses during the incongruent presentation by the total number of incongruent stimulus presentations. The results showed that the participants produced a greater number of errors during the incongruent colour-word presentations. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

Analysis also revealed a significant main effect of blocks ($F_{2, 48} = 50.104$, $p < 0.001$), where the greatest number of errors (collapsed across both congruent and incongruent presentations) was demonstrated during the presentation of the stimuli in the first block of

presentations (block 1 - block 2: $t_{24} = 7.169$, $p > 0.001$, block 1 - block 3: $t_{24} = 7.019$, $p > 0.001$). However, no response difference was seen during the blocks 2 and 3 stimulus presentations ($t_{24} = 1.00$). The same pattern results were observed in the congruence and blocks interaction ($F_{2, 48} = 14.568$, $p = 0.001$) in that significant response inhibition deficit was shown during the first block of stimulus presentations in both the congruent (block 1 - block 2: $t_{24} = 3.894$, $p = 0.001$, block 1 - block 3: $t_{24} = 3.894$, $p = 0.001$) and incongruent (block 1 - block 2: $t_{24} = 6.731$, $p > 0.001$, block 1 - block 3: $t_{24} = 6.414$, $p > 0.001$) colour-word presentations, as shown in Figure 3-8b. No significant response inhibition deficit was observed during the blocks 3 and 4 of either the congruent ($t < 1$) or incongruent ($t_{24} = 1.00$) colour-word presentations (Figure 3-7b). With respect to congruence, a greater level of response inhibition was demonstrated during the incongruent stimulus presentations in block 1 compared to the congruent presentations ($t_{24} = 3.756$, $p = 0.001$), whereas no such difference between the congruent and incongruent colour-word presentations was observed during blocks 2 and 3 (max $t_{24} = 1$).

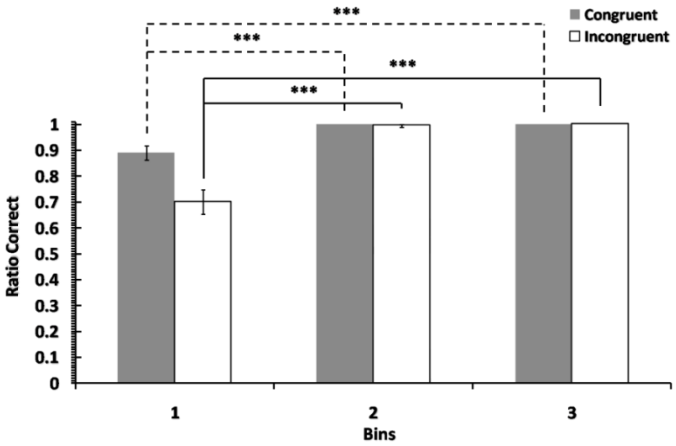

Figure 3-8: The effects of (congruence and presentation blocks on response inhibition during the colour-word Stroop task. A greater degree of omission and commission errors were made during the first block of colour-word presentations compared to the remaining blocks. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

The analysis of the effect of individual difference behavioural measures on response inhibition as measured by the colour-word Stroop task revealed no significant interaction between congruence, blocks or congruence and blocks with respect to ADHD (max $F < 1$), TS (max $F < 1$), BAS (max $F_{2, 46} = 1.574$), BIS (max $F_{1, 23} = 1.373$), and yawning (max $F_{2, 46} = 2.088$) behavioural measures.

With regards to response times, the data from one participant were excluded from the response time analysis due to the failure to produce any correct responses during block 1. However, the data from this subject was not excluded from the number of errors analysis described above, as the failure to produce a correct response during block 1 prevented this subject from producing a response time for the first block (which can be obtained only from correct responses), but the data from this subject was still valid for the number of errors analysis. A significant effect of congruency was observed in terms of the participant response time ($F_{1, 23} = 61.189$, $p < 0.001$) where the participants demonstrated slower response times during the incongruent colour-word presentations than the congruent presentations (Figure 3-9).

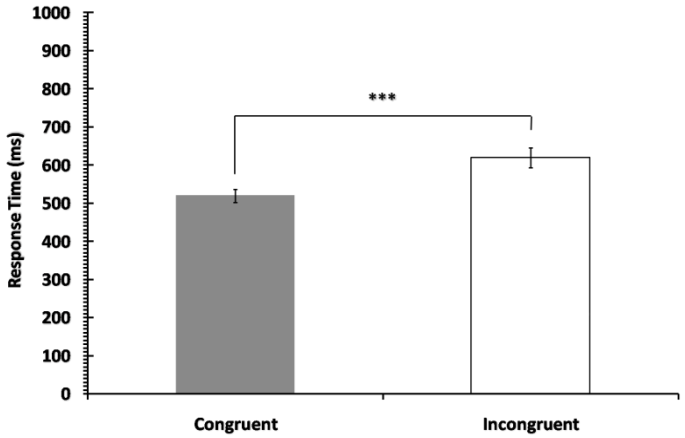

Figure 3-9: The effects of congruence on the colour-word Stroop task, where incongruent colour-word presentations results in longer response times. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The analysis of response times revealed a significant effect of blocks ($F_{2, 46} = 5.91$, $p < 0.01$). As seen in Figure 3-10, the results show that the participants produced the fastest response times during block 3 of the colour-word presentations compared to either block 1 ($t_{23} = 2.716$, $p < 0.05$) or block 2 ($t_{23} = 4.058$, $p < 0.001$), whereas no difference in response times was observed between blocks 1 and 2 ($t < 1$). No significant interaction between congruence and the response blocks was noted ($F_{2, 46} = 1.317$).

The analysis of the effect of individual difference behavioural measures on response times as measured by the colour-word Stroop task revealed no significant effect of congruence, blocks or congruence and blocks with respect to ADHD (max $F < 1$), TS (max $F_{2, 44} = 1.303$), BAS (max $F_{2, 44} = 1.522$), BIS (max $F_{1, 22} = 2.646$), and yawning (max $F < 1$) behavioural measures.

3.2.2.3.1: CORRELATIONAL ANALYSIS

Correlational analysis revealed a significant negative correlation between the response inhibition (as measured by the number correct responses made during the incongruent colour-word presentations) and BAS Reward Responsiveness ($r_{24} = -0.422$, $p < 0.05$). No other significant correlations between response inhibition measures of the colour-word Stroop task (mean correct response on the incongruent and congruent colour-word presentations) and the different individual difference behavioural measures were found (max $r_{25} = -0.379$).

A significant negative correlation was found between the response time during the congruent colour-word presentations and the BAS drive ($r_{24} = -0.415$, $p < 0.05$) as well as

the overall BAS score (r_{24} = -0.407, $p < 0.05$). However, no other correlations were observed between the individual difference behavioural measures and the response times in the congruent and incongruent presentations (max r_{24} = -0.346).

3.2.2.4: THE MISSION TO MARS TASK

A significant effect of inhibition was observed ($F_{1, 24}$ = 15.021, p = 0.001) where the participants successfully demonstrated conditioned inhibition as measured by the task (Figure 3-10).

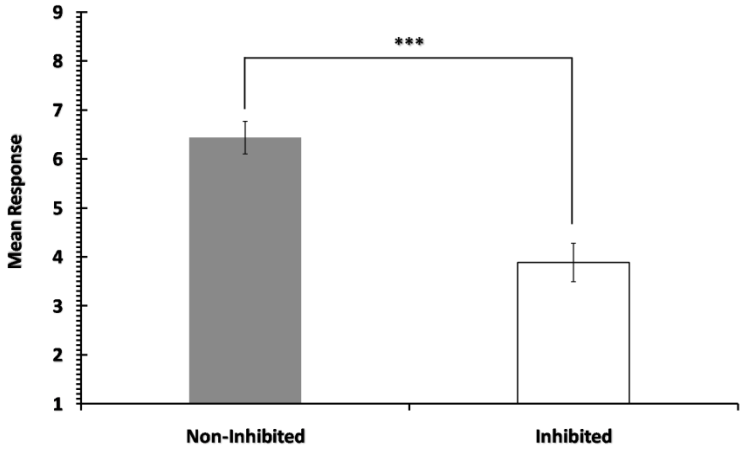

Figure 3-10: A significant main effect of inhibition was obtained indicating the successful expression of conditioned inhibition by the task. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

A significant interaction between stimulus type and inhibition was noted ($F_{1, 24}$ = 5.115, p < 0.05). However, as shown in Figure 3-11, post hoc analysis failed to reveal a significant difference between responding to the transfer and generalized stimuli for either inhibitory or excitatory responding (max t_{24} = 1.94), as conditioned inhibition was demonstrated for both the transfer (t_{24} = 4.626, p < 0.001) as well as the generalized stimulus (t_{24} = 2.883, p < 0.01).

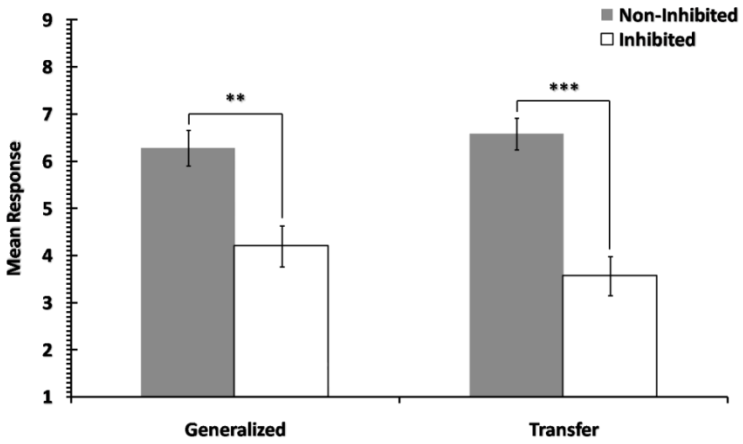

Figure 3-11: An interaction between inhibition and stimulus type was observed. However, no difference between the generalized and transfer stimuli were found with regards to inhibitory or excitatory responding as both stimuli passed the summation test. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

A significant 3-way interaction was observed between inhibition, stimulus and presentation ($F_{2.53, 60.71} = 5.115$, $p < 0.05$). As seen in Figure 3-12, post hoc analysis showed a significant difference between the inhibitory responding to the transfer and generalized stimulus during third stimulus presentation ($t_{24} = 2.883$, $p = 0.01$). No other significant difference between the transfer and generalized stimulus was observed (max $t_{24} = 1.457$). With regards to presentation, conditioned inhibition responding was observed during the first ($t_{24} = 2.744$, $p = 0.01$), second ($t_{24} = 2.8381$, $p < 0.05$) and the fourth ($t_{24} = 4.522$, $p < 0.001$) presentation of the generalized stimulus and the second ($t_{24} = 3.32$, $p < 0.01$), third ($t_{24} = 3.645$, $p = 0.01$), fourth ($t_{24} = 4.672$, $p < 0.001$) and fifth ($t_{24} = 2.951$, $p < 0.01$) presentation of the transfer stimulus.

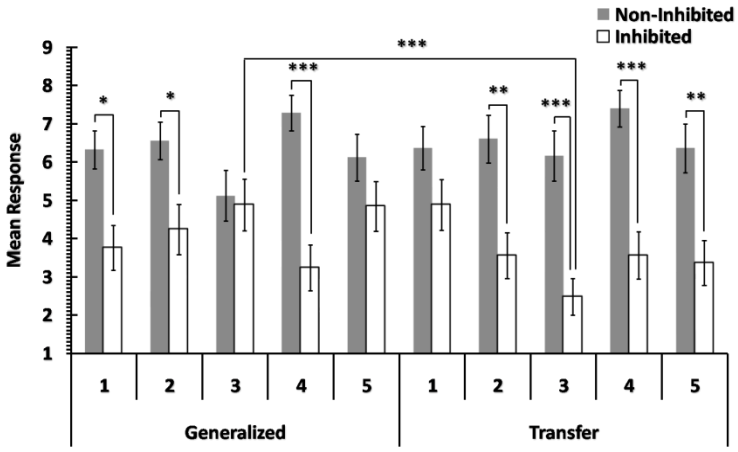

Figure 3-12: An interaction between inhibition, presentation and stimulus type was observed. However, only during the third presentation of the inhibitory stimulus was a difference between the generalized and transfer stimulus observed. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

The Median split analysis by individual difference behavioural measures showed a significant interaction between the BAS behavioural measure and the inhibition-stimulus interaction ($F_{1, 23} = 5.787$, $p < 0.05$). As seen in Figure 3-13a, post hoc analysis revealed a significant difference on the responding to the non-inhibited generalized stimulus between the participants scoring below or equal and those above median ($t_{23} = 2.671$, $p < 0.05$), whereas no other significant difference in responding was noted (max $t < 1$). The BAS behavioural measure also showed a significant interaction with the inhibition-stimulus-presentation interaction ($F_{2.56, 58.79} = 3.16$, $p < 0.05$). Post hoc analysis revealed a significant difference between the participants scoring below or equal and those above median on the responding to the non-inhibited generalized stimulus in the second ($t_{23} = 2.036$, $p < 0.05$) and fourth presentation ($t_{23} = 2.321$, $p < 0.05$), to the inhibited transfer stimulus in the third ($t_{13.29} = 2.195$, $p < 0.05$) and fourth presentation ($t_{17.53} = 2.287$, $p < 0.05$). No other significant difference in responding was noted (max $t_{23} = 1.902$).

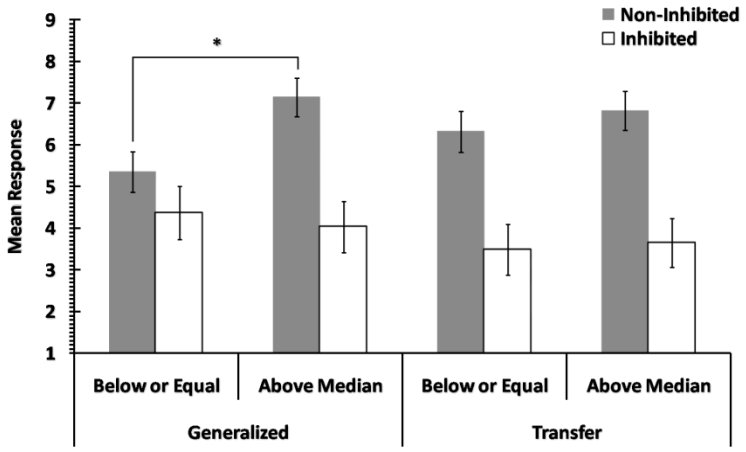

Figure 3-13: An interaction between median split of the BAS behavioural measure and inhibition-stimulus was observed. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

No other interactions between measures of conditioned inhibition and the ADHD (max $F_{1, 23} = 1.427$), TS (max F < 1), BIS (max F < 1), and yawning (max $F_{1, 23} = 1.523$) behavioural measures were found.

3.2.2.4.1: CORRELATIONAL ANALYSIS

A significant negative correlation was found between the BAS fun seeking behavioural measure and the level of conditioned inhibition demonstrated summarized by the conditioned inhibition ratio ($r_{25} = -0.443$). However, there was no other correlation between the individual difference behavioural measures (overall or in relation to the subscales) and performance on the conditioned inhibition task summarized by the conditioned inhibition ratios (max $r_{25} = 0.306$).

3.2.3: DISCUSSION

Looking at the Go/NoGo task, the results showed that response inhibition (as measured by the number of commission errors compared to the number of omission errors committed)

was successfully measured by the task. The level of response inhibition demonstrated was not due to inattention as the number of omission errors that acts as a measure of sustained attention (Berwid, et al., 2005), was close to zero. Moreover, the results also showed the participants demonstrated a high level of response inhibition. Although the participants produced significantly more commission errors than omission errors, the number of commission errors produced was still quite low.

With regards to the response time measured during the Go signal presentations, the gradual increase in response times through the progression of the testing may have been due to fatigue in that although the response times did get worse as the experiment wore on, increase in response time was approximately 50 ms greater than those measured during the first block.

The participants in the current investigation failed to demonstrate the Simon effect, which is contrary to a number of previous findings (Buckolz, O'Donnell, & McAuliffe, 1996; Peterson, et al., 2002; Simon, 1969; Simon & Berbaum, 1990; Simon & Rudell, 1967). However, Georgiou et al. (1995), in an experiment evaluating the performance of TS and control participants using a Simon task reported that unlike the TS participants, the matched controls failed to demonstrate the Simon effect. In the Simon task, response times served as an indirect measure of accuracy. In this task the commission of errors was not recorded, and the trial continued until the participant produced the correct response. Thus, it can be asserted that a greater response time generated during a trial would in general be as a result of the participant producing the wrong response, realizing that action, and acting to produce the correct response needed to continue on to the next trial.

Based on the latency results, the participants produced significantly more errors during the 100ms delay measure as compared to the 900ms response delay. This may be due to the participants having more time to plan their actions following a 900ms delay before making a response. However, the lack of a significant interaction between spatial correspondence and delay implies that similar number of errors was produced for both spatially correct and incorrect locations.

In a series of experiments performed by Notebaert, Soetens, and Melis (2001), the authors reported that a key component for the Simon effect to occur are attention shifts, explained as the disengagement of attention from the previously presented stimulus location to the fixation cross in preparation for the next presentation of the stimulus. Thus although the next stimulus presentation occurred as soon as the correct response was produced, 100ms may not have been ample enough time for the gaze to disengage and shift back to the fixation cross and to the new location (unlike the 900ms response delay presentations). As such, this may have led to more errors being produced (signified by the longer response times) in the 100ms presentations irrespective of presentation-response congruency.

Looking at the results of the colour-word Stroop task, it was observed that a Stroop effect was successfully measured in the population. The slower response times during the incongruent presentation were as a result of an inhibition of a response (as it would take longer for a participant to cease an incorrect ongoing response and apply a correct response). However, the participants were successful in the inhibition of an incorrect response as both the congruent and incongruent correct response means were close to a value of 1. Moreover, the lack of a significant difference between the congruent and

incongruent colour-word presentations response times during the later response blocks (as well as a gradual decrease in response times) implies that response inhibition became easier and more automatic with practice.

Looking at Mission to Mars task, as expected (based on the results outlined in chapter 2); the participants successfully demonstrated conditioned inhibition. Moreover, similar to the results outlined in chapter 1, both the transfer as well as the generalized stimuli successfully passed summation test.

With regards to the individual difference behavioural measures, the lack of correlations between the behavioural measures and the Simon task implies that ADHD and TS-like behaviours have possibly little impact on response inhibition (as measured by the Simon task). Previously, in their investigation, Georgiou et al. (1995) reported a significantly greater level of Simon effect in the TS patients compared to matched controls. However, as reported by Stern, Blair, and Peterson (2008), Georgiou et al. failed to report whether any comorbidity existed within the TS group. Thus, the results obtained by Georgiou et al. may have been due to the influence from possible comorbid disorders (such as ADHD).

Looking at the Go/NoGo task, the current results revealed that ADHD-like behaviours may adversely affect response inhibition. Previous investigations have consistently found a deficit in response inhibition as measured by the Go/NoGo task in ADHD individuals (Berwid, et al., 2005; Bitsakou, et al., 2008; Iaboni, et al., 1995). Thus, although none of the participants in the current investigation were diagnosed with ADHD, the positive correlation between the ADHD behavioural measure and commission errors indicate that ADHD-like behaviours may have an adverse effect on response inhibition. Unlike the

results obtained in the Go/NoGo response inhibition task, ADHD and TS-like behaviours were not found to adversely impact response inhibition as measured by the colour-word Stroop task. The effects of ADHD on performance on the Stroop task have yielded varying results. While some previous investigations had found that response inhibition measured by the Stroop task was adversely effected by ADHD (Lansbergen, et al., 2007; Nigg, 2000; Seidman, et al., 1997; Young, et al., 2006), others have failed to observe any effect (Gaultney, et al., 1999; Schwartz & Verhaeghen, 2008). Similarly, the present results also failed to demonstrate any significant effect of either ADHD or TS-like behaviours on the level of conditioned inhibition demonstrated by the participants as measured by the Mission to Mars task.

Several significant correlations were observed with regards to the BAS system. The correlation between the BAS Reward Responsiveness and the measure of response inhibition (as number of correct responses during the incongruent colour-word Stroop task) implies that greater degree reward responsiveness led to a decrease in the level of response inhibition. Perhaps correct responding during the incongruent colour-word presentations became a reward in itself (as good performance is generally considered a rewarding experience) and individuals who rated higher in BAS reward responsiveness were more impulsive with their responses which in turn led to a greater number of errors. However, the absence of a correlation between the overall BAS (or any of the other BAS sub score measures) does not lend support to the explanation presented. However, the finding of a negative correlation between the BAS (as well as the BAS Drive) and response time (during congruent colour-word presentations) implies that those with stronger

goal/reward driven behaviours responded faster during the congruent presentations. This correlation was not seen on the incongruent presentations.

A relationship between the BAS and conditioned inhibition was observed, where a negative correlation between BAS fun seeking behavioural measure and the conditioned inhibition ratio of the Mission to Mars task was obtained. This result is similar to those of Migo et al (2006) who reported a negative correlation between the conditioned inhibition ratio and the BAS reward responsiveness measure, as unsurprisingly, significant correlation exists between all of the BAS sub-scales. This correlation implies that those with higher level of fun seeking behaviours demonstrated a higher level of conditioned inhibition as measured by the Mission to Mars task. Median split analysis also showed that the BAS system had an effect on the level of conditioned inhibition demonstrated as individuals who scored lower than (or equal to) the median on the BAS measure demonstrated less excitatory learning when presented with the more novel generalized stimulus (in the absence of the inhibitor); so much so that individuals who scored lower than (or equal) the median on the BAS measure failed to demonstrate conditioned inhibition when presented with the generalized stimulus. However, inhibitory responding was unaffected by the BAS system. This result indicates that individuals with lower BAS behaviours demonstrated less stimulus generalization, which had no effect on the level of inhibition demonstrated. According to Matthews and Gilliland (1999) BAS individuals would have enhanced conditioning when conditioned with conditioned reward stimuli. It may be that the game nature and the absence of aversive stimuli in the Mission to Mars task makes the task an appetitive one, which in turn makes it more sensitive to the BAS system. As such, performance on the task

(and in turn the level of conditioned inhibition measured) is greater for individuals measuring higher on the BAS behavioural measure.

In the current experiment, the participants successfully demonstrated response inhibition and conditioned inhibition using the computer keyboard as the method of response input (for the behavioural inhibition tasks only as the conditioned inhibition task used the computer mouse). However, does using a colour coded response pad have an effect on response accuracy and the response times produced in each of the three behavioural inhibition tasks? Does the use of a keyboard introduce a variable delay in the measure of response time? Although it must be admitted that if a variable delay was introduced by the use of the keyboard as the response input device of choice, this delay would be added on to all of the conditions (for example to both the congruent and incongruent conditions in the colour-word Stroop task). However, while this temporal fidelity may not affect the results obtained per se, it does provide information with regards to how much of a temporal variance the use of a keyboard introduces compared to a response pad, if any. The following experiment investigates this question by conducting the series of tasks on a new set of participants using a commercially designed response pad (Cedrus RB-730 Response Pad) with colour-coded keys (to be used for the Stroop as well as the Simon tasks) to see whether the substitution of the response pad for the computer keyboard produces any significant changes in the results obtained. Responding for the Mission to Mars conditioned inhibition task was recorded using a mouse same as in experiment 3-1 as responding in the task in question was untimed.

3.3: EXPERIMENT 2B - THE INVESTIGATION OF RESPONSE INHIBITION IN THE NORMAL POPULATION USING A RESPONSE PAD AS THE RESPONSE INPUT DEVICE

3.3.1: STIMULI & MATERIAL

3.3.1.1: PARTICIPANTS

Thirty participants (Male: n = 17, Female: n = 13) were recruited from the University of Nottingham student population (Mean age = 24.27 years). The participants were paid a £5 inconvenience allowance for their participation in their study. The procedures conformed to the guidelines set by the School of Psychology, University of Nottingham Ethics Committee.

3.3.1.2: MATERIALS

The stimuli and materials used follow those outlined in Experiment 2A, with the exception of the substitution of a Cedrus RB-730 Response Pad for the computer keyboard as the response input device used for the response-inhibition tasks. All responding was made using a computer mouse for the Mission to Mars conditioned inhibition task.

3.3.1.3: PROCEDURES

3.3.1.3.1: THE GO/NOGO TASK

The procedures of the Go/NoGo task followed those outlined above in Experiment 2A. However, instead of a computer keyboard, the participants used a response pad (Cedrus

RB-730 Response Pad) to input their responses. The participants were required to press a button on the response pad marked “Go” whenever the Go signal was presented and not to do so when presented with the NoGo signal.

3.3.1.3.2: THE SIMON TASK

The procedures of the Simon task followed those outlined above in Experiment 2A. However, instead of a computer keyboard, the participants used a response pad (Cedrus RB-730 Response Pad) to input their responses. The participants were required to press a green coloured button located on the left side of the response pad following the presentation of the Go signal whenever a green coloured box appeared on screen and to press a red coloured button located on the right side of the response pad following the presentation of the Go signal whenever a red coloured box appeared on screen. Responses were made using the left hand index finger for the “green” button presses using the right hand index finger for the “red” button presses.

3.3.1.3.3: THE COLOUR-WORD STROOP TASK

The procedures of the Simon task followed those outlined above in Experiment 2A. However, instead of a computer keyboard, the participants used a response pad (Cedrus RB-730 Response Pad) to input their responses. The participants were required to press a green, blue or red coloured button located on the response pad in response to the colour of the word that appeared on screen. The buttons were green, blue and red in the order of left to right on the response pad.

3.3.1.3.4: THE MISSION TO MARS TASK

The procedure of this paradigm is outlined in chapter 2.

3.3.1.3.5: INDIVIDUAL DIFFERENCE MEASURES

The individual difference behavioural measures and their administration procedures are outlined above in Experiment 2A.

3.3.1.4: DESIGN AND ANALYSIS

The Design and Analysis of the Go/NoGo, the Simon, colour-word Stroop and the Mission to Mars tasks follow those outlined in Experiment 2A

3.3.2: RESULTS

3.3.2.1: THE GO/NOGO TASK

A significant difference between the number of errors committed in the Go and the NoGo trials was found ($F_{1, 29} = 15.719$, $p < 0.001$). As shown in Figure 3-14, the participants made significantly greater number of commission errors compared to omission errors, of which none was made. No significant effect of block or an interaction between the omission/commission errors and blocks was found (max F <1). Thus, the remaining response inhibition analysis was collapsed across blocks.

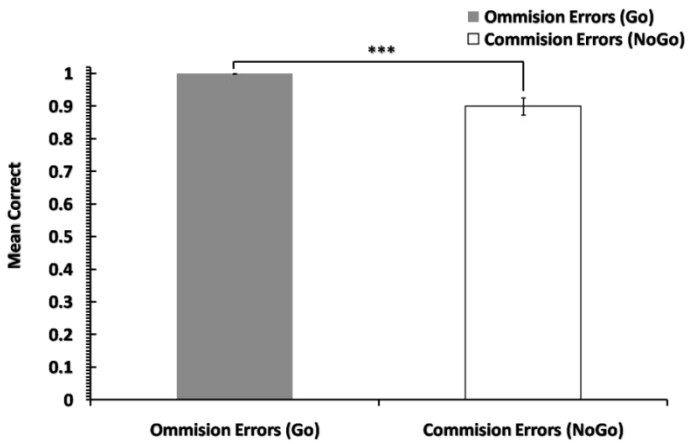

Figure 3-14: The overall number of omission and commission errors committed in the Go/NoGo Task. The participants produced a greater number of commission errors (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

Median split analysis of individual difference behavioural measures (performed individually for each measure) revealed no significant interaction between omission/commission errors and ADHD, TS, BIS, BAS, or the yawning individual difference behavioural measures (max $F_{1, 28} = 1.352$).

The results of the response time during the presentation of the Go signal showed no significant effect of blocks ($F_{3, 87} = 2.422$). The analysis of the effect of individual difference behavioural measures on response times did not reveal a significant interaction between response time blocks and ADHD, TS, BIS, BAS, and the yawning individual difference behavioural measure (max $F < 1$).

3.3.2.1.1: CORRELATIONAL ANALYSIS

No significant correlation between the different individual difference behavioural measures and measure of response inhibition (mean commission errors committed) or the measure of attention (mean omission errors committed) was observed (max $r_{30} = - 0.35$).

Response time analysis revealed a significant positive correlation between the mean response times and the BAS Drive ($r_{30} = 0.407$, $p < 0.05$) as well as with the total BAS score (max $r_{30} = 0.359$, $p = 0.05$). No other significant correlation between the individual difference behavioural measures and the response time was observed (max $r_{30} = 0.253$).

3.3.2.2: THE SIMON TASK

The analysis of the Simon task revealed a significant effect of delay ($F_{1, 29} = 163.373$, $p < 0.001$). As shown in Figure 3-15a, the participant response times were slower following a 100ms response request delay compared to a 900ms delay. No significant main effect of spatial correspondence was found ($F_{1, 29} = 1.034$), as seen in figure 3-15b.

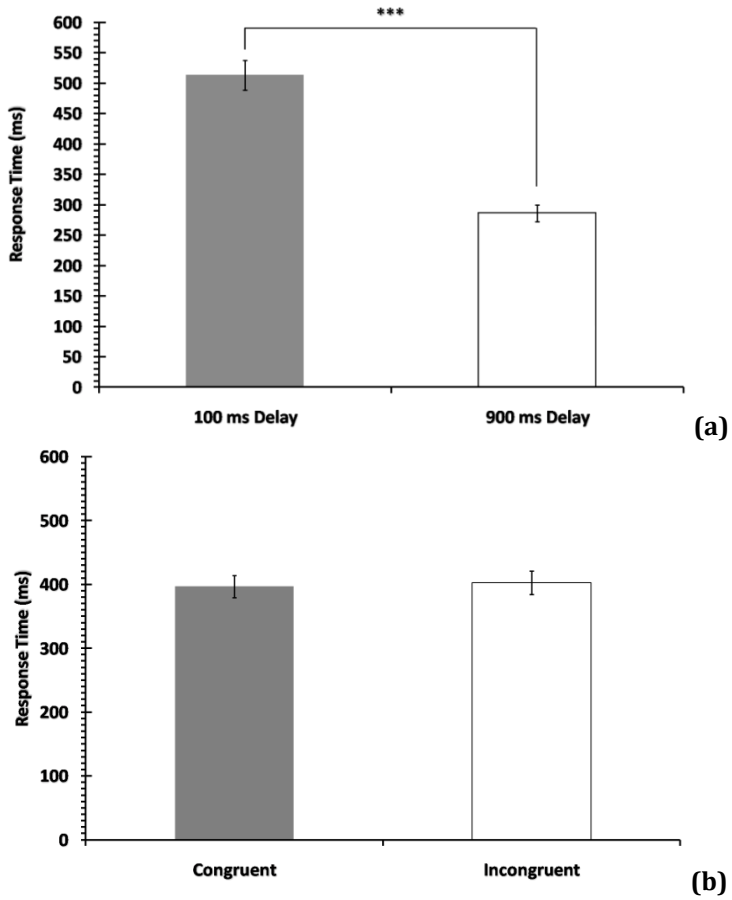

Figure 3-15: The effects of (a) response request delay in the Simon task, where a shorter delay between stimulus presentation and response request appears to cause longer response times. Analysis of Spatial correspondence (b) revealed no demonstration of Simon effect by participants. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The results showed a significant effect of blocks ($F_{1, 29} = 3.656$, $p < 0.01$) as seen in Figure 3-16a. Post hoc analysis revealed that the participants responded significantly slower during the first block of responses compared to the remaining nine blocks (Min $t_{29} = 5.812$, $p < 0.001$, max $t_{29} = 10.997$, $p < 0.001$). No other significant difference was found between the response times in any of the other response blocks (max $t_{29} = 1.925$). As seen in figure 3-16b, the results also showed a significant three-way interaction between spatial correspondence, delay and block ($F_{9, 261} = 2.006$, $p < 0.05$). Post hoc analysis showed that a significant difference between the two delay times was observed in all of the spatially

congruent and incongruent stimulus presentations (Min $t_{29} = 2.143$, $p < 0.05$, max $t_{29} = 3.526$, $p = 0.01$). With regards to spatial correspondence, a significant difference in the sixth response block for the 900ms delay was found ($t_{29} = 2.368$, $p < 0.05$) whereas no other significant difference between the spatially congruent and incongruent presentations was noted (max $t_{29} = 1.98$). No significant two-way interaction between spatial correspondence, delay and response blocks was found ($F_{9, 261} = 1.693$).

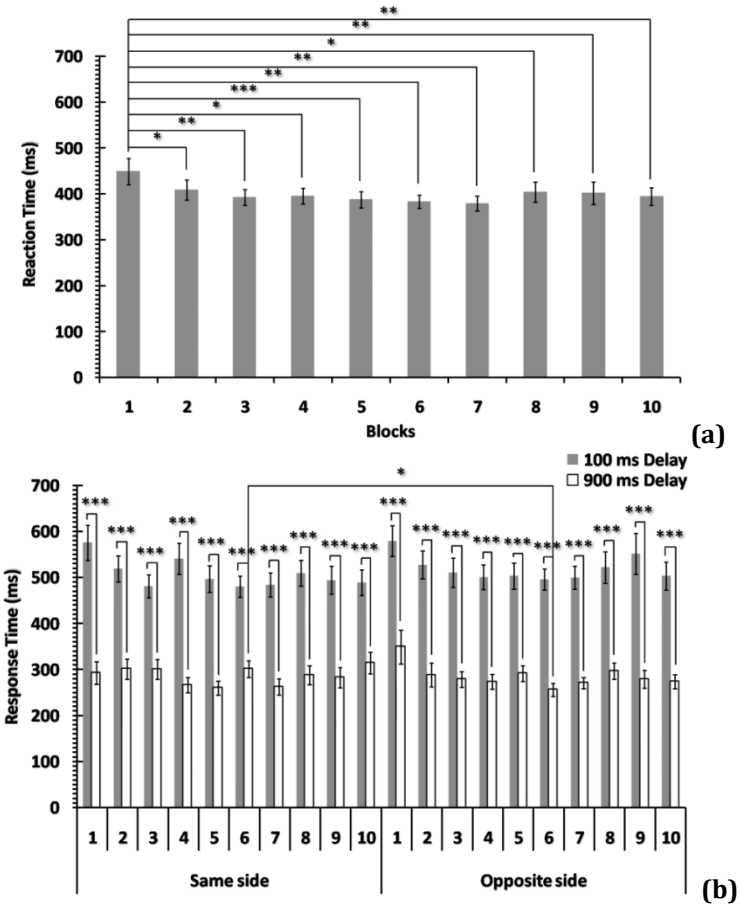

Figure 3-16: A significant effect of in participant response times was found in the (a) response blocks, and (b) three-way spatial correspondence-delay- response block interaction. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

Median split analysis of the individual difference behavioural measures and the performance on the Simon task showed no significant interaction between the measures of

the Simon task (spatial correspondence or Delay) and the ADHD, TS, BAS, BIS, or yawning individual difference behavioural measures (max $F_{1, 28} = 4.03$).

3.3.2.2.1: CORRELATIONAL ANALYSIS

Correlational analysis revealed no significant correlation between the measures of the Simon task (spatial correspondence and delay) and the different individual difference behavioural measures (max $r_{30} = -0.312$).

3.3.2.3: THE COLOUR-WORD STROOP TASK

The analysis of the errors produced in the colour-word Stroop task did not reveal a significant effect of congruence, response blocks, or an interaction between congruence and blocks (max $F < 1$).

Response time analysis revealed a significant effect of congruency ($F_{1, 29} = 39.283$, $p < 0.001$) where the participants demonstrated slower response times during the incongruent colour-word presentations than the congruent presentations (Figure 3-17).

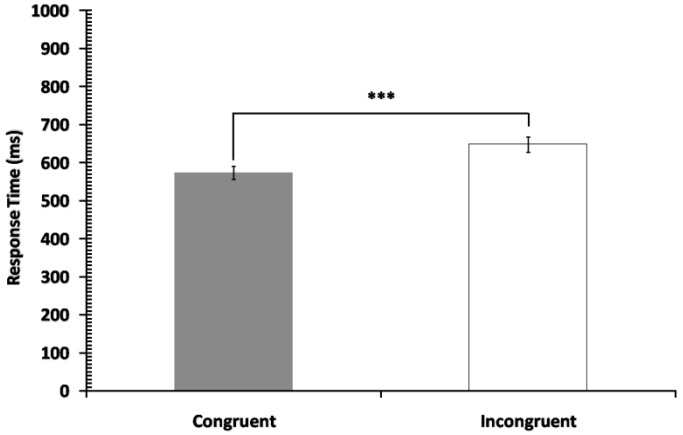

Figure 3-17: The effects of congruence on the colour-word Stroop task, where incongruent colour-word presentations appear to produce longer response times. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The response times analysis also revealed a significant effect of blocks ($F_{2, 58} = 10.403$, $p = 0.01$). As seen in Figure 3-18, the results show that the participants produced the slowest response times during block 1 of the colour-word presentations compared to either block 2 ($t_{29} = 3.42$, $p < 0.01$) or block 3 ($t_{29} = 3.452$, $p < 0.01$). However, no difference in response times was observed between blocks 2 and 3 ($t_{29} = 1.692$). No significant interaction between congruence and response blocks was found ($F_{2, 58} = 2.917$).

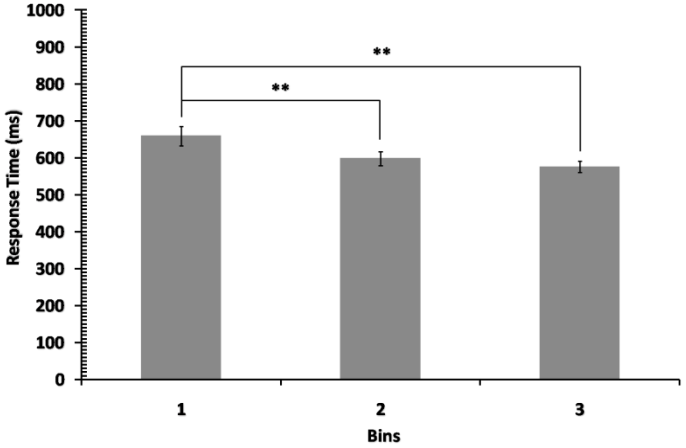

Figure 3-18: The effects of stimulus presentation blocks on the colour-word Stroop task. The results show that the slowest response time was produced in the first presentation block. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The analysis of the effect of individual difference behavioural measures on response times as measured by the colour-word Stroop task revealed no significant interaction between congruence, blocks or congruence and blocks with respect to either ADHD (max $F_{1, 28} = 1.164$), TS (max $F_{2, 44} = 1.303$), BAS (max $F_{1, 28} = 1.242$), BIS (max $F_{2, 56} = 2.655$), or yawning (max $F < 1$) behavioural measures.

3.3.2.3.1: CORRELATIONAL ANALYSIS

Correlational analysis revealed no significant correlation between response inhibition measures of the colour-word Stroop task (mean correct response on the congruent and

incongruent presentations) and the different individual difference behavioural measures were found (max r_{30} = 0.294).

Moreover, no correlations were observed between the individual difference behavioural measures and the response times in the congruent and incongruent presentations (max r_{30} = 0.254).

3.3.2.4: THE MISSION TO MARS TASK

A significant main effect of inhibition was found ($F_{1, 29}$ = 19.735, $p < 0.001$) as conditioned inhibition was successfully demonstrated by the participants (Figure 3-19). No significant interaction between inhibition and stimulus, or presentation was found (max $F < 1$). As such, the remaining analysis was collapsed across stimulus and presentation.

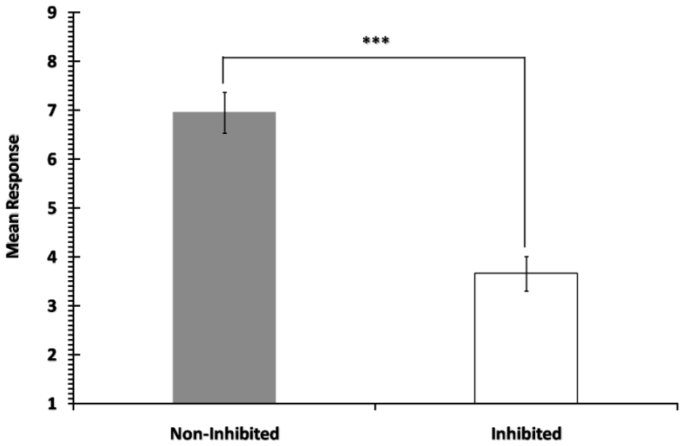

Figure 3-19: A significant main effect of inhibition was obtained indicating the successful expression of conditioned inhibition by the task. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

The median split analysis of the individual difference behavioural measures failed to show a significant interaction between inhibition and the ADHD, TS, BIS, BAS and the yawning behavioural measures (max $F_{1, 28}$ = 2.323).

3.3.2.4.1: CORRELATIONAL ANALYSIS

Correlational analysis did not reveal a significant correlation between the individual difference behavioural measures (overall or in relation to the subscales) and performance on the conditioned inhibition task summarized by the conditioned inhibition ratio (max r_{30} = 0.343).

3.3.3: DISCUSSION

Similar to experiment 2A, the results showed that response inhibition was successfully measured by the Go/NoGo task as the participants committed a greater number of commission errors than omission errors. This effect was not as a result of inattention as the number of omission errors produced by the participants was close to zero. Also, overall the participants demonstrated a high level of response inhibition as the number commission errors produced was still quite low compared to the number of correct responses produced. This result is similar to those reported by Cragg and Nation (2008). With regards to the response time measured during the Go signal presentations, the gradual decrease in response time observed in experiment 2A was not observed in this current analysis.

Similar to the previous experiment, the participants failed to demonstrate a Simon effect. Looking at the delay in responding results, the response times produced during the 100ms responding delay trials were significantly longer than those of the 900ms trials. This pattern was observed for each and every trial. As explained in experiment 2A, it is assumed that response times served as an indirect measure of accuracy. Thus, it can be inferred that the participants in the current investigation produced significantly more errors during the

100ms response input delay as compared to the 900ms response input delay. This may be due to the participants have more time to plan their actions following a 900ms delay before making a response.

However, the lack of a significant interaction between spatial correspondence and delay implies that similar number of errors was produced for both spatially congruent and incongruent locations. Another possible reason for the slow responses in the 100ms delay trials may be as an indirect result of the 900ms delay trials. The prolonged delay in responding in the 900ms trials may indirectly cause the participants to delay their responding in the 100ms delay trials even though the Go signal has already been presented. However, it must be noted that any responses produced after the presentation of the stimulus and prior to the presentation of the Go signal were not recorded (as the response times recorded only the correct response produced after the presentation of the Go signal following the delay). Thus, all the errors produced during the 900ms delay trials may have become lost in the delay. Regardless, any spatial correspondence error that may have been lost during the 900ms delay should have been observed in the 100ms delay trials. However, the response times produced for spatially congruent and incongruent stimulus presentations were not significantly different, thereby reaffirming the absence of the Simon effect in the present population.

Looking at the colour-word Stroop task, while participants in both experiments 2A and 2B successfully demonstrated the Stroop effect, the results of the colour-word Stroop tasks in the current investigation were different than those of experiment 2A. Unlike experiment 2A, no difference between congruent and incongruent colour-word presentations were

observed in this experiment. Thus it would appear that the participants were more accurate with their responses in this experiment compared to those in experiment 2A. However, the absence of a Stroop effect may perhaps be due to the colour coded buttons on the response pad making the selection of correct responses easier during the incongruent presentations.

Regardless, the participants in both experiments demonstrated response inhibition as measured by the colour-word Stroop task. As shown by the means of correct responses, the participants appeared to successfully inhibit erroneous responses during the incongruent colour-word presentations. This conclusion is also supported by the response time data, as the slower response times during the incongruent presentation can be assumed to be as a result of the inhibition of an erroneous response, as it would take longer for a participant to cease an incorrect ongoing response and apply a correct response. On the other hand, the increase in response times during the incongruent presentations in turn may be as a result of both the response inhibition as well as the participants shifting their gaze to the response pad to find and select the correct colour. Moreover, the gradual decrease in response times over the blocks implies that response inhibition became easier and more automatic with practice.

Finally, similar to the results in the previous experiment, the participants successfully demonstrated conditioned inhibition in the Mission to Mars task. Moreover, similar to previous results, summation test was successfully passed on the transfer as well as the generalized stimuli.

With regards to the individual difference behavioural measures, the results of the current investigation failed to show any effect of TS and ADHD-like behaviours on conditioned inhibition or response inhibition measured by the Simon, the colour-word Stroop or the Go/NoGo tasks. However, since none of the participants in the current investigation reported being diagnosed with ADHD or TS, any TS and ADHD-like behaviours measured by the two individual difference measures were presumably normal and the difference between the variance in TS and ADHD like behaviours among the participants to be minimal.

The correlation between the BAS (as well as the BAS Drive) and response time measured in the Go/NoGo task showed that those with more pronounced goal/reward driven behaviours responded slower to the Go signal. Previously, Berkman, Lieberman and Gable (2009) had found that individuals scoring high on the BAS Drive and overall BAS scale produced faster correct responses regardless of stimulus type, leading the authors to conclude that the BAS is sensitive to reward learning and is distinct from impulsivity. This result is contrary to the result obtained in the current experiment. Unlike the results obtained in experiment 2A, no other correlations were found between the BAS behavioural measure and performance on any of the other remaining tasks.

The results of the current experiment showed that while the use of a response pad produced similar pattern of results in some of the tasks (Namely the Go/NoGo and the Simon tasks), there were some differences from the pattern of result seen in experiment 2A, especially within the colour-word Stroop task. Thus, in the following analysis, the performance by the participants in experiment 2A and 2B is compared on each of the four

tasks. With respect to the response inhibition task, the analysis serves to see whether the use of a response pad produced any significant difference in overall performance on any of the three tasks.

3.4: RESPONSE AND CONDITIONED INHIBITION IN THE NORMAL POPULATION – COMBINED ANALYSIS OF EXPERIMENTS 2A AND 2B

3.4.1: DESIGN AND ANALYSIS

The design and analysis of the Go/NoGo, the Simon, colour-word Stroop and the Mission to Mars tasks follow those outlined in Experiment 2A. In the current analysis, the participants from experiments 2A and 2B were separated into the keyboard and the response pad groups respectively and analyzed as a between subjects factor with the data from the response inhibition measure on a repeated measures ANOVA. Where no significant difference was found between the two groups, the results were combined and analyzed as detailed in Experiment 2A.

3.4.2: RESULTS

3.4.2.1: THE GO/NOGO TASK

The between subject analysis revealed no significant effect of group (max $F < 1$) and as such the results from the keyboard and the response pad groups were combined and analyzed as one dataset.

A significant difference between the number of errors in the Go and the NoGo trials was found ($F_{1, 53} = 41.536$, $p < 0.001$), in that the participants made significantly greater number of commission errors compared to omission errors, as shown in Figure 3-20. No significant effect of block or omission/commission errors-by-block interaction was found (max $F < 1$). All further Go/NoGo response inhibition analysis was collapsed across blocks.

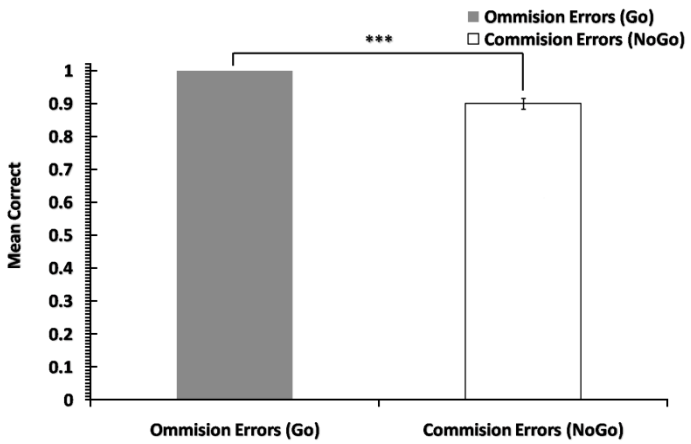

Figure 3-20: The overall number of omission and commission errors committed in the Go/NoGo Task. The participants produced a greater number of commission errors. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

Median split analysis of the individual difference behavioural measures did not reveal a significant interaction between omission/commission errors and either the ADHD, TS, BIS, BAS, or the yawning individual difference behavioural measure (max $F_{1, 53} = 1.197$).

With regards to response times, no significant effect of group was found ($F_{2.37,\ 125.57} = 4.748$), and as such, the analysis were collapsed across group and analyzed as a combined dataset. Analysis of the response time during the presentation of the Go signal showed a significant effect of blocks ($F_{2.37,\ 125.57} = 4.748$, $p < 0.01$). Post hoc analysis revealed a significant difference between the participant response times during block 1 and block 4 ($t_{54} = 2.033$, $p < 0.05$), between blocks 2 and 3 ($t_{54} = 2.592$, $p < 0.05$), as well as blocks 2 and 4 ($t_{54} = 4.408$, $p < 0.0015$) as it was observed that response times increased during the later blocks compared to the earlier ones (Figure 3-21). No other significant difference between the response times in each block was found (max $t_{54} = 1.552$).

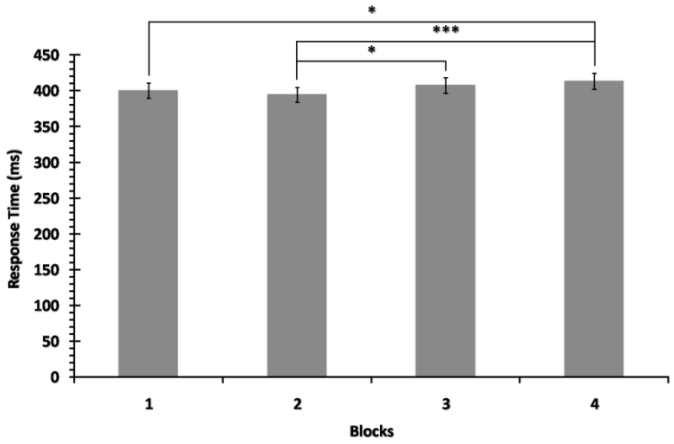

Figure 3-21: Overall response time following the presentation of the Go signal. The participants responded with slower response times in the later blocks or presented Go stimuli compared to the earlier blocks. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The analysis of the effect of individual difference behavioural measures on response times did not reveal a significant interaction between the response time and ADHD, TS, BIS, BAS, and the yawning behavioural measure (max $F_{3, 159} = 1.468$).

3.4.2.1.1: CORRELATIONAL ANALYSIS

Correlational analysis revealed no significant correlation between the different individual difference behavioural measures and measure of response inhibition (mean commission errors committed) or the measure of attention (mean omission errors committed) (max $r_{30} = - 0.259$).

Correlational analysis of the response time (in Go signal presentations) revealed a significant positive correlation between the BAS Drive subscale ($r_{55} = 0.316$, $p < 0.05$) as well as with the total BAS score (max $r_{55} = 0.289$, $p < 0.05$). No other significant correlation between the individual difference behavioural measures and the response time was observed (max $r_{55} = 0.208$).

3.4.2.2: THE SIMON TASK

The analysis of response inhibition as measured by the Simon task revealed a significant interaction between group and delay ($F_{1, 53} = 14.553$, $p < 0.01$). Post hoc analysis showed that while no difference in response time existed in the 900ms delay condition ($t < 1$), the keyboard group responded significantly faster in the 100ms delay condition compared to the response pad group ($t_{45.43} = 3.816$, $p < 0.001$), as shown in Figure 3-22. No significant interaction between group and congruence, blocks, spatial correspondence-by-delay, spatial correspondence-by-blocks, or congruence-by-delay-by-blocks was found (max $F_{8.53, 452.09} = 1.763$).

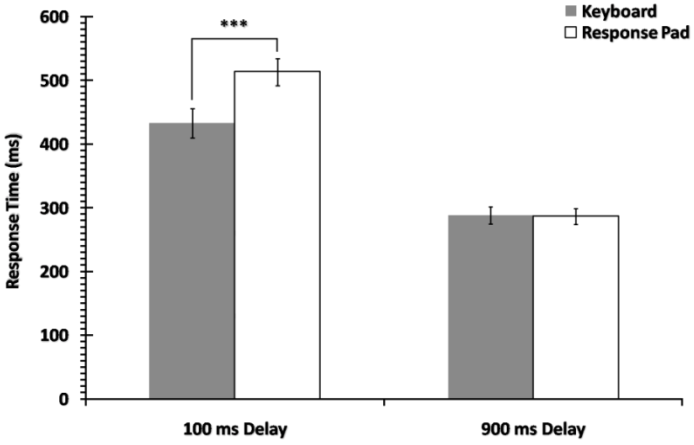

Figure 3-22: The effects of group (Keyboard and Response pad response input) on the delay condition in the Simon task. The participants who responded using the computer keyboard produced faster response times than the participants whom entered their responses using the response pad in the 100ms delay condition, whereas the speed of responding between the two groups was the same in the 900ms delay condition. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

3.4.2.3: THE COLOUR-WORD STROOP TASK

The analysis revealed a significant between-subject group effect ($F_{1, 53} = 25.162$, $p < 0.001$), in that the response pad group produced a higher degree of correct response than the keyboard group in the colour-word Stroop task (Figure 3-23).

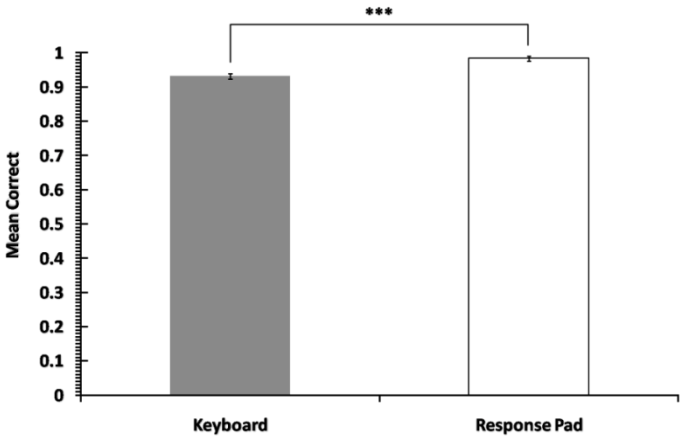

Figure 3-23: The effects of group (Keyboard and Response pad response input) in the colour-word Stroop task. In general, the participants who responded using the computer keyboard produced more errors than the participants whom entered their responses using the response pad. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The analysis of response inhibition as measured by the colour-word Stroop task revealed a significant interaction between group and congruence ($F_{1, 53} = 9.999$, $p < 0.01$) as shown in Figure 3-24. Post hoc analysis revealed that the response pad group produced significantly greater number of correct responses than the keyboard group for both congruent ($t_{33.23} = 2.213$, $p < 0.05$) as well as the incongruent ($t_{32.02} = 4.483$, $p < 0.05$) colour-word presentations.

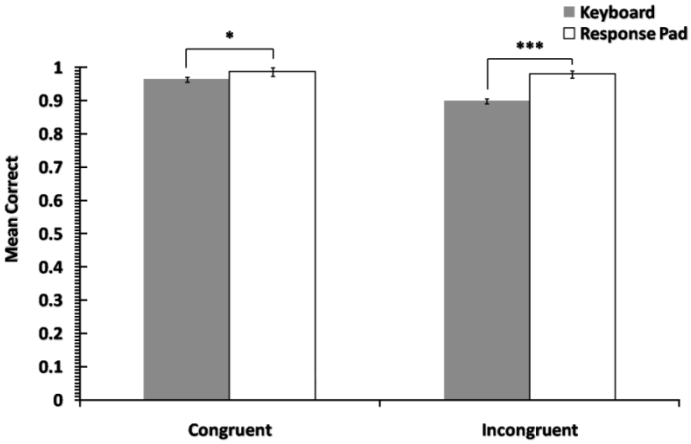

Figure 3-24: The effects of group (Keyboard and Response pad response input) on the level of correct responses produced during congruent and incongruent colour-word presentations. The participants who responded using the computer keyboard produced more errors than the participants whom entered their responses using the response pad during both congruent and incongruent colour-word presentations. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

A significant interaction between group and the response blocks was found ($F_{1.1,\ 58.34} = 52.426$, $p < 0.001$). Although significantly more correct responses were made by the response pad group compared to the keyboard group during block 1 ($t_{26.498} = 6.287$, $p < 0.001$), the keyboard group made more correct response than the response pad group during both block 2 ($t_{36.32} = 2.492$, $p < 0.05$) and block 3 ($t_{29} = 2.971$, $p < 0.01$). In addition, group had a significant effect on the congruence-block interaction ($F_{1.1,\ 58.34} = 52.426$, $p < 0.001$) (Figure 3-25). Post hoc analysis showed that while the response pad group produced fewer incorrect responses in block 1 ($t_{28.9} = 3.118$, $p < 0.001$), in block 2, the keyboard group produced more correct responses than the response pad group ($t_{29} = 2.112$, $p < 0.05$) during the congruent colour-word presentations. No significant difference between groups was seen in block 3 of the congruent colour-word presentations ($t_{29} = 1.439$). A similar pattern of results was seen during the incongruent colour-word presentations as the response pad group produced fewer incorrect responses during block 1 of the presentations ($t_{25.37} = 5.974$, $p < 0.001$), whereas in block 3, the keyboard group produced more correct responses than the response pad group ($t_{29} = 4.408$, $p < 0.05$). No significant difference between groups was seen in block 2 of the congruent colour-word presentations ($t_{40.06} = 1.649$).

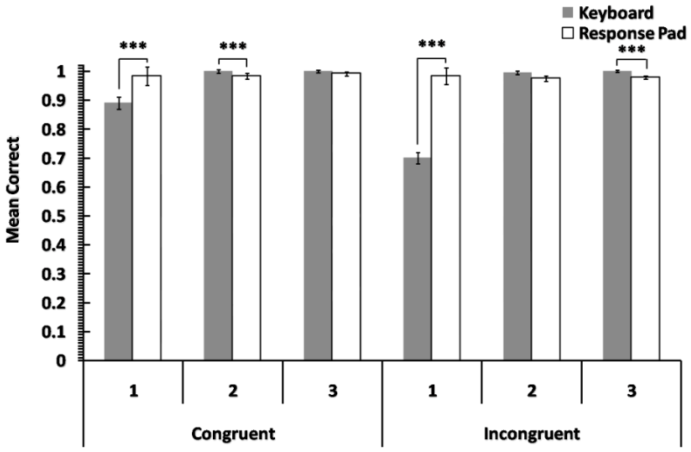

Figure 3-25: The effects of group (Keyboard and Response pad response input) on the level of correct responses produced during the blocks of congruent and incongruent colour-word presentations. It was observed that while the response pad group produced a greater number of correct responses during the first block of presentations, it was the keyboard group that responded more accurately during the later presentation blocks. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

With regards to response time, no significant effect of group (keyboard or response pad) on either congruency or blocks was found (max $F_{1.57,\ 81.43} = 2.736$). As such, the remaining analysis of response time was collapsed across group. A significant effect of congruency was observed in terms of the participant response time ($F_{1,\ 52} = 99.187$, $p < 0.001$) as the participants demonstrated overall slower response times during the incongruent colour-word presentations than the congruent presentations (Figure 3-26).

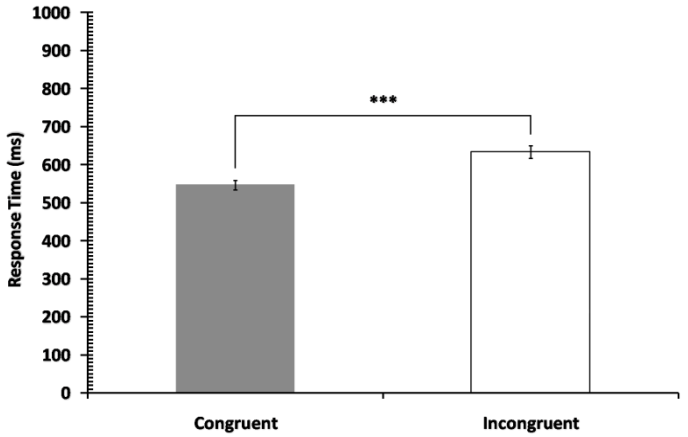

Figure 3-26: The effects of congruence on the colour-word Stroop task, where incongruent colour-word presentations appear to produce longer response times (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$).

A significant effect of blocks was also observed in the response time analysis ($F_{1.57, 81.43} = 13.227$, $p < 0.001$). The results showed that the participants produced the slowest response times during block 1 of the colour-word presentations compared to either block 2 ($t_{53} = 2.556$, $p < 0.05$) or block 3 ($t_{53} = 4.352$, $p < 0.001$). In addition, the participants' response times were lower during block 2 compared to block 3 ($t_{53} = 3.727$, $p < 0.001$).

As shown in Figure 3-27, a significant interaction between congruence and blocks was obtained ($F_{2, 104} = 3.707$, $p < 0.05$). Post hoc analysis showed that responding during the incongruent colour-word presentations was consistently slower than the congruent presentations in each of the three stimulus presentation blocks (Block 1: $t_{53} = 7.352$, $p < 0.001$, Block 2: $t_{53} = 7.577$, $p < 0.001$, Block 3: $t_{53} = 5.176$, $p < 0.001$).

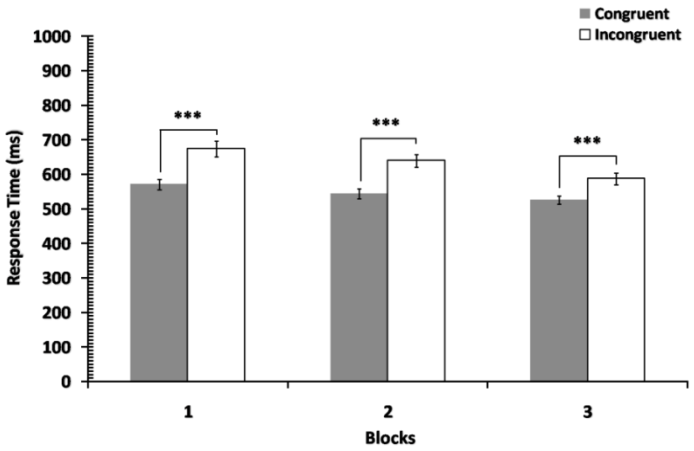

Figure 3-27: The effects of (a) stimulus presentation blocks and (b) congruent and incongruent colour-word presentation in each block on the measured response time in colour-word Stroop task. (*** = $p < 0.001$, ** = $p < 0.01$, * = $p < 0.05$)

The analysis of the effect of individual difference behavioural measures on response times as measured by the colour-word Stroop task revealed no significant interaction between congruence, blocks or congruence and blocks with respect to the ADHD (max $F_{2, 104} =$

2.048), TS (max $F_{1, 52}$ = 1.033), BAS (max F < 1), BIS (max $F_{1.56, 82.92}$ = 2.368, degrees of freedom adjusted for sphericity), and the yawning (max F < 1) behavioural measures.

3.4.2.3.1: CORRELATIONAL ANALYSIS

No significant correlations response inhibition (as measured by the congruent and incongruent mean correct ratios) in the Stroop task and the individual difference behavioural measures were found (r_{55} = -0.237).

Correlational analysis revealed a significant correlation between mean response times during the congruent colour-word stimulus presentations and the TS behavioural measure (r_{54} = 0.29, P < 0.05). No other correlations were observed between the individual difference behavioural measures and the response times during the congruent and incongruent presentations (max r_{54} = 0.223).

3.4.2.4: THE MISSION TO MARS TASK

The analysis of the Mission to Mars results revealed no significant effect of group on performance on the task (max $F_{4, 212}$ = 1.076). Thus, all further analysis was collapsed across group. The combined analysis revealed a significant main effect of inhibition ($F_{1, 53}$ = 33.434, p < 0.001) as conditioned inhibition was successfully demonstrated by the participants (Figure 3-28).

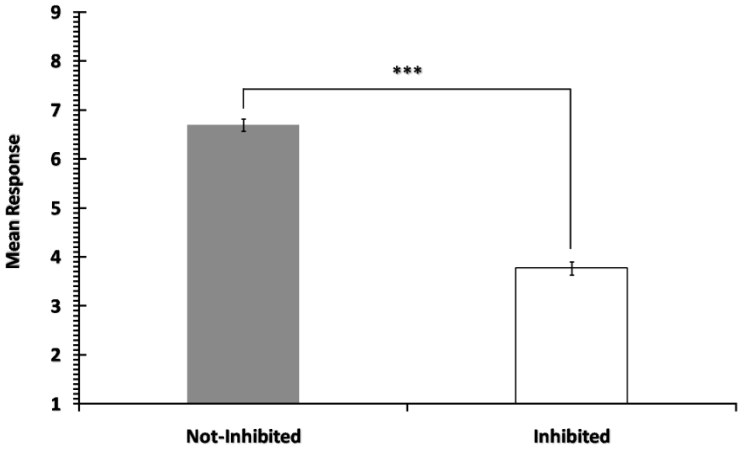

Figure 3-28: A significant main effect of inhibition was obtained indicating the successful expression of conditioned inhibition by the task. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

A marginally significant interaction between stimulus type and inhibition was noted ($F_{1, 53} = 3.891$, $p = 0.054$). However, no significant difference between the stimulus types was found during the either the inhibitory or excitatory stimulus presentations (max $t_{54} = 1.549$), as conditioned inhibition was successfully demonstrated by both the generalized ($t_{54} = 4.887$, $p < 0.001$) and the transfer stimuli ($t_{54} = 6.449$, $p < 0.001$) as shown in Figure 3-29.

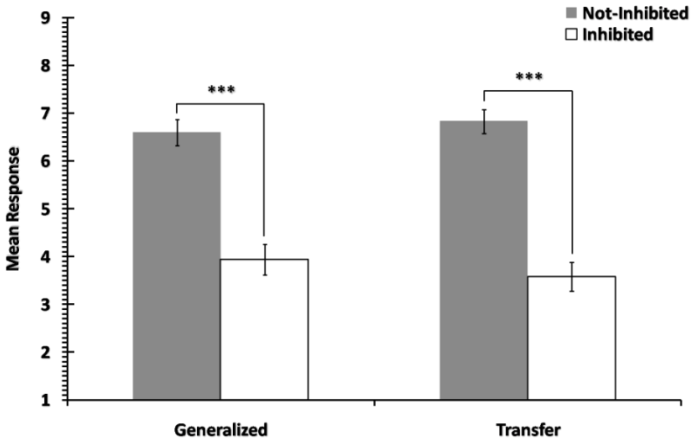

Figure 3-29: An interaction between inhibition and stimulus type was found. However, both the transfer as well as the generalized stimuli successfully passed the summation test. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

A significant 3-way interaction between inhibition, presentation and stimulus type was obtained ($F_{4, 212} = 2.468$, $p < 0.05$). As shown in Figure 3-30, while conditioned inhibition was successfully demonstrated by both the transfer and generalized stimuli in each of the five presentations (Min $t_{54} = 2.547$, $p < 0.05$, max $t_{54} = 5.926$, $p < 0.001$), a significant difference between responding to the transfer and the generalized stimulus was found during the first ($t_{54} = 1.99$, $p = 0.052$), third ($t_{54} = 2.506$, $p < 0.05$) and fifth ($t_{54} = 2.214$, $p < 0.05$) inhibitory presentations. Thus, while a greater level of inhibited responding to the generalized stimulus was shown during the first presentation, it was the transfer stimulus that showed a greater level of inhibited responding during the third and fifth presentation.

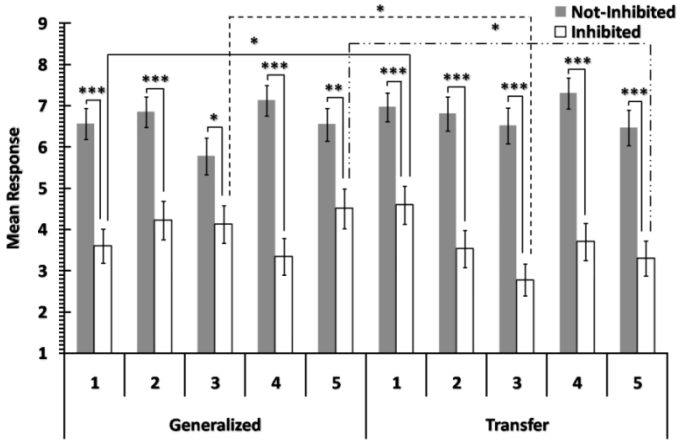

Figure 3-30: An interaction between inhibition, presentation and stimulus type was found. Both the transfer as well as the generalized stimuli successfully passed the summation test in each of the five presentations. However, there was a significant difference between the stimulus types during the first, third and fifth inhibitory presentations. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

The median split analysis of the individual difference behavioural measures failed to show a significant interaction between inhibition and the ADHD, TS, BIS, BAS and the yawning behavioural measures (max $F_{1, 53} = 3.476$).

3.4.2.4.1: CORRELATIONAL ANALYSIS

Correlational analysis did not reveal a significant correlation between the individual difference behavioural measures (overall or in relation to the subscales) and performance on the conditioned inhibition task summarized by the conditioned inhibition ratio (max r_{55} = -0.226).

3.4.2.5: CORRELATION BETWEEN THE DIFFERENT INDIVIDUAL DIFFERENCE MEASURES (COMBINED ACROSS GROUPS)

A significant positive correlation between the TS behavioural scale and the BAS Drive (r_{55} = 0.362, $p < 0.01$) as well as with the total BAS score (r_{55} = 0.283, $p < 0.05$) was found. Moreover, the TS behavioural measure was also positively correlated with the yawning behavioural measure (r_{55} = 0.43, p = 0.001). No other significant correlations between the different behavioural measures were found (max r_{55} = 0.261).

3.4.2.6: CORRELATION BETWEEN THE DIFFERENT S-R TASKS

In order to analyse whether the Go/NoGo, the colour-word Stroop and the Simon tasks measured the same underlying inhibitory process, a correlation between the performance S-R tasks was performed. The results were analyzed separately for the Keyboard and the Response pad groups as a significant group effect was observed in the analysis of the colour-word Stroop task. Performance on the tasks were measured as thus: the colour-word Stroop (the difference between the number of congruent errors and the number of incongruent errors), the Simon task (the difference between the response times during spatial corresponding presentations and those during spatial non-corresponding

presentations), and the Go/NoGo (the difference between the number of omission errors and the number of commission errors).

The results showed that a significant correlation between the colour-word Stroop and the Simon task in both the Keyboard ($r_{25} = 0.545$, $p < 0.01$), as well as the Response pad group ($r_{30} = -0.514$, $p < 0.01$). No significant correlation was found in either group with respect to the Go/NoGo task (max $r_{30} = 0.337$).

3.4.3: DISCUSSION

Looking at the Go/NoGo task, the results showed that the method of recording the participant's responses had no effect on the performance on the Go/NoGo task. This is not surprising as the Go/NoGo required pressing a single button when the Go signal was presented, and as such it made little difference whether responding was done through pressing a single button on the response pad or the spacebar on the keyboard. Experiment 2B was also performed to investigate whether a slight lag time existed between the pressing of the spacebar in response to the Go signal and the time when the response is recorded (specifically, does the use of a keyboard introduce a unaccounted hardware lag time increasing the response times recorded). The absence of significant response time difference between the participants in experiment 2A and 2B can be interpreted as either the supposed lag time being absent or quite negligible.

Combined analysis of experiment 2A and 2B populations showed that the Go/NoGo task successfully measured response inhibition in the combined population. In general, while a greater number of commission errors were committed by the participants compared to

omission errors, the participants demonstrated a high degree of response inhibition, demonstrated by the low number of commission errors produced. Moreover, the observed results were not due to inattention, as little or no omission errors were recorded (Berwid, et al., 2005). The participants showed a general increase in response times over the four blocks of stimulus presentations, which may have been due to general fatigue as the experiment wore on. Moreover, although the response times did get worse through the course of the experiment, the difference was only about 50ms, which is quite small.

With regards to the Simon task, a significant difference between the two populations groups and responding in the two response-delay (100ms, 900ms) presentations, where, although no significant difference was observed between the two populations in terms of responding after the 900ms delay, the participants in experiment 2A (who were using the keyboard as the device for responding) were significantly faster than the participants in experiment 2B who used the response pad. This result seems to indicate that the use of a keyboard made responding easier and more accurate in the 100ms responding delay trials, which unlike the 900ms delay trials, allow notably less time for the participants to plan and execute their responses.

It would seem that having the two colours visible (as they were for the response pad group of participants) did not assist the participants in making the planning and execution of their responses easier in the Simon task. It may be that the coloured buttons acted more as a distraction, as perhaps the participants shifted their gaze to the coloured buttons as a reassurance that they were making the correct responses before executing their decided action. If so, the 900ms delay would provide ample amount of time for the participants to

shift their gaze to the buttons on the response pad and produce a response, whereas 100ms would not (resulting in a delay in responding). However, this is all speculative as no recording of the participants gaze was undertaken in the current investigation. The results however did show that having the colours present had no influence on the Simon effect itself as there was no significant interaction between the method of responding and spatial consistency.

A significant difference between the two population groups was also observed in the colour-word Stroop task as the use of the colour coded response pad significantly reduced the number of omission and commission errors made by the participants in experiment 2B compared to the participants in experiment 2A. This was especially evident during the first block of stimulus presentations. However, this effect changed during the second and the third block of presentations as responding was slightly yet significantly more accurate for the keyboard group as opposed to the participants using the response pad. One possible explanation for this result may be that the participants in the response pad group became more impulsive over time sacrificing accuracy. However, no difference in the response times was found between the groups for either the measure of congruency or the response blocks, which does not support the hypothesis stated above. A more likely explanation would be that once the participants became more confident in what key represented what colour on the computer keyboard, the advantage that the colour coded response pad had disappeared. Moreover, unlike the first block of stimulus presentations (during which the participants in experiment 2B were significantly more accurate in their responding to both the congruent and incongruent colour-word presentations), the difference between the two groups (as shown in figure 3-26b) was much smaller in the second and the third stimulus

presentation blocks (where the use of a keyboard resulted in more accurate responding than the use of the response pad). Thus, maybe as the experiment wore on, having the colours present became more of a distraction resulting in a slightly less accurate responding.

As noted above, the use of a response pad did not result in faster responding by the participants as opposed to using a keyboard, as no difference between the two populations was observed with regards to the response times. Overall, the response times produced during the congruent colour-word presentations was significantly less than those during incongruent stimulus presentations. This result supports the demonstration of response inhibition by the participants in the colour-word Stroop task, as the difference between the response times during the congruent/incongruent colour-word presentations may be as a result of the time taken to inhibit an ongoing behaviour and initiate an alternate behaviour. This result is analogous to those obtained by Stroop (1935) who found that it took longer for his participants to read incongruent colour names compared to the control sets.

Looking at the overall performance on the Mission to Mars task, the combined analysis showed that the expression of conditioned inhibition was successfully demonstrated by the participants. However, while a significant stimulus by inhibition interaction was observed, no significant difference in either excitatory or inhibitory responding between the generalized or the transfer stimuli was found. Moreover, summation test was successfully demonstrated by both the transfer as well as the generalized stimuli (Rescorla, 1969) overall as well as during each of the five stimulus presentations.

With regards to the individual difference behavioural measures, ADHD and TS-like behaviours were found to have no impact on neither response inhibition measured by Go/NoGo nor conditioned inhibition as measured by the Mission to Mares task. TS-like behaviours however were found to have an effect on response times in the colour-word Stroop task, as individuals who demonstrated higher levels of TS-like behaviours responded more slowly during the congruent colour-word presentations. This effect was not observed during incongruent colour-word presentations. This result is contrary to those found by Channon, et al. (2009) who found no difference between the response times of the matched controls and the TS group in the Stroop task. However, as noted, this result was confined only to responding in the congruent colour-word presentations. Moreover, none of the participants tested reported being diagnosed with TS, and as such the level of TS-like behaviours reflected variation within the normal range.

The results also showed a positive correlation between the BAS as well as the BAS Drive and the response time as measured during the Go signal presentations. This indicates that the more impulsive individuals with more pronounced goal/reward driven behaviours responded slower to the Go signal, which is quite surprising as the opposite effect would be expected in the more impulsive individuals. However, this result was confined to the Go/NoGo measure as no effect of the BAS behaviours was observed with respect to response times measured during the Stroop task.

Correlational analysis was conducted by collapsing the data for individual difference behavioural measures across the two experiments (experiments 2A and 2B). The results showed that individuals demonstrating greater levels of TS-like behaviours also

demonstrated higher drive for obtaining rewards as well as higher levels of impulsivity as measured by the BAS scale. Moreover, the finding of a positive correlation between the TS and the yawning behavioural measures provides support for the theory that excessive yawning may be associated with TS (Dalsgaard, et al., 2001; Sandyk, 1996; Walusinski, 2009).

Finally, looking at the S-R tasks themselves, the correlational analysis revealed that while the Simon and the colour-word Stroop may be measuring the same underlying inhibitory process, the Go/NoGo is not. However, due to the fact that participants in both the keyboard as well as the response pad groups failed to significantly demonstrate the Simon effect (while successfully demonstrating the Stroop as well as inhibitory responding in the Go/NoGo task), one cannot consider the results observed as firm evidence for both the Stroop and the Simon tasks measuring the same underlying inhibitory function. Moreover, in Simon task, the similarity of the results for the response times during spatial corresponding presentations and the spatial non-corresponding presentations may have been the reason why the correlation with the colour-word Stroop task was positive for the response pad group and negative for the keyboard group, whereby such a difference between the keyboard and the response pad results may not have existed if the Simon effect was obtained (in that response times for the spatial non-corresponding presentations were significantly greater than those of the spatial corresponding presentations). Thus, while the results support Nigg's assertion that the Stroop and the Go/NoGo may measure different inhibitory processes (Nigg, 2000), with respect to the Simon task, this question still remains unanswered.

The purpose of the current analysis was to see whether the use of response pad provided any advantage over using a keyboard in response inhibition paradigms. It was found that while the response pad produced an advantage early on in the colour-word Stroop task, this advantage disappeared as the task continued. Moreover, the presentation of the colours used in the Simon task may have acted more as a distraction than an aid in the Simon task. The results also indicated that the response pad produced no advantage over the use of a computer keyboard in providing more accurate response times. Based on the results obtained, the use of a response pad provides no significant advantage over the use of an ordinary computer keyboard when testing measures of behavioural inhibition.

With regards to the measure of conditioned inhibition, it must be noted that all the participants in experiments 1A, 1B, 1C, 2A and 2B all performed the Mission to Mars conditioned inhibition task, as well as all of individual difference behavioural measures. Therefore, in the final section of this chapter, a combined analysis of conditioned inhibition as measured by the Mission to Mars task, the possible influence of temperament as measured by the individual difference behavioural measures was performed.

3.5: THE COMBINED ANALYSIS OF THE MISSION TO MARS TASK AND INDIVIDUAL DIFFERENCE BEHAVIOURAL MEASURES

A combined analysis of conditioned inhibition as measured by the Mission to Mars task and the individual difference behavioural measures was performed in the current section. Combined, 137 participants from experiments 1A, 1B and 1C as well as 2A and 2B have performed the Mission to Mars conditioned inhibition task as well as all four individual difference behavioural measures: the ADHD measure (Kessler, et al., 2005) (Shown in table 2-2), the TS measure (Shown in table 2-3), Carver & White (1994) BIS/BAS behavioural measure, as well as the yawning (Greco & Baenninger, 1993) behavioural measure (Shown in table 2-4). This analysis provides the best opportunity to investigate whether the various types of behaviours measured by the individual difference measures have an effect on the level of conditioned inhibition demonstrated, as this section marks the final analysis of the individual difference measures before moving on to the investigation of inhibition within clinical populations.

3.5.1: DESIGN AND ANALYSIS

The design and analysis of the current analysis followed those outlined in section 2.2.1.4.

To determine what factors make up the novel TS individual difference behavioural measure used throughout the studies outlined in chapters 2 and 3, a two-factor confirmatory factor analysis of the novel TS individual difference behavioural measure was performed using quartimax rotation with Kaiser Normalization. A factor loading value of 0.50 was applied.

Moreover, to discount the possibility of the CI acting as an occasion setter (if there further learning occurring during the testing trials, which the absence of an effect of presentation discounts) as opposed to a conditioned inhibitor, a conditioned inhibition ratio was calculated from the first presentation of the CS_t ($[I,CS_t]/CS_t$) as the absence of prior presentations of the CI with the CS_t prevents the possibility of the CI acting as an occasion setter. Following this calculation, a bivariate correlation on the two factors of the TS individual difference behavioural measure was performed with the first CS_t presentation conditioned inhibition ratio as well as the overall conditioned inhibition ratio (overall [CI,CS]/CS) in order to analyse whether a relationship existed between the separate factors of the TS individual difference behavioural measure and the measure of conditioned inhibition.

3.5.2: RESULTS

As shown in figure 3-31a, an overall effect of inhibition was found ($F_{1, 136} = 68.628$, $p < 0.001$). Moreover, a significant interaction between stimulus and inhibition was observed ($F_{1, 136} = 68.628$, $p < 0.001$), as shown in figure 2-31b. Post hoc analysis showed that while excitatory responding was significantly greater when presented with the transfer stimulus as opposed to the generalized stimulus ($t_{136} = 1.954$, $p = 0.053$), summation test was successfully passed by both stimulus variants. The participants demonstrated significant conditioned inhibition for both the transfer ($t_{136} = 2.507$, $p = 0.01$) as well as the generalized stimulus ($t_{136} = 2.269$, $p < 0.05$).

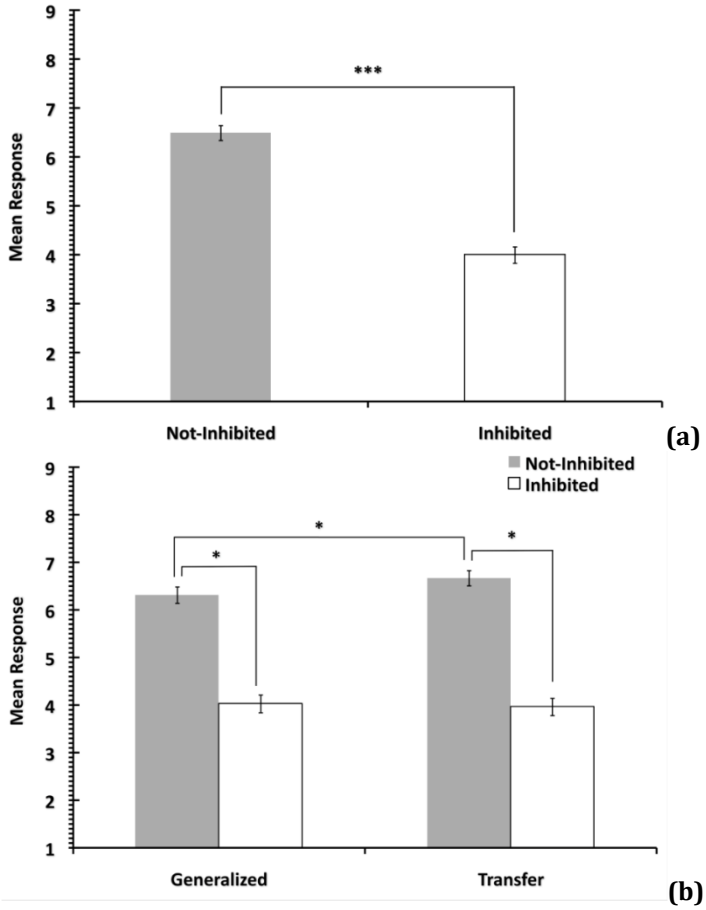

Figure 3-31: A significant (a) main effect of inhibition and (b) inhibition-by-Stimulus interaction were obtained. Although significantly less excitatory responding was expressed when presented with the generalized stimulus compared to the presentation of the transfer stimulus, conditioned inhibition was significantly demonstrated for both stimulus variants. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

A significant interaction between inhibition and presentation was observed ($F_{4, 544} = 2.525$, $p < 0.001$). However, conditioned inhibition was clearly demonstrated in each of the five stimulus presentations (Min $t_{136} = 6.146$, $p < 0.001$, max $t_{136} = 9.018$, $p < 0.001$) as shown in figure 3-32.

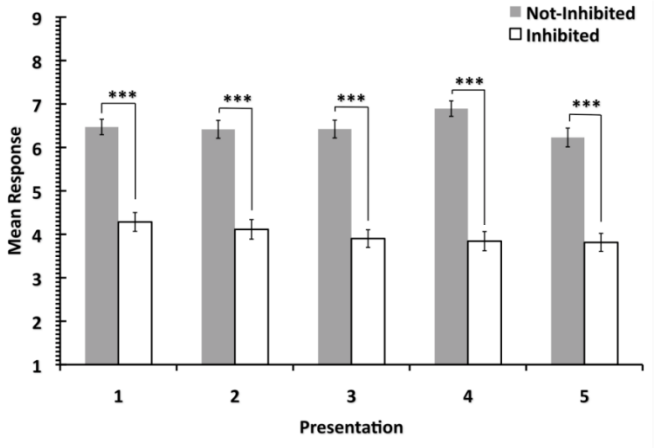

Figure 3-32: A significant inhibition-by-Stimulus interaction was obtained. However, conditioned inhibition was significantly demonstrated in each of the five stimulus presentations. (* = P < 0.05, ** = P < 0.01, *** = P < 0.001)

Median split analysis of the four individual difference behavioural measures failed to show any interaction between level of conditioned inhibition demonstrated on the Mission to Mars Task and the ADHD, TS, BIS, BAS or the yawning behavioural measures (max F < 1).

3.5.2.1: SEX DIFFERENCES

Repeated measure analysis of the data with the sex of the participants (male: n = 48, female: n = 89) as the between subjects factor failed to reveal a significant interaction between inhibition and the sex of the participant (F = 0.003).

3.5.2.2: CORRELATIONAL ANALYSIS

No significant correlation between the individual difference behavioural measures (overall or in relation to the subscales) and performance on the conditioned inhibition task summarized by the conditioned inhibition ratio were observed (max r_{137} = -0.08).

Correlational analysis between the individual difference behavioural measures showed a positive correlation between the ADHD and the TS-like behavioural measures (r_{137} = 0.383,

$p < 0.001$). A positive correlation was also found between the ADHD-like and the BIS behavioural measures ($r_{137} = 0.291$, $p = 0.001$). Moreover, the ADHD behavioural scale was also positively correlated with the yawning behavioural measure ($r_{137} = 0.354$, $p < 0.001$).

A positive correlation between the TS-like behaviours and the yawing behavioural measure was found ($r_{137} = 0.548$, $p < 0.001$). The correlation with the yawning behavioural measure remained when the analysis was repeated with the yawing item on the TS scale removed from analysis ($r_{137} = 0.541$, $p < 0.001$). Moreover, similar to the ADHD behavioural measure, a positive correlation between the TS and the BIS behavioural measure was found ($r_{137} = 0.352$, $p < 0.001$). Also, a positive correlation between the BIS and the yawning behavioural measure was found ($r_{137} = 0.273$, $p = 0.001$). No other correlations between the individual difference behavioural measures were noted ($r_{137} = 0.161$).

3.5.2.2: TS INDIVIDUAL DIFFERENCE BEHAVIOURAL MEASURE FACTOR ANALYSIS

A two factor confirmatory factor analysis of the TS individual difference behavioural measure revealed that the 18 items of the TS measure loaded into two factors (factor loading of 0.5) where three OCD items loaded onto factor two (items 3, 6 and 15) and fifteen TS items loaded onto factor 1 (the remaining items as shown in table 2-3). During the development of the TS individual difference behavioural measure Dr. Cassaday and I had knowingly included three OCD items in the behavioural measure in question as OCD is often comorbid in TS. However, the factor analysis confirmed the separate OCD and TS factors that had made up the items of the TS individual difference behavioural measure.

Moreover, none of the TS items loaded onto the OCD factor or vice versa. The choice for choosing two factors was also confirmed by the Scree plot obtained (figure 3-32).

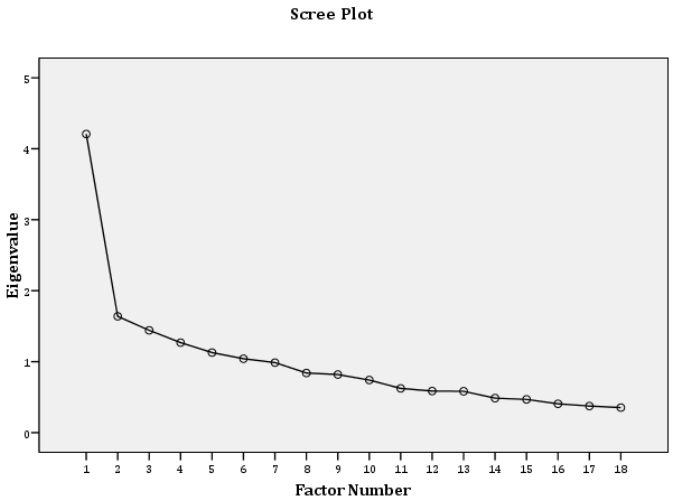

Figure 3-32: The Scree plot of the confirmatory factor analysis of the TS individual difference behavioural measure. As shown the choice of two factors is confirmed by the above plot as the factors begin to plateau after the second plot point.

Bivariate correlational analysis on the two factors of the TS individual difference behavioural measure failed to show a relationship between overall conditioned inhibition ratio and the either the OCD ($r_{137} = 0.033$) or the TS factors ($r_{137} = 0.101$) on the TS individual difference behavioural measure.

Similarly, correlational analysis on the two factors of the TS individual difference behavioural measure failed to show a relationship between conditioned inhibition ratio of the first CS_t presentation and either the OCD ($r_{137} = -0.025$) or the TS factors ($r_{137} = 0.089$) on the TS individual difference behavioural measure.

3.5.3: DISCUSSION

The participants successfully demonstrated significant level of conditioned inhibition on the Mission to Mars task. Moreover, the summation test was passed by both the transfer (that had never been paired with the CI during training) as well as the generalized (a stimulus which had never been introduced during training) stimuli. Thus, conditioned inhibition was successfully measured by the task (Rescorla, 1969). These results were similar to those previously obtained by Migo et al. (2006).

The results showed that excitatory responding was significantly less when presented with the generalized stimulus compared to the transfer stimulus during testing. This result was not surprising as the transfer stimulus was presented in absence of a conditioned inhibitor throughout the training phase, whereas the first time the participants encountered the generalized stimulus was during the training phase. As such, it was to be expected that a stronger excitatory response would be produced by the participants when presented with the more familiar transfer stimulus as opposed to the more novel generalized stimulus. The results also showed that the level of conditioned inhibition demonstrated was found to be independent of the participant's gender.

The results of both the median split as well as the correlational analysis revealed that conditioned inhibition was not affected by TS, ADHD as well as impulsive (as measured by the BAS) or anxious behaviours (as measured by the BIS). This finding is different than those reported by Migo et al (2006) who found a significant positive correlation between the level of conditioned inhibition shown and BAS Reward Responsiveness. However, although the Mission to Mars task was adapted from the task used by Migo et al, several

differences exist between the two tasks such as the inclusion of a storyline as well as the reduction in the number of presentations in both training as well as testing phases in the Mission to Mars task. Another significant different between Migo et al and the current analysis is that the number of participants in the current analysis was significantly greater than those in the Migo et al experiment.

It has been previously suggested (Jeffrey Alan Gray, 1987; Matthews & Gilliland, 1999) that individuals that rate high in BIS would exhibit enhanced conditioning when conditioned with aversive stimuli, whereas high BAS individuals would demonstrate enhanced conditioning when conditioned with rewarding stimuli. Thus it may be that the relative neutrality of the stimuli used in the Mission to Mars task (being that the task is neither appetitive or aversive) may have left the level of conditioning demonstrated unaffected by the differing levels of BIS or BAS behaviours demonstrated by the participants. However, in an investigation of the validity of the revised version of Gray's Reinforcement Sensitivity Theory (RST) using novel task that crossed appetitive/aversive unconditioned stimuli with approach/avoidance conditioned responses, Berkman et al. (2009) had found that high BAS (especially BAS Drive) individuals produced faster correct responses to all trial types regardless of whether the stimulus was hedonistically aversive or appetitive, reinforcing the hypothesis that the BAS is sensitive to reward learning and is distinct from impulsivity. The results of the current analysis however failed to show any effect by the BAS measure on the level of conditioned inhibition demonstrated.

With regards to ADHD-like behaviours, previously Pliszka, Hatch, Borcherding, and Rogeness (1993) reported that ADHD had no effect on the level of conditioning

demonstrated in an aversive Pavlovian conditioning paradigm. However, while the findings by Pliszka et al showed the absence of an effect of ADHD behaviours on the level of S-S associations demonstrated, the current results showed that ADHD-like behaviours had no effect on the inhibition of S-S associations.

Similar to the findings reported in chapter 2, the well acknowledged TS-ADHD comorbidity in clinical groups (Comings & Comings, 1987; Gilbert, et al., 2004; Sheppard, et al., 1999; Spencer, et al., 1998) supports the finding of a strong positive correlation between the scores obtained on the TS and the ADHD scale. This helps lend credibility to the newly created TS scale used in the current investigation. Also, the strong positive correlation found between the yawning scale with both the TS and the ADHD scales and lends support to the view that excessive yawning may be as a result of an underlying predisposition to TS and/or ADHD (Dalsgaard, et al., 2001; Sandyk, 1996; Walusinski, 2006, 2009).

The positive correlation between the BIS behavioural measure and the ADHD and well as the TS measures indicate that individuals that demonstrate higher degrees of anxious behaviours also demonstrate greater levels of TS and ADHD-like behaviours. This is finding is contrary to the hypothesis that disorders of behavioural inhibition such as ADHD and TS would be associated with a higher degree of impulsive behaviours and a lesser degree of inhibitory behaviours (Nigg, 2001; Quay, 1997). This result is also contrary to the findings by Johnson, Turner, and Iwata (2003) who found no correlation between ADHD and the BIS/BAS. However, due to the fact that none of the participants reported being diagnosed with ADHD or TS, such findings cannot be considered conclusive until such findings are noted in clinically diagnosed TS and/or ADHD participants. As previously stated, the TS and

ADHD scales employed during the current analysis were not used as diagnostic tools, and thus high ratings in the noted scales cannot be inferred as the presence of TS and/or ADHD in the subject.

As the TS individual difference behavioural measure was developed in house, it had not undergone any analysis to check whether it contained more than one dimension (i.e. just measuring TS). Thus, the results obtained may have been due to the influence other factors as opposed to just TS-like behaviours. Factor analysis revealed that the TS individual difference behavioural measure was composed of two distinct factors, and that while the majority of the items (15 of the 18 items) were measures of TS behaviours, an OCD factor was also found (3 items). However, correlational analysis of the two distinct factors (TS and OCD) failed to show a relationship with the measure of conditioned inhibition (represented by the conditioned inhibition ratio).

Moreover, it had been suggested that while the inhibitory responding observed throughout the analysis may be as a result of an inhibitory CI-UCS relationship (where the CI would mark the absence of the UCS), it may also be possible that the inhibitory responding may be as a result of occasion setting (whereby the presence of the CI modulates the CS-UCS responding). Accordingly, a simple means for discounting the possibility of the CI acting as an occasion setter as opposed to a conditioned inhibitor was to analyse the first presentation of the [CI, CS_t]. Prior to this first presentation, CS_t had never been presented along with the CI, and as such, during this first presentation, the CI cannot act as an occasion setter (whereas this would not hold true with repeated presentations of the [CI, CS_t]). However, linear regression analysis of the two distinct factors failed to show a

relationship with the measure of conditioned inhibition during the first presentation of the CS_t. Thus, this analysis reaffirms that at least within the normal population, TS-like behaviours do not affect the level of conditioned inhibition demonstrated.

In conclusion, the Mission to Mars task appears to act as a good translational paradigm of conditioned inhibition to be used in human participants. While neither ADHD nor TS-like behaviours were shown to have an effect on the level of conditioned inhibition demonstrated, the results obtained cannot be assumed to be representative of possible results when the level of conditioned inhibition is measured in clinical TS and ADHD populations (as discussed in chapters 4 and 5). With regards to the behavioural measures, the results also support the validity of the newly developed TS scale as a possible measure of TS-like behaviours. Finally, the strong correlation between the yawning and the TS and well as the ADHD behavioural measures provide support to the hypothesis that excessive yawing may serve as a possible marker for TS and/or ADHD. However, no firm conclusion can be drawn until such time that the same result is obtained in clinical TS and ADHD populations.

CHAPTER 4: TOURETTE SYNDROME – PERFORMANCE ON THE CONDITIONED INHIBITION PARADIGMS

4.1: INTRODUCTION

Tourette Syndrome (TS) is a developmental disorder characterized by involuntary, repetitive, stereotypic tics, both motor and vocal (Albin & Mink, 2006; Chowdhury, 2008; Jankovic, 2001; James F. Leckman, 2003; Robertson, 2000, 2006; Sheppard, et al., 1999; Spencer, et al., 1998; Swerdlow, 2001; The Tourette Syndrome Classification Study Group, 1993). Developmentally, tics typically start between the ages of 3 and 8 years, peak early in the teens, and reduce by the age of 19 or 20 years (Chang, et al., 2004; Chowdhury, 2008; Dooley, et al., 1999; James F. Leckman, 2003; James F. Leckman, et al., 1998).

Bouts of motor and phonetic tics occur during the course of a day and in the longer term wax and wane in the level of severity (Jankovic, 2001; James F. Leckman, 2003; The Tourette Syndrome Classification Study Group, 1993). Motor and phonetic tics are often preceded by premonitory sensations or thoughts (such as 'burning' of the eye before a eye blink tic, sore throat preceding grunting, aggressive ideas, environmental stimuli such as a person's cough or gesture), which are alleviated by the performance of the tic (Conelea & Woods, 2008; Jankovic, 2001; James F. Leckman, 2003; J. F. Leckman, et al., 1993; Prado, et al., 2008; The Tourette Syndrome Classification Study Group, 1993).

Based on the presenting symptoms, inhibitory deficits are thought to be fundamental to TS (Brand, et al., 2002; Comings & Comings, 1987; Georgiou, et al., 1995; Gilbert, et al., 2004; Sheppard, et al., 1999; Swerdlow, et al., 1996). Accordingly, inhibitory processes have been a focus of experimental studies of TS. For example, Georgiou et al. (1995) reported that the classic Simon effect (faster responding on congruent compared to incongruent trials) was greater for TS participants compared to matched controls indicating a possible deficit in

cognitive inhibition. However, the majority of investigations into cognitive and behavioural deficits in TS have failed to demonstrate any significant deficits compared to matched controls in participants without co-morbid attention deficit hyperactivity disorder. For example, participants with TS have been reported to perform as normal on Go/NoGo measures of response inhibition (Roessner, et al., 2008; Serrien, et al., 2005). Similarly, unless the inhibitory demands of the task are increased (Channon, et al., 2009), TS participants show no significant performance deficits in the colour-word Stroop task or the flanker task (Channon, et al., 2009; Channon, et al., 2006; Channon, et al., 2003).

Nonetheless, TS is a neuropsychological disorder with clear evidence for neural abnormalities in the basal ganglia (Cheon, et al., 2004; Giedd, et al., 2001; Hyde, et al., 1995; Mink, 2001; Minzer, et al., 2004; Peterson, et al., 1998; Sheppard, et al., 1999; Stern, et al., 2000) and the motor cortex (Gilbert, et al., 2004; Serrien, et al., 2005). Moreover, in line with the established role of the basal ganglia, dopamine antagonists have been used in the treatment of the symptoms TS (Gilbert, 2006). Reduction in the peripheral symptoms of anxiety has also been claimed to reduce tics. For example, it was reported by Findley et al (2003) that compared to controls, TS and OCD (Obsessive Compulsive Disorder) children experienced more stressful life events. Therefore, agents such as the noradrenergic α_2 agonist clonidine, which have anxiolytic properties, may be preferred over dopamine antagonists, also in part because they produce fewer side effects (Srour, Lesperance, Richer, & Chouinard, 2008). Thus, the range of neural circuitries and neuromodulatory pathways implicated in TS are consistent with a range of deficits, wider than the response inhibition that has been most extensively investigated to date. Moreover, when performance on procedural learning tasks was systematically compared with that on a task

requiring associative learning (S-S as well as S-R) in TS, the underlying learning systems were found to be dissociable (Marsh, Alexander, Packard, Zhu, & Peterson, 2005).

S-S associations provide a mechanism through which environmental events can act as symptom triggers and can thus explain the variability in frequency of symptoms and time course (Ferguson & Cassaday, 1999; Lishman, 1987; Siegel, 1977; Stewart, de Wit, & Eikelboom, 1984; Watson, 1924). In TS, a variety of associative triggers for tics have been documented, for example a person's cough or gesture (Conelea & Woods, 2008; James F. Leckman, 2003). Likewise premonitory urges in the form of somatic sensations ('burning' of the eye before a eye blink tic, sore throat preceding grunting), and the life situations that affect pre-tic urges and sensations (J. F. Leckman, et al., 1993) provide a source of stimuli that could become associated with tic-generated stimuli through S-S associations. Moreover, such antecedent stimuli have recently been targeted in behavioural treatments for TS (Conelea & Woods, 2008; Verdellen, et al., 2008; Woods, Walther, Bauer, Kemp, & Conelea, 2009).

A number of investigations have looked at S-S associations in TS. An earlier study of 'latent inhibition' (the reduction of S-S associative learning due to stimulus pre-exposure) found this effect to be normal in TS participants (Swerdlow, et al., 1996). However, while latent inhibition procedures retard later learning they do not render the pre-exposed stimulus truly inhibitory (Baker & Mackintosh, 1977). It is however by establishing a stimulus selectively to predict the occasions on which an otherwise expected outcome will not occur that a stimulus can become truly inhibitory (Pavlov, 1927; Rescorla, 1969).

To date, no research has explicitly examined the inhibition of S-S associations (i.e. 'conditioned inhibition') in TS. In conditioned inhibition procedures, a conditioned stimulus (CS) is presented immediately prior to an unconditioned stimulus (UCS), except on those occasions when it is preceded by the conditioned inhibitor (CI). Thus the CI comes to inhibit the CS-UCS association. According to Rescorla (1969), the conditioned inhibitor must be described in relation to the same UCS as that used in identifying the conditioned excitor, as well as the tendency that is assumed to be under the control of the conditioned inhibitor must be in direct opposite of the of the conditioned excitor. Moreover, Rescorla further states that for a stimulus to be identified as a conditioned inhibitor, it needs to pass the summation test and the retardation test. The summation test can be described the inhibition of excitatory responding produced by a transfer stimulus (a conditioned excitor that had not been previously paired with a conditioned inhibitor) by the CI, whereas the retardation test is described as retarded excitatory acquisition by a CI compared to a novel stimulus. As outlined in chapter 2, while both the retardation and summation tests have been reported predominantly in animal learning paradigms, a notable number of human learning paradigms report only having used the summation test as the test for conditioned inhibition (Grillon & Ameli, 2001; Karazinov & Boakes, 2004; Migo, et al., 2006; Neumann, et al., 1997).

As outlined in chapter 2, two video game style conditioning procedures have been developed that demonstrate reliable conditioned inhibition and are suitable for younger participants (Migo, et al., 2006). The conditioned inhibition tasks employed in this investigation were a serial-presentation conditioned inhibition task with implicit task instructions (Mission to Mars task) and a simultaneous-presentation conditioned inhibition

task with explicit task instructions (Weapon X task). In the present study, the participants were children and adolescents with a clinical diagnosis of TS (in the absence of co-morbid attention deficit hyperactivity disorder) and as well as age and sex matched controls.

As mentioned above, medication for TS has traditionally been with dopamine antagonists, of which the atypical neuroleptics are currently the drugs of choice, and at the lowest effective dose, to reduce the incidence of side effects (Srour, et al., 2008). Moreover, medication (with neuroleptics) has previously been reported to improve the learning of S-R associations in experimental studies of TS (Marsh, et al., 2004). However, because of concern over side effects with dopamine antagonists, a variety of other drugs have been used to control tics. The majority of the current sample was medicated with clonidine which reduces activity in the noradrenergic system through a pre-synaptic mechanism of action. This action is of a priori interest given the body of evidence to suggest a role for noradrenaline as a key modulator of behavioural inhibition and anxiety (Jeffrey Alan Gray, 1982).

4.2: METHODS AND MATERIALS

4.2.1: PARTICIPANTS

Fifteen TS participants (12 males, 3 females, mean age = 13 years 11 months, range = 10–20 years) were recruited for the current study (The Child and Adolescent Clinic, Psychiatry Department, Queen's Medical Centre, Nottingham). All of the clinical TS participants met the DSM-IV criteria for TS. Of thirty five potential controls tested, nineteen were matched for age (within 6 months as measured on the day of testing) and sex with the TS

participants. All TS participants had met DSM IV (American Psychiatric Association, 2000) criteria for TS. This yielded a control sample of fifteen males and four females (mean age = 13 years 5 months, range = 10–20 years). All TS participants were assessed using the Yale Global Tic Severity Scale (YGTSS) within two months of testing in the present study (same day scores were available for eleven of the fifteen participants). The available IQ scores (n = 13 TS and n = 9 matched controls) had been measured with the Wechsler Abbreviated Scale of Intelligence (WASI).

With respect to medication at the time of testing, seven participants were on clonidine (50–100 mcg), one participant was on clonazepam (500 mcg), one was on the atypical antipsychotic aripiprazole, three had previously been on clonidine but were off medication at the time of testing (doses 50-200 mcg), one was drug free that day (previously treated with aripiprazole), two had never received any medication for their TS symptoms. Participant details are summarized in Table 4-1.

				Medication		YGTSS			
Subject	Age (months)	Sex	IQ	Type	Dosage	Motor	Phonic	Impairmet	Total Score
TS-1	137	Male	103	Clonazepam	500	14	13	25	52
TS-2	209	Male	107	(Aripiprazole)	2.5*	n/a	n/a	n/a	66
TS-3	176	Female	95	Clonidine	25-50	0	0	0	0
TS-4	151	Male	101	(none)	n/a*	5	0	0	5
TS-5	151	Male	135	(Clonidine)	50*	5	0	0	5
TS-6	163	Male	120	Clonidine	100	11	0	20	31
TS-7	161	Female	96	Clonidine	75-100	11	10	15	36
TS-8	193	Male	76	Clonidine	50	9	9	0	18
TS-9	197	Male	111	(Clonidine)	200*	7	2	20	29
TS-10	155	Male	111	Clonidine	50	18	11	10	39
TS-11	127	Male	-	(none)	n/a*	12	9	10	31
TS-12	190	Male	95	Clonidine	50	15	14	30	59
TS-13	247	Male	112	(Aripiprazole)	n/a*	13	19	15	47
TS-14	121	Male	-	Clonidine	50	5	0	0	5
TS-15	136	Female	97	(Clonidine)	n/a*	14	14	10	38

Table 4-1: Demographics, medication and symptom scores for the TS participants. TS = Tourette Syndrome participant code; mcg = micrograms medication dosage per day; YGTSS = Yale Global Tic Severity Scale; n/a = data not available or not applicable, () = Previous medication type (subject was off medication at time of test), * = Previous medication dosage (subject was off medication at time of test).

This study was approved by NHS Research Ethics (Derbyshire REC, reference 08/H0401/34, approved April 2008). All participants received an inconvenience allowance of £5-£10 to cover their travel expenses.

4.2.2: MATERIALS

The task programs were produced in E-studio and utilized E-prime (Psychology Software Tools Inc., Pittsburgh, USA) to present the material to the participants. The programs were run on personal computers with 17" monitors or on a portable 15" laptop computer when travel to the participant was required for testing. Participants' responses were made using a mouse. The stimuli presented during each of the two tasks are shown in Figure 4-1.

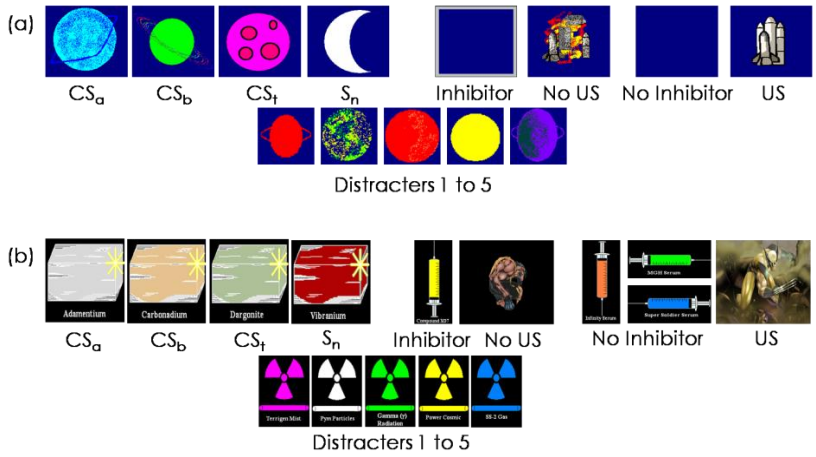

Figure 4-1: The stimuli presented during (a) Mission to Mars and (b) Weapon X task variants.

4.2.3: PROCEDURE

The procedure for the Mission to Mars and the Weapon X conditioned inhibition tasks followed those outlined in chapter 2.

4.2.4: DESIGN AND ANALYSIS

Analysis of variance (ANOVA) was run in a mixed design with up to four within-subjects factors to assess the development of conditioned inhibition: inhibition (the presence or absence of the CI); task (Mission to Mars versus Weapon X); stimulus type (summation test with the generalized stimulus versus the previously trained transfer stimulus); presentation, of which there were five levels.

Diagnosis and medication were between subjects factors, examined in successive analyses. The effect of diagnosis was examined overall. The effect of medication was examined within the TS group. An on-anxiolytic group were under treatment with clonidine (n=7) or clonazepam (n=1) at the time of behavioural testing. An off-anxiolytic group (n=7) were not under treatment with clonidine or clonazepam at the time of behavioural testing, but this group included one participant under treatment with aripiprazole. Analyses were collapsed across task, stimulus type and presentation where these factors did not affect the development of conditioned inhibition. Planned comparisons (t-tests at $p \leq 0.05$) were conducted to examine effects of a priori interest. Also, effect size calculations (Cohen's d calculations – denoted as "d") were conducted for the medication analysis.

The dependent variable to assess conditioned inhibition was the participants' expectancy scores (for appearances of an intact rocket in task 1 or the successful transformation of Logan into Wolverine in task 2). In addition, a conditioned inhibition ratio was calculated by dividing the average expectancy score for non-inhibited stimulus presentations by the average expectancy score for inhibited stimulus presentations. Thus, conditioned inhibition

is indicated by a ratio less than one and the absence of conditioned inhibition by a ratio greater than or equal to one. The interrelationship between the level of conditioned inhibition summarized by the ratio and symptom severity scores (measured by the YGTSS) was explored by Pearson's r correlation (the total YGTSS scores were available for all participants; the subscale scores were available for all but one participant). Where the data were available (for twelve of the fifteen TS participants), the same analyses were repeated to examine conditioned inhibition performance on each of the tasks in relation to TS participants' IQ. Similarly, the effect of medication was further examined by correlational analysis, using both the raw duration and a ratio to adjust for participants' age (length of time on medication divided by the age of the participant).

4.3: RESULTS

There was a main effect of inhibition ($F_{1, 32} = 28.184$, $p < 0.001$). Figure 4-2 shows that the TS participants demonstrated an overall equivalent level of inhibition to the matched controls, and this was confirmed statistically as there was no significant interaction between the diagnosis and inhibition ($F = 0.079$). Performance was equivalent in the two task variants in that there were no significant interactions involving task and inhibition ($F_{1, 32} = 1.439$). Similarly, there were no effects of stimulus type (generalized or transfer) or presentation with respect to inhibition ($F_{1, 32} = 3.725$).

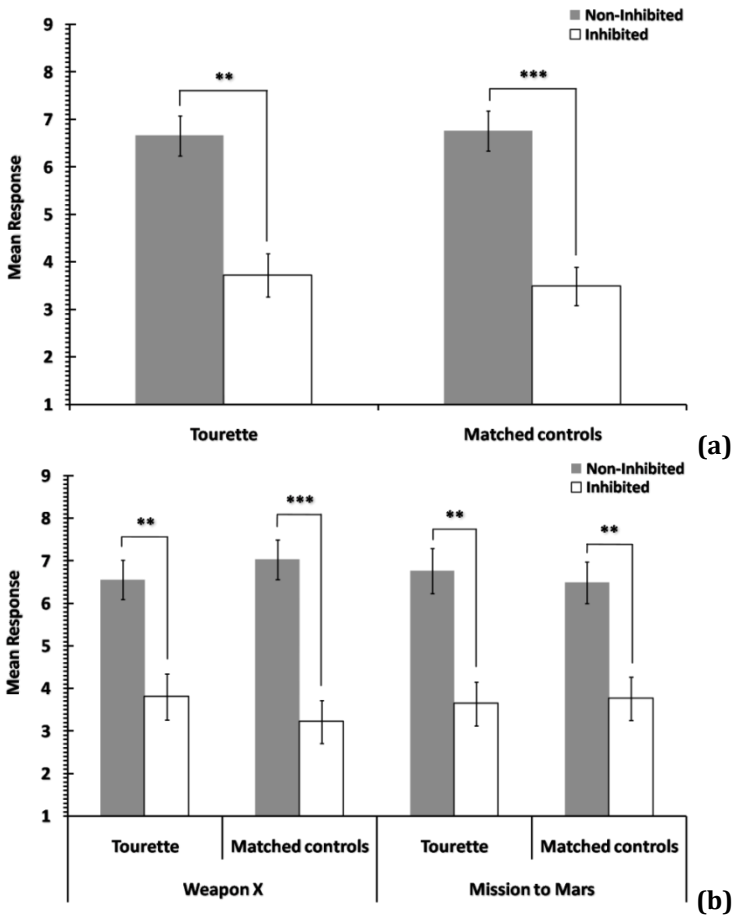

Figure 4-2: The overall effect of inhibition with respect to diagnostic group overall (a) and by each task variant (b). Conditioned inhibition was significant in all groups (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$).

Figure 4-3 shows that conditioned inhibition was reduced by anxiolytic medication in the TS sample. This impression is confirmed statistically by a significant interaction between medication and inhibition ($F_{1, 13} = 5.881$, $p < 0.05$). Exclusion of the single participant on clonazepam from the on-anxiolytic group, primarily composed of participants on clonidine, does not change the conclusion that conditioned inhibition was impaired by medication in that the interaction between medication and inhibition remained significant ($F_{1, 12} = 5.359$, $p < 0.05$). The participant on clonazepam is therefore included with the participants on clonidine, in the on-anxiolytic group, for the subsequent analyses.

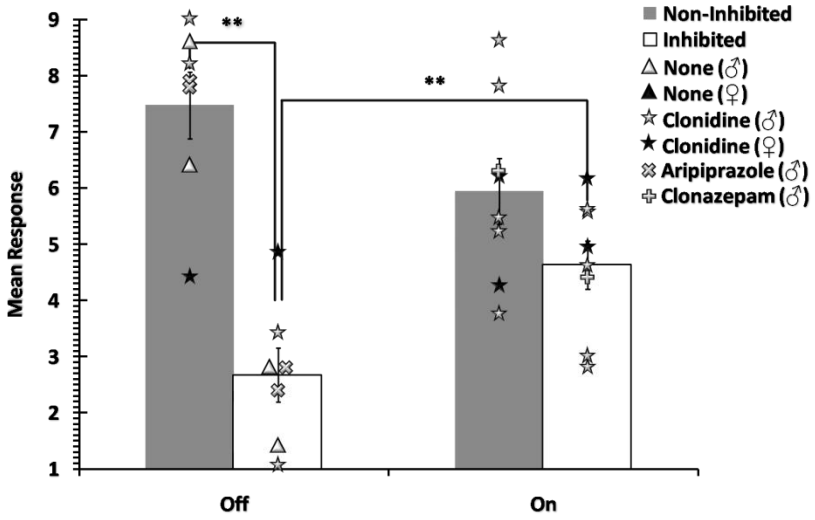

Figure 4-3: The effect of inhibition in relation to anxiolytic medication. The individual data points show the medication status and sex of the participants. In the off-anxiolytic group, three participants had formerly been on clonidine, one was on aripiprazole (atypical antipsychotic), one was drug free that day (formerly on aripiprazole), and two had never been on any medication. In the on-anxiolytic group all of participants were on clonidine save one who was on clonazepam. Conditioned inhibition was significant in the off- but not in the on-anxiolytic group because of a reduction in inhibitory learning in the on-anxiolytic participants (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$).

Conditioned inhibition (shown as the difference between non-inhibited and inhibited response scores) was clearly demonstrated in TS participants who were off-anxiolytic at the time of testing ($t_6 = 4.626$, $p < 0.01$, effect size: $d = 3.62$). By contrast, conditioned inhibition was absent in TS participants who were on-anxiolytic at the time of testing ($t_7 = 1.323$, $d = 0.97$). Further planned comparisons showed that the reduction in conditioned inhibition arose primarily because of a difference between the inhibited responding between the groups in relation to medication status ($t_{13} = 3.061$, $p < 0.01$, $d = 1.7$). There was no significant difference in excitatory learning measured in the non-inhibited groups in relation to medication status ($t_{13} = 1.82$, $d = 1.12$).

To address possible confounds of medication with age (as age may have affected conditioned inhibition) and/or tic severity (as those TS participants on- or off-anxiolytics

may have had a different symptom profile), analyses of covariance were conducted using age and/or scores of the YGTSS as covariates of medication for the TS group. It was found that the significant interaction between inhibition and medication remained intact regardless of the age ($F_{1, 13} = 5.46$, $p < 0.05$) and YGTSS scores ($F_{1, 13} = 5.501$, $p < 0.05$) of the TS participants.

Finally, in order to assess the level to which the conditioned inhibition discrimination was learned by the end of the training phase, the data from the first test presentation of the non-inhibited transfer stimulus (which was used during training phase) were analyzed. Univariate analysis of the first presentation of the transfer stimulus showed no overall significant difference between the TS groups (on- or off-anxiolytics) and the matched controls ($F_{2, 31} = 1.999$, $p=0.153$). Neither was there any difference by task: Weapon X task ($F = 0.498$, $p=0.612$); Mission to Mars task ($F_{2, 31} = 1.437$, $p=0.253$).

4.3.1: CORRELATIONAL ANALYSIS

There was no correlation between symptom severity measured by the YGTSS (overall or in relation to the subscales) and performance on either of the conditioned inhibition tasks summarized by the conditioned inhibition ratios (maximum $r_{14} = 0.315$). There was a significant relationship between IQ and the Mission to Mars conditioned inhibition ratio ($r_{12} = -0.606$, $p < 0.05$), but this was inconsistently demonstrated in that there was no such correlation between IQ and the Weapon X conditioned inhibition ratio ($r_{12} = -0.350$). For TS participants in the on-anxiolytic group, there was no correlation between medication

duration or medication duration as a proportion of age and performance on the conditioned inhibition tasks (maximum $r_{8} = -0.555$).

4.3.2: SEX DIFFERENCE

There were overall sex differences in conditioned inhibition in the sample of TS participants and their matched controls (Figure 4-4). This was demonstrated statistically as a significant interaction between inhibition and sex ($F_{1, 32} = 7.56$, $p = 0.01$) whereby conditioned inhibition was overall demonstrated by the male participants ($t_{26} = 6.157$, $p < 0.001$, $d = 2.32$) but not the females ($t_{6} = 0.413$, $d = 0.29$).

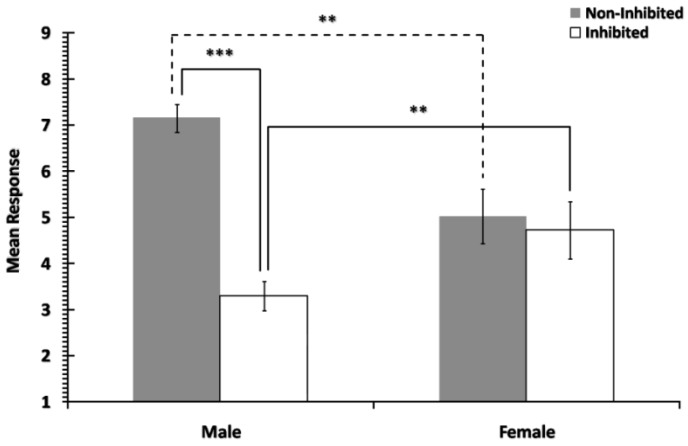

Figure 4-4: The overall effect of inhibition with respect to sex. Male participants demonstrated greater levels of conditioned inhibition compared to female participants (* = p<0.05, ** = p<0.01, *** = p<0.001).

This difference in conditioned inhibition arose because, compared to the females, the male participants showed greater level of excitatory learning (non-inhibited) responses ($t_{32} = 3.20$, $p < 0.01$, $d = 1.4$) as well as greater inhibition, shown as a lower level of inhibited responses ($t_{17.84} = 2.886$, $p = 0.01$, $d = 0.9$).

This sex difference is irrelevant to our overall conclusion in that controls were matched by sex as well as age in order to examine conditioned inhibition in TS. Moreover, there were

only 3 female participants with TS and 4 age-matched female controls. However, medication status was determined by factors outside of our control and whilst one female was in the off-anxiolytic group, two females were on-anxiolytics. Thus the sex difference in conditioned inhibition could in principle contribute to the apparent effect of treatment with anxiolytics. Accordingly, the key analysis to examine inhibition by medication was also run with the female participants excluded. When this was done, the interaction between inhibition and medication remained significant, both with ($F_{1, 10} = 7.79$, $p = 0.02$) and without ($F_{1, 9} = 6.40$, $p < 0.05$) inclusion of the participant on clonazepam

4.4: DISCUSSION

The results of the current investigation showed that the inhibition of S-S association was not affected by the presence of TS. The learning of conditioned inhibition was confirmed by the summation test for conditioned inhibition (Rescorla, 1969), specifically by the transfer of inhibition to a CS not previously presented with the CI during training (CS_t) and to a novel stimulus from the same category, to which participants would generalized their excitatory responding (S_g). On this criterion test, conditioned inhibition was clearly demonstrated in the present study, using two task variants suitable for younger participants, including those with TS. Statistically, there was no difference in the level of conditioned inhibition shown, either by stimulus type or task. The equivalence of results across the two stimulus types, and in two task variants, provides strong evidence that the inhibitory properties of the CIs transferred both to a stimulus with which it had never previously been experienced and to a new stimulus with which they had no explicit prior training of any kind. The tasks were very different in terms of content but formally

identical with respect to design and procedure, in all aspects other than the task instructions. That there was no difference in performance by task also suggests that explicit learning instructions are not necessary to show conditioned inhibition with the procedures in use. Moreover, the absence of a difference between the simultaneous-presentation Weapon X task and the serial-presentation Mission to Mars task provides evidence against previous reports that conditioned inhibition can only be demonstrated through simultaneous-presentation of the stimuli (Baeyens, et al., 2004; Holland, 1984; Holland & Lamarre, 1984).

The earlier acquisition of the discrimination between inhibited and non-inhibited stimuli was not directly assessed in the training phase due to the implicit nature of the Mission to Mars task instructions. However, for both task variants, trial 1 responding to the transfer stimulus provided a measure of the level of excitatory learning and the means to measure any differences between groups prior to the introduction of a CI for this association. Analysis of excitatory conditioning to the transfer stimulus showed no differences between the diagnostic groups, or by medication for TS participants, either overall or in either task.

As mentioned, participants with TS showed no difference in the expression of conditioned inhibition. Thus, learning to inhibit prodromal S-S associations could be an effective behavioural approach to symptom control. However, when the participants with TS were examined with respect to their medication, a clear difference was seen in the level of conditioned inhibition demonstrated by each of the two medication groups. As noted, the majority of the participants were medicated with clonidine which possesses anxiolytic properties. Thus, the two medication groups examined were identified as either on- or off-

anxiolytic medication. The results showed that while excitatory responding was unaffected by anxiolytic medication, participants in the on-anxiolytic medication group demonstrated significant deficit in inhibitory responding compared to the off-anxiolytic medication group.

The participants treated with the atypical antipsychotic aripiprazole (of which only one was on medication at the time of behavioural testing) were categorized as 'off-anxiolytics' as the mechanism of action of aripirazole does not include a reduction in noradrenergic activity. While aripiprazole has recently been reported to relieve some symptoms of anxiety and depression, this efficacy has only been demonstrated as an adjunctive treatment in the context of residual symptoms that are resistant to treatment with serotonin reuptake (SSRIs) anti-depressants (Adson, Kushner, & Fahnhorst, 2005; Worthington, Kinrys, Wygant, & Pollack, 2005) and has been attributed to the drug's serotonergic mechanisms of action (Pae, Serretti, Patkar, & Masand, 2008). Also, the lone clonazepam participant was included in the on-anxiolytic group due to the anxiolytic properties of clonazepam as a benzodiazepine. Although the effects of benzodiazepines on the noradrenergic system are indirect, similar to clonidine however, they reduce noradrenergic activity (Jeffrey Alan Gray, 1982).

Symptom severity, that in principle confounds medication, provided no obvious account for the results obtained, as the results remained the same when the symptom severity level (measured by the YGTSS) was taken into account. Furthermore, there was no overall relation between conditioned inhibition and symptom severity scores. Similarly, the analysis with respect to IQ provided no account of the results. Although a negative

correlation between IQ and the conditioned inhibition ratio was shown, this however was only significant for one of the tasks in use. Moreover, this direction of relationship meant greater rather than less conditioned inhibition was shown in participants with lower IQ.

Together these results point to the conclusion that anxiolytic medication in TS has a selective effect on an aspect of associative learning that could potentially be relevant to both the symptom profile and the ability to control tics which have identified triggers. Importantly, the fact that the effect of anxiolytic medication in TS was selective to inhibition, in that excitatory learning was not significantly affected, suggests that there was no general learning impairment as one would expect with a non-specific effect. In other words, there was no evidence that clonidine affected arousal, attention or motivation to engage with the task in the present study.

From a theoretical perspective, the selective effect on inhibitory as opposed to excitatory learning could be related to clonidine's anxiolytic actions on the Behavioural Inhibition System (BIS). According to Gray (1982), anti-anxiety drugs impair the processing of signals of nonreward (similar to those provided by the CIs used in the present study). The gray frame (Mission to Mars task) and the yellow syringe (Weapon X task) specifically predicted that the normal contingency was not in place (represented by the alternate outcomes of an exploded rocket in the Mission to Mars task and a feral Logan in the Weapon X task). As shown by the results, such CI processing was clearly impaired in participants under anxiolytic medication for TS.

In other tasks, there is evidence for improved cognitive control in TS, particularly in relation to suppressing prepotent S-R associations (Mueller, et al., 2006). In some cases of

TS, stimuli provided by environmental events and thoughts are recognised to trigger associations that precede tics (James F. Leckman, 2003; James F. Leckman & Peterson, 1993; Prado, et al., 2008; Verdellen, et al., 2008). Similarly, other environmental events and thoughts provide stimuli with the potential to become learned inhibitors of these unwanted associations. Through impaired conditioned inhibition, medication with drugs like clonidine could impair potential cognitive control mechanisms for the suppression of tics (through an action on the associative chain that generates triggers). Specifically, impaired inhibition of S-S associations may leave TS sufferers less able to inhibit the unwanted thoughts and premonitory associations that can lead to tics. Such contextual triggers have recently become the focus of behavioural treatments for TS: through extinction of the excitatory association (Verdellen, et al., 2008); and in their capacity as discriminative stimuli in relation to tic reinforcement (Woods, et al., 2009).

The present study shows a selective effect in TS in that within the same participants excitatory learning was unaffected by clonidine. In other words, under clonidine, the learning of S-S associations was as normal, in line with observations that, importantly, clonidine is without effect on many aspects of cognition. However, normal excitatory learning also means that associative triggers for tics are not directly suppressed by this treatment. Thus, while treatment with anxiolytics may improve aspects of the symptom profile in TS, the consequences of impaired inhibitory learning should be taken into account when considering clonidine as a form of treatment for TS (Srour, et al., 2008). Thus, it can be concluded that the cognitive side effects of drugs like clonidine should be further investigated (Tiplady, Bowness, Stien, & Drummond, 2005).

Notwithstanding the medication effect, the current investigation showed that in general, the inhibition of S-S associations was not affected by the presence or the symptom profile of TS. However, as mentioned, while a number of investigations failed to demonstrate any significant deficits in non-comorbid TS participants compared to matched controls, in TS-ADHD comorbids the presence of inhibitory deficits have often been attributed to the presence of ADHD (Brand, et al., 2002; Channon, et al., 2003; Como, 2001; Gilbert, et al., 2004; Ozonoff, et al., 1998). As such, the following chapter investigates the inhibition of S-S associations in a clinical ADHD population.

CHAPTER 5: ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) – PERFORMANCE ON CONDITIONED INHIBITION PARADIGMS

5.1: INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder, the diagnosis of which depends on the emergence of symptoms by 7 years of age (Barkley, 1998; Kytja & Voeller, 2004; Schachar, et al., 2000). ADHD is characterized by the display of inattention and hyperactivity/impulsivity that are manifested in a manner that is uncharacteristic of the child's current level of development (American Psychiatric Association, 2000; Barkley, 1998; Kytja & Voeller, 2004). The prevalence of ADHD has been variably estimated as high as 10% (Kytja & Voeller, 2004), 18% (Faraone, et al., 2003) or as low as 5.29% (Polanczyk, et al., 2007). On conservative estimates of 2-6% children in the US meet DSM-IV criteria. Reported prevalence rates in the UK of the equivalent 'hyperkinetic' disorder following ICD-10 criteria are still lower, of the order of 2% (Rohde, et al., 2005) as the diagnosis of hyperkinetic disorder by ICD-10 criteria is markedly more stringent than the diagnosis of ADHD by DSM-IV criteria (Foreman, Foreman, Prendergast, & Minty, 2001; Santosh, et al., 2005; Singh, 2009).

ADHD is a disorder that is often comorbid with other neurological disorders. According to Barkley (1998), approximately 87% of clinically diagnosed ADHD patients have one or more comorbid disorder and about 67% have two or more comorbid disorders. A comorbid disorder of note for ADHD is TS (Erenberg, 2005; Kytja & Voeller, 2004; Robertson, 2000, 2006; Sheppard, et al., 1999; Spencer, et al., 1998; Srour, et al., 2008). It has been estimated that the comorbidity of ADHD in TS patients is at approximately 48% of the cases (Comings & Comings, 1987). Being diagnosed by ADHD does not increase the risk of comorbidity with TS; to the contrary, being diagnosed with TS does increase the risk of

ADHD comorbidity, whereby in these cases ADHD often precedes TS in the TS-ADHD comorbids (Barkley, 1998). It is not surprising that with respect to neural structural factors, ADHD and TS share some commonalities. According to Banaschewski et al., the involvement of the corpus callosum (reduced size) and the basal ganglia (reduced volume of the caudate nuclei) has been indicated in both TS and ADHD (Banaschewski, et al., 2007).

Neuroanatomical studies have suggested several regions that may be responsible for ADHD, such as the cerebellum (Castellanos, et al., 1996; Castellanos, et al., 2001), the frontal lobe (Giedd, et al., 2001; Gitten, Winer, Festa, & Heindel, 2006) and the basal ganglia (Casey, et al., 1997; Casey, et al., 2001; Giedd, et al., 2001). Casey et al. (1997; 2001) hypothesized that the basal ganglia are involved in the inhibition of inappropriate behaviours; the disruption of which results in abnormalities in behavioural control. They further stated that the frontal cortex is involved in the maintenance of action by monitoring relevant information, whereby disruptions in this region result in deficits in performing relevant actions. Studies have also implicated the involvement of the basal ganglia circuits in the acquisition of classical conditioning. Winstanley, Baunez, Theobald, & Robbins (2005), in an investigation the effects of lesioning of the subthalamic nucleus (STN) and its effects on Pavlovian autoshaping behaviours found that lesions to the STN creates a fundamental deficit in the formation of Pavlovian CS-UCS associations (this deficit was not observed if the acquisition of the autoshaping task occurred prior to the STN lesion). In addition, in a PET scan study of conditioned eyeblink paradigm in healthy human subjects, Logan and Grafton (1995) found activation of the ventral striatum being significantly correlated with learning.

Similar to TS, it has been suggested that ADHD is a disorder of inhibition (Nigg, 2001; Quay, 1997; Schachar & Logan, 1990; Schachar, et al., 2000; Young, et al., 2006). According to, Nigg (2001) there are two categories of inhibition. The first, *executive inhibition*, involves the suppression of a cognition or response directed at achieving an internally represented goal at a later time, measured by such tasks as the stop signal and the Go/NoGo (whereby the Go response is set up as the dominant response by being presented the most and as the response that is required to be withheld when the more rare NoGo signal is presented). The second, identified by Nigg as *motivational inhibition* involves the cessation of actions and behaviours that are driven by fears or anxieties resulting from signals of danger, punishment, or unexpected stimuli. Motivational inhibition is derived from Gray's (1982) BIS theory . However, there has not been much experimental support for motivational inhibition deficit in ADHD, as most investigations have failed to find any relationship between the BIS system and ADHD (Johnson, et al., 2003; Pliszka, et al., 1993).

Several investigators have stated that ADHD results from a deficit in executive inhibition (Barkley, 1998). A great number of studies have demonstrated support for the existence of a deficit in response inhibition in ADHD (Seidman, et al., 1997; Trommer, et al., 1988; Young, et al., 2006). In an investigation of inhibitory control in ADHD children using three tests of response inhibition (the Stop signal, the Go/NoGo and a modified version of the Stroop task), Bitsakou, Psychogiou, Thompson, & Sonuga-Barke (2008) found that ADHD children demonstrated significant deficits compared to the controls on all of the inhibitory tasks, supporting the presence of inhibitory deficits in ADHD. Further evidence was provided by Oosterlaan and Sergeant (1998) who investigated the possibility of ADHD being as a result of a deficit in two aspects of executive functioning, namely response

inhibition and response re-engagement. Using a variation of the stop signal task called the change task, the authors found that both the ADHD and the disruptive participants did demonstrate impaired response inhibition compared to the normal controls, unlike the anxious group who demonstrated a higher degree of inhibition compared to the controls, providing support to the theory that ADHD involves a deficit in response inhibition. Moreover, working under the hypothesis that ADHD is a disorder of inhibitory control in an investigation of the development and pathology of inhibitory control through the stop-signal paradigm, Schachar et al. (1990; 2000) found that the ADHD group demonstrated deficient inhibitory control compared to all other groups (normal controls, learning disorder, emotional disorder, conduct disorder and comorbid ADHD-conduct disorder). Further evidence of the presence of inhibitory deficit in ADHD was provided by Iaboni, Douglas, & Baker (1995) who observed that ADHD children produced more commission errors in a Go/NoGo paradigm compared to controls irrespective of reward/cost, indicating that ADHD involves a more generalized inhibition impairment.

While the majority of the researches in the existence of inhibitory deficits in ADHD have investigated deficits in response inhibition (S-R paradigms such as the Stroop, the Go/NoGo and the Stop signal to name a few), few investigations have examined the inhibition deficits in S-S associations. In a study of 'conditioned blocking' Oades and Müller (1997) found that the development of conditioned blocking was impaired in ADHD children (compared to matched controls). Although conditioned blocking utilizes S-S association, it is not a true measure of inhibition, in that the former association of a conditioned stimulus (CS) with an unconditioned stimulus (UCS) prevents a novel CS from gaining association with the UCS. Stimulus inhibition demonstrated by establishing a stimulus selectively to predict the

occasions on which an otherwise expected outcome will not occur (Pavlov, 1927; Rescorla, 1969). A reliable measure of the inhibition of S-S association is though conditioned inhibition (Pavlov, 1927; Rescorla, 1969), where a CS is associated with a particular outcome or an UCS, except on occasions where the CS is presented with a conditioned inhibitor (CI). The absence of the UCS during the trials where the CI is presented makes the CI an inhibitor of the CS-UCS association. To date, no research has explicitly examined the inhibition of S-S associations (formally 'conditioned inhibition') in ADHD. In conditioned inhibition procedures, a conditioned stimulus (CS) is presented immediately prior to an unconditioned stimulus (UCS), except on those occasions when it is preceded by the conditioned inhibitor (CI). Thus, the CI comes to inhibit the CS-UCS association. We have developed video game style conditioning procedures that demonstrate reliable conditioned inhibition and are suitable for younger participants (Migo, et al., 2006). In the present study, the participants were children and adolescents with a clinical diagnosis of ADHD (in the absence of co-morbid TS) and typically developing age and sex matched controls.

The current study investigated the possible disturbance of the inhibition of S-S associations using two conditioned inhibition paradigms adapted from a conditioned inhibition task developed by Migo et al. (2006) that is suitable for use of younger participants. In the present investigation, the performance of children diagnosed with ADHD (in the absence of TS comorbidity) was compared to those of age and sex matched controls.

Medication for ADHD has traditionally been with dopamine agonists, of which methylphenidate is currently the drug of choice (Langleben, et al., 2006; Lopez, et al., 2003). The ADHD participants tested in the present study were all medicated with

methylphenidate; treatment was thus confounded with diagnosis. However, medication dosage and duration of treatment were taken into account statistically.

5.2: METHODS AND MATERIALS

5.2.1: PARTICIPANTS

Twelve ADHD participants (12 males: mean age = 13 years 11 months; range = 11 years 9 months – 16 years 9 months) were recruited for the current study (The Child and Adolescent Clinic, Psychiatry Department, Queen's Medical Centre, Nottingham). The ADHD participants were provided by Dr. Martin Batty, who had followed the standard screening procedure. The screen procedure of the ADHD participants included a battery of tests including the Development and Well Being Assessment (DAWBA) (Goodman, Ford, Richards, Gatward, & Meltzer, 2000), the Social Communications Questionnaire (SCQ) (Berument, Rutter, Lord, Pickles, & Bailey, 1999), the Strength and Difficulties Questionnaire (SDQ) (Goodman, 1997) as well as The Conners' Parent Rating Scale – Revised: Long (CPRS-R: L) (Conners, Sitarenios, Parker, & Epstein, 1998). Also, contact with the school and the completion of the Teachers version of the DAWBA, SDQ and the CPRS-R: L was also completed. Following these tests, ADHD diagnosis was confirmed or overturned following a clinical consensus diagnostic meeting involving Dr. Chris Hollis and another experienced child and adolescent psychiatrist, which included a full review of the participant's medical history, parent and teacher DAWBA transcripts (including computer generated predictions) and the questionnaires. Further assessment of the participants with Weschler Abbreviated Scale of Intelligence (WASI), Test of Word Reading Efficiency

(TOWRE), and Annett Handedness Questionnaire followed. The ADHD participants involved in this study were right handed participants with a DSM-IV diagnosis of ADHD with no comorbid disorders (excluding oppositional defiant disorder (ODD), conduct disorder (CD) and anxiety disorder who were included in the study) who had demonstrated a positive response to stimulant medication with an IQ of 70 and above.

Of the thirty five controls tested, eleven were matched for age and sex with the ADHD participants (11 males: mean age = 13 years 11 months; range = 11 years 7 months - 17 years 1 month). The range of IQ of the participants was 75-108 for the ADHD (n = 12) and 102-107 in the matched control (n = 5) participants. CPRS-R: L was the test of choice for the ADHD assessment. All of the ADHD participants were on medication (Concerta – an extended-release preparation of methylphenidate) at the time of testing. Participant details are summarized in Table 5-1.

	Subjects	ADHD-1	ADHD-2	ADHD-3	ADHD-4	ADHD-5	ADHD-6	ADHD-7	ADHD-2	ADHD-9	ADHD-10	ADHD-11	ADHD-12
	Age (months)	201	190	161	141	144	167	169	190	145	142	153	194
	IQ (WASI)	75	87	77	108	79	98	77	103	94	105	104	85
Medication	Dosage (mg/kg)	0.85	1.08	1.93	1.03	0.82	0.89	0.77	0.57	1.33	0.83	1.23	1.42
Medication	Time on Medication (Months)	63	41	51	5	19	22	18	92	11	54	59	27
Medication	Medication duration corrected for age	0.31	0.22	0.32	0.04	0.13	0.13	0.11	0.48	0.08	0.38	0.39	0.14
CPRS-R: L	Oppositional	80	84	90	87	85	90	89	54	83	85	75	90
CPRS-R: L	Cognitive Problems	62	74	74	59	78	75	77	57	63	74	78	77
CPRS-R: L	Hyperactivity	85	57	85	87	90	90	90	80	85	90	80	90
CPRS-R: L	Anxious	54	44	61	45	79	90	47	51	63	45	63	68
CPRS-R: L	Perfectionism	65	43	49	69	77	77	55	50	58	41	69	52
CPRS-R: L	Social Problems	72	60	73	69	65	90	81	90	45	90	77	80
CPRS-R: L	Psychosomatic	61	61	42	63	88	90	90	90	58	48	83	58
CPRS-R: L	ADHD Index	70	77	77	73	77	83	79	60	75	82	76	75
CPRS-R: L	Global Restless Score	63	70	86	77	82	90	86	70	80	86	75	81
CPRS-R: L	Emotional Lability	90	73	83	78	72	90	83	61	72	72	83	79
CPRS-R: L	Global Total	72	72	88	80	81	90	88	69	80	84	80	83
CPRS-R: L	DSM Inattentive	69	76	77	65	80	81	71	58	65	80	77	78
CPRS-R: L	DSM Hyperactive	86	63	81	87	90	90	87	81	81	90	81	90
CPRS-R: L	DSM Total	78	73	81	77	88	90	80	69	74	90	81	89
CPRS-R: L	DSM Inattentive Count	8	9	9	7	9	8	8	2	6	9	9	9
CPRS-R: L	DSM Hyperactivity Count	6	2	7	9	9	9	9	6	7	9	8	8

Table 5-1: Demographics, medication and symptom scores for the ADHD participants. All participants were male and were on *Concerta* ADHD medication. ADHD = Attention deficit hyperactivity disorder participant code; mg/kg = milligrams medication per kilogram body weight dosage per day; CPRS-R: L = Conners Parent Rating Scale – Revised: Long; WASI: Wechsler Abbreviated Scale of Intelligence.

This study was approved by NHS Research Ethics (Derbyshire REC, reference 08/H0401/34, approved April 2008). All participants received an inconvenience allowance of £5-£10 to cover their travel expenses.

5.2.2: MATERIALS

All of the programs were produced in E-studio and utilized E-prime (Psychology Software Tools Inc., Pittsburgh, USA) to present the material to the participants. The programs were run on personal computers with 17" monitors or on a portable 15" laptop computer when travel to the participant was required for testing. The participants responded using a mouse. The stimuli presented during each of the two experiments are shown in Figure 5-1.

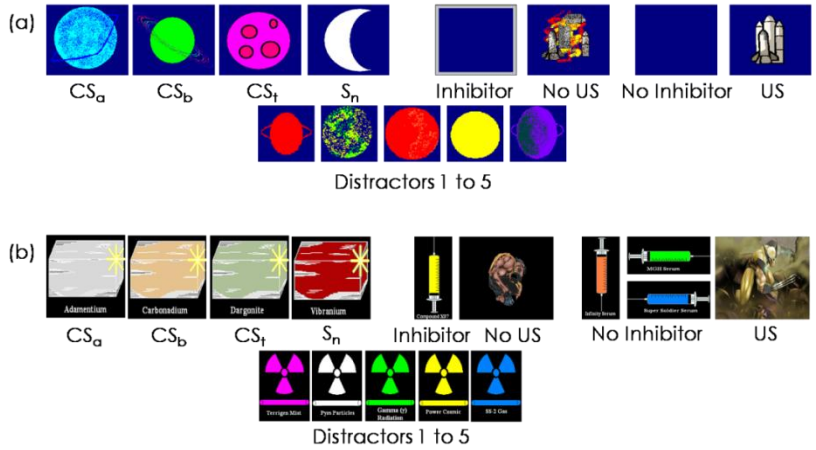

Figure 5-1: The stimuli presented during (a) Mission to Mars, and (b) The Weapon X task variants.

5.2.3: PROCEDURES

The procedure for the Mission to Mars and the Weapon X conditioned inhibition tasks follow those outlined in chapter 2.

5.2.4: DESIGN AND ANALYSIS

Analysis of variance (ANOVA) was run in a mixed design with up to four within-subjects factors to assess the development of conditioned inhibition: inhibition (the presence or absence of the CI); task (Mission to Mars versus Weapon X); stimulus type (summation test with the generalized stimulus versus the previously trained transfer stimulus); presentation (of which there were five levels). Diagnosis was the between subjects factors. All of the ADHD patients were on medication (Concerta) at the time of testing. In order to investigate any possible effects of medication, median split analyses were conducted with respect to time on medication and the dosage of medication (mg/kg). These were distinct parameters in that time on and dose of medication were not correlated (see below).

Median split analysis was also used to examine the effect of symptom severity (measured using the CPRS-R: L) on the expression of CI. Analyses were collapsed across stimulus type and presentation where these factors did not affect the development of conditioned inhibition. The dependent variable to assess conditioned inhibition was the participants' expectancy scores (for appearances of an intact rocket in task 1 or the successful transformation of Logan into Wolverine in task 2). Planned comparisons (t-tests at $p \leq 0.05$) were conducted to examine effects of a priori interest.

In addition, a conditioned inhibition ratio that was calculated by dividing the average expectancy score for non-inhibited stimulus presentations by the average expectancy score for inhibited stimulus presentations. Thus conditioned inhibition is indicated by a ratio less than one and the absence of conditioned inhibition by a ratio greater than or equal to one. The interrelationship between the level of conditioned inhibition summarized by the ratio

and symptom severity scores (measured by the CPRS-R: L) was explored by Pearson's r correlation, 2-tailed. Where the data were available (for all ADHD participants and six matched controls), the same analyses were repeated to examine conditioned inhibition performance on each of the tasks in relation to ADHD participants' IQ. Similarly, the effect of medication was further examined by correlational analysis, using duration of medication, duration of medication adjusted by age (time on medication divided by the age of the participant) and medication dosage (mg/kg).

5.3: RESULTS

Analysis with respect to the diagnostic groups (ADHD and matched controls) confirmed that there was a significant main effect of inhibition ($F_{1, 21} = 24.782$, $p < 0.001$). However, there was no significant interaction between diagnostic group and inhibition ($F_{1, 21} = 0.763$) as both the matched controls ($t_{11} = 3.624$, $p < 0.005$, $d = 2.16$) and the ADHD group ($t_{11} = 3.374$, $p < 0.01$, $d = 1.94$) demonstrated significant levels of conditioned inhibition (Figure 5-2a). Although there was no three-way interaction between task, inhibition and diagnostic groups ($F_{1, 21} = 0.029$), there was a marginal task by inhibition interaction ($F_{1, 21} = 4.11$, $p = 0.055$) reflecting some differences in performance by task shown in Figure 5-2b. While both the ADHD ($t_{11} = 3.309$, $p < 0.01$, $d = 1.9$) and the matched control participants ($t_{10} = 3.694$, $p < 0.01$, $d = 2.06$) demonstrated significant level of conditioned inhibition on Weapon X task, only the matched controls demonstrated a significant level of inhibition on the Mission to Mars task ($t_{10} = 2.527$, $p < 0.05$, $d = 1.38$) whereas the ADHD participants failed to do so ($t_{11} = 2.053$, $d = 1.12$). No significant interaction between inhibition and

diagnostic groups was found with respect to either stimulus, and/or presentation (max $F_{1, 21} = 4.111$).

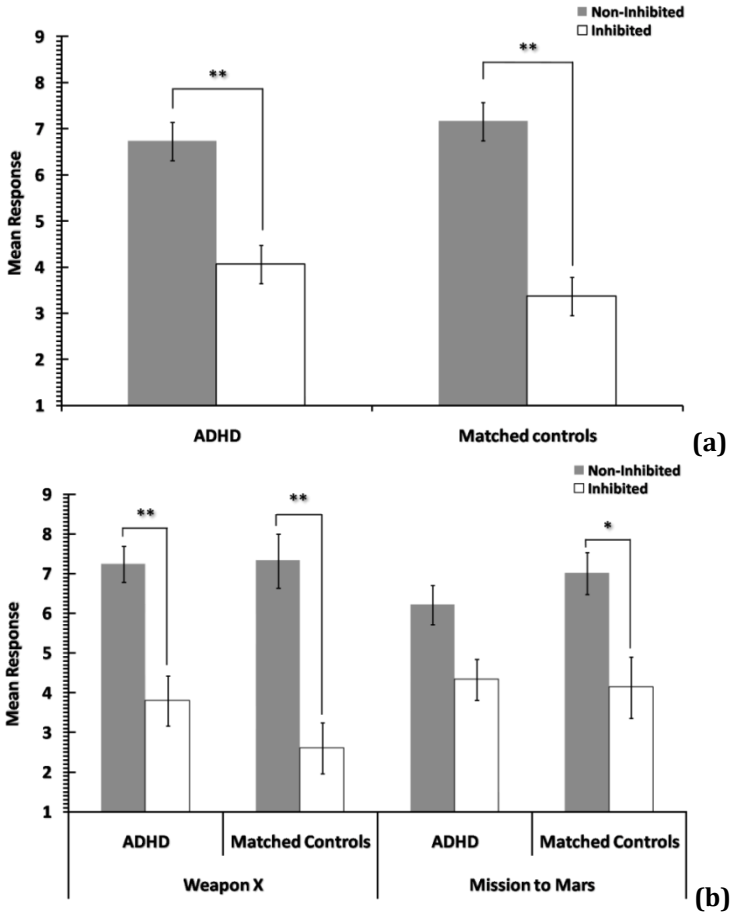

Figure 5-2: A main effect of inhibition was demonstrated overall (a). As shown, both the ADHD and matched control participants demonstrated significant level of inhibition. As shown in (b) although no significant effect of inhibition was observed for the ADHD group in the Mission to Mars task, no significant interaction between task and inhibition was noted with respect to the diagnostic groups. (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$)

The analysis of effects of medication was confined to the ADHD group alone. As would be expected, the effect of inhibition remained significant ($F_{1,11} = 11.384$, $p < 0.01$). Since there were no significant interactions between inhibition and stimulus or presentation (max $F_{1,21} = 1.388$), all further analyses were collapsed across the factors of stimulus and presentation. However, analyses were conducted separately by task as a result of the differences by task identified above. Participants who were below or equal to the median in

relation to medication dose (figure 5-3a), time on medication (figure 5-3b) or medication adjusted by age (figure 5-3c) did not show a clear conditioned inhibition effect on either of the two conditioned inhibition task variants (max t_5 = 1.955, d = 0.99). Significant conditioned inhibition in the Weapon X task was demonstrated by participants above the median for dose (t_5 = 5.167, $p < 0.01$, d = 4.5), time of medication (t_5 = 3.042, $p < 0.05$, d = 2.62), as well as time of medication adjusted by age (t_5 = 3.042, $p < 0.05$, d = 2.62). However, it was non-inhibited rather than inhibited ratings that differed between participants above median and those below or equal the median (t_{10} = 2.237, $p < 0.05$, d = 1.41). No other differences between the levels of inhibited and non-inhibited ratings reached significance (max t_{10} = 1.341, d = 0.85).

Although somewhat enhanced in participants with longer duration of treatment, the level of conditioned inhibition demonstrated was not significant in the Mission to Mars task variant for participants above the median (max t_5 = 1.671, d = 1.4).

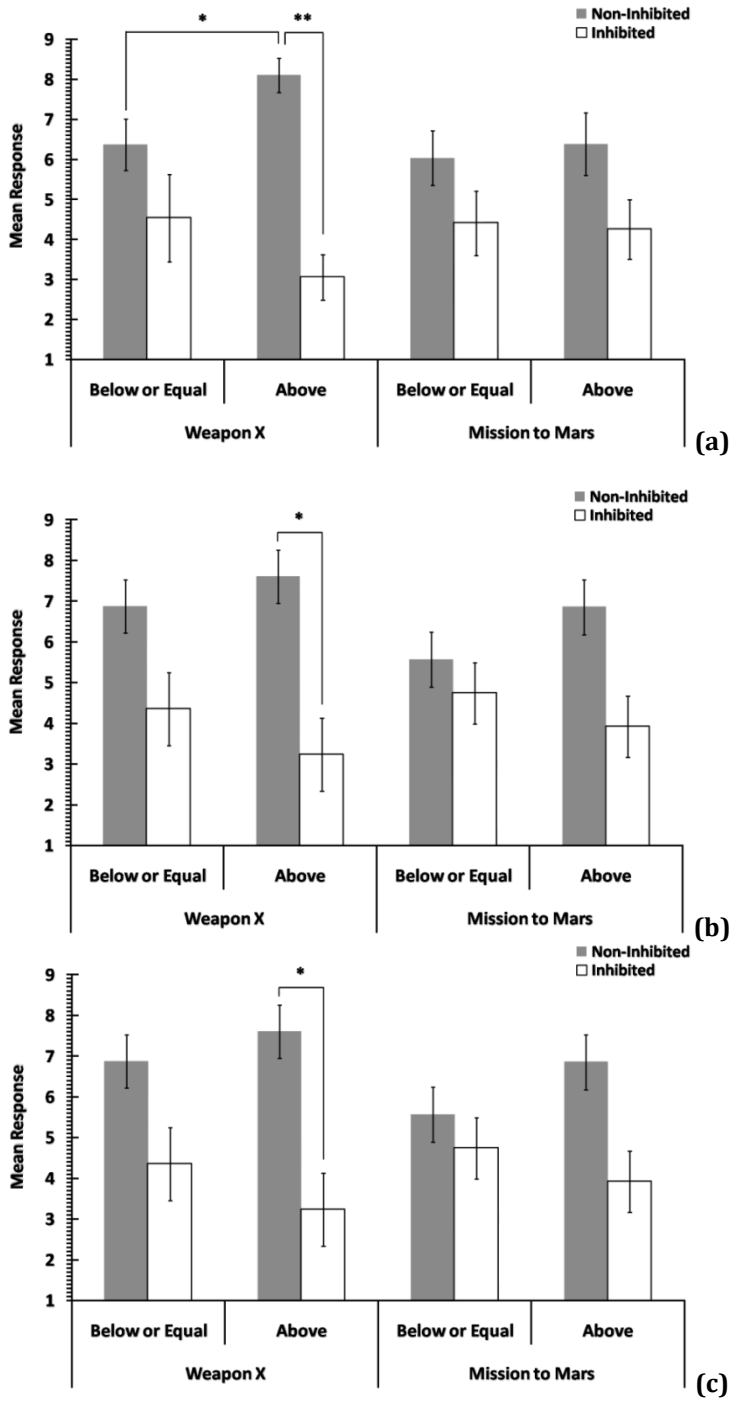

Figure 5-3: The effects of medication on conditioned inhibition with respect to (a) dosage [mg/kg], (b) time on medication and (c) Time on Medication adjusted by age. As observed in both (a) (b) and (c), no significant effect of inhibition was observed for the ADHD group below or equal the median in either task variant. The ADHD groups above the median for dosage (a) time on medication (b) and Time on Medication adjusted by age (c) demonstrated significant level of inhibition in the Weapon X task only. A significant difference between the above and the below or equal the median groups were found during the excitatory responses in the weapon X task in the medication dosage analysis (a) only. (* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$)

Within the ADHD group, there was no interaction between symptom level (median split on CPRS-R ratings) and inhibition or inhibition by task (max F = 0.666). Thus, participants with high and low symptom severities demonstrated equivalent levels of conditioned inhibition. Nevertheless, participants may have shown individual variation on the task in relation to symptom severity. To address the likely confound between medication status and ADHD symptom severity, ANCOVA was applied to the median split analyses for the ADHD group, using the ADHD index of the CPRS-R: L as covariate. A significant interaction between time on medication and inhibition was found ($F_{1, 9} = 5.748$, $p < 0.05$). Inspection of the adjusted means shows that when symptom severity was taken into account, overall conditioned inhibition was more pronounced in participants above the median time on medication (mean inhibited ratings = 3.37, s.e.m. = 0.526; mean non-inhibited ratings = 7.519, s.e.m. = 0.405) compared with the level of conditioned inhibition seen in participants below the median time on medication (mean inhibited ratings = 4.747, s.e.m. = 0.526, mean non-inhibited ratings = 5.922, s.e.m. = 0.405). No other interactions were significant (max F < 1). Moreover, there were no significant interactions between dose and inhibition (max $F_{1, 9} = 1.629$).

Due to the design of the two tasks, no data were collected during the training phase of the procedure. However, in order to analyze whether the participants had demonstrated learning of the conditioned inhibition at the end of the training phase, the data on the first presentation of the non-inhibited transfer stimulus during the test phase were analyzed. Univariate ANOVA of the first presentation ratings demonstrated no significant difference between the ADHD group and the matched controls overall for the Weapon X task (F =

0.271), the Mission to Mars task ($F_{1, 21} = 2.248$), or over both tasks combined (F = 0.266). Moreover, in order to observe whether learning under methylphenidate had affected the acquisition of the conditioned inhibition, the analysis was repeated with medication dosage (mg/kg) median split, and with time on medication (month) median split as the between subject variable. Univariate ANOVA of the first presentation ratings demonstrated no significant difference between the two medication dosage groups for the Weapon X task (F = 0.156), the Mission to Mars task (F = 0.015), or over both tasks combined (F = 0.084). Moreover, there were no significant difference between the two time on medication (months) groups for the Weapon X task ($F_{1, 10} = 1.607$), the Mission to Mars task (F = 0.015), or over both tasks combined (F = 0.236).

5.3.1: CORRELATIONAL ANALYSIS

Within the ADHD sample, there was no significant correlation between dose or the duration of medication and performance on either task as summarized by the conditioned inhibition ratios (max $r_{12} = -0.408$). Dose and duration were distinct medication parameters in that there was no correlation between the measures of participants' time on medication and medication dosage was found ($r_{12} = -0.168$). Similarly, there was no correlation between symptom severity measured by the CPRS-R: L (either overall or by its subscales; max $r_{12} = -0.511$). Neither was there any correlation with regard to IQ and the summary scores provided by the conditioned inhibition ratios for either task (max $r_{12} = -0.549$). Moreover, the overall correlation between conditioned inhibition and IQ across both the ADHD and matched controls was similarly insignificant for both task variants (max $r_{17} = -0.426$).

5.4: DISCUSSION

Conditioned inhibition was successfully demonstrated in the younger participants used in the present study. The summation test confirmed the presence of the conditioned inhibition (Rescorla, 1969) where inhibition was transferred to a CS that had not been previously presented with the CI during training (CS_t) as well as to a novel stimulus from the same category to which excitatory responding was generalized to (S_g). Thus, ADHD participants successfully suppressed S-S associations. Statistically, the participants did not demonstrate significantly different levels of inhibition to either of the two stimulus variants. However, while statistically the participants did not show different levels of conditioned inhibition with regards to the task variants, there was some indication from Figure 5-2b that the level of conditioned inhibition was not equivalent across the two tasks in use. As previously demonstrated (Holland, 1984; Holland & Lamarre, 1984), this may in part be due to the way in which the stimuli are presented in each paradigm as conditioned inhibition was clearly demonstrated by the Weapon X task (simultaneous stimulus presentation) and less so in the Mission to Mars task (serial stimulus presentation). As stated by Holland (Holland, 1984; Holland & Lamarre, 1984) it may be that the effectiveness of a stimulus to act as an inhibitor depends on the temporal arrangement of the stimuli. Holland had found that while a CI trained in a simultaneous presentation paradigm successfully inhibited suppression to a transfer stimulus during the summation test, no such transfer was noted in the serially presented paradigm. However, this may not be the case for this experiment in that while conditioned inhibition was notably less pronounced the serial presentation paradigm (Mission to Mars) compared to the

simultaneous presentation paradigm (Weapon X), statistically, both task variants passed the summation test.

Previously, in TS participants (as outlined in the previous chapter), medication with clonidine was found to impair the expression of conditioned inhibition, as measured by the identical procedures outlined in the current investigation. However in the current study, the entire sample of ADHD participants was medicated with methylphenidate (Concerta), and thus, medication was confounded with diagnosis. As stated above, the level of CI was not equivalent across the two tasks in use. Specifically, the ADHD group did not show significant conditioned inhibition on the Mission to Mars task. Accordingly, within the ADHD sample the effects of medication were examined separately by task. Correlational analyses did not suggest any linear relationship between the level of CI and medication dose or duration in either task variant.

However, median split analyses to divide the ADHD group in to low vs. high dose and short vs. long duration of treatment showed that (according to either of these medication parameters) treatment with methylphenidate tended to improve expression of the conditioned inhibition. This was particularly true for the Weapon X task. As observed on the dose (but not on the treatment time), higher doses of methylphenidate resulted in significant improvement in excitatory learning, but not inhibitory learning. This difference by CI variant is not straightforwardly related to task difficulty in that the Weapon X task supported an overall stronger CI effect (presumably in consequence of its explicit learning instructions and simultaneous rather than serial presentation of the conditioned inhibitor in relation to CS_t and S_g). Although it is unlikely that dose and duration measures are to be

independent either of each other, or of symptom severity, the results however showed no significant correlation between the dosage and time on medication.

Figure 5-3 (a) seems to suggest that while a higher dose of methylphenidate appears to significantly enhance excitatory learning, it also appears that the higher dosage methylphenidate may also enhance inhibitory responding as well. However, while inhibitory responding does appear to be greater in the above the median group with respect to methylphenidate treatment dosage in the Weapon X task compared to the less than or equal the median group, this difference was not statistically significant. Furthermore, no such enhanced learning (in either excitatory or inhibitory responding) was observed in the Mission to Mars task as the results were just not significant. Moreover, the difference in performance seen in the Weapon X task was demonstrated as improved summation test discrimination. The level of performance demonstrated in the summation test is a reflection of the expression of earlier learning (which was not measured directly in either of the two tasks as a result of the implicit nature of the Mission to Mars task, and the attempt to keep both the structures of both Weapon X and Mission to Mars tasks as similar as possible). However, as mentioned in the results above, no significant effect of medication status (with respect to neither dosage nor duration) was observed with respect to performance in the first presentation of the CS_t (which provided the best measure of excitatory learning). Thus, the present result only allow the conclusion that methylphenidate improved the expression of prior learning.

There has been evidence that methylphenidate has an effect on performance on tests of inhibition. In a study of the sensitivity of the colour-word Stroop to methylphenidate

treatment by observing the performance on the Stroop task by ADHD and matched controls both on and off methylphenidate, Lansbergen, Kenemans, & van Engeland, (2007) found that performance in both groups (ADHD and controls) improved when on methylphenidate compared to when tested off-medication. Also, a study was conducted by Scheres et al. (2003) investigating the effects of methylphenidate on three forms of response inhibition; the inhibition of an on-going response (measured by the Circle Tracing task and the 'Follow task' which involved participants following a target stimulus onscreen using a mouse until when presented with a stop signal), interference control (Measured by the Word-Colour Stroop and the Flanker tasks), and inhibition of a prepotent response (Measured by the Stop paradigm). Scheres et al. reported that while methylphenidate had no significant effect on the interference control tasks, it significantly improved performance on tasks measuring the inhibition of an on-going response (the Follow task only) and those measuring the inhibition of a prepotent response. Thus, these studies demonstrate that methylphenidate seems to improve certain inhibitory functions in ADHD participants. However, it must also be noted that none of these studies involved tests of the inhibition of S-S associations and as such the effect of methylphenidate on inhibitory S-S associations in unknown.

The absence of significant correlation between the Conners scores (and its subscales) and the level of inhibition demonstrated in either task variant seems to indicate that conditioned inhibition was not affected by symptom severity. This lack of correlation between symptom severity and CI may be due to a ceiling effect resulting from the relatively restricted range of scores in the patient sample who all met conservative diagnostic criteria for ADHD, and/or the limited available sample size. However, there was some indication in the data that the effect of medication was more than would be expected

on the basis of symptom severity: when symptom severity was taken into account statistically (by analysis of covariance), there was an interaction between time on (but not dose of) medication and inhibition, in this case overall rather than separately by task. This result shows that, when symptom severity was taken into account, the summation test discrimination was overall reduced in participants treated with methylphenidate over a shorter time frame.

While a number of the ADHD participants scored a lower than average IQ, there was no correlation between IQ and the level of inhibition demonstrated, either within the ADHD sample, or including the matched controls where the data were available. Conventional tests of inhibition used with ADHD participants (the Stop signal, the Go/NoGo and a modified version of the Stroop task), similarly showed a deficit in relation to ADHD but no association with IQ (Bitsakou, et al., 2008). In the present study, it was not possible to match controls also on the basis of IQ as IQ scores were not available for all participants. However, there are arguments against matching on the basis of IQ in that a disorders such as ADHD may be a likely cause of depressed IQ scores in young participants: the matching fallacy whereby participants may be 'overmatched' on variables which are not independent of the disorder in question (Seidman, et al., 1997).

The current investigation demonstrated that conditioned inhibition appears to be overall unaffected by the symptoms of ADHD. While there seems to be a possible performance difference on serially presented task compared to the task employing simultaneous stimuli presentation, once cannot discount the possibility that this may be an artefact resulting from the limited number of participants used in this investigation and may disappear (or

possibly become statistically significant) if a larger population sample is employed. Moreover, medication may also play a role in some capacity in the level of conditioned inhibition demonstrated by the ADHD population. Thus, to conclusively analyze the effect of methylphenidate on the expression of conditioned inhibition demonstrated, the current study needs to be further investigated using a drug-free population sample.

CHAPTER 6: GENERAL DISCUSSION

The aim of this thesis was to investigate the deficient inhibitory control theory of ADHD and TS; specifically, the examination of deficits resulting from the disorders in question on the inhibition of S-S associations as measured by a translational test of inhibition using Pavlovian procedures.

Investigators have used the Go/NoGo (Tamm, et al., 2004; Trommer, et al., 1988), the Stroop (Channon, et al., 2003; Marsh, et al., 2007) and a number of other S-R associative tasks to investigate inhibitory deficits resulting from ADHD and TS. However, to date no investigation has looked at the possible inhibitory deficits in S-S associations as a result of TS or ADHD. With regards to TS, the onset and variations in tics have to some extent, been attributed to S-S associations (Conelea & Woods, 2008; James F. Leckman, 2003). For example, observations have shown that contextual and environmental events, such as the presence of a patient's father (Conelea & Woods, 2008) or the sound of a cough (James F. Leckman, 2003) have initiated and/or increased the frequency of tics in the observed TS patient. Moreover, premonitory urges such as a tickly throat, or burning sensation around the eyes can become associated with certain events or contexts, especially if they induce feelings of stress and anxiety, which can trigger tics in individuals with TS (J. F. Leckman, et al., 1993). Thus, the observed symptomology of TS may in part result from deficits in the inhibition of such S-S associations.

Based on the high comorbidity of TS and ADHD (Comings & Comings, 1987; Erenberg, 2005; Robertson, 2006) and the fact that ADHD may contribute to or possibly be responsible for inhibitory deficits observed in TS (Brand, et al., 2002; Channon, et al., 2003; Como, 2001; Gilbert, et al., 2004; Ozonoff, et al., 1998), it was hypothesized that a deficit in

the inhibition of S-S associations would be observed in the clinical ADHD population as well.

6.1: INDIVIDUAL DIFFERENCE BEHAVIOURAL MEASURES

Chapter 2 and chapter 3 of the current thesis were concerned with the investigation of the effects of individual different behaviours on the expression of the inhibition of S-S (chapter 2 and 3) and S-R (chapter 3) association in the normal population. Within the normal population, the expression of the inhibition of S-S (as measured by conditioned inhibition) and S-R (as measured by the Go/NoGo, the colour-word Stroop, and the Simon task) were observed with respect to individual differences in ADHD-like behaviours, TS-like behaviours, impulsive (as measured by the BAS), and anxious (measured by the BIS) behaviours.

Prior to the discussion of the individual different measures, it must be noted that conditioned inhibition was successfully demonstrated in the normal populations equally by both the Weapon X as well as the Mission to Mars conditioned inhibition task variants. Moreover, the normal population also demonstrated successful inhibition of S-R associations as measured by the Go/NoGo, the colour-word Stroop as well as the Simon task. In addition, the normal population sample tested (in experiments 2A and 2B) did not demonstrate deficits in attention (as measured by the number of omission errors produced in the Go/NoGo task).

A significant correlation between the expression of conditioned inhibition (i.e. conditioned inhibition ratio) for the Weapon X task and the ADHD individual difference behavioural

measure was observed, where the expression of conditioned inhibition in the Weapon X task diminished with increasing ADHD-like behaviours in the normal population. Interestingly, as noted above, the analysis of the ADHD clinical group (chapter 5) revealed that conditioned inhibition was demonstrated by the ADHD clinical group only in the Weapon X task. It must be noted however that the correlation with the ADHD individual difference and the expression of conditioned inhibition was only observed in the Weapon X task and not the Mission to Mars task. As no significant difference between tasks were observed in experiment 1C, one would suspect that if ADHD like behaviours produced an adverse effect on the expression of conditioned inhibition, it should also be observed in the Mission to Mars task as well. However, this was not so. Moreover, the analysis of the Weapon X task with respect to the individual difference measures only occurred in experiment 1C, whereas the Mission to Mars task was used in all the studies reported in chapters 2 and 3. Thus, the population sample where this correlation was observed (n = 33) was quite smaller than that of the Mission to Mars task (n = 137, following a combined analysis of the entire Mission to Mars task presentations) where no correlation was between ADHD-like behaviours and the expression on conditioned inhibition was observed.

With the exception of the Weapon X task and ADHD individual difference behaviours in experiment 1C, the results showed that in the normal population, TS and ADHD-like individual difference behaviours have no effect on either S-S, or S-R inhibition. Moreover, median split analysis of the TS and ADHD individual difference behavioural measures also failed to reveal any significant interaction between the behavioural measures and the performance on the S-S as well as S-R inhibition tasks. Previous investigations showed that

in the clinical population, while deficits in S-R were much less observed in the TS population (Channon, et al., 2009; Channon, et al., 2003; Marsh, et al., 2007; Ozonoff, et al., 1994; Roessner, et al., 2008; Serrien, et al., 2005; Stebbins, et al., 1995), a deficit is often observed in the ADHD population (Bitsakou, et al., 2008; Iaboni, et al., 1995; Lansbergen, et al., 2007; Seidman, et al., 1997; Trommer, et al., 1988; Young, et al., 2006). However, since none of the of the participants reported being diagnosed with TS or ADHD (even after the purpose of the investigation and how it relates to TS and ADHD clinical populations were revealed at the end of each experiment) it maybe that the reason no correlations were observed was due to the possibility that the ADHD and TS-like behaviours measured in the normal populations were – as might be expected - within the normal range.

Looking at the measure of impulsivity and anxiety like behaviours, previously Migo et al (2006) reported a negative correlation between the expression of conditioned inhibition and a sub-score (BAS Reward Responsiveness) of the BAS individual difference measure. However, while the opposite result (a positive correlation between BAS Reward Responsiveness and the expression of conditioned inhibition in the Weapon X task) was observed in the Weapon X-Mission to Mars analysis (Experiment 1C in chapter 2), there were no other correlations between either the BIS, or the BAS (as well as the BAS sub-scores) in the large combined sample analysis of the Incredible Hulk-Mission to Mars (chapter 2) or the large sample analysis of the Mission to Mars task (chapter 3). Thus, these results indicate that impulsivity (as measured by the BAS) and anxiety (as measured by the BIS) have little or no influence on the inhibition of S-S associations. Moreover, since the observations were made within a normal population, there may not have been a great

degree of variation in the impulsive/anxious behaviours demonstrated by the population sampled.

With regards to the inhibition of S-R tasks, a significant positive correlation between the response times measured in the Go/NoGo task and the BAS as well as the BAS Drive individual difference measures were found. This result was quite unexpected, in that it implies that the more impulsive individuals (who scored higher on the BAS scale) responded slower when presented with presumably activating stimuli, such as the Go signal in the Go/NoGo task. However, since responding to the Go signal serves a measure of sustained attention (Berwid, et al., 2005), these results may show that higher degree of impulsivity resulted in greater lapses in sustained attention. This result is not surprising as higher impulsivity has been shown to be associated with lower levels of attention (Sheppard, et al., 1999; Trommer, et al., 1988). However, being that the participants were in the normal (i.e. non-clinical) population, the loss of attention measured was insufficient to result in significantly greater number of errors in the Go signal compared to those individuals rating lower on the BAS scale.

6.1.1: CORRELATIONS BETWEEN THE INDIVIDUAL DIFFERENCE BEHAVIOURAL MEASURES

Looking at the individual difference measures themselves, a significant correlation between the TS and the ADHD measure was observed a number of times, including in the combined Mission to Mars analysis (section 3.5, chapter 3). This is not surprising as ADHD and TS are often comorbid in the clinical population (Comings & Comings, 1987; Sheppard, et al., 1999; Spencer, et al., 1998). While this observation provides a degree of validation to

the in-house developed TS individual difference behavioural measure, one cannot claim validation for the TS measure until it has been tested on clinical TS population.

It had been previously reported that excessive yawning might be a possible tic observed in TS (Dalsgaard, et al., 2001; Sandyk, 1996; Walusinski, 2009). For example, while investigating the theory that TS results from increased dopamine activity caused by postsynaptic dopamine receptor sensitivity, Sandyk (1996) found that administration of small doses of apomorphine (a dopamine D2 autoreceptor agonist) produced yawning in both animals as well as humans. Moreover, Sandyk also observed that the exposure to brief extracranial applications of picotesla flux electromagnetic fields produced yawning followed by increased motor tic activity in two TS patients. In the current thesis investigation, this hypothesis was tested in the normal population using a yawning questionnaire (table 2-4) developed by Greco and Baenninger (1993). Throughout chapters 2 and 3, Correlational analysis of the individual difference behavioural measures in the combined analysis of the Mission to Mars task showed that the measure of yawning was positively correlated with both TS and ADHD-like individual difference behavioural measures. While this finding does not provide unequivocal proof for yawing as a marker of TS (as the yawing questionnaire was not tested in a TS clinical population), it does however provide some evidence for possible association of excessive yawning and TS and warrants further study among clinical population.

6.2: THE EXPRESSION OF CONDITIONED INHIBITION IN CLINICAL POPULATIONS

As demonstrated in chapters 4 and 5, the result of the investigation in the TS and ADHD clinical populations showed no significant deficit in the inhibition of S-S associations in either the clinical TS or ADHD populations compared to the matched controls. Conditioned inhibition was clearly demonstrated by the TS and matched control populations in both conditioned inhibition task variants, as the summation test (Rescorla, 1969) was successfully passed in both task variants and by all populations. However, as reported in chapter 5, conditioned inhibition was not equally demonstrated across both task variants as ADHD participants failed to demonstrate conditioned inhibition in the Mission to Mars task. Nonetheless, conditioned inhibition was significantly demonstrated both overall as well as in the Weapon X task by the clinical ADHD population. Thus, the results do indicate that overall, the suppression of S-S associations appears to be unaffected by the presence of TS and/or ADHD disorders. As reviewed above, individual difference analysis in the normal population revealed similar observations, as no relationship was observed between the expression of conditioned inhibition and TS and ADHD-like individual difference behaviours in the normal population. This was further reaffirmed upon the factor analysis of the TS individual difference behavioural measure, whereby no relationship between TS like behaviours and the expression of conditioned inhibition was observed when the OCD factor was removed from the analysis or when the possibility of the CI acting as a occasion setter (by analysing the level of conditioned inhibition demonstrated during the first presentation of the [CI,CS_t]). Thus, at least with regards to the inhibition of S-S associations, the expression of inhibition in TS and ADHD populations seem to be unaffected by the presence of the disorders in question.

As mentioned, with the exception of the ADHD participants, conditioned inhibition was similarly expressed in both task variants. Previously, Holland (Holland, 1984; Holland & Lamarre, 1984) observed that conditioning to the feature negative stimulus can only be obtained through simultaneous presentation of the stimuli in a conditioned inhibition paradigm. In their series of experiments, Holland reported the feature negative stimulus failed to pass summation test following serial presentation training. Similar results were also reported by Baeyens et al (2004), who reported that the transfer of an inhibition by a conditioned inhibitor to a transfer stimulus was perfect in a simultaneous presentation paradigm, irrespective of the learning history of the transfer stimulus (B+/YB- vs. B+ only group). Yet, in a sequential presentation paradigm, the authors found that the transfer of inhibition by the conditioned inhibitor (X) to the transfer stimulus was successful only if the transfer stimulus had been involved in another sequential feature negative training (B+/YB-) but not if the transfer stimulus had been consistently reinforced (B+). However, in the experiments reported in this thesis, the summation test was passed by both the transfer stimulus (that was trained in the B+ manner described above by Baeyens et al.) as well as novel generalized stimulus that had not been presented during training. Thus, conditioned inhibition was expressed equally in both simultaneously presented Weapon X task as well as the serially presented Mission to Mars task.

The two task variants varied not only in their simultaneous/serial stimulus presentations but also with respect to the implicit or explicitness of the instructions provided. Previously, Arcediano et al. (1996), in their non-aversive 'conditioned suppression' computer based human learning paradigm reported a significant difference in the responses produced

between a group of participants trained with implicit task instructions and those who received explicit task instructions (with greater learning demonstrated by the explicit instructions group). However, the absence of a task difference in the majority of experiments reported in this thesis implies that the implicitness (Mission to Mars) or explicitness (Weapon X as well as the Incredible Hulk task variant in experiments 1A and 1B) of the task instructions did not produce a change in the learning demonstrated; in particular there was no evidence for any difference in the expression of conditioned inhibition in relation to task.

6.3: DOPAMINE AND THE BASAL GANGLIA

According to the dopamine prediction-error theory of learning, the learning of an association between a stimulus and event is as a result of dopamine neuron activity (Schultz, 2007; Schultz, et al., 1997; Schultz & Dickinson, 2000; Waelti, et al., 2001). According to Schultz and Dickinson (2000), dopamine neurons show homogeneous short latency response to attention-inducing stimuli, which results in an activation-depression sequence, and to reward-related stimuli (as well as auditory/visual stimuli that predict such rewards) that result in pure activations. Dopamine neurons code errors in the prediction of reward in that primary rewards that are unpredictable during the initial behavioural reaction elicit neuronal activations, which decrease with continuing experience where reward becomes preceded by the conditioned stimuli. Over time, the conditioned reward-predicting stimulus induces pure activations similar to the reward itself. However, if the predicted reward fails to occur resulting in an error in responding, a depression in the dopamine neuron is observed at the time when the reward would have

been presented (which in turn shows that dopamine neurons not only code for the expected reward but also for the specific time of the reward as well). As such, dopamine neurons are responsible for the acquisition and expression of conditioned inhibition.

Evidence for the dopamine prediction error model has been provided by Tobler, Dickinson, & Schultz (2003) who, following an electrophysiological investigation reported that while the conditioned excitor lead to the activation of all the analysed dopamine neurons (242% above baseline), the conditioned inhibitor produced a depression of approximately 70% of the neurons tested (median level of 35% below baseline), while producing minor activation in the remaining 30% (median level of 69% above baseline), indicating that dopamine neurons distinguish between a conditioned excitor and a conditioned inhibitor.

Looking at TS and ADHD, various lines of evidence have reported the involvement of the dopamine system in the pathologies of TS and ADHD (Banaschewski, et al., 2007; Barkley, 1998). Neuroanatomically (as reviewed in chapter 1), abnormalities in the basal ganglia have been observed by a number of investigations in both ADHD (Casey, et al., 1997; Castellanos, et al., 1996; Giedd, et al., 2001) as well as TS patients (Cheon, et al., 2004; Hyde, et al., 1995; Minzer, et al., 2004; Yazgan, Peterson, Wexler, & Leckman, 1995). Further evidence is provided by pharmaceutical treatments of the disorders in question, in that the use of dopamine agonists has been widely employed in the treatment of TS and ADHD. Antidopaminergic agents such as haloperidol and pimozide have been widely used in the treatment of TS (Gilbert, 2006). Moreover, stimulants such as methylphenidate (a dopamine agonist) have been widely used treatment of ADHD (Krause, et al., 2000; Kurlan, et al., 2002; Lopez, et al., 2003; Pelham, et al., 2001; Solanto, 2002).

Thus, based the high level of comorbidity between TS and ADHD, it was expected that compared to the normal population a deficit in conditioned inhibition be observed in the TS and ADHD populations. However, no such deficit (at least overall and with respect to the Weapon X task in the ADHD participants) was observed. A possible explanation for such a finding may be due to medication. Due to the limitations placed up the current investigation by the NHS research ethics, the medication status of the participants were not altered in any way for the investigation. As such, as reported in chapter 4 (TS) as well as Chapter 5 (ADHD) of the current thesis, a number of TS participants and all of the ADHD participants were on medication at the time of testing. I had no knowledge of medication status until the time of (or soon after) the experiment and medication status of the participants could be changed at any time prior to the experiment. Thus, the analysis of medication on conditioned inhibition was unplanned. The effect of medication on the expression of conditioned inhibition is discussed below.

6.4: MEDICATION EFFECT

While the results of the current investigation revealed no deficits in the inhibition of S-S association in the TS and ADHD clinical populations, unplanned comparisons revealed interesting drug effects on the measure of conditioned inhibition in both TS and ADHD populations. The comparisons with medication were unplanned, as the medication status of the participants was not altered due to constraints placed by the experimental ethics clearance.

6.4.1: THE EFFECTS OF MEDICATION IN THE TS POPULATION

Within the TS population, it was found that the majority of the participants were medicated with clonidine, which has anxiolytic properties. Thus, the medication status of the TS population was categorized as either on or off anxiolytic medication. Due to aripiprazole being an atypical antipsychotic with a different profile of action that does not include a reduction in noradrenergic activity (unlike clonidine which is a α2 noradrenergic agonist), the participants treated with aripiprazole (of which only one was currently medicated at the time of behavioural testing) were categorized as 'off-anxiolytics'. Moreover, the clonazepam participant was included in the 'on-anxiolytic' group due of the anxiolytic properties of clonazepam as a benzodiazepine, which similar to clonidine reduces noradrenergic activity despite benzodiazepines having indirect effects on the noradrenergic system (Jeffrey Alan Gray, 1982).

Unplanned comparisons revealed a notable difference in the level of conditioned inhibition demonstrated between the medicated (at the time of testing) and unmedicated TS participants. The results showed that inhibitory responding was significantly reduced in the medicated 'on-anxiolytic' group compared to the unmedicated group, while no significant difference in excitatory responding was found between the two groups. Any confounds resulting from symptom severity (as measured by the YGTSS) were dismissed as no relation between symptom severity and conditioned inhibition was found. In addition, the results remained unchanged when the analysis was repeated with symptom severity as a covariate. The inclusion of the clonazepam participant among the "on-medication"

clonidine group was not responsible for the results obtained as similar results were observed when the analysis was repeated with the exclusion of the clonazepam participant.

A previous investigation had found that clonidine produces significant impairment in tasks requiring attention, most notably on tasks measuring attention in presence of distractors, such as the flanker task (Tiplady, et al., 2005). However, the finding that anxiolytic medication (i.e. clonidine) produced no effect on excitatory responding (reducing only inhibitory responding), suggests that clonidine did not have a general effect on attention, arousal or a general impairment on learning.

Yet, why does clonidine only act on inhibitory learning and not to excitatory learning as well? According to Gray (1982), anti-anxiety drugs impair the processing of signals of non-reward (similar to the CI in the current conditioned inhibition tasks, which signalled the absence of an expected event, i.e. the UCS), which are under the control of the BIS system. Gray (1982, 1988) further stated that anxiolytics act by reversing the stressed induced activity in the ascending noradrenergic and serotonergic fibres, in that selective neurotoxic lesions of the ascending noradrenergic bundle (which arises in the locus coeruleus and supplies the noradrenergic inputs into the hippocampus) produces the same effect on the septal driving of theta as the those of anxiolytic drugs (McNaughton & Gray, 2000). Thus, according to Gray's model, the anxiolytic action of clonidine (a functionally noradrenergic antagonist) on the BIS system may have impaired the procession of the CI stimulus that act as signals of a non-event, as observed in the TS study. However, it must be said that Gray's inception of the BIS was to examine anxiety and not conditioned inhibition. As such, the explanation provided above would only account for rewarding outcomes. In that vein, it

could be argued that premonitory urges can be viewed as aversive in that they create a sense of frustration for the TS patient (James F. Leckman, 2003; James F. Leckman & Peterson, 1993), and that the removal of the urge by a tic can provide a "rewarding" sense of relief for the individual. Thus, the premonitory urge-tic relationship may be observed from an operant conditioning perspective.

However, would this observed reduction in S-S inhibition by clonidine translate into the exacerbation the TS symptoms as opposed to reduction of them? Clonidine is prescribed to reduce tics in TS patients, and the effectiveness of clonidine in the reduction of tic in TS patients have been observed in a number of studies (Borison, Ang, Hamilton, Diamond, & Davis, 1983; Fulton, Shady, & Champion, 1988; Jimenez-Jimenez & Garcia-Ruiz, 2001; Kurlan, et al., 2002; Truong, Bressman, Shale, & Fahn, 1988). It may be that, clonidine moderates the expression of the TS symptoms at some other stage beyond the initial S-S association. Thus, Clonidine may act on the S-R associations between discriminative stimuli that give rise to tic responses that follow the onset of the premonitory sensation (as a result of an S-S association). However to date, no experimental research has been conducted to study the effects of clonidine on S-R associations in TS patients. Thus, whether clonidine acts on S-R associations to modulate the level of tics experienced by TS patients is currently unknown.

Thus, stemming from the current results it can be inferred that anxiolytic medication in TS has a selective effect on an aspect of associative learning that could potentially be relevant to both the symptom profile and the ability to control tics that have identified triggers.

6.4.1: THE EFFECTS OF MEDICATION IN THE ADHD POPULATION

With regards to the ADHD investigation, unlike the TS participants, all of the ADHD participants were under medication (methylphenidate) at the time of testing. As such, there were no off-medication ADHD participant comparison group (like those in the TS investigation) to investigate the effects of medication against. Thus, in order to investigate the effects of methylphenidate on the expression of conditioned inhibition, the ADHD participants were divided into high and low medication groups based on the time on medication as well as the medication dosage using the median scores to split the sample into two categorical groups.

The results showed than an improved performance was demonstrated by the participants on the higher dosage of (or longer treatment time with) methylphenidate on the Weapon X task (consistent with the overall performance of the ADHD participants). Moreover, it was observed that a higher dosage of (but not a longer duration of treatment with) methylphenidate resulted in significant improvement in the excitatory (but not the inhibitory) learning demonstrated on the Weapon X task. While no correlations between symptom severity (as measured by the CPRS-R: L) and the expression of conditioned inhibition was found, when symptom severity was taken into account (as a covariate) a interaction between time on medication and inhibition was observed, both overall as well as separated by task. There was no such interaction when the sample was split by medication dosage. The results showed that when symptom severity was taken into account, summation test discrimination was overall reduced in participants treated with

methylphenidate over a short time frame. Possible confounds based on IQ were dismissed as no correlation between IQ and the expression of conditioned inhibition was found.

Thus, these results show that (at least with regards to the Weapon X task) learning in the conditioned inhibition task was improved by methylphenidate, though inhibition as such was not significantly improved. This result is in line with those of Harmer and Philips (1999) who reported enhanced conditioned inhibition in rats following repeated pre-treatments with d-amphetamine (a dopamine agonist with similar mechanism of action as methylphenidate). However, unlike the d-amphetamine treatment by Harmer and Phillips which resulted in improved inhibitory and excitatory responding in the rats, the treatment with methylphenidate in the present investigation produced significant improvement in excitatory responding only.

It has been previously observed that methylphenidate and d-amphetamine bind to dopamine transporters blocking reuptake (Solanto, 2002). However, unlike methylphenidate, d-amphetamine also facilitates the release of dopamine. Perhaps the different mechanism of action of d-amphetamine results in a more generalized improvement in learning. While both dopamine and noradrenaline are catecholamines, noradrenaline may have a different effect on learning than dopamine in that increased noradrenaline may result in enhanced inhibitory responding. Methylphenidate, which shows greater selectivity for the dopaminergic system than d-amphetamine, resulted in enhanced excitatory learning. While d-Amphetamine, which acts to increase both noradrenaline and dopamine in the brain (Carr & Moore, 1969) enhanced both excitatory and inhibitory learning, as observe by Harmer and Phillips (1999).

6.5: HOW WERE THE TASKS SOLVED?

Previous work in this laboratory established that an earlier variant of the Mission to Mars task produced equivalent results irrespective of whether the absence of the rocket UCS outcome was specified by the presentation of a blank screen or an exploded rocket (Migo, et al., 2006). This study used normal adult participants, mostly students. In the present task variants, simplified for use with younger participants, including those with diagnosed ADHD and TS, the absence of the target UCSs was represented by the presentation of the alternative outcomes of the exploded rocket (in the Mission to Mars variant) or feral Logan (in the Weapon X variant). Moreover, since the number of trials also needed to be reduced, unpredicted presentations of the exploded rocket and feral Logan, so-called 'minus' trials intended to reduce the likelihood of direct associative solutions (Migo, et al., 2006) were not used in the experiments reported in the this thesis. This raises the possibility that direct associations between the inhibitors (the grey frame or the yellow syringe) could have contributed to participants' ability to guess the outcome because of a direct association between the inhibitors and alternative outcomes (the exploded rocket or feral Logan, respectively). Indeed this logical objection applies to all such tasks, irrespective of how the absence of the outcome to be predicted (in the present study the rocket or Wolverine) is specified.

In the animal literature, non-events can support learning. This was clearly demonstrated in a study by Mackintosh, Bygrave & Pickton (Mackintosh, Bygrave, & Picton, 1977) in an unblocking experiment based on surprising shock omission. Blocking is reliably

demonstrated when after training with a particular CS for particular UCS, a second CS that predicts nothing new is 'blocked' from gaining any associative strength. However, if the UCS is altered the second CS is said to be 'unblocked' and new learning can occur. Where the UCS was two shocks, one after the other, the omission of the second shock was sufficient to produce unblocking in rats. Moreover, the new learning was excitatory rather than inhibitory as would be predicted on Rescorla-Wagner theory (Dickinson, 1980; Mackintosh, et al., 1977).

In human studies, what the participants report can be used in evidence as to the likely basis of task solution. This issue was investigated during task development with undergraduate and postgraduate participants who were naïve to the topic under study (Migo, et al., 2006). For example, at the conclusion of the experiment when the nature of the tasks was described, the majority of the participants (regardless of whether they were in the clinical groups or among the non-clinical normal population) expressed surprise when the identity of the CI was revealed. Taken together with the result that conditioned inhibition was significantly demonstrated throughout by any population throughout this thesis, this reaction by the participants could be interpreted as the absence of (conscious) knowledge about the true nature of the CI, even though the association between the CI and the absence of the UCS was demonstrated.

Whilst generally informative, such self-report data is difficult to analyse formally and inevitably confounded by participants' age, verbal abilities and their general levels of experience as participants in experimental studies. Younger participants in the experiments reported in this thesis did report some comments but, as might be expected,

these were generally unsophisticated, such as 'no idea what was going on', 'it was the yellow syringe' or 'oh, I thought that was a glitch in the program' (when informed about the grey border as the CI in the Mission to Mars task).

However, these comments were not suitable for any formal analysis and - without prompting that might have led the participants – do not necessarily tell us anything about the underlying associative structure. For example, the comment 'it was the yellow syringe' could reflect direct awareness of the contingency between the notional inhibitor used in the Weapon X task and the alternative outcome of feral Logan, or it could reflect the intended implicit or explicit learning of the inhibitory function of this stimulus. Similarly, O'Boyle and Bouton (1996) investigated conditioned inhibition in human subjects in a multiple category learning paradigm, using a game called "Clues and Culprits" where subjects were asked to judge the predictive strength of the clues paired with culprits in a series of hypothetical burglaries, where one clue was paired with one culprit when presented on its own, yet, when presented with a second clue, it was paired with a second culprit (A→culprit 1, AX→culprit 2). According to the authors, X should acquire inhibitory status for the first culprit (A+, AX-) in this feature negative procedure, as it should acquire greater inhibitory strength than a differential cue merely associated with a second culprit (A→culprit 1, X→culprit 2). However, O'Boyle and Bouton reported that inhibition occurred in both the feature negative as well as the differential procedures and that the level of inhibition did not differ between procedures. Thus, the association of the conditioned inhibitor (i.e. negative feature) and the differential cue with culprit 2 was

sufficient to inhibit culprit 1. Moreover, similar to the current investigation, O'Boyle and Bouton used the summation test only as a test for the negative feature association.

In any event, the use of direct associations was minimised in the Mission to Mars task by (1) the implicit task instructions (participants were directed to count rockets during the training phase) and (2) the serial nature of the design and the presentation of intervening distractor stimuli. This argument does not apply to the Weapon X task, which used explicit learning instructions and simultaneous presentation of CSs, distractors and the inhibitor. However, with the exception of the effect of methylphenidate reported in Chapter 5, and it should be noted that the accentuation of the conditioned inhibition effect was mediated by increased ratings on non-inhibited test trials, there were no differences by task in the experiments reported in this thesis.

Moreover, medication did not seem to have an effect on learning in the acquisition stage. The effect of clonidine in TS participants reported in Chapter 4 only reached significance on the non-inhibited test trials. If the same underlying learning mechanism (simple excitatory learning) was responsible for this drug effect on the putative inhibitory learning in these participants, then the drug effect should have been the same in both conditions. Not only was the drug effect on the non-inhibited test trials insignificant, in both the TS and ADHD studies there were no effect of diagnostic group or medication status on first test trial responding to the transfer stimulus. These analyses were included as learning was not directly assessed in the training phases of the tasks due to the implicit nature of the Mission to Mars task and the need to keep the tasks formally equivalent as far as possible.

That being said, further improvement to the tasks used here should be considered for future studies. For example, provided the task is not made too lengthy or difficult for the target group of interest, the retardation test should ideally be used to supplement the summation test (Rescorla, 1969).

6.6: FUTURE DIRECTIONS

Due to a number of constraints placed on the current project (such as NHS research ethics approval and the limited time allowed for the completion of the PhD), several potential avenues of research had to be eliminated from the current doctoral research. Thus, the inclusion of the lines of investigation listed here in future studies would better clarify many of the questions left unanswered in this doctoral thesis investigation.

As outlined, due to NHS ethics limitations placed upon the studies of the clinical ADHD and TS population approval, the medication status of the clinical participants was not under experimental control. Thus, a number of the TS and all of the ADHD participants were under medication treatment at the time of testing. Although, as outlined in chapters 4 and 5 as well as above, the medication treatments yielded some interesting and unexpected results, as noted, medication had produced an effect on the expression of conditioned inhibition. Moreover, while a number of the TS participants were tested drug free (as they were off-medication for some time prior to testing); there were only a few in numbers (whereas none of the ADHD population was tested drug free). Thus, in order to test the effects of ADHD and TS on the expression of conditioned inhibition without the possible influence of medication, the experiments would need to be replicated on drug-free TS and

ADHD populations. Moreover, following the same line of argument, a drug free population sample would also provide a fair sized control group to more clearly investigate the effects of medication on the expression of conditioned inhibition in both clinical populations.

Moreover, the limited time allowance of a doctoral thesis investigation did not allow a larger population sample to be tested. Although the population sample was similar to those used by other investigations (Georgiou, et al., 1995; Gitten, et al., 2006; Stern, et al., 2000), the sample size was nonetheless quite small. Admittedly, while clinical populations of TS and ADHD were quite limited, over time, new ADHD and TS patients became available for testing. However, often it would take months before new clinical participants became available for testing. Moreover, the age of the participants (as the cut-off age was set at 9 years of age) as well as parental consent and availability of the participants for testing also produced limitations on the available population sample. Thus, with greater time allowance for testing, a larger population sample would provide greater experimental power.

Looking at the individual difference behavioural measures, the restriction of the analysis to the normal population left a number of questions unanswered. While a number of interesting results were obtained using a population sample of normals, a number of inferences were made to the clinical populations that could have been more definitively answered if the analysis were replicated in the clinical populations in question. However, the ethics approval did not allow testing of the individual difference measures on the ADHD and TS clinical populations. Also, since these measures were developed for use with adult samples, a number of the items were not age appropriate for the young participants tested.

Thus, while the TS and ADHD individual difference measured were consistently correlated in the multiple investigations undertaken with the normal population in the current doctoral investigation, one cannot say for sure whether the same results would be observed if tested on the clinical population. For example, while it can be assume that the behavioural measures successfully measured TS and ADHD-like behaviours, it is not known for sure whether this assumption is true until such time when the behavioural measures in question are applied to the clinical TS and ADHD populations. As such, validation for the newly developed TS individual difference behavioural measure would only provided if the same results observed are obtained following testing on clinical TS and ADHD populations. The same argument also applies to the yawning individual difference measure, whereby the possibility of excessive yawing as a marker of TS (and or ADHD) can be made if similar results outlined in chapters 2 and 3 are observed in clinical TS and ADHD populations.

An important issue that bears more discussion is that of the variable application of the concept of inhibition. Terms such as cognitive and behavioural inhibition have been used to describe performance in diverse forms of procedures. Similarly, the terms cognitive and behavioural inhibition have been used to refer to wide ranging underlying cognitive processes - executive function, working memory, among others. However, the use of these terms has been quite inconsistent due to the lack of any universally agreed taxonomy for manifestations of inhibition (but see Nigg, 2000). For example, while the term behavioural inhibition has often been used to describe the inhibition of S-R associations, through associative chains environmental events can follow a predictable succession culminating in internal events, such as thoughts and emotions though further S-S associations, as well potentially triggering responses through S-R links. In this sense, the inhibition of S-S

associations can also lead to the inhibition of behaviour. On the other hand, to the extent only thoughts rather than behaviours are directly associated, the inhibition of S-S associations could be considered more akin to the cognitive inhibition described by Nigg (2000).

The question lies with what is exactly meant by the term inhibition. In psychology, inhibition often refers to slow response times (as measured by such tasks as the Simon task) or increased errors relative to a baseline condition (as measured by tasks such as the Go/NoGo). On the other hand, conditioned inhibition involves neither one of these factors, as it is the measure of the inhibition of an association between a conditioned and unconditioned stimuli. Moreover, inhibition may not necessarily involve an act of suppression or cancellation. For example, while the presentation of the NoGo signal in the Go/NoGo task may result in the cancellation of a prepared response, it may be that the participants may not prepare a response in advance but rather wait until the target appears before deciding to response or withhold a response.

Stemming from this argument, another issue regarding inhibition arises from the inhibitory measures themselves. While tasks such as the Go/NoGo, the Stroop and the Simon task have been identified as measures of the inhibition of S-R associations; they may not necessarily measure the same underlying inhibitory process. A number of investigators view inhibition not as a unitary construct but as a family of functions (Friedman & Miyake, 2004; Nigg, 2000). According to Nigg (2000), tasks such as the Stroop measure interference control (the prevention of influence by competing distractors), while the Go/NoGo measures behavioural inhibition (the suppression of automatic or cued but inappropriate

responses). The correlational analysis between the various tasks undertaken in Chapter 3 provided evidence for this view as no correlation between the performance on the Go/NoGo task and the colour-word Stroop tasks were observed. It must be noted that while significant correlation between the colour-word Stroop and the Simon task was observed, the absence of a Simon effect throughout the investigation prevents using this finding as evidence for concluding that the Simon and the colour-word Stroop tasks tap the same underlying inhibitory processes.

Another issue with the inhibition of S-R association tasks concerns the difficulties of the tasks themselves. It may have been that the S-R tasks employed in chapter 3 were too easy for the adult (undergraduate and postgraduate) population. For example, the absence of a time constraint for responding in the Simon task may have been the cause behind the absence of a Simon effect. Perhaps the participants may have (subconsciously) felt that they could sacrifice speed in favor of accuracy as they sensed no pressure to response as quickly as possible regardless of whether the S-R were spatially correspondent or not. Similarly, the 2000ms presentation of the Go and the 1500ms presentation of the NoGo stimuli may have provided ample time for the critical decision making period creating a ceiling effect. This view is similar to those taken with regards to the Incredible Hulk conditioned inhibition task (Chapter 2), in that, while conditioned inhibition was clearly demonstrated by the task, the task was deemed too easy to be a reliable measure of conditioned inhibition. Thus, the introduction of a time constraint for responding in the Simon, as well as more stringent time constraints in the Go/NoGo as well as the colour-word Stroop tasks would eliminate the possibility of the existence of a ceiling effect in the results.

6.7: CONCLUSION

The aim of the current doctoral thesis was investigate the deficient inhibitory control theory of ADHD and TS; specifically, the examination of deficits resulting from the disorders in question on the inhibition of S-S associations as measured by a translational test of Pavlovian conditioned inhibition. A driving component of the research hypothesis of this doctoral thesis was that the unwanted behaviours observed in TS and ADHD are as a result of inhibitory deficits in S-S associations which precede and influence S-R associations that result in a particular unwanted behaviour or response. While inhibitory deficits observed in TS and ADHD have been predominantly attributed to deficits in response inhibition (such as the notion that the symptoms of TS are as a result failing to successfully inhibit motor and tic responses), the main assumption behind the current research was that the symptoms of TS and ADHD may arise as a result of a deficit in a cognitive process prior to the onset of the unwanted behavioural response.

Continuing on with the symptom profile of TS, let us suppose that exposure to a particular stimulus results in the onset or exacerbation of a particular tic (such as exposure to the waiting room of a doctor's office may result in the onset of coughing or sniffing tic in a TS patient). This in itself would be a simple S-R association (Doctors office $\rightarrow$ tic). However, there may be other type of associations that preceded the S-R association that result in the onset of the tic. Suppose that a sound of a cough heard in the waiting room or the doctor's office itself may become associated with the thought of illness (which itself may be associated with the idea of uncontrollable coughing) resulting in a premonitory urge that in

turn leads to the coughing tic in the TS patient. Thus, a S-S association may form between a certain stimulus (for example, an ill patient waiting for the doctor in the same waiting room, or the sound of a cough) giving rise to a premonitory urge to tic (as a result of the thought of illness being associated with coughing which may build up to an urge for a coughing tic). Thus, this S-S association giving rise to the premonitory urge precedes the S-R response that results in a tic response. As such, deficits in the inhibition of the formations of such S-S associations would result in a greater level of failure to inhibit such premonitory urges that ultimately (further down along the chain) may result in the onset and/or exacerbation of tics in TS patients. The same line of thought would hold true with respect to the initiations of unwanted behaviours in ADHD.

However, the results showed that in general, the inhibition of S-S associations were unaffected by the presence of TS and ADHD, in so far as can be concluded given the overall small sample and the few (TS) or non-existent (ADHD) unmedicated clinical population sample. Thus, in line with the results obtained, if TS and ADHD are due to inhibitory deficits which result in the symptom profiles of the disorders (i.e. tics and unwanted behaviours respectively), this inhibitory deficit should occur further down the associative chain (perhaps some point in the S-R associations) leading to the onset of the unwanted behaviours. However, as previously mentioned, the results of previous studies in S-R inhibitory deficits in TS and ADHD have been mixed. Yet, it may be that the tasks chosen for the measure of the inhibition of the S-R associations may have failed to truly measure the type S-R associations that may be responsible for the symptoms of TS and ADHD.

Despite the absence of a deficit in the inhibition of S-S association in TS and ADHD, the pharmaceutical treatment of the disorders in question appears to have significant effect on the level of conditioned inhibition and excitation demonstrated. It was observed that while anxiolytic medication (clonidine) adversely affected inhibitory learning in the TS participants, treatment with methylphenidate produced enhanced excitatory learning in the ADHD participants.

Such findings warrant further investigations with special focus on the effects of medication on the expression of conditioned inhibition and the efficacy of behaviour therapy. For example, TS children with impaired inhibition due to medication may be less able to inhibit tics in the presence of the premonitory urge when cues to inhibit are present in the environment. To give a concrete example, for children with tics, the inhibitory process measured by conditioned inhibition, could moderate cognitive processes along the following lines: "is there something in this environment that tells me not to tic (parent, bully, teacher, potentially embarrassing situation), even though I have the urge". Children with intact inhibitory process (and who have learned suppression) should potentially recognize these kinds of cue and inhibit their tics, even if the urge is there.

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