ELECTROPHYSIOLOGICAL CORRELATES OF LEARNING AND COGNITIVE CONTROL IN CHILDREN WITH TICS WITH AND WITHOUT ADHD SYMPTOMS

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ABSTRACT

The aims of this study were to explore the nature of comorbid Tourette syndrome and attention-deficit/hyperactivity disorder (TS+ADHD), in particular whether additive, independent or symptomatic phenocopy models of comorbidity can explain the co-occurrence of these two conditions, and to investigate the impact of comorbid ADHD symptoms on cognitive functions related to the control of tic symptoms in young people with TS. Electrophysiological activity and behavioural performance were measured during three cognitive tasks designed to assess goal-directed reinforcement learning, habit-based reinforcement learning, and cognitive control and were compared between young people with TS, ADHD, TS+ADHD and unaffected young people aged 9 to 17 years. The extent to which severity of tics, ADHD and comorbid oppositional-defiant disorder (ODD) symptoms predicted behavioural and electrophysiological correlates of reinforcement learning and cognitive control was also examined. The TS+ADHD and ADHD groups were impaired in goal-directed learning and modification of new behaviours using reinforcement feedback. ADHD symptoms were negatively associated with adaptive changes in the feedback-related negativity (FRN) ERP that were indicative of compensatory strategies employed to improve learning in the TS+ADHD group. In contrast, the TS+ADHD and ADHD groups showed intact habit-learning performance compared with unaffected controls. The TS+ADHD and ADHD groups were impaired in the ability to withhold inappropriate responses to Nogo stimuli during the Go/Nogo cognitive control task compared with TS and controls. Both ADHD groups also showed greater intra-individual variability than TS and controls. Concurrently, the TS+ADHD group were enhanced in the ability to withhold inappropriate Nogo responses and showed enhancement of the error-related negativity (ERN) ERP relative to the ADHD group. The TS group exhibited enhanced ERN ERPs and post-error slowing, a measure of the ability to adjust performance following errors. These findings are consistent with an additive, but interactive, model of comorbidity, and indicate that comorbid ADHD symptoms introduce impairments in young people with TS that will negatively impact upon the ability to control tics.

DEDICATION

This thesis is dedicated to my mum, Valerie, and to the memory of my dad, Colin.

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1.1 OVERVIEW

In the context of psychiatry, *comorbidity* refers to the co-occurrence of two psychiatric conditions in the same individual at a rate that is higher than could be expected by chance (Caron & Rutter, 1991). Comorbidity occurs in a large proportion of children with neurodevelopmental conditions, including Tourette syndrome (TS) (Costello et al., 2003; Merikangas et al., 2010; Scharf et al., 2012). Attention-deficit/hyperactivity disorder (ADHD) is one of the most frequently co-occurring disorders in TS and may be the most impairing form of comorbidity due to the significant behavioural, social and educational deficits that accompany ADHD and the difficulties involved in treating children with comorbid TS and ADHD (TS+ADHD) (see 1.3 - 1.5 for a full discussion). At present, the causes of TS+ADHD and the effects of comorbid ADHD symptoms on cognitive function in TS are unclear. Greater understanding of these issues is crucial to facilitate improvements in treatment and reduce impairments in children with TS+ADHD.

1.2 TOURETTE SYNDROME: CLINICAL CHARACTERISTICS, COURSE AND TREATMENT

TS is a neurodevelopmental disorder that affects approximately 1% of school-aged children and is defined by the chronic presence of multiple motor and one or more phonic tics for one year or more (APA, 2000). Tics are sudden, repetitive, involuntary and unwanted movements and sounds that occur in frequent bursts and can be simple or complex in nature (Bruun & Shapiro, 1972). Simple tics resemble meaningless fragments of behaviours, for example excessive blinking, head or limb jerking, sniffing and throat clearing, while

complex tics can appear similar to voluntary, purposive behaviours, such as facial expressions, kissing gestures and uttering words or phrases (Bruun & Shapiro, 1972; Moldofsky et al., 1974). In some TS sufferers (<50%) complex tics take socially inappropriate and embarrassing forms including coprolalia (uttering obscenities), copropraxia (obscene movements), echopraxia and echolalia (echoing movements or utterances of others) (Comings & Comings, 1985; Kano et al., 1997; Sweet et al., 1973). Tics follow a characteristic waxing and waning pattern in that they fluctuate in severity, type and number over the long-term course of TS (Bruun & Shapiro, 1972).

TS typically onsets between the ages of 4-8 years (Comings & Comings, 1985; Kano et al., 1998; Leckman et al., 1998). Simple motor tics affecting the face and head are the most common first signs of TS, followed a few years later by simple phonic tics (Fernando, 1967; Kano et al., 1998). As childhood progresses, complex motor and phonic tics develop and symptoms increase in frequency, severity and number to reach a worst-ever tic severity at approximately 8-12 years (Bloch et al., 2006; Leckman et al., 1998). Concurrently, most children develop an ability to suppress or withhold their tics temporarily in certain situations, for example in the classroom (Banaschewski et al., 2003a; Comings & Comings, 1985). However, tic suppression is effortful and tiring and can lead to a build-up of uncomfortable *premonitory phenomena*, i.e. unpleasant urges or bodily sensations that precede tics and are relieved by tic expression (Banaschewski et al., 2003a; Kane, 1994; Kwak et al., 2003). Tic symptoms tend to attenuate in late adolescence and symptoms remit in the majority of patients by early adulthood (Bloch et al., 2006; Leckman et al., 1998; Fernando, 1967).

Nevertheless, tics can impair child development considerably. Impairments in social, emotional and educational functioning frequently accompany tics and are inversely associated with, and/or predict, tic severity (Carter et al., 2000; Conelea et al., 2011; Elstner et al., 2001; Storch et al., 2007; Zhu et al., 2006). For example, children and adults with TS have difficulties making and maintaining friendships, experience teasing and restricted social lives as a result of tics, and have lower quality of life and higher anxiety and depressive symptoms than unaffected individuals (Carter et al., 2000; Champion et al., 1988; Conelea et al., 2011; Debes et al., 2010;

Elstner et al., 2001; Packer, 2005; Rizzo et al., 2011; Storch et al., 2007; Sukhodolsky et al., 2003; Zhu et al., 2006). Children with TS experience greater school problems than unaffected children (Carter et al., 2000; Debes et al., 2010; Storch et al., 2007). Concerns about ticcing and/or the effort of suppressing tics can lead to difficulties concentrating on schoolwork (Roessner et al., 2011a) and children report that tics can interfere with handwriting, reading and speaking up in class (Packer, 2005).

Pharmacological and behavioural therapies to help individuals cope with tics and reduce symptom severity may be offered if functional impairments are severe. Medications include dopamine-blocking antipsychotic drugs such as Haloperidol, Pimozide, Risperidone and Aripiprazole, and the noradrenergic-inhibiting drugs Clonidine and Guanfacine (Huys et al., 2012; Párraga et al., 2010; Thomas & Cavanna, 2013). These drugs have been shown to be successful in reducing tic severity in children and adults, although their efficacy varies across individuals and some patients do not respond to treatment (Bubl et al., 2006; Gaffney et al., 2002; Huys et al., 2012; Lombroso et al., 1995; Sallee et al., 1997). Due to the harmful side-effects associated with medication, including extra-pyramidal symptoms with Haloperidol and Pimozide, and sedation with Risperidone, Aripiprazole, Clonidine and Guanfacine, clinical guidelines recommend the use of pharmaceutical therapy for only severely affected patients (Roessner et al., 2011a).

Behavioural therapy provides a safer alternative to medication. Habit-reversal based therapies, Habit Reversal Therapy (HR) (Azrin & Nunn, 1973; Woods et al., 1996) and the Comprehensive Behavioural Intervention for Tics (CBIT) (Piacentini et al., 2010), have been the most rigorously assessed. Habit-reversal therapies consist of training the patient to self-monitor for signs that tics are imminent, for example by being aware of premonitory urges, and to produce voluntary competing responses in place of tics (Azrin & Nunn, 1973; Woods et al., 1996). Children and adults experience significant reductions in tic frequency and severity following 8-14 sessions of HR or CBIT, and symptom improvements remain at 6 month follow-ups (Bate et al., 2011; Deckersbach et al., 2006; Franklin et al., 2011; Piacentini et al., 2010; Woods et al., 1996).

Another effective behavioural treatment is Exposure and Response Prevention (ER), which involves suppressing tics for increasingly extended periods (2 hours) while enhancing attention to urges (Hoogduin et al., 1997). The aim of ER is to habituate patients to the uncomfortable pre-tic sensations, thereby reducing the urge to tic and thereafter the occurrence of tics (Hoogduin et al., 1997). The rationale of ER is supported by experimental studies which show that severity of tics and perceived urges decrease after periods of rewarded suppression (Specht et al., 2013; Verdellen et al., 2007; Woods et al., 2008). ER reduces tic symptom severity to a degree comparable with HR and results in significantly decreased perceived severity of urges in children and adults (Hoogduin et al., 1997; Verdellen et al., 2008; Verdellen et al., 2004). ER may be the more advantageous behavioural treatment because suppression is targeted at improving severity of all tics at once, while HR/CBIT targets only one or two tics at a time for improvement in the course of therapy (Verdellen et al., 2004). Although clearly effective, HR/CBIT and ER are limited by the high degree of motivation, effort and time required from patients and families to achieve success with therapy, and by the varying ability of children to exert control over tics.

1.3 COMORBID ADHD SYMPTOMS IN TOURETTE SYNDROME: CLINICAL CHARACTERISTICS AND ASSOCIATED IMPAIRMENTS

Recent studies report that clinically significant ADHD symptoms are present in 55% of clinical and 23% of community samples of children and adults with TS (Freeman, 2007; Scharf et al., 2012). ADHD is one of the most common neurodevelopmental disorders, affecting approximately 5% of children worldwide (Polanczyk et al., 2007; Willcutt, 2012). The disorder is characterised by developmentally inappropriate and impairing symptoms of inattention, for example being unable to finish tasks or sustain attention without being distracted by extraneous stimuli, hyperactivity, for instance climbing or running about in inappropriate situations and being unable to calm down upon request, and impulsivity, for example being unable to wait for

things such as the end of a question or a turn in a game (APA, 1994). The Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) subdivides ADHD into Combined Type (inattentive and hyperactive-impulsive symptoms), Predominantly Inattentive Type (inattentive symptoms only), and Predominantly Hyperactive-Impulsive Type (symptoms of hyperactivity and impulsivity only) (APA, 1994).

ADHD onsets early in childhood, by definition before age 7, and usually earlier than TS (APA, 1994; Bloch & Leckman, 2009). Moderate-to-severe disorder symptoms persist into adulthood in a larger proportion of patients with ADHD (65% in boys, 77% in girls) compared with the small proportion of patients with TS who experience continuing tic symptoms in adulthood (26%) (Biederman et al., 2012; Bloch & Leckman, 2009; Faraone et al., 2006). Therefore, illness duration is likely to be longer for children with comorbid TS+ADHD than children with TS alone. Indeed, comorbid ADHD symptoms have been found to be associated with earlier appearance of tic symptoms in children with TS+ADHD compared with children with TS and other comorbidities (Roessner et al., 2007a).

Debilitating neurodevelopmental conditions such as oppositional defiant disorder (ODD), conduct disorder (CD), and symptoms of autistic spectrum disorders (ASD) are highly comorbid with ADHD (Gillberg et al., 2004; Mulligan et al., 2009; Rommelse et al., 2009; Yoshimasu et al., 2012), which places children with TS+ADHD at an increased risk for these disorders. Correspondingly, higher rates of ODD/CD have been reported in children with TS+ADHD compared with children with TS or TS and comorbidities other than ADHD (Roessner et al., 2007a). Children with TS+ADHD have also been found to have greater numbers of comorbid conditions than children with TS or ADHD alone (Spencer et al., 1998).

ADHD is associated with significant functional impairments. Children and adolescents with ADHD have significantly lower educational attainment, self-esteem and quality of life, and significantly higher rates of juvenile criminality, special education requirements, and family, peer relationship and school dysfunction than unaffected young people (Brammer & Lee, 2011; Bussing et al., 2010; Klassen et al., 2004). These ADHD-related impairments create or exacerbate social, educational and behavioural problems in children

with TS+ADHD. For example, higher rates of disruptive behaviour and family dysfunction have been reported in children with TS+ADHD compared with unaffected children, while children with TS have not differed from controls (Sukhodolsky et al., 2003). School dysfunction is comparable in children with TS+ADHD and ADHD and is higher than in unaffected children (Spencer et al., 1998). Children with TS+ADHD have greater attention, social, aggressive and delinquent problems than children with TS, and these difficulties are significantly associated with ADHD symptoms rather than tics (Carter et al., 2000; Hoekstra et al., 2004; Roessner et al., 2007b; Sukhodolsky et al., 2003). Finally, quality of life ratings are significantly lower in children with TS+ADHD compared with children with TS, ADHD, TS and comorbid obsessive-compulsive disorder (OCD), and unaffected children (Rizzo et al., 2011; Spencer et al., 1998).

It is clear that comorbid ADHD symptoms have detrimental effects on the lives of children with TS. Effective treatments to reduce symptoms and the severity of associated functional impairments are therefore essential for children with these comorbid conditions. However, treatment for TS+ADHD can be problematic (discussed in 1.5 below). This is at least partly because the neurobiological mechanisms involved in comorbid TS+ADHD are not sufficiently well understood to guide decisions about appropriate pharmacological therapy. Moreover, knowledge of how comorbid ADHD symptoms affect cognitive functions that are involved in tic suppression and behavioural therapies for tics is lacking. Increasing understanding of these issues will be instrumental in improving treatments for TS+ADHD.

1.4 CAUSES OF TS, ADHD AND TS+ADHD

1.4.1 Why do TS and ADHD co-occur?

There are several possible explanations for why TS and ADHD co-occur. First, TS+ADHD may reflect true comorbidity in that two separate disorders, TS and ADHD, with distinct neuropathologies manifest in one individual (Banaschewski et al., 2007; Caron & Rutter, 1991). This is known as the *additive model* of comorbidity and could arise because TS and ADHD

share risk factors or have similar causal pathways, for example particular genetic or neurobiological abnormalities, which creates a vulnerability to both disorders (Rothenberger et al., 2007; Rutter, 1997). If the additive model is correct, children with TS+ADHD should exhibit genetic or neurobiological features, or correlates of those features, of TS and of ADHD.

Second, TS+ADHD might be an independent, or partially independent, disorder from TS and ADHD with its own distinct aetiology (Banaschewski et al., 2007; Rothenberger et al., 2007; Rutter, 1997). If this independence model holds, children with TS+ADHD should show some neuropathological characteristics that are different from those in TS and ADHD individually. Finally, Banaschewski et al. (2007) suggest that tics might mimic ADHD symptoms in some children but those symptoms are not genuine expressions of ADHD. For example, tics could be misconstrued as hyperactivity, suppressing tics could result in apparent problems with attention and concentration, and acting on urges to tic could be misinterpreted as impulsivity. In this account TS+ADHD is referred to as a *symptomatic phenocopy* and children would exhibit only characteristics of TS and not those of ADHD.

It is not known which of these models is accurate but such knowledge has important implications for treatment of children with comorbid TS+ADHD. For instance, if TS+ADHD is an independent condition with its own aetiology, treatments used for TS and ADHD may be inappropriate or ineffective. Likewise, if ADHD symptoms in TS are a symptomatic phenocopy and do not reflect pathological mechanisms involved in ADHD, administering treatments for ADHD, such as stimulant medication, would be redundant and potentially harmful. In order to evaluate these models, a good understanding of the causes of TS and ADHD individually is required. Evidence for the neurobiological bases of TS and ADHD will be reviewed in the following section before considering the evidence for which model of comorbidity applies to TS+ADHD.

1.4.2 Neurobiology of TS, ADHD and TS+ADHD

The neurobiological mechanisms underlying TS and ADHD have not been identified but considerable evidence suggests that abnormalities in cortico-basal ganglia-thalamo-cortical (CBTC) circuits are involved. There are

several CBTC circuits in the brain which reciprocally connect parts of the basal ganglia nuclei (caudate and putamen (striatum), globus pallidus, substantia nigra, subthalamic nucleus) to regions of cortex via the thalamus (Alexander & Crutcher, 1990). Each circuit involves different cortical areas and forms a distinct but interactive processing loop which serves to regulate particular aspects of behaviour, including sensory and motor behaviour (sensorimotor loop), cognition (fronto-striatal loops), and emotion and reward processing (limbic loop), depending on the cortical regions involved in the loop (primary motor and somatosensory cortices (M1/S1), supplementary motor area (SMA) and premotor cortex in the sensorimotor loop, dorsolateral prefrontal cortex (dlPFC) and lateral orbitofrontal cortex (lOFC) in the fronto-striatal loops, anterior cingulate cortex (ACC), medial OFC (mOFC), hippocampi and amygdalae in the limbic loop) (Alexander & Crutcher, 1990; Haber & Calzavara, 2009; Redgrave et al., 2011).

It has been proposed that tics reflect the anomalous activation of neurons in the striatum causing, via disinhibition of the thalamus, excitation of cortical sensorimotor loop regions and the production of involuntary (tic) behaviours (Albin & Mink, 2006; Leckman et al., 2006). A similarly deviant activation of limbic loop regions and the interaction of those regions with the sensorimotor circuit might be involved in orchestrating more complex tics and uncomfortable premonitory urges (Albin & Mink, 2006; Peterson et al., 2007). Neural communication in the CBTC circuits relies heavily on the neurotransmitter dopamine, and it is suggested that hyperactive or imbalanced dopamine signalling triggers inappropriate striatal activity (Albin & Mink, 2006; Buse et al., 2012). This suggestion is consistent with the successful reduction of tics with dopamine-blocking antipsychotic drugs (Gaffney et al., 2002; Huys et al., 2012; Lombroso et al., 1995; Sallee et al., 1997). In support of this model, neuroimaging studies have reported abnormalities in sensorimotor and limbic CBTC regions in TS. These include atypical volumes of the thalamus, putamen, caudate and sensorimotor regions, and cortical thinning of the sensorimotor and anterior cingulate cortices in children with TS compared with unaffected children (Fahim et al., 2009; Fahim et al., 2010; Lee et al., 2006; Makki et al., 2009; Miller et al., 2010; Peterson et al., 2001; Peterson et al., 2003; Roessner et al., 2011b).

A *Frontal Lobe Compensation* hypothesis was proposed by Leckman et al. (2006) which suggests that compensatory activation of prefrontal brain systems modulates aberrant neuronal activity in the cortico-striatal circuitry involved in tics and premonitory urges. Repeated engagement of this compensatory circuitry results in tic suppression and even voluntary manipulation of tic behaviours (Leckman et al., 2006). Consistent with this hypothesis, studies examining neural activation during tic suppression compared with free-ticcing suggest that fronto-striatal circuitry is recruited to control tics and regulate activity in the sensorimotor loop. Peterson et al. (1998) found significantly increased BOLD activation in PFC and caudate, which was negatively associated with decreased activation in motor execution regions, during tic suppression compared with free ticcing in adults with TS. Similarly, Serrien et al. (2005) reported increased electrophysiological activity in the alpha frequency band, which has been associated with motor inhibition, between electrode sites at the front of the scalp when adults with TS suppressed tics.

It must be noted that interpreting findings in adults with TS requires caution because these individuals may be atypical of TS since they do not follow the usual remitting disorder course. However, Hong et al. (2013) recently reported increased electrophysiological activity in the theta frequency band, which is associated with voluntary control and monitoring of thought and behaviour, between scalp sites over prefrontal and motor cortices in children with TS during voluntary tic suppression compared with spontaneous tic expression. Importantly, the strength of theta activity was positively associated with tic severity, such that children with the most severe motor tics showed the greatest activity between PFC-motor sites during tic suppression. Moreover, increased PFC BOLD activation has been found in children with TS compared with unaffected children during suppression of tic-like involuntary movements (blinks), indicating children with TS recruit prefrontal regions to a greater degree than unaffected children to control tic-like behaviours (Mazzone et al., 2010).

Several other neural atypicalities reported in TS have been attributed to compensatory neural changes occurring as a result of controlling tics. Peterson et al. (2007) found increased volumes of the amygdalae and hippocampi in

children and adults with TS compared with unaffected individuals. These increases were negatively associated with tic severity, which led the authors to suggest that the changes were compensatory, and could reflect the result of controlling tics or compensating for abnormal activity in the limbic loop. Peterson et al. (2001) found increased dlPFC volumes in children and reduced dlPFC volumes in adults with TS. Reduced corpus callosum (CC) areas in children but increased CC sizes in adults have also been reported (Moriarty et al., 1997; Peterson et al., 1994; Plessen et al., 2004). Plessen et al. (2004) found CC areas were positively correlated with tic severity and negatively correlated with PFC volumes. The authors suggested that reduced CC size in children reflects a compensatory decrease in cross-hemisphere communication to enable greater within-hemisphere PFC control of tics. Increased CC volumes and decreased PFC volumes in adults with TS might signify inefficient prefrontal tic control, reflecting the persistence of tics into adulthood (Leckman et al., 2006).

Hypoactive dopaminergic functioning within the fronto-striatal circuits has been proposed as core to the neuropathology of ADHD (Sagvolden et al., 2005; Tripp & Wickens, 2008). Given that the fronto-striatal circuits are vital in controlling motor behaviour, attention and cognition, this proposal is consistent with the behavioural symptoms of ADHD. Three lines of evidence support this proposal. First, stimulant drugs such as methylphenidate that block the re-uptake of dopamine are the recommended medication for ADHD (in addition to psycho-educational and behavioural therapy) and are effective in reducing ADHD symptoms (Taylor et al., 2004). Second, abnormalities in genes involved in the expression of dopamine receptors and dopamine re-uptake mechanisms (dopamine transporters), as well as changes in the receptors and transporters themselves that are consistent with hypoactive dopamine function, have been found in genetic and neuroimaging studies in ADHD (Li et al., 2006; Volkow et al., 2009).

Finally, neuroimaging studies have consistently reported alterations in fronto-striatal loop regions that suggest activity within these circuits is dysfunctional in ADHD. Significant reductions in dlPFC, OFC and basal ganglia volumes, frontal white matter, and BOLD activity in the dlPFC and basal ganglia during cognitive tasks and at rest have been reported in children

and adults with ADHD compared with unaffected controls (Casey et al., 2007; Castellanos et al., 2002; Dickstein et al., 2006; Ivanov et al., 2010; Kates et al., 2002; Qui et al., 2009; Silk et al., 2005; Sobel et al., 2010; Zang et al., 2007). Moreover, these structural and metabolic atypicalities become more normalised, i.e. like those of unaffected individuals, when methylphenidate is administered (Casey et al., 2007; Ivanov et al., 2010; Sobel et al., 2010).

Additionally, parietal and cerebellar regions have been found to be reduced in volume and show hypoactive BOLD responses in ADHD during rest and cognitive tasks (Casey et al., 2007; Castellanos et al., 2002; Dickstein et al., 2006; Silk et al., 2005). It has been suggested that these findings are consistent with poor control of motor and attentional functions in ADHD, with abnormalities in parietal cortex contributing to attentional control dysfunction and those in the cerebellum involved in motor dysregulation (Brennan & Arnsten, 2008; Casey et al., 2007). Finally, Plessen et al. (2006) reported increased volumes of the hippocampi in children with ADHD compared with controls, which correlated inversely with severity of ADHD symptoms. This finding is akin to the increased hippocampal volumes in TS which correlated with tic severity (Peterson et al., 2007). Plessen et al. (2006) concluded that these increases in ADHD reflect compensatory responses to coping with ADHD symptoms, for example, the hippocampi might be recruited to a greater degree than normal to improve cognitive functioning.

With contrasting dopamine abnormalities associated with TS and ADHD it seems somewhat paradoxical that these two conditions should co-occur. To the best of this author's knowledge, no study has examined dopaminergic functioning in children or adults with TS+ADHD to elucidate how these opposing abnormalities are expressed in the comorbid form. There are several dopaminergic pathways in the brain and so one possibility is that some, TS-related, dopaminergic pathways tend towards hyperactivity while other, ADHD-related, pathways are hypoactive. Another possibility is that TS+ADHD is an independent disorder and dopamine is altered in a distinct way from TS and ADHD individually. Considering the use of medications with opposite effects on dopaminergic function in TS and ADHD, further research in this area is important.

Research investigating the structure and function of neural regions in TS+ADHD is also sparse. Castellanos et al. (1996) examined PFC and basal ganglia volumes in children with ADHD with and without comorbid TS and found reversed asymmetry of globus pallidus volume in these groups compared with unaffected children. This indicates that children with TS+ADHD share neurobiological abnormalities with children with ADHD, which is suggestive of an additive model of comorbidity. However, the omission of a TS group without ADHD symptoms limits strong conclusions to be drawn from this study. Fredericksen et al. (2002) reported increased white matter in the right frontal lobe in children with TS, but no differences in children with TS+ADHD or ADHD, compared with controls. In contrast, children with TS+ADHD and ADHD had smaller grey matter volumes in the left frontal lobe compared with controls, with no differences in this region in TS. These findings provide some support for the additive model of comorbidity in TS+ADHD, with children with comorbidity showing ADHD-related neural atypicalities, although TS-related abnormalities might also have been expected. Importantly, Fredericksen et al.'s (2002) findings also suggest that fronto-striatal control of tics might be compromised by ADHD-related deficits in frontal lobe functioning in children with TS+ADHD (Leckman et al., 2006). Hypothetically, this might affect the development of compensatory neural changes in these regions in children with TS+ADHD, which may affect the likelihood that their tics will remit in adulthood. It is clear however that further research investigating the neural basis of TS+ADHD is needed.

1.5 TREATMENT FOR TS+ADHD

A large-scale study examining treatment history in children and adolescents with TS with and without comorbid conditions (n=314) found that children with TS+ADHD were more likely to receive pharmacological treatment than children with TS without comorbidity or with comorbid OCD (Debes et al., 2009). However, pharmacological treatment for children with TS+ADHD can be complicated. The clinician must identify which symptoms are the most impairing and should be treated (usually the ADHD symptoms)

and determine the optimal medication, or combination of medications, to treat both sets of symptoms (Graham et al., 2011; Rizzo et al., 2013).

Theoretically, the first-line pharmaceutical treatment for ADHD, i.e. dopamine-enhancing stimulant medications, should exacerbate tics since these behaviours are associated with hyperactive dopamine. Accordingly, in the past stimulants were not advised as treatments of choice in children with TS+ADHD (Bloch et al., 2009). Recent reviews of the literature have found however that stimulant administration does not exacerbate tics in the majority of patients (85-90%) and in the minority who do experience exacerbation of symptoms, the withdrawal of medication promptly reverses increases in tic severity (Graham et al., 2011). Alpha-2 agonists, stimulants, and Atomoxetine (a noradrenergic enhancing drug) have been shown to reduce both tic and ADHD severity (Bloch et al., 2009; Rizzo et al., 2013) but efficacy of each drug varies across individuals. The side-effects associated with each drug must also be considered, particularly if a combination of medications, for example stimulants and Clonidine, are to be administered (Döpfner & Rothenberger, 2007).

Behavioural tic therapies in place of tic medication might therefore be particularly valuable for children with comorbid TS+ADHD. It is unclear however whether ADHD-related impairments in frontal lobe functioning negatively impact upon the ability of children with TS+ADHD to engage effectively in such therapies, which likely rely on fronto-striatal control mechanisms. No study has examined the efficacy of behavioural treatments for TS+ADHD but this is a necessary avenue for future research. Döpfner & Rothenberger (2007) point out that modifications to behavioural tic therapies might be required to assist children with TS+ADHD in achieving successful reduction of symptoms, such as incorporating rewards or employing cognitive strategies to overcome attention difficulties.

1.6 AIMS OF THIS THESIS

The first aim of this thesis is to investigate the basis of TS+ADHD, particularly in terms of which model of comorbidity (additive, independence,

or symptomatic phenocopy) applies to this combination of neurodevelopmental disorders. The second aim is to examine the neurocognitive impact of having comorbid ADHD symptoms in children with TS with particular focus on how neurocognitive functions likely involved in controlling tics are affected by ADHD. Investigating the basis and impact of comorbid ADHD in TS, or indeed any form of psychiatric comorbidity, is not straightforward. An optimal method of identifying the pathogenesis of this comorbidity would be to examine the expression and interaction of genetic and neurobiological markers for TS and ADHD in children with TS+ADHD (Rutter, 1997). However, as was made clear in section 1.4, there are no such markers for these conditions.

An appropriate alternative approach is to examine neurocognitive correlates of the probable pathology of each disorder in children with TS+ADHD (Roessner et al., 2007c; Rutter, 1997). Following the latter method, this thesis investigates how neural correlates of cognitive functions that are implicated in the pathology of TS and ADHD, namely learning and cognitive control, differ in children with TS+ADHD compared with children with TS or ADHD alone and unaffected children. Evidence suggests that impairments in learning are involved in the pathology of tics and ADHD symptoms, while atypicalities in cognitive control have been linked with the causes of ADHD and compensatory mechanisms to cope with tics in TS. These two cognitive functions are therefore ideally suited to investigating the causes and impact of comorbid ADHD symptoms in TS. This will be discussed in detail in chapter 2.

Electrophysiology was selected as the method of measuring neural correlates of learning and cognitive control. To briefly describe this technique, electrical brain activity, the electroencephalogram (EEG), is recorded from electrodes placed in a cap on a participant's head. EEG is a real-time measure of brain activity, with a temporal resolution in the millisecond time-range. This is in contrast to fMRI which has a slower temporal resolution in the second time-range. The spatial resolution of EEG is inferior to that of fMRI, but it is possible to state with some confidence that electrophysiological activity measured over the front of the scalp reflects frontal brain activity for example. EEG was selected rather than fMRI because learning and cognitive control are fluid, flexible processes that can arguably be most accurately captured by a technique with high temporal resolution. EEG is also less susceptible to loss of

data due to movement artefacts than fMRI, which is important to consider when studying young people with tic disorders and hyperactivity.

EEG data can be analysed in the frequency domain to examine oscillatory electrophysiological activity, or in the time-domain to examine electrophysiological activity associated with the occurrence of particular events in time, such as the onset of a stimulus in an experimental task. Time-domain activity is extracted from the on-going EEG by segmenting the EEG data into small segments (epochs) that are the same length with reference to an event of interest (stimuli for example). These epochs are then averaged to create an event-related potential (ERP). There are well-established ERP correlates of learning and cognitive control, and therefore, the EEG data were analysed in the time-domain in this research.

2. LEARNING AND COGNITIVE CONTROL IN TS, ADHD AND TS+ADHD: A LITERATURE REVIEW

2.1 OVERVIEW

Learning can broadly be defined as the acquisition of new behaviours. *Cognitive control* refers to a range of self-regulatory processes that facilitate voluntary control of thoughts, emotions and actions. These cognitive functions were selected as tools for investigating the causes and impact of comorbid ADHD symptoms in TS for several reasons. The neural substrates of learning and cognitive control overlap with neural circuitry that has been shown to be atypical in TS and ADHD. Theoretical models based on this neural overlap and on empirical investigations of learning and cognitive control in TS and ADHD propose that alterations in these cognitive functions are fundamentally related to the core disturbances or compensatory mechanisms characteristic of these disorders. Specifically, abnormal learning processes have been implicated in the causes of both TS and ADHD (discussed in full in 2.2), while atypicalities in cognitive control have been linked with the causes of ADHD symptoms and compensatory mechanisms related to the control of tic symptoms in TS (discussed in 2.3).

Therefore, investigation of learning and cognitive control processes in TS+ADHD compared with TS and ADHD should reveal insights into the basis of this comorbidity; for example, the presence of TS-related and ADHD-related characteristics in TS+ADHD would support an additive model of comorbidity. Moreover, the examination of cognitive control characteristics in TS+ADHD should clarify whether comorbid ADHD symptoms negatively affect aspects of cognition involved in tic control in young people with TS. This chapter presents the theoretical models and empirical evidence for the roles of learning and cognitive control in TS and ADHD, and reviews the research to date investigating these cognitive functions in comorbid

TS+ADHD. This chapter is presented in two parts; section 2.2 is focused on learning and section 2.3 focuses on cognitive control.

2.2 LEARNING

Abnormalities in learning that is subserved by basal ganglia circuitry, that is, *reinforcement learning*, are increasingly being proposed as core to the neuropathology of TS and ADHD. Reinforcement learning describes the processes by which new behaviours are learned if they are followed by positive consequences (positive reinforcements) or not learned if they are followed by negative consequences (negative reinforcements). A host of research examining basal ganglia function during learning episodes using fMRI in human participants and fMRI and cellular recordings in non-human primates and rodents has elucidated the mechanisms of reinforcement learning (Maia, 2009; Pasupathy & Miller, 2005; Schultz, 2002).

In particular, dopaminergic neurons in the striatum (caudate and putamen of the basal ganglia) increase their firing rate when the outcome of a performed behaviour is better than expected and decrease firing rate when the outcome is worse than expected (Maia, 2009; Schultz, 2002). These bursts and depressions in dopaminergic transmission are termed positive and negative prediction errors respectively and are used by the basal ganglia, along with information provided from cortical regions concerning the organism's state, to determine which behaviours are advantageous and should be performed in future and which are disadvantageous and should be prevented (Maia & Frank, 2011; Schultz, 2002). Repeated experience of a positive prediction error following a particular behaviour leads to the learning and reproduction of that behaviour in future, likely via neuroplastic changes strengthening neural pathways underlying the behaviour, while recurrent negative prediction errors leads to extinction of the behaviour (Schultz, 2002; Schultz et al., 2003). The ACC, dlPFC and OFC also show activity that is consistent with prediction errors and are thought to be involved in this learning system (Pasupathy & Miller, 2005; Schultz, 2002; Schultz et al., 2003).

The outcomes of reinforcement learning can be goal-directed behaviours or habitual behaviours (habits) (Maia, 2009; Redgrave et al., 2010; Yin & Knowlton, 2006). Goal-directed behaviours are flexible, consciously controlled actions that are sensitive to and are modified in accordance with motivational states and anticipations of the outcome of performing the behaviour; for example, telling a joke to friends but not in an important business meeting (Redgrave et al., 2010; Yin & Knowlton, 2006). In contrast, habits are defined as rigid, largely non-conscious and automatic behaviours that are performed regardless of motivational state and are insensitive to reward anticipation, for example automatically turning on a light switch despite knowledge that the light bulb requires changing (Redgrave et al., 2010; Seger & Spiering, 2011; Yin & Knowlton, 2006). It has been proposed that dorsal regions of the striatum and the sensorimotor cortico-basal ganglia-thalamo-cortical (CBTC) loop are involved in habit-learning, while ventral regions of the striatum and prefrontal cortex (fronto-striatal CBTC loop) are involved in goal-directed learning (Maia, 2009; Seger & Spiering, 2011; Yin & Knowlton, 2006). A behaviour can be learned initially as a goal-directed action but after repeated practice becomes habitual, such as is the case with driving a car.

Theories have been proposed to account for the symptoms of TS and ADHD in terms of particular reinforcement learning abnormalities. These theories will be presented in the following sections, and the research to date examining reinforcement learning in TS and ADHD shall be discussed. Finally, consideration will be given to how the study of reinforcement learning in TS+ADHD can be employed to improve understanding of this comorbidity.

2.2.1 Reinforcement learning in TS

In TS, it has been suggested that excessive dopaminergic activity in the striatum leads to the inappropriate formation of strong associations between external or internal sensory stimuli and motor responses (motor and phonic tics), resulting in hyper-learned tic 'habits' (Leckman & Riddle, 2000; Maia & Frank, 2011; Worbe et al., 2011). According to this view, like other habits tics are ingrained behaviours that are inflexible, executed largely automatically, and are difficult to consciously control. The success of habit-reversal therapy in treating tics supports this proposal, since this therapy trains the ability to break

and re-form well-learned associations between sensory urges to tic and tic actions (see chapter 1 section 1.2). In contrast to the hyper-learning hypothesis, Marsh et al. (2004) proposed that the ability to form habitual behaviours is impaired in TS due to structural and functional alterations in basal ganglia nuclei. Marsh et al. (2004) describe a concatenation process in habit-learning by which individual actions, such as those involved in brushing one's teeth (putting toothpaste on brush, brushing teeth, rinsing mouth), become chunked into a whole habitual behaviour (brushing teeth) by changes in dopaminergic firing. The authors suggested that this concatenation mechanism is impaired in TS and results in the execution of fragmentary actions (tics) that would normally be part of sequenced, coherently executed habitual behaviours.

Despite these well-formulated hypotheses concerning the nature of learning abnormalities underlying tic symptoms, little empirical work has investigated reinforcement learning in TS. Moreover, studies that have been conducted have produced mixed findings. For instance, Crawford et al. (2005) compared adolescents with TS and unaffected controls on a gambling task designed to assess reinforcement learning. On each trial, participants chose a card associated with a monetary reward or loss from one of four decks with the aim of winning as much money as possible. Two decks were 'bad', with cards giving large rewards or larger losses, and two decks were 'good', giving small rewards but smaller losses. Across 100 trials of learning about the monetary rewards/losses of each deck by trial and error, the TS and control groups showed no significant differences in the percentage of choices made from bad decks, or in RT to select a card. The authors concluded that individuals with TS and unaffected individuals were equivalent in learning ability. Channon et al. (2006) also reported no performance differences between adults with TS and controls on a rewarded object-alternation task. Across 50 trials, participants learned that to win a rewarding object (a coin), they had to search for the object in the opposite location to the one it had just been found. The TS and control groups did not differ in accuracy for selecting the alternate location, suggesting comparable learning in these two groups.

In contrast, Kéri et al. (2002) reported impaired learning performance in children with TS compared with controls on the Weather task. This task involves predicting good or bad weather (rain or sunshine) based on

combinations of 1, 2, or 3 symbolic cues, when each cue is probabilistically associated with rain and sunshine (e.g. one cue predicts rain 74% of the time and sun 26% of the time). Feedback concerning the accuracy of each weather prediction is provided to facilitate learning of the correct associations. The assumption of this task is that the complex probabilistic associations between cues and weather outcome force learning of the associations to take place non-consciously within the habit-learning system, rather than consciously within learning systems outside of the basal ganglia. Kéri et al. (2002) found that children with mild TS and controls showed a significant linear increase in accuracy in predicting weather across trials, while children with severe TS showed no such learning effect. Tic severity scores correlated negatively with accuracy, indicating children with most severe tics were poorest at learning the cue-weather associations. The authors concluded that children with TS were impaired at stimulus-response learning and suggested this might be due to deficient habit-learning functions of the dorsal basal ganglia. Marsh et al. (2004) replicated these findings with the Weather task in children and adults with TS, and additionally reported significantly less learning-related decrease in RT across trials in TS than controls. Again, greater tic severity was associated with poorer learning performance. The authors suggested that impaired habit-learning is central to the pathology of TS, and proposed that dysfunction of the basal ganglia concatenation mechanism underlies this impairment and tic symptoms (described in paragraph 1 of this section).

However, interpreting findings from the Weather task is problematic. The assumption that only the habit-learning system is involved in learning the cue-weather associations is unsupported by research showing that disrupting habit-learning does not impair performance on this task (Price, 2009). The extreme complexity of the Weather task further complicates interpretation of deficits. With four possible symbolic cues presented in combinations of one-to-three cues on each trial and each having a different probability of predicting good and bad weather, it is clear that this task places considerable demands on non-learning functions such as working memory. Therefore, the extent to which deficits in Weather task performance in TS reflect impairments in habit-learning specifically is unclear.

More informative findings of reinforcement learning in TS were provided by a set of carefully designed experiments from Palminteri and colleagues (Palminteri et al., 2009; Palminteri et al., 2011; Worbe et al., 2011). These experiments were designed based on the premise that if dopamine signalling is hyperactive in TS then individuals with TS should show intact, or perhaps over-active, learning from positive reinforcements but should be impaired on learning from negative reinforcements (Palminteri et al., 2009; Palminteri et al., 2011). The reason for this is that over-active dopaminergic transmission would result in more frequent or larger dopamine bursts following rewards, rendering it more likely that a positively reinforced behaviour will be learned. Simultaneously, raised dopamine levels would prevent or diminish depressions in dopaminergic signalling following negative reinforcements which would interfere with learning from punishments.

In the first of these studies, Palminteri et al. (2009) compared subliminal reinforcement learning between adults with TS receiving dopamine antagonist medication (neuroleptics), which reduces dopaminergic transmission, adults with TS not receiving neuroleptic treatment, and unaffected control adults. The task consisted of 'guessing' whether to respond or not respond on each trial and viewing the outcome of the choice. The outcome could be no reward (€0), positive reward (€1), or punishment (- €1). Associated with these outcomes were symbolic cues (one cue per outcome) which were presented subliminally (flashed on screen surrounded by masks) prior to participants' 'guesses'. Across the task, participants learned the associations between subliminally presented cues and reward outcomes. Learning from rewards was measured by the amount of money gained at the end of the task, while learning from punishment was measured by the amount of money not-lost. Palminteri et al. (2009) found that un-medicated adults with TS successfully learned from rewards but were poor at learning from punishments, while medicated adults with TS were able to avoid punishments but not learn from positive reward. Furthermore, individuals with TS showed a greater bias for learning from positive rewards compared with the control group, and this difference was larger when comparing the un-medicated adults with controls than the medicated adults with controls. The authors interpreted these findings as indicating that adults with TS exhibited signs of hyper-

dopaminergic activity when dopamine transmission was not regulated by neuroleptic medication. These effects are consistent with the hypothesis that tics are hyper-learned via excessive dopaminergic activity in reinforcement learning pathways, but further research is required to clearly link tic symptoms with hyperactive dopaminergic transmission during reinforcement learning.

Palminteri et al. (2011) extended these findings using a motor sequence learning task in adults with TS (medicated with neuroleptics and un-medicated) and unaffected controls. In this task, participants produced motor sequences consisting of three-key combinations of keyboard button presses in response to corresponding key combination images presented on screen. The outcome of each motor sequence was displayed on screen immediately following production. Outcome was minimal reward (1 cent) or high reward (€10). Half of the motor sequences were associated with minimal reward and the other half with high reward. Across 15 trial blocks, each motor sequence was produced 10 times. Learning of the motor sequences was assessed by decreases in RT across blocks for minimal reward and high reward sequences. Palminteri et al. (2011) found that learning was better for the highly rewarded sequences than the minimally rewarded sequences, which they termed a reinforcement learning effect. This reinforcement learning effect was significantly greater in un-medicated adults with TS than unaffected controls and medicated adults with TS. The authors concluded that these findings were consistent with hyper-dopaminergic activity in reinforcement learning circuitry in TS.

Importantly, these findings contradict Marsh et al.'s (2004) proposal that habit-learning concatenation functions are impaired in TS. Palminteri et al. (2011) noted the discrepancy between their findings and the impairment in habit-learning reported by Kéri et al. (2002) and Marsh et al. (2004), and suggested that this may reflect the fact that successful performance on the Weather task required learning from both positive and negative reinforcements, since each cue was associated probabilistically with good and bad weather outcomes. Palminteri et al. (2011) pointed out that reward and punishment learning would be differentially affected in TS by hyper-dopaminergic activity, and therefore it is crucial to examine these processes separately. It is possible that poor learning from negative reinforcements (bad weather outcomes) due to over-active dopamine transmission drove the impairment in the Weather task

rather than the impaired concatenation mechanism that Marsh et al. (2004) proposed. Consistent with this suggestion, Worbe et al. (2011) found that un-medicated adults with TS were slightly poorer at learning probabilistic associations between cues and good/bad outcomes than controls. The cue-outcome associations predicted good and bad outcomes simultaneously and were similar to the cue-outcome associations in the Weather task.

In summary, early studies of reinforcement learning in TS did not support the theory that tics reflect hyper-learned habitual behaviours arising from over-active dopaminergic transmission. Rather, studies reported no differences in reinforcement learning between individuals with TS and unaffected individuals (Channon et al., 2006; Crawford et al., 2005) or impaired learning in children and adults with TS, suggestive of a deficient habit-learning mechanism (Kéri et al., 2002; Marsh et al., 2004). In contrast, the recent studies from Palminteri and colleagues indicate that un-medicated adults with TS show greater learning of stimulus-response associations and motor action sequences from positive reinforcements but poorer learning from negative reinforcements than unaffected adults. These more recent findings are indicative of hyperactive dopaminergic signalling in TS and are consistent with the view that dopamine-mediated hyper-learning is involved in tic symptoms.

However, there are a number of issues concerning reinforcement learning in TS that remain to be addressed. Importantly, the involvement of hyper-learning in tics has yet to be clearly established. Palminteri and colleagues did not report how the differences in reinforcement learning in TS were associated with tic symptomatology. If tics are hyper-learned habits, it can be expected that more severe tics would be associated with greater hyper-learning from positive reinforcements and poorer learning from negative reinforcements. It is possible that the negative associations between tic severity and learning performance in the Weather task studies reflected an association between poor punishment learning (from the cues associated with bad weather outcomes) and more severe tics, but this is speculation and clearer evidence for the involvement of hyper-learning in tics is required. Moreover, findings of hyper-learning in TS have not been reported in children. Adults with TS are atypical of the condition because tics usually remit or abate in early adulthood. It is therefore important to establish whether the reinforcement learning effects

reported in Palminteri et al.'s adult samples are generalisable to children with TS.

Another issue is the extent to which atypical reinforcement processes in TS are restricted to habit-learning or also affect goal-directed learning. Different striatal-cortical circuits are thought to be involved in habit-learning (sensorimotor cortices and dorsal striatum) and goal-directed learning (ventral striatum and prefrontal and limbic cortices). Therefore, establishing whether both of these learning systems or just habit-learning is atypical in TS could reveal important insights into the neural mechanisms underlying tic symptoms. With the exception of the Weather task studies which focused specifically on habit-learning (Kéri et al., 2002; Marsh et al., 2004) the previous research in TS has not distinguished between habit-learning and goal-directed learning. Finally, the extent to which individuals with TS can control and modify behaviours learned by reinforcement has not been examined. This is an important area for investigation because it would be informative of the degree to which individuals with TS can control tics, assuming tics are well-learned behaviours. In the current research, in addition to the main aims of this thesis to investigate the basis and impact of comorbid ADHD symptoms in young people with TS, these issues concerning reinforcement learning in TS were explored. Performance of young people with TS was compared with unaffected controls on two tasks designed to measure habit-learning and goal-directed learning separately, and the degree to which individuals could modify the learned behaviours and how tic symptom severity predicted learning performance on each task was examined.

2.2.2 Reinforcement learning in ADHD

In ADHD, it is suggested that reinforcement processes are inefficient due to hypoactive dopaminergic transmission in cortico-striatal pathways involving the ventral striatum, limbic and prefrontal cortices, creating a steepened *delay of reward gradient* (Johansen et al., 2009; Maia & Frank, 2011; Sagvolden et al., 2005). Delay of reward gradient is a term used to refer to the length of time or number of items in between which the production of a behaviour and a rewarding dopamine burst can be associated to ensure the behaviour is strengthened and reproduced in future (Johansen et al., 2009;

Maia & Frank, 2011; Sagvolden et al., 2005; Sonuga-Barke, 2002). A steepened delay of reward gradient in ADHD would result in impaired learning from positive reinforcements unless a sufficiently short time or sufficiently few behaviours occurred in the interim between the to-be-learned behaviour and its reward (Johansen et al., 2009; Sagvolden et al., 2005). Additionally, low dopaminergic activity is proposed to diminish the impact of negative prediction errors (depressions in dopamine firing) in ADHD, thereby creating impairments in learning from punishments (Johansen et al., 2009; Sagvolden et al., 2005). Difficulties learning appropriate behaviours and extinguishing inappropriate behaviours are proposed to underlie the inattentive, hyperactive and impulsive symptoms of ADHD (Johansen et al., 2009; Sagvolden et al., 2005).

Support is accumulating for this account of reinforcement learning in ADHD. For instance, Frank et al. (2007) compared reinforcement learning performance of adults with ADHD, tested on and off their methylphenidate (dopamine agonist) medication, and unaffected adults. The authors hypothesised that adults with ADHD would be impaired at learning from rewards when off medication compared with controls due to hypoactive dopamine transmission, but this deficit would improve on medication due to the enhancing effects of methylphenidate on dopamine. Frank et al. (2007) further predicted that learning from negative reinforcements would not improve with medication administration because enhancing dopamine would not normalise negative prediction errors.

Participants were presented with pairs of stimuli and were required to choose one of the stimuli in each pair. The stimulus pairs were constructed such that in one pair, one stimulus was correct 80% of the time and the other stimulus was correct 20% of the time, in another pair the stimuli were correct 70% and 30% of the time, and in a third pair the stimuli were correct 60% and 40% of the time. Feedback was presented after each choice to enable learning of the probabilistic associations between stimuli and correct responses across trials. Learning could proceed by positive reinforcement (learning that one stimulus in each pair was correct 80%, 70% or 60% of the time) or by negative reinforcement (learning that one stimulus in a pair was incorrect 20%, 30% or 40% of the time). Frank et al. (2007) reported that, as predicted, adults with

ADHD off medication were significantly poorer at learning from positive and negative reinforcements than controls. On medication, positive reinforcement learning was improved in ADHD to the point that these individuals did not differ from controls, but the impairment in learning from negative reinforcements remained. This pattern of findings provides compelling support for the hypothesised hypo-dopamine mediated impaired reinforcement learning in ADHD.

Difficulties with reinforcement learning have also been reported in children with ADHD. Luman et al. (2009) used a simple reinforcement learning task in which children with ADHD (off stimulant medication) and unaffected controls learned across trials, by positive and negative feedback, to associate two presented pictures with left hand responses and another two pictures with right hand responses. In addition to positive and negative feedback informing children of the correctness of their responses, on some trials the children received a small (2 cent) or large (8 cent) reward for correct responses. The frequency of rewards varied from infrequent (12.5% of trials) to frequent (50% of trials). Luman et al. (2009) hypothesised that large, frequent rewards would enhance learning performance in ADHD. The authors found that children with ADHD and unaffected controls increased in accuracy across trials, indicating both groups learned the stimulus-response (S-R) associations. However, accuracy throughout the task was lower in children with ADHD and, unlike controls, the ADHD group showed no learning-related decrease in RT across trials. Luman et al. (2009) suggested that the S-R associations were weaker in ADHD than controls, and concluded the children with ADHD had difficulty with reinforcement learning. Learning performance in the ADHD group was uninfluenced by frequency and magnitude reward manipulations, which led the authors to suggest that the difficulty in learning may have been driven by working memory or other non-reinforcement related impairments. However, increasing reward frequency and magnitude need not necessarily improve the functioning of positive and negative prediction errors, particularly in the case of this study in which the frequent rewards were not especially frequent (only 50% of trials) and the difference between large and small rewards may not have been meaningful.

Itami and Uno (2002) examined the ability to reverse behaviours learned by reinforcement and extinction of previously-learned behaviours in ADHD. Children with ADHD (off stimulant medication) and unaffected control children completed two reinforcement learning tasks. Both tasks began with a learning phase in which the children learned to associate one of two presented figures with a button click and the other figure with no button click. Feedback was presented after each trial and a point was awarded for every correct response to the click figure and every correct omission of response to the not-click figure. Once a criterion of 9/10 correct trials in a row was reached the children proceeded to either a reversal phase in one task or an extinction phase in the second task. In the reversal task, the associations between figures and responses reversed unexpectedly, such that the previous click figure became the not-click figure and the previous not-click figure became the click figure. Positive and negative feedback following responses were provided so that children could learn the new, reversed associations. In the extinction task, after the learning phase it became inappropriate to click either figure. This was indicated by negative feedback following a response to either the previous click or previous not-click figures.

In both tasks, all children showed an increase in points won during the learning phase, indicating they successfully learned the figure-response associations, a decrease in points won at the beginning of the reversal and extinction phases, and an increase again towards the end of the extinction/reversal phases. However, the children with ADHD required more trials than controls to reach criterion in the learning phases of each task, indicating a difficulty with acquiring the figure-response associations. Moreover, the ADHD group made more errors than controls in the extinction and reversal phases, suggesting that children with ADHD were less able to learn the new reversed associations and learn by negative reinforcement to extinguish the previously-learned associations than unaffected children. Additionally, the children with ADHD performed more poorly in the extinction phase than in the reversal phase, indicating greater impairment in extinction than reversal learning processes, while the control children produced equivalent performance in the extinction and reversal phases. These findings provide clear support for the theory that depleted dopamine leads to impaired

learning of new behaviours from positive rewards and impaired extinction of previously acquired behaviours by negative punishments. Further, Itami and Uno's (2002) results indicate that children with ADHD experience difficulty when behaviours learned by reinforcement must be modified.

Habit-learning learning paradigms have also been employed to investigate reinforcement learning in ADHD. For example, Karatekin et al. (2009) examined incidental learning of motor sequences in the serial-reaction time task (SRT) in adolescents with ADHD (off stimulants) and unaffected controls. In the SRT task (Nissen & Bullemer, 1987) participants make rapid button-press responses to a stimulus that moves between different locations on screen, using a different response button for each screen location. In some task blocks, stimulus movement occurs in a repeating sequence of screen locations, while in other task blocks stimulus movement is pseudorandom. Participants are not informed of the repeating sequence and their aim is simply to respond to the stimulus as quickly as possible. Despite being unaware of the repeating sequence, participants show increasingly fast RTs on sequence blocks and slower RTs on pseudorandom blocks, indicating that the sequence was learned incidentally (without awareness) and that this learning facilitated better performance on sequence blocks and disrupted performance on non-sequence blocks.

Although the SRT does not involve learning from tangible rewards or punishments, neuroimaging studies have revealed that striatal dopamine release during SRT performance is consistent with positive prediction errors (Badgaiyan et al., 2007; Rauch et al., 1998). Therefore, it is appropriate to class the SRT as a reinforcement learning task. Further, the SRT can be considered to measure mainly habit-learning because the sequence learning is not goal-directed. Karatekin et al. (2009) found that both ADHD and control groups showed typical SRT learning effects. RTs decreased during the sequence blocks, and increased when a pseudorandom block was presented after the sequence blocks. These findings indicate that children with ADHD were not impaired in incidental sequence learning, which implies that the habit-learning system is not affected, or is relatively less affected, than the goal-directed learning system in ADHD.

However, Barnes et al. (2010) reported atypical sequence learning RT effects in ADHD during a modified version of the SRT paradigm, which involved incidental learning of alternating response sequences. Specifically, while control children showed the typical decrease in RT across sequence blocks, reflecting learning of the alternating sequence, children with ADHD showed a pattern of decrease-increase-decrease in RT across sequence blocks. Barnes et al. (2010) concluded that sequence learning was atypically variable in children with ADHD. These results could reflect an impairment in habit-learning in children with ADHD, or possibly fatigue or boredom effects in the middle of the task in these children.

To summarise, empirical work examining goal-directed reinforcement learning in children and adults with ADHD has provided clear support for the theory that learning from positive rewards and negative punishments is impaired in ADHD, and that hypoactive dopamine transmission underlies this deficit. It is less clear whether habit-learning is also affected by abnormal dopamine in ADHD, although the findings to date provide greater support for this form of learning to be spared rather than impaired. Nevertheless, further research investigating habit-learning in ADHD is warranted and would be valuable in terms of understanding the neural circuits affected in ADHD. Furthermore, knowledge that habit-learning is unimpaired in ADHD would be useful in understanding which aspects of cognition are relatively strong in children with ADHD and could be harnessed in therapeutic management of symptoms. Therefore, in addition to the main aims of this thesis in investigating comorbid TS+ADHD, the extent to which goal-directed and habit-learning are atypical in ADHD compared with unaffected young people was explored.

2.2.3 Reinforcement learning in TS+ADHD

Considering the opposing atypicalities in dopamine and reinforcement learning in TS and ADHD, with increased dopamine and hyper-learning in TS and decreased dopamine and impaired learning in ADHD, it seems counterintuitive that these conditions should co-occur. One possibility is that TS+ADHD is a symptomatic phenocopy, and that the ADHD symptoms observed are in fact misinterpreted tics (see chapter 1, section 1.4.1 for a full

explanation of this comorbidity model). Another possibility is that dopamine abnormalities are restricted to habit-learning circuitry in TS and goal-directed circuitry in ADHD, and both of these atypicalities occur in TS+ADHD. This suggestion would support an additive model of comorbidity. A final possibility is that TS+ADHD is an independent condition and does not share the same dopamine-related pathological mechanisms as TS and ADHD. An important question then for understanding the basis of TS+ADHD is to establish how reinforcement learning, and by inference dopaminergic striatal-cortical pathways, manifests in young people with TS+ADHD.

To the best of this author's knowledge, only one published study has examined reinforcement learning in TS+ADHD. Channon et al. (2003) compared incidental sequence learning during the SRT task in young people with TS (n = 14), TS+ADHD (n = 9), TS+OCD (n = 6) and unaffected controls (n = 21). The authors reported no significant group differences in the degree of RT decrease across sequence blocks and concluded that individuals with TS with or without comorbid ADHD or OCD did not show impairment in incidental learning. However, Channon et al. (2003) did not control for confounding effects of medication on performance. Eight young people with TS were receiving neuroleptic medication for tic symptoms, one participant was receiving methylphenidate, which was not withdrawn, for ADHD symptoms, and another five participants with TS were taking other medications such as SSRIs, which do not target dopamine signalling directly but likely influence dopamine levels indirectly via their effects on serotonin. As the studies in TS and ADHD have shown, TS-related and ADHD-related atypicalities in reinforcement learning diminish strikingly with administration of neuroleptics and methylphenidate (Frank et al., 2007; Palminteri et al., 2009; Palminteri et al., 2011). Therefore, Channon et al.'s (2003) SRT findings in TS and TS+ADHD may reflect medication effects rather than disorder effects.

Clearly, reinforcement learning requires further investigation in TS+ADHD. In the current research, habit-learning and goal-directed reinforcement learning tasks were employed to thoroughly explore which aspects of reinforcement learning are affected in TS+ADHD and how functioning of these learning systems differs or is similar to those in TS and ADHD alone.

2.2.4 Approach and hypotheses for learning in the current research

The main aim of examining reinforcement learning in this thesis was to improve understanding of the basis of TS+ADHD, particularly whether additive, independent or symptomatic phenocopy models best fit this form of comorbidity. Two additional aims were firstly, to compare habit-learning and goal-directed learning in TS compared with unaffected children to investigate whether atypicalities are restricted to habit-learning, whether tic symptoms are associated with these atypicalities, and how well young people with TS can control well-learned behaviours. The second additional aim was to explore whether both goal-directed and habit-learning systems are affected in ADHD.

The approach taken was to compare reinforcement learning performance of young people with TS, TS+ADHD, ADHD and unaffected controls on a habit-learning task and a goal-directed learning task. The SRT task was selected as a measure of habit-learning due to the robust nature of this task in eliciting learning effects in typically developing children and adults (Eimer et al., 1996; Jackson et al., 1995; Meulemans et al., 1998; Nissen & Bullemer, 1987; Thomas & Nelson, 2001; Thomas et al., 2004). A novel task involving learning of simple S-R associations by positive and negative feedback was designed to assess goal-directed learning (described in full in chapter 4, section 4.1.1). This task was based on paradigms used previously to study dopamine prediction error activity during reinforcement learning in non-human primates (Pasupathy & Miller, 2005) and was pilot tested in typically developing children and adults to ensure it elicited behavioural and electrophysiological reinforcement learning effects (see appendix A for the pilot study, which has been produced for publication and is under review with *Developmental Cognitive Neuroscience*). Both habit and goal-directed learning tasks consisted of an initial learning phase followed by a control phase in which the learned habitual or goal-directed behaviours required modification. This was done to assess how well young people in each group were able to alter well-learned behaviours.

In addition to examining behavioural task performance, neural mechanisms underlying reinforcement learning were investigated using electrophysiology. EEG analyses were restricted to the goal-directed learning task because the SRT task is not particularly amenable to electrophysiological

recording due to the rapid presentation of stimuli and because electrophysiological correlates of habit-learning are not well established. Two ERP components were selected as electrophysiological correlates of goal-directed reinforcement learning, the stimulus-locked P3 and the feedback-locked feedback-related negativity (FRN). The P3 is a positive deflection in the averaged ERP waveform at approximately 300-600ms following a stimulus. In learning situations the P3 is maximal at parietal scalp sites and decreases across trials as to-be-learned behaviours are acquired (Rose et al., 2001; Shephard et al., *under review* (see appendix A)). The P3 is thought to reflect increasing consolidation of to-be-learned behaviours, such as the strengthening of S-R associations (Rose et al., 2001; Shephard et al., *under review* (see appendix A)).

The FRN is a negative deflection in the averaged ERP waveform that is maximal at fronto-central scalp and occurs at approximately 250ms following positive and negative feedback (Miltner et al., 1997; Oliveira et al., 2007). The FRN was originally thought to occur only, or maximally, following negative feedback and was suggested to reflect negative prediction errors (Holroyd & Coles, 2002; Miltner et al., 1997). More recently however it has been demonstrated that the FRN is also elicited by positive feedback (Oliveira et al., 2007), and varies in amplitude depending on participants' expectancy of feedback. That is, the FRN is larger when feedback is unexpected regardless of whether it is positive or negative, and smaller when feedback is expected (Bellabaum & Daum, 2008; Luque et al., 2012; Oliveira et al., 2007). Consequently, the FRN is thought to index positive and negative prediction errors (Luque et al., 2012; Oliveira et al., 2007). In typically developing children and adults the FRN decreases in amplitude as behaviours are learned by reinforcement, likely reflecting decreasing magnitude of prediction errors (Eppinger et al., 2009; Holroyd & Coles, 2002; Shephard et al., *under review* (see appendix A)).

This component has not been studied previously in individuals with TS or TS+ADHD, but has been examined during non-learning, reward and punishment processing in ADHD (Holroyd et al., 2008; van Meel et al., 2011). These studies reported no differences in FRN amplitude during rewarded and punished guessing tasks in children with ADHD compared with unaffected

controls, suggesting dopamine prediction errors were equivalent in individuals with and without ADHD. These findings are in stark contrast to the reinforcement learning studies in ADHD showing methylphenidate mediates performance impairments in ADHD (Frank et al., 2007), and require further investigation.

Two methods of analysing behavioural and electrophysiological correlates of reinforcement learning were employed. First, performance and ERP measures were compared between the four participant groups to investigate how the TS and ADHD groups differed from the control group, and how the TS+ADHD group differed or were similar to the TS and ADHD groups and the unaffected controls. Second, regression analyses were conducted to examine how well severity of tics and ADHD symptoms predicted reinforcement learning measures. The aim of regression analyses was to clarify the involvement of reinforcement learning in tic and ADHD symptoms in the TS and ADHD groups respectively, and to establish whether such relationships were also present in the TS+ADHD group.

It was hypothesised that young people with TS would show hyper-learning during the habit-learning task compared with controls but not during the goal-directed learning task. Further, the TS group were expected to show impairment in controlling the learned habitual behaviours relative to controls, which would be consistent with the intractable nature of hyper-learned habits and the difficulty involved in controlling tics. It was predicted that young people with TS with more severe tics would show greater hyper-learning in the habit-learning task and poorer control over the learned habitual behaviours than young people with less severe tics. Conversely, young people with ADHD were predicted to show impaired learning of and control over goal-directed behaviours compared with controls but equivalent habit-learning ability. Greater ADHD symptom severity was expected to be associated with more impaired goal-directed learning. Due to the scarcity of previous research, no specific predictions were made for reinforcement learning in the TS+ADHD group. Rather, the extent to which young people with TS+ADHD showed similar reinforcement learning characteristics to the TS and ADHD groups and the presence of relationships between tic and ADHD symptom severity and reinforcement learning in TS+ADHD were explored. The methods and results

for the habit-learning and goal-directed learning tasks are presented in chapters 4 and 5 respectively.

2.3 COGNITIVE CONTROL

The self-regulatory processes referred to by the term cognitive control include withholding inappropriate and/or impulsive behaviours, suppressing irrelevant external or internal stimuli that interfere with goal-directed behaviour, monitoring and resolving conflict in incoming information or in our own internal thoughts and behaviour plans, monitoring and adjusting our behaviour for errors, switching flexibly between different cognitive and behavioural tasks (cognitive flexibility), and regulating our on-going behaviour to ensure it is optimal for the current environment (Pennington & Ozonoff, 1996). Cognitive control develops gradually across childhood, reaching maturity in late adolescence or early adulthood (Bunge et al., 2002; Casey et al., 1997; Dimoska et al., 2007; Hogan et al., 2005; Johnstone et al., 2005; Johnstone et al., 2007; Jonkman, 2006; Koolschijn et al., 2011; Ladouceur et al., 2007; Rubia et al., 2006; Rueda et al., 2004; Velanova et al., 2008). The protracted development of cognitive control is thought to reflect the slow maturation of its frontal neural substrates, such as the dlPFC, OFC and ACC, and their connections with key posterior and subcortical regions, including the tempero-parietal cortices and the basal ganglia (fronto-striatal circuit) (Bunge et al., 2002; Casey et al., 1997; Fair et al., 2007; Rubia et al., 2006; Velanova et al., 2008). Since the neural circuitry involved in the typical development of cognitive control has been shown to be altered in TS and ADHD (see 1.4.2) there is good reason to expect young people with these disorders to exhibit atypicalities in cognitive control.

2.3.1 Cognitive control in TS

Based on the observation that individuals with TS appear to have great difficulty with preventing the expression of motor and phonic tic behaviours, it has frequently been proposed that TS is associated with a fundamental deficit in cognitive control (Kane 1994; Marsh et al., 2007; Pennington & Ozonoff,

1996; Roessner et al., 2008). However, research investigating cognitive control in children and adolescents with TS has provided little evidence for such a deficit. The majority of recent studies (summarised in table 2-1) have reported no differences in cognitive control performance between young people with TS and age-matched controls. These studies have employed several different experimental tasks designed to measure a range of cognitive control processes, including the ability to suppress irrelevant and interfering information, withhold the execution of an inappropriate prepotent or prepared response, and switch flexibly between performing different tasks. Thus, cognitive control appears to be intact in young people with TS across an array of processes measured and experimental paradigms employed. This pattern of findings cannot easily be attributed to normalising or enhancing effects of medication on performance because several of the studies included medication-naïve (never medicated) or medication-free (not currently medicated) participants (Baym et al., 2008; Roessner et al., 2008).

Interestingly, several recent studies have found cognitive control to be enhanced in young people with TS compared with unaffected young people. For instance, Mueller et al. (2006) used an oculomotor task consisting of switching between execution of pro- and anti- saccadic eye movements towards or away from a target every two trials. The saccade type required on each trial was cued at long or short preparation times. The authors found that young people with TS performed better than controls, producing significantly fewer errors and faster RTs on trials with the highest cognitive control demands (short preparation switch trials). Jackson and colleagues replicated the enhancement in other samples of young people with TS when switching predictability and preparation time in the oculomotor task were reduced (Jackson et al., 2007) and using a manual version of the oculomotor switching task (Jackson et al., 2011, Experiment 1). Other research groups have also reported enhanced performance in young people with TS on switch trials of a combined switching and interference suppression paradigm (Greimel et al., 2011) and on Go and Nogo trials of a Go/Nogo task, requiring execution and prevention of a prepotent motor response respectively (Debes et al., 2011).

Table 2-1

Summary of studies investigating cognitive control in children and adolescents with TS and unaffected controls (Co)

Authors (year)	TS n (age in years); Co n (age in years)	% TS+ comorbid ADHD/OCD	% TS on medication	Tasks employed (main cognitive control processes assessed)	Cognitive control effects
Ozonoff et al. (1998)	46 (11.9); 22 (12.5)	50%	60%	Negative Priming (interference suppression)	TS = Co TS- = Co; TS+ < Co[a]
Ozonoff et al. (1999)	30 (12.6); 29 (12.1)	46%	Not specified	Stroop (interference suppression), ToH (planning), WCST (interference suppression/cognitive flexibility)	TS = Co (all tasks) TS- = Co; TS+ = Co[a] (All tasks)
Crawford et al. (2005)	20 (14.4); 20 (14.3)	0%	25%	Flanker (interference suppression), Sentence Completion (interference suppression)	TS < Co (all tasks)
Li et al. (2006)	30 (12.0); 28 (12.1)	43%	93%	Stop Signal Task (withholding prepared response)	TS = Co
Mueller et al. (2006)	9 (13.1); 19 (13.3)	0%	55%	Combined antisaccade + Switching (withholding prepotent response + cognitive flexibility)	TS > Co
Jackson et al. (2007)	7 (14.2); 12 (14.0)	0%	57%	As above	TS > Co
Marsh et al. (2007)	32 (12.8); 20 (13.5)	37%	71%	Stroop	TS = Co
Baym et al. (2008)	18 (10.4); 19 (10.3)	55%	0%	Nemo task (rule learning, cognitive flexibility, interference suppression)	TS = Co
Roessner et al. (2008)	20 (12.5); 15 (12.8)	0%	0%	Go/Nogo (withholding prepotent response)	TS = Co

Church et al. (2009)	27 (12.5); 27 (12.4)	44%	70%	Stroop, TMT (cognitive flexibility), Verbal Fluency (cognitive flexibility)	TS = Co (all tasks)
Eichele et al. (2010)	19 (12.6); 19 (13.1)	47%	52%	Go/Nogo	TS = Co
Sukhodolsky et al. (2010)	56 (10.9); 71 (11.4)	0%	64%	CPT (sustained attention + withholding prepotent response), Stroop	TS = Co (both tasks)
Debes et al. (2011)	39 (13.9); 37 (13.8)	43%	0%	Go/Nogo, Stroop	TS- > Co (Go/Nogo); TS = Co (Stroop)
Greimel et al. (2011)	21 (11.3); 27 (12.0)	0%	0%	Set shifting (cognitive flexibility + interference suppression), Go/Nogo	TS > Co (Set Shifting) TS = Co (Go/Nogo)
Jackson et al. (2011)					
Exp. 1:	13 (14.2); 13 (14.0)	0%	53%	Exps 1 and 3: Combined switching + conflict	Exp1: TS > Co
Exp. 3:	10 (13.7); 15 (14.3)	0%	Not specified	(cognitive flexibility + interference suppression)	Exp3: TS = Co
Drury et al. (2012)					
(Exp.1)	16 (13.4); 27 (14.1)	0%	50%	Stroop + Switching (interference suppression + cognitive flexibility)	TS = Co

[a] TS- refers to children with TS without comorbid ADHD/OCD; TS+ refers to children with TS and comorbid ADHD and/or OCD.

One possible explanation for the enhancement in TS is that cognitive control processes measured in experimental tasks are routinely employed by individuals with TS to control their tics in daily life. Due to the frequent engagement of cognitive control during tic control these processes become heightened, which might reflect a compensatory strengthening of cognitive control neural circuitry (Jackson et al., 2007). This suggestion is consistent with Leckman et al.'s (2006) frontal lobe compensation hypothesis (described in 1.4.2) proposing that repeated engagement of prefrontal regions to modulate activity in basal ganglia and motor cortical regions involved in tic production leads to compensatory enhancement of prefrontal circuitry and the ability to voluntarily control tics. Importantly, the behavioural findings of enhanced cognitive control in TS indicate that the compensatory enhancement can be measured in the laboratory using experimental tasks.

Furthermore, studies investigating structure and function of fronto-striatal circuitry associated with cognitive control task performance have indicated that compensatory neural changes in TS can be detected using neuroimaging methods in tandem with cognitive control paradigms. For example, Jackson et al. (2011, Experiment 2) reported alterations in the integrity of white matter tracts underlying the frontal lobes in young people with TS which were consistent with compensatory changes in cognitive control networks. Several functional neuroimaging studies have reported fronto-striatal activation to be greater in individuals with TS than unaffected controls during performance of demanding cognitive control task trials (Baym et al., 2008; Jackson et al., 2011, Experiment 3; Marsh et al., 2007). These neuroimaging findings suggest that individuals with TS recruit cognitive control circuitry to a greater degree than controls to achieve successful task performance and are consistent with Jackson et al.'s (2007) proposal that such circuitry is strengthened.

Several findings in adults with TS have also supported the proposal that enhanced cognitive control is associated with tic control and arises from strengthened fronto-striatal cognitive control networks. It must be noted that findings in adults are somewhat problematic to interpret because by definition, adults with TS do not follow the typical remitting course of the disorder and hence findings in adult participants may not be typical of TS. This might be

particularly true for findings of cognitive control because if, as the above findings suggest, this function is intimately linked with compensatory mechanisms to cope with tics, then adults with non-remitting TS may not have undergone such changes. Inefficient cognitive control ability and an associated lack of neuroplastic adaptation to tics might explain why symptoms do not diminish with age in these individuals. Consistent with these suggestions, findings of cognitive control performance in adults with TS are more mixed than in children. These studies are summarised in table 2-2.

Nevertheless, four studies conducted with adult participants are particularly relevant to this thesis and the compensatory hypotheses and shall be considered. First, Deckersbach et al. (2006) examined associations between cognitive control performance on a task measuring interference suppression, the visuospatial priming (VSP) task, and response to habit-reversal therapy (HRT) in adults with TS. TS showed poorer performance than controls, indicating impairment in the ability suppress interfering information. Importantly, post-HRT decreases in tic severity were associated with better performance on the VSP task. That is, adults who experienced the greatest decrease in tic severity with HRT had more efficient cognitive control than adults who responded less well to HRT. These findings indicate that more efficient cognitive control performance on laboratory tasks is associated with better tic control and may be a useful predictor of the likelihood that an individual will respond to behavioural tic therapy.

The remaining three relevant studies employed electrophysiological measures of neural activity associated with cognitive control. Since EEG has rarely been used to study cognitive control in children with TS, the findings from the adult studies were used to guide methods and hypotheses concerning electrophysiological correlates of cognitive control in young people in this thesis. The earliest study was conducted by Johannes et al. (2001) and examined ERP correlates of withholding prepared responses in the Stop-Signal Task (SST). The SST involves responding promptly to a Go stimulus except when it is followed by a Stop stimulus. Stop trials therefore require the prepared Go response to be withheld. The authors found no group differences in task performance, but ERPs associated with withholding the response on Stop trials were larger in amplitude at frontal scalp sites in TS than controls.

Table 2-2

Summary of research investigating cognitive control in adults with TS and unaffected controls (Co)

Author (year)	TS n (age in years); Co n (age in years)	% TS+ comorbid ADHD/OCD	% TS on meds	Task(s) (cognitive control processes assessed)	Cognitive control effects
Georgiou et al. (1995)	10 (31.0); 10 (31.0)	Not specified	50%	Switching + interference suppression paradigm	TS < Co
Johannes et al. (2001)	10 (34.4); 10 (33.7)	50%	40%	Stop Signal Task (withholding prepared response)	TS = Co
Channon et al. (2004)	15 (33.8); 23 (33.7)	0%	Not specified	Hayling Sentence Completion (interference suppression), WCST (interference suppression + cognitive flexibility)	TS < Co (Hayling) TS = Co (WCST)
Serrien et al. (2005)	9 (28); 9 (29)	22%	0%	Go/Nogo (withholding prepotent responses)	TS = Co
Watkins et al. (2005)	20 (31.5); 20 (36.6)	15%	70%	Verbal Fluency (cognitive flexibility), Set-Shifting (cognitive flexibility), Go/Nogo	TS < Co (set-shifting) TS = Co (Go/Nogo, Fluency)
Channon et al. (2006)	20 (31.0); 25 (28.8)	0%	50%	Combined Flanker + Switching (interference suppression + cognitive flexibility), Sentence Completion (interference suppression)	TS < Co (Sentence Completion) TS = Co (Flanker/Switching)
Deckersbach et al. (2006)	28 (35.1); 20 (34.3)	53%	57%	Visuospatial Priming (VSP) (interference suppression)	TS < Co

Rankins et al. (2006)	6 (49.); 6 (47.7)	0%	33%	Switching + interference suppression paradigm	TS < Co
Thibault et al. (2009)	15 (37); 20 (40)	0%	0%	Stroop, combined Go/Nogo and interference suppression paradigm	TS > Co (both tasks)
Beirmann-Ruben et al. (2012)	12 (37), 12 (37)	0%	0%	Go/Nogo	TS = Co
Eddy et al. (2012)	40 (32); 20 (27.3)	0%	60%	Verbal Fluency, Stroop	TS < Co (both tasks)
Wylie et al. (2013)	27 (26.1); 28 (26.6)	0%	39%	Simon task (interference suppression)	TS < Co

The ERP components examined were an early frontal negativity and the NoGo-Anteriorisation (NGA). The early frontal negativity was defined by the authors as a negative deflection in the time-range 100-400ms following the Go stimulus, and likely partially corresponds to the N2 ERP component. The N2 is a negative deflection occurring 200-400ms post-stimulus at fronto-central scalp sites and is larger in amplitude for task trials with high versus low cognitive control demands (Jodo & Kayama, 1992). The N2 has been linked with several cognitive control processes such as resolving conflict, suppressing interfering information, and withholding prepotent responses (Enriquez-Geppert et al., 2010; Folstein et al., 2008; Jodo & Kayama, 1992). The NGA refers to a shift in P3 topography from the typical centro-parietal maximum observed on low cognitive control trials to a frontal maximum on trials when cognitive control is engaged, particularly when a prepotent response must be withheld (Enriquez-Geppert et al., 2010; Fallgatter et al., 1997; Fallgatter & Strik, 1999). Source analyses investigating the neural generators of the N2 and NGA suggest that these components reflect the engagement of frontal cognitive control mechanisms (Enriquez-Geppert et al., 2010; Fallgatter et al., 2004; van Veen et al., 2002).

Johannes et al.'s (2001) findings are consistent with the fMRI findings in children (Baym et al., 2008; Jackson et al., 2011; Marsh et al., 2007) indicating that individuals with TS engage cognitive control circuitry to a greater degree than unaffected individuals during experimental tasks. Thibault et al. (2009) corroborated Johannes et al.'s (2001) NGA findings using a combined Nogo and interference suppression task. Adults with TS performed better than controls on trials requiring suppression of interfering response information, and as well as controls in preventing prepotent responses to Nogo stimuli. The NGA, measured as the difference between Nogo and Go trials, showed a more frontal maximum in TS than in controls, indicating greater activity in frontal control circuitry during Nogo trials in the TS group. These ERP studies indicate that the N2 and NGA ERP components are sensitive electrophysiological indices of the strengthened engagement of cognitive control circuitry in TS.

Finally, in their study examining electrophysiological activity in the alpha frequency band during tic suppression in adults with TS (see 1.4.2),

Serrien et al. (2005) also examined alpha activity during performance of a Go/Nogo task. The adults with TS performed the task as well as controls, but exhibited greater alpha coherence between frontal and central scalp sites during Nogo trials than controls. Coherence is a measure of the extent to which changes (e.g. increases or decreases) in oscillatory EEG activity in a given frequency band at a particular scalp location are associated with the same changes in activity at other scalp sites, and is thought to index the recruitment of neural networks underlying the scalp sites examined. The same increase in alpha coherence between fronto-central sites was found while adults with TS suppressed tics compared with freely executed tics. Serrien et al. (2005) therefore concluded that frontal neural circuitry involved in cognitive control over motor behaviour was enhanced in TS and could be recruited to gain control over tics. These findings provide further support for the association between cognitive control measured on laboratory tasks and processes engaged to control tics, the compensatory increased engagement of cognitive control circuitry in TS, and the sensitivity of electrophysiological measures in detecting this increased engagement.

In summary, there is growing evidence that cognitive control ability measured on experimental tasks is closely associated with an individual's ability to control tics in daily life, and that neural circuitry underlying cognitive control is engaged more greatly in TS than in unaffected individuals. This could reflect a compensatory response to tics that can result in enhanced behavioural performance on cognitive control tasks in the laboratory and can be measured using fMRI and electrophysiological techniques. Cognitive control ability and increases in frontal activation during cognitive control tasks may be useful as a marker for the likelihood that an individual will respond well to behavioural therapies for tics. Understanding how comorbid ADHD symptoms affect cognitive control ability and underlying neural circuitry in young people with TS is therefore of great importance. As will be discussed in the following section, ADHD has been robustly associated with impaired cognitive control at the behavioural and neural level, suggesting comorbid ADHD symptoms might impair cognitive control, and therefore tic control, in TS.

2.3.2 Cognitive control in ADHD

Cognitive control impairments have been proposed as central to ADHD, underlying inattentive, impulsive and hyperactive symptoms (Barkley, 1997). Correspondingly, empirical investigations have revealed a range of cognitive control deficits in ADHD. Impaired ability to withhold prepotent or prepared inappropriate responses has been strongly associated with the disorder, with numerous reports of significantly higher rates of Stop and Nogo errors in children and adults with ADHD compared with controls (Benikos & Johnstone, 2009; Casey et al., 1997; de Zeeuw et al., 2008; Durston et al., 2003; Groom et al., 2008; Groom et al., 2010a; Johnstone & Clarke, 2009; Liotti et al., 2005; Tamm et al., 2004; Vaidya et al., 2005; Wiersema et al., 2005). There have also been consistent reports of impaired circuitry underlying the ability to withhold inappropriate behaviours, including hypoactivity and reduced connectivity in fronto-striatal regions (Cubillo et al., 2010; Durston et al., 2003; Rubia et al., 1999; Rubia et al., 2010; Smith et al., 2006; Tamm et al., 2004; Vaidya et al., 2005), and significantly reduced frontal amplitudes of N2 and NGA ERPs (Albrecht et al., 2005; Benikos & Johnstone, 2009; Fallgatter et al., 2004; Groom et al., 2008; Groom et al., 2010b; Johnstone & Clarke, 2009; Johnstone et al., 2007; Liotti et al., 2005; Wild-Wall et al., 2009) during successful Stop and Nogo trials.

Impairments in other cognitive control processes have also been reported. Children and adults with ADHD have produced significantly poorer performance on tasks such as the Stroop and Flanker paradigms and reduced activation of fronto-striatal and temporal circuitry during these tasks compared with age-matched controls (Casey et al., 1997; Jonkman et al., 2007; King et al., 2007; van Meel et al., 2007; Vaidya et al., 2005), suggesting a deficit in the ability to suppress interfering information. Evidence is also accumulating for a switching deficit in ADHD, with reports of disproportionately increased error rates and slowed RTs on switch trials in children with ADHD than controls (Cepeda et al., 2000; Oades et al., 2008). Children and adults with ADHD have also shown significantly lower metabolic activations in fronto-striatal, parietal and temporal regions recruited significantly by controls on switch trials (Cubillo et al., 2010; Rubia et al., 2010; Smith et al., 2006).

Monitoring and adjusting performance for errors has also been found to be impaired in ADHD, although the findings are less consistent for this aspect of cognitive control. Error monitoring and adjustment are assessed behaviourally by the degree to which responding is adaptively slowed following error commission, termed *post-error slowing* (PES), and with electrophysiology by the error-related negativity (ERN) and error-positivity (Pe) ERPs. The ERN is a negative deflection in the waveform that occurs in the -50 to +100ms time-range surrounding an erroneous response and is maximal at fronto-central scalp sites (Falkenstein et al., 1991; Gehring et al., 1993). The Pe is a positive deflection in the waveform occurring 150-300ms following an erroneous response and is maximal at centro-parietal scalp (Falkenstein et al., 1991). It is thought that the ERN indexes an automatic error-detection mechanism which compares actual and intended behaviour and is generated by dopaminergic transmission between the basal ganglia and the ACC (Falkenstein et al., 1991; Gehring et al., 1993; Holroyd & Coles, 2002). The Pe on the other hand is thought to reflect conscious evaluation of an error and is related to corrective adjustments to performance or cognitive strategies such as PES (Falkenstein et al., 1991; Niewenhuis et al., 2001).

Mixed findings of impaired PES (Wiersema et al., 2005) and intact PES (Groom et al., 2010a; van Meel et al., 2007; Wild-Wall et al., 2009) have been reported in children with ADHD compared with controls. Reduced amplitude of the ERN in ADHD has been reported in some studies (van Meel et al., 2007) but not others (Groom et al., 2010a; Wiersema et al., 2005; Wild-Wall et al., 2009). Similarly, Pe amplitude has been found to be reduced in some samples of children with ADHD (Wiersema et al., 2005) but not others (Groom et al., 2010a; Wild-Wall et al., 2009). Groom et al. (2010a) reported a decrease in power and inter-trial coherence, that is, the extent to which electrophysiological activity is consistent across task trials, during error trials in the theta frequency range in children with ADHD compared with controls. The theta frequency has been linked with error monitoring and is thought to contribute to the ERN ERP (Cavanagh et al., 2009).

Finally, increased intra-individual variability (IIV) has been proposed as a core feature of ADHD (Castellanos & Tannock, 2002). IIV refers to frequent fluctuations in an individual's behaviour that occur in the

second/millisecond time-range and are thought to reflect momentary lapses in attention and intention (Castellanos & Tannock, 2002; Kofler et al., 2013). The meaning of increased IIV is currently unclear; for example it may reflect abnormalities in the fine-tuning or timing of motor behaviour underpinned by cerebellar and basal ganglia circuitry (Castellanos & Tannock, 2002) or impairments in bottom-up or top-down regulation of behaviour due to decreased integrity and efficiency of frontal circuitry and depleted dopaminergic transmission (MacDonald et al., 2006; Tamm et al., 2012). Abnormal noradrenergic transmission has also been linked with increased variability in ADHD (Frank et al., 2007). IIV is measured in experimental settings by RT variability, that is, the degree to which RT varies across trials within individuals. Increased RT variability in children and adults with ADHD compared with controls is a robust finding and has been reported in many different experimental tasks, including Go trials of SST and Go/Nogo paradigms (Banaschewski et al., 2003b; de Zeeuw et al., 2008; Groom et al., 2010a; Liotti et al., 2005; Uebel et al., 2010), interference suppression tasks (Castellanos et al., 2005), and repeat and switch trials of cognitive flexibility tasks (Oades et al., 2008; Smith et al., 2006).

Clearly, widespread cognitive control impairments are associated with ADHD. It remains unclear specifically which cognitive control deficits are most central to ADHD neuropathology, but impaired ability to withhold inappropriate behaviours and increased IIV might be the most likely candidates due to the large number of consistent reports of these deficits. This suggestion is in line with findings of recent meta-analyses examining the effect sizes of differences in these cognitive control abilities between ADHD and controls and discriminant function analyses examining the classificatory power of these deficits in differentiating ADHD cases from controls (Holmes et al., 2010; Kofler et al., 2013; Willcutt et al., 2005). It must be noted that considerably fewer studies have investigated error monitoring and switching in ADHD, which may explain why alterations in these aspects of cognitive control have been less strongly linked with the disorder. In light of the findings from this literature review, it is clear that comorbid ADHD symptoms might introduce impairments in a range of cognitive control processes in young people with TS which could affect their ability to control tics.

2.3.3 Cognitive control in TS+ADHD

Compared with the wealth of research investigating cognitive control in TS and ADHD individually, relatively few studies have examined this ability in comorbid TS+ADHD (summarised in table 2-3). Moreover, there have been methodological problems with several of the studies exploring cognitive control in TS+ADHD. For example, Mostofsky et al. (2001) sought to investigate whether comorbid ADHD symptoms affected the ability of young people with TS to produce prosaccade and antisaccade eye movements. The authors examined these oculomotor behaviours in boys with TS or TS+ADHD and unaffected boys. The TS+ADHD group tended to produce more antisaccade errors than the TS group and produced significantly more variable prosaccade latencies (increased IIV) than the TS and control groups. Mostofsky et al. (2001) concluded that impairments in withholding inappropriate, prepotent behaviours in TS are associated with comorbid ADHD symptoms, and children with comorbid TS+ADHD show alterations in sensorimotor response preparation (increased IIV) compared with children with TS alone. These findings are important as they imply that ADHD-related cognitive control deficits are manifested in individuals with TS+ADHD, but the lack of an ADHD-only comparison group limits such strong conclusions. Later studies were also limited by the failure to include an ADHD-only comparison group (Channon et al., 2003) or a TS-only group (Greimel et al., 2008).

Roessner et al. (2007c) addressed this limitation by examining cognitive control performance of children with TS, TS+ADHD, ADHD and unaffected control children on a Stroop task and the Wisconsin Card Sorting Test (WCST). The Stroop task involves reporting the ink colour of presented colour-name words when ink and name colours are congruent (e.g. the word ‘red’ printed in red ink) or incongruent (the word ‘red’ printed in green ink). On incongruent trials the colour name is read automatically and interferes with reporting the ink colour. The WCST involves sorting cards according to changing task rules which must be inferred from performance feedback. As such, the WCST measures the ability to suppress interfering information (previously correct sorting rules) and switch flexibly between sorting rules.

Table 2-3

Summary of research investigating cognitive control in young people with TS+ADHD

Author (year)	TS+ADHD n (age in years); Co n (age in years); TS n (age in years); ADHD n (age in years)	Task(s) (cognitive control processes assessed)	Cognitive control effects
Mostofsky et al. (2001)	14 (11.7); 10 (10.6); 11 (10.8); no ADHD	Prosaccade/antisaccade task (withholding prepotent eye movements – antisaccades; IIV – prosaccade latency)	TS+ADHD < TS (antisaccades) TS+ADHD > TS, Co (IIV)
Channon et al. (2003)	9 (12.3); 21 (13.6); 14 (13.7); no ADHD	Hayling Sentence Completion (interference suppression), Stroop (interference suppression), Fluency (cognitive flexibility), TMT (cognitive flexibility), simplified WCST (interference suppression + cognitive flexibility)	TS+ADHD = TS & < Co (Hayling) TS+ADHD = TS, Co (all other tasks)
Roessner et al. (2007c)	15 (11.3); 15 (11.3); 15 (11.3); 16 (11.2)	Stroop, WCST	TS+ADHD < Co, ADHD (Stroop) ADHD < Co (WCST) No group interactions
Greimel et al. (2008)	20 (11.3); 20 (11.5); no TS; 20 (11.2)	Go/Nogo (withholding prepotent responses), Set-Shifting (interference suppression + switching)	TS+ADHD = ADHD & < Co (Go/Nogo) TS+ADHD = ADHD, Co (Set-Shifting)
Sukhodolsky et al. (2010)	45 (11.2); 71 (11.4); 56 (10.9); 64 (11.6)	Stroop, Go/Nogo (CPT version)	TS+ADHD = ADHD & < Co (Go condition of Go/Nogo: accuracy & RT variability) ADHD < Co (Stroop)

Greimel et al. (2011)	25 (11.7); 27 (12.0); 21 (11.3); 23 (11.9)	As in Greimel et al. (2008)	ADHD-yes < ADHD-no (both tasks) TS-yes > TS-no (Set-Shifting) No group interactions
Yordanova et al. (1997)	11 (11.3); 11 (11.4); 11 (11.5); 10 (11.3)	Frontal lobe control task (see text). PINV ERP measured as correlate of frontal control functions	Group interaction for PINV amplitude (lack of control); opposite TS-present and ADHD-present effects for loss of control condition (see text)

The authors were particularly interested in exploring which model of comorbidity, additive, independent or phenocopy, might represent the basis of TS+ADHD and employed two analysis methods to address this issue.

First, performance measures for each task were statistically compared between the four groups to examine how the groups differed from one another. Second, to examine whether comorbid TS+ADHD was consistent with an additive model of comorbidity, the authors employed a 2x2 factorial approach. This approach involves creating two between-subjects group factors with two levels each: TS-present with the levels TS-yes (TS and TS+ADHD) and TS-no (ADHD and controls), and ADHD-present with the levels ADHD-yes (ADHD and TS+ADHD) and ADHD-no (TS and controls). Both between-subjects variables are entered into ANOVA models for each performance measure. Significant main effects of TS-present or ADHD-present indicate a difference between children with TS or ADHD compared with children without those conditions. A lack of significant interaction between the two group factors is said to indicate that an additive effect of TS and ADHD characteristics in TS+ADHD is supported, suggesting any effects observed in TS+ADHD reflect the sum of those present in TS and ADHD alone (Roessner et al., 2007c).

On the Stroop task there was a trend for greater interference scores in the TS+ADHD group than the ADHD and control groups, suggesting children with comorbid TS+ADHD were poorest at suppressing irrelevant interfering information. There were no main effects of TS-present or ADHD-present and no interaction between these group factors. In contrast, there was a significant main effect of ADHD-present on WCST perseverative errors (failures to change sorting rule) but no effect of TS-present or interaction between the group factors, and a trend for higher perseverative errors in the ADHD group compared with the TS group. Roessner et al. (2007c) concluded that ADHD symptoms impair cognitive control while tic symptoms do not, and comorbid ADHD symptoms should be the focus of treatment in children with TS+ADHD. Further, due to the lack of group interactions, the authors stated that their findings were consistent with an additive model of comorbidity and suggested that both TS and ADHD coexist independently in children with TS+ADHD.

However, it can be argued that Roessner et al.'s (2007c) conclusions are not fully justified from their findings. If ADHD symptoms impair cognitive control in TS+ADHD then children with ADHD and TS+ADHD should show the same impairment profile. This was not the case in the analysis of the four participant groups. Another limitation of Roessner et al.'s (2007c) study is that the tasks used, particularly the WCST, are insensitive for measuring specific aspects of cognitive control. For instance, switching to a new rule of card sorting on the WCST requires, in addition to the ability to switch from one task to another and suppress interference from the previously used rule, the deductive inference that a new rule is required, efficient learning of the new rule, and holding and manipulating rule information in working memory (Ozonoff et al., 1998). To fully understand the nature of deficits related to ADHD symptoms in TS+ADHD the particular cognitive control processes affected must be identified and this can best be achieved by ensuring the tasks employed are optimally sensitive and specific to the processes they are designed to measure.

Greimel et al. (2011) noted the importance of task selection and examined performance of children with TS, TS+ADHD, ADHD and controls on Go/Nogo and set-shifting tasks. The Go/Nogo task involves responding to frequently presented Go stimuli and withholding responses to infrequent Nogo stimuli. The high frequency of Go stimuli builds up a prepotent response tendency and renders withholding responses to Nogo stimuli challenging. The task is simple with minimal learning and memory demands and therefore can be considered a sensitive measure of the ability to withhold inappropriate behaviours. The set-shifting task was designed carefully to measure switching and interference suppression with minimal demands on other cognitive functions required by the WCST.

Greimel et al. (2011) also used the 2x2 factorial method. The authors found that the ADHD-yes group (TS+ADHD, ADHD) produced significantly longer RTs for Go trials in the Go/Nogo task and tended to produce longer RTs and more errors on trials requiring interference suppression on the set-shifting task than the ADHD-no group (TS, controls). In contrast, the TS-yes group (TS, TS+ADHD) produced significantly faster RTs on interference suppression trials of the set-shifting paradigm than the TS-no group (ADHD, controls). The

authors concluded that ADHD is associated with impaired cognitive control while the TS findings supported the frontal lobe compensation hypothesis (Leckman et al., 2006), and that the lack of group interactions supported an additive model of comorbidity for TS+ADHD. Greimel et al. (2011) also suggested that compensatory mechanisms associated with TS might ameliorate cognitive control deficits associated with ADHD in children with TS+ADHD. This latter suggestion has important implications for understanding how ADHD symptoms affect cognitive control and tic control in TS+ADHD. The absence of group interactions also bolsters the support for an additive model of TS+ADHD comorbidity provided by Roessner et al. (2007c).

However, interpreting Greimel et al.'s (2011) findings is problematic due to several issues with the 2x2 factorial approach. Firstly, significant main effects of TS-present or ADHD-present reveal cognitive control characteristics that are associated with TS with and without ADHD, or ADHD with and without TS, but little about how participants with TS+ADHD differ from or are alike those with TS or ADHD alone. Characteristics that are specific to the comorbid group may be undetectable when the comorbid group is combined with a TS or ADHD only group. Therefore, although Greimel et al.'s (2011) findings provide important evidence for impaired cognitive control associated with ADHD and enhanced cognitive control associated with TS, it is unclear whether the TS+ADHD group showed both of these characteristics. In order to understand the cognitive control profile in individuals with comorbid TS+ADHD, analyses comparing the four participant groups should be conducted.

Secondly, the assumption that an absent group interaction is indicative of an additive model of comorbidity is questionable. The rationale for this assumption is that if there is no interaction, then when combined with the TS group the TS+ADHD group do not differ from the ADHD group, and when combined with the ADHD group they do not differ from the TS group. This suggests that TS and ADHD characteristics are both present in TS+ADHD; otherwise, the comorbid group would differ from one of the TS-only or ADHD-only groups and this would produce a significant interaction. However, Banaschewski et al. (2007) emphasised that an absent interaction can simply reflect a lack of statistical power or the influence of methodological

peculiarities. More than this, if an interaction was present it need not necessarily reflect a non-additive model. A difference between controls and one of the other groups might drive an interaction effect, since like the TS+ADHD group, the controls are paired with ADHD in one group factor and TS in the other group factor. Furthermore, an additive model might truly represent TS+ADHD but the characteristics of the two disorders might interact and produce different behavioural manifestations from TS or ADHD alone. In light of these considerations, Roessner et al.'s (2007c) and Greimel et al.'s (2011) support for an additive model of comorbidity seems less convincing.

Sukhodolsky et al. (2010) took a more traditional approach to investigating TS+ADHD and examined group differences between large samples of children with TS (n=56), TS+ADHD (n=45), ADHD (n=64) and controls (n=71) in performance on a Stroop task and a Go/Nogo-type task (the Continuous Performance Test, CPT). The ADHD and TS+ADHD groups produced significantly poorer Go accuracy (higher rates of omitted Go responses) and RT variability than the control group on the CPT, while on the Stroop task children with ADHD showed significantly poorer interference suppression than control children. The TS group did not differ from controls on either task. The authors concluded that some aspects of cognitive control are similarly impaired in TS+ADHD and ADHD (sustained attention on the CPT and increased IIV), while other aspects (interference suppression) are less impaired in TS+ADHD than ADHD. Therefore, in contrast to Roessner et al.'s (2007c) and Greimel et al.'s (2011) suggestions that TS+ADHD reflects the additive effects of TS and ADHD, Sukhodolsky et al.'s (2010) findings indicate that the basis of TS+ADHD is more complex, and that some TS and ADHD characteristics might be expressed while others are not.

In summary, behavioural studies examining cognitive control in children with TS+ADHD have produced mixed findings. There has been some indication that ADHD symptoms impair cognitive control in children with TS+ADHD, and also that compensatory mechanisms related to TS might diminish ADHD-related deficits. In terms of the particular aspects of cognitive control affected by comorbid ADHD symptoms, Roessner et al.'s (2007c) study suggested the ability to suppress interfering information might be impaired, but as discussed there are problems with proposing this deficit is

related to ADHD symptoms per se. Sukhodolsky et al.'s (2010) findings indicate that interference suppression is not impaired in TS+ADHD but that children with this comorbidity show increased IIV and poor performance on Go trials like children with ADHD. Further research is needed to clarify which particular aspects of cognitive control are most affected by ADHD symptomatology in TS+ADHD. Likewise, the basis of TS+ADHD is still uncertain. Greimel et al. (2011) and Roessner et al. (2007c) suggest that this form of comorbidity is additive in nature, although there are difficulties drawing this conclusion due to the 2x2 factorial approach employed in these studies. In contrast, Sukhodolsky et al. (2010) propose TS+ADHD might be more complex than a simple additive effect of TS and ADHD characteristics. Again, further research is required to elucidate the basis of TS+ADHD.

It is also important to investigate the neural mechanisms underlying cognitive control in TS+ADHD. Such examination could reveal greater engagement of control circuitry in TS+ADHD which would support the suggestion that TS-related enhancements are present in children with this comorbidity. Alternatively, impaired engagement of cognitive control circuitry in TS+ADHD would support the view that ADHD-related deficits in cognitive control are expressed in the comorbid form. To the best of this author's knowledge, only one study has investigated neural activity associated with cognitive control in children with TS, TS+ADHD, ADHD and unaffected control children. Yordanova et al. (1997) examined ERP correlates of frontal lobe function in children with TS and low levels of ADHD symptoms (TS group), TS and high levels of ADHD symptoms (TS+ADHD group), ADHD, and unaffected children. A novel task was designed to measure frontal lobe function. A tone was presented followed by a white noise stimulus that could be stopped by pressing a button. In block 1 a button press always stopped the white noise (control condition, CC). In block 2 the button press only stopped the noise for the first half of the block, thereby introducing a loss of control condition (LoCC) in the second half of the block. In block 3 the button press never stopped the noise, creating a lack of control condition (LaCC). The post-imperative negative variation (PINV), a slow negative deflection associated with control functions of the frontal lobes, was measured 600-1200ms

following the white noise. The 2x2 factorial approach was used to investigate the basis of comorbid TS+ADHD.

In CC, there were no main effects of TS-present or ADHD-present and no group interactions. In LoCC, there were no main effects but there was a significant group interaction. This was further investigated and shown to reflect greater PINV amplitudes in the ADHD group compared with control and TS+ADHD groups. Yordanova et al. (1997) suggested this pattern of findings indicated that a simple additive model of comorbidity may not be adequate to explain TS+ADHD. In LaCC, there were significant main effects of TS-present and ADHD-present and no group interaction. Children with TS showed smaller PINV amplitudes than children without TS, while children with ADHD exhibited larger amplitudes than children without ADHD. The authors suggested that these effects indicated that TS and ADHD are associated with unique patterns of frontal lobe activity and that children with TS+ADHD might experience both TS-related and ADHD-related disruptions (additive effects of TS and ADHD). Yordanova et al.'s (1997) findings suggest that depending on the particular cognitive process assessed the expression of TS-related and ADHD-related characteristics varies in children with TS+ADHD. The findings therefore support Sukhodolsky et al.'s (2010) suggestion that the basis of TS+ADHD is complex and may not conform to one particular model. The drawbacks of Yordanova et al.'s (1997) study however are the use of the 2x2 factorial approach without investigating differences between the four groups (unless there was a significant interaction), and the unusual and rather confusing task which is difficult to relate to instances of cognitive control in daily life, including tic control. As with the behavioural studies in TS+ADHD, further research investigating electrophysiological correlates of cognitive control in this comorbidity are required.

2.3.4 Approach and hypotheses for cognitive control in the present research

The aim of investigating cognitive control in this thesis was to explore the basis of comorbid TS+ADHD and to improve understanding of how comorbid ADHD symptoms affect aspects of cognition that are involved in tic control. The approach taken was designed to address limitations of the previous

research in this area. Firstly, aspects of cognitive control for examination were carefully selected based on their likely involvement in controlling tics and/or their robust association with ADHD symptomatology. Based on the findings from the literature review above, the processes selected were the ability to withhold inappropriate prepotent behaviours, which clearly relates to tic suppression and has been robustly associated with ADHD, IIV as measured by RT variability due to its robust association with ADHD, and monitoring and adjusting performance for errors, which may be important in tic control in that the ability to monitor for tics and adjust on-going behaviour following a tic should improve an individual's ability to cope with tic symptoms.

The Go/Nogo paradigm was selected as a means of measuring these aspects of cognitive control due to its simplicity, with minimal learning and memory demands, and its robustness in eliciting behavioural and electrophysiological cognitive control effects in typical and atypical developmental populations (e.g. Johnstone et al., 2005). Electrophysiological correlates of cognitive control selected for study were well established ERP components, the N2, P3, ERN and Pe. The N2 and P3 have been extensively investigated in ADHD and have been shown to be sensitive indices of enhanced engagement of cognitive control circuitry in adults with TS. The ERN and Pe have been used previously to investigate error monitoring in ADHD.

The approach taken for analysis was to first, compare cognitive control performance and electrophysiological activity between young people with TS, TS+ADHD, ADHD and unaffected young people to investigate how the TS+ADHD group differed or were similar to the TS and ADHD groups. Second, regression analyses were conducted to examine how well tic and ADHD symptoms predicted performance and ERP correlates of cognitive control. This regression method has rarely been used in studies of TS+ADHD but is important because it can reveal how tic and ADHD symptoms contribute to cognitive control characteristics in young people with TS+ADHD, thereby providing insight into the basis of this comorbidity.

It was hypothesised that young people with TS without comorbid ADHD symptoms would show enhanced performance and increased amplitudes of ERPs compared with the control group, reflecting enhanced

cognitive control in TS. Young people with ADHD without comorbid tics were expected to show poorer behavioural performance and decreased amplitudes of ERPs relative to controls, indicative of impairment in cognitive control processes measured. Consistent with the view that ADHD symptoms impair cognitive control in TS+ADHD it was predicted that aspects of cognitive control that are sensitive to ADHD (withholding inappropriate responses, RT variability) would be impaired in young people with TS+ADHD relative to young people with TS. Furthermore, in line with Greimel et al.'s (2011) suggestion that TS-related enhancements ameliorate ADHD-related cognitive control deficits in TS+ADHD, it is hypothesised that the ability to withhold prepotent responses will be better in TS+ADHD than in ADHD. IIV is not proposed to play a role in tic control and therefore it is hypothesised that TS+ADHD and ADHD groups will show a similar level of impairment in RT variability. Error monitoring, which might be less strongly related to ADHD but is proposed to be involved in tic control, is hypothesised to be enhanced in TS+ADHD relative to ADHD and comparable in the two TS groups. In the regression analyses, it is hypothesised that tic symptoms will be predictive of better behavioural performance and larger ERP amplitudes, while ADHD symptoms will predict poorer performance and smaller ERP amplitudes. In terms of which model of comorbidity represents TS+ADHD, no specific prediction is made in light of the mixed previous findings, but the pattern of group differences in cognitive control characteristics along with examination of how tic and ADHD symptoms relate to cognitive control in the TS+ADHD group should provide insight into which model best applies to this form of comorbidity. The methods and results for the investigation of cognitive control are presented in chapter 6.

3. METHOD

3.1 ETHICAL APPROVAL

Full ethical approval for the study was obtained from the East Midlands (Leicester) NHS Research Ethics Committee and the Research and Development departments of the Nottinghamshire Healthcare, Nottingham University Hospitals, and Lincolnshire Partnership Foundation NHS trusts. Additional ethical approval was granted from the University of Nottingham Medical School Ethics Committee for recruitment and testing of a subsample of the TS group via TS support groups, such as Tourette's Action. Testing procedures approved by NHS and Medical School ethics committees were identical. Approval from the Medical School committee hastened recruitment and testing at the beginning of the study while R&D approvals were pending.

3.2 PARTICIPANTS

Young people aged 9-17 years were recruited to take part in the current study. Participants were included in one of the following groups: TS, TS+ADHD, ADHD, Control. A power calculation was performed to determine the number of participants required for each group. Power calculations conducted in G*Power indicated that 25 to 35 participants would be required in each group in order to detect significant main effects and interactions (based on moderate-to-large effect sizes (Yordanova et al., 1997), an alpha level of .05 and power of .90). Participant inclusion and exclusion criteria and group characteristics are described in the following sections. The clinical and socio-demographic characteristics for each group are summarised in table 3-1.

3.2.1 Inclusion and exclusion criteria

Young people were included in the study if they met the following criteria:

- Aged 9-17 years
- Fluent spoken English

- Met DSM-IV/DSM-IV-TR diagnostic criteria for TS and/or ADHD (clinical groups)

Young people with the following were excluded from the study:

- Learning disability (IQ estimates below 70)
- Symptoms of ASD
- Any neurodevelopmental or psychiatric condition (Control group)

Diagnoses of TS and ADHD were confirmed using the Development and Well-Being Assessment (DAWBA, see 3.3.1 below). The DAWBA was used to confirm that young people in the clinical groups did not meet diagnostic criteria for ASD, and that young people in the Control group did not meet diagnostic criteria for any disorder. The Wechsler Abbreviated Scale of Intelligence (WASI, see 3.3.2 below) was used to screen for learning disability. Children in clinical groups with other comorbid psychiatric conditions such as OCD and ODD were not excluded due to the high co-occurrence of these conditions with TS and ADHD (Freeman, 2007; Gillberg et al., 2004; Rommelse et al., 2009; Scharf et al., 2012). Clinical or subclinical symptoms of TS, ADHD, OCD and ODD were measured in all participants (see 3.3 for measures). Symptom severity scores were used in analyses with performance and electrophysiological measures (described in chapters 4, 5 and 6).

3.2.2 TS group

Sixty young people with TS were approached via Nottinghamshire healthcare NHS Trust Child and Adolescent Mental Health Services (CAMHS) and TS support groups run by the charity Tourette's Action. Eighteen of those individuals agreed to take part and were included in the study. All participants had received a formal clinical diagnosis of TS from a consultant psychiatrist, community paediatrician, or GP, without a comorbid diagnosis of ADHD.

Table 3-1
Socio-demographic and clinical characteristics for each participant group. Values are group means with standard deviations in parentheses.

	TS (n=18)	TS+ADHD (n=17)	ADHD (n=13)	Control (n=20)	Group differences
Age (months)	158.0 (33.3)	148.2 (33.9)	168.5 (32.9)	156.3 (34.8)	n/s
Gender (% males)	77.8	94.1	92.3	80.0	n/s
Handedness (% right handed)	83.3	88.2	92.3	80.0	n/s
SES	2.1 (1.4)	1.8 (1.2)	2.1 (1.5)	1.5 (1.1)	n/s
IQ	111.2 (11.8	110.1 (12.2)	96.3 (15.6)	112.6 (11.2)	ADHD < TS*/TS+ADHD*/Controls**
Motor tic severity (YGTSS Motor)	13.6 (7.5)	15.9 (4.5)	0 (0)	0 (0)	TS > ADHD/Controls** TS+ADHD > ADHD/Controls**
Phonic tic severity (YGTSS Phonic)	5.5 (5.8)	12.1 (7.9)	0 (0)	0 (0)	TS > ADHD/Controls** TS+ADHD > TS*/ADHD**/Controls**
Total tic severity (YGTSS Total)	19.3 (12.1)	28.1 (11.3)	0 (0)	0 (0)	TS > ADHD/Controls** TS+ADHD > TS*/ADHD**/Controls**
CPRS-R ADHD Index	54.0 (9.0)	72.8 (9.3)	76.1 (16.0)	47.6 (6.5)	TS > Controls* ADHD > TS/Controls** TS+ADHD > TS/Controls**

CPRS-R Inattentive	50.4 (7.6)	70.5 (8.6)	72.8 (18.5)	47.3 (6.9)	ADHD > TS/Controls** TS+ADHD > TS/Controls**
CPRS-R Hyper-Impulsive	56.5 (11.7)	74.7 (11.2)	81.1 (20.9)	48.6 (6.8)	TS > Controls* ADHD > TS**/TS+ADHD*/Controls** TS+ADHD > TS/Controls**
CPRS-R ODD	52.3 (10.4)	65.4 (13.0)	75.6 (21.0)	47.2 (9.3)	ADHD > TS**/TS+ADHD*/Controls** TS+ADHD > TS/Controls**
ADHD Rating Scale IV	54.9 (30.4)	95.2 (4.4)	97.1 (2.5)	38.4 (27.3)	ADHD > TS/Controls** TS+ADHD > TS/Controls**
SDQ Hyperactivity	4.6 (3.1)	8.1 (2.0)	8.3 (2.0)	2.7 (2.6)	ADHD > TS/Controls** TS+ADHD > TS/Controls**
SDQ Conduct	1.1 (1.6)	3.6 (2.1)	7.1 (3.0)	.80 (1.2)	ADHD > TS+ADHD*/TS**/Controls** TS+ADHD > TS/Controls**
CY-BOCS	6.6 (9.8)	2.1 (5.3)	.62 (1.7)	.05 (.22)	TS > Controls*
Comorbid conditions	OCD (n=3) OCB (n=5) Depression (n=3) Anorexia (n=1) GAD (n=1)	OCD (n=2) ODD (n=5) Social phobia (n=2) Specific phobia (n=1) GAD (n=2) Separation anxiety (n=1) Dyslexia (n=1)	ODD (n=4) CD (n=2) Dyslexia (n=1) Dyspraxia (n=1)	--	

Medication	Clonidine (n=3) Aripriprazole (n=2) Citalopram (n=1) Fluoxetine (n=1) Not med. (n=3)[a] Med. naïve (n=9)	Methylphenidate (n=2) Aripriprazole (n=2) Fluoxetine (n=1) Not med. (n=3) [a] Med. naïve (n=8)	Methylphenidate (n=9) Atomoxetine (n=2) Not med. (n=1) [a] Med. naïve (n=2)	--
Behaviour therapy	HR (n=4) CBT (n=1) No therapy (n=1)[b] Therapy naïve (n=12)	Mindfulness (n=1) No therapy (n=1) [b] Therapy naïve (n=15)	No therapy (n=1)[b] Therapy naïve (n=12)	--

* = p < .05, ** = p < .01.
GAD = Generalised anxiety disorder. CBT = Cognitive Behavioural Therapy.
[a] Not medicated = off medication for 1 year minimum prior to participation. [b] No behavioural therapy for 1 year minimum prior to participation

3.2.3 TS+ADHD group

Forty-eight young people with TS+ADHD were invited to take part via Nottinghamshire Healthcare NHS Trust and Lincolnshire Partnership NHS Foundation Trust CAMHS. Seventeen young people with a formal clinical diagnosis of TS (n=16) or chronic motor tics (n=1) and either a formal clinical diagnosis of ADHD (n=10) or clinically-significant ADHD symptoms rated on the DAWBA and ADHD rating scales (described in 3.3) (n=7) agreed to take part. ADHD subtypes were Combined Type (n=15) or Predominantly Inattentive Type (n=2). Participants receiving stimulant medication (methylphenidate) for ADHD symptoms withdrew medication for 24 hours prior to experimental testing.

3.2.4 ADHD group

Seventy-seven young people with ADHD were approached via Nottinghamshire and Lincolnshire Child and Adolescent Mental Health Services. Thirteen young people with a formal clinical diagnosis of ADHD (all Combined Type) and no comorbid diagnosis of tics agreed to take part. Stimulant medication (methylphenidate) was withdrawn for 24 hours prior to experimental testing.

3.2.5 Control group

Twenty typically developing young people without psychiatric conditions were recruited from Nottinghamshire primary and secondary schools for the control group. Participants were matched on age, gender, socioeconomic status and IQ to participants in the clinical groups (see table 3-1).

3.2.6 Group matching

Participant groups were matched as closely as possible on the following socio-demographic variables: age (within 10 months either side of current age), gender, socio-economic status (SES) as assessed by the National Statistics Socio-economic Classification (NS-SEC, see 3.3.7 below) (within 1 point either side of SES), and IQ assessed by the WASI (within 10 IQ points either side of scores). Between-groups analyses were conducted to assess group

differences in the socio-demographic variables presented in table 3-1. Variables were checked for normal distributions with Shapiro-Wilk tests (p values < .05 indicate non-normally distributed data). One-way ANOVA tests were used for normally distributed variables; Kruskal-Wallis tests were used for variables that were not normally distributed. Significant group effects were further investigated using parametric independent-samples t-tests or non-parametric Mann-Whitney U tests (as appropriate) to compare each pair of groups. Chi-square tests were used to examine group differences in frequencies of gender type and handedness. The results of these analyses are presented in table 3-1.

3.3 SCREENING AND CLINICAL SYMPTOM ASSESSMENT

A screening and clinical symptom assessment was carried out with every participant's parent/carer to confirm the presence or absence of TS, ADHD and comorbid psychiatric diagnoses, and to measure the presence and severity of clinical and subclinical symptoms of TS, ADHD and other psychiatric disorders. The assessment tools are summarised in table 3-2 and described in the following sections.

3.3.1 Development and Well-Being Assessment (DAWBA)

The DAWBA (Goodman et al., 2000) is a set of measurements, including a structured interview schedule, the Strengths and Difficulties Questionnaire (SDQ) and the Social Aptitude Scale (SAS), which assess the presence of symptoms of TS, ADHD, OCD, ODD, CD, anxiety (generalised, separation), specific phobia, social phobia, depression, eating disorders, and ASD. A set of structured questions based on DSM-IV and ICD-10 diagnostic criteria is administered to assess symptoms of each disorder. Skip rules are included in each set of questions to enable the interviewer to move forward to the next section of the interview if disorder symptoms are clearly absent. If responses indicate disorder symptoms are present, the structured questions are completed and open-ended questions are used to gain further information about

the young person's symptoms. An online system (www.dawba.net) is available to enter the interviewee's responses into an online form. The online system provides computer-generated predictions of the likelihood that a young person meets diagnostic criteria for each disorder, which can be used by the researcher to make DSM-IV and ICD-10 diagnostic ratings. In the current study, the DAWBA was carried out in person with the participant's parent/carer and the DAWBA online system was used to process responses and assist in diagnostic ratings. Parent and Teacher versions of the DAWBA are available. The Parent version was used in the current study. The interview takes approximately 1-2 hours to complete depending on the number of symptoms present.

3.3.2 Wechsler Abbreviated Scale of Intelligence (WASI)

The WASI (Wechsler, 1999) is a quick-administration test of general intelligence from which an IQ estimate can be obtained in approximately 20 minutes. The 2-subtest version of the WASI was used, consisting of the Vocabulary test of crystallised intelligence and the Matrix Reasoning test of fluid intelligence. In the Vocabulary test, participants are required to provide definitions of English words which increase in difficulty as the test progresses. In the Matrix Reasoning test, participants are presented with pattern matrices, each with one piece of the matrix missing, and must decide which of five possible patterned pieces would complete the matrix. The matrices increase in difficulty across the test. Participants' scores on each test are scaled according to normed age-appropriate scores and an IQ estimate is obtained from the sum of the two scaled test scores. IQ estimates of 70 or less are indicative of learning disability. This cut-off score was used in the present study to screen out children with learning disabilities.

3.3.3 Yale Global Tic Severity Scale (YGTSS)

The YGTSS (Leckman et al., 1989) is a rating scale used to assess the presence and severity of tic symptoms over a one-week period prior to administration. The scale is administered as an interview with the young person and parent/carer. A tic inventory is completed first to identify the type of motor and phonic tics present in the past week. Six further items assess the number, frequency, intensity and complexity of current tics and the level of interference

and overall impairment caused by tics. Scores for Total Motor Tics (0-25), Total Phonic Tics (0-25), Impairment due to tics (0-50), and Global Severity Score (0-100) can be calculated. The Total Motor Tic (YGTSS Motor), Total Phonic Tic (YGTSS Phonic) and Total Tic Score (motor score + phonic score, YGTSS Total) were used as measures of motor, phonic and total tic severity in this study.

3.3.4 Conners Parent Rating Scale-Revised (CPRS-R)

The CPRS-R is an 80-item paper-format questionnaire in which the parent/carer rates the presence of ADHD and other behaviours in the past six months (Conners et al., 1998). Gender- and age-scaled indices of DSM-IV ADHD symptoms are produced, as well as indices of other problematic aspects of behaviour such as oppositional and social problems. The ADHD Index, Inattentive Score, Hyperactive-Impulsive Score, and ODD Score were used as indices of parent-rated ADHD traits, inattention, hyperactivity-impulsivity, and ODD traits respectively.

3.3.5 ADHD Rating Scale IV

The ADHD Rating Scale-IV (DuPaul et al., 1998) is a paper-format questionnaire-style rating scale used to assess the severity of ADHD symptoms within the past week. The scale consists of 18 items based on DSM-IV criteria for ADHD and produces age- and gender-scaled scores to evaluate the severity of Inattentive symptoms, Hyperactive-Impulsive symptoms, and total ADHD symptoms (the sum of the Inattentive and Hyperactive-Impulsive scores). The scores are interpreted as the percentile of the population at which the score is higher. For example, the total ADHD score could be higher than 99% of the population, which would indicate significant ADHD symptoms. The questionnaire is completed by the parent/carer with reference to the young person's behaviour over the last week. The total ADHD score index was used as a measure of participant's current ADHD symptom severity in this study.

3.3.6 Strengths and Difficulties (SDQ) Hyperactivity and Conduct Scales

The SDQ is administered as part of the parent-rated DAWBA and is a 25-item questionnaire-style rating scale. Symptoms of emotional, conduct and

Table 3-2
Summary of measures used in screening and clinical symptom assessment

Assessment measure	Summary	Purpose of assessment	Indices employed in the current study
Development and Well-Being Assessment (DAWBA) (Goodman et al., 2000)	Structured interview to assess presence of psychiatric disorders in children	Clinical groups: confirm TS/ADHD diagnoses, absence of ASD symptoms and assess presence of other comorbid symptoms. Control group: confirm absence of psychiatric conditions and assess presence of subclinical symptoms	Predictions of disorder risk
Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999)	Brief test of general intelligence	Screen for the presence of learning disability in all groups	2-subtest IQ scores (cut-off: scores < 70)
Yale Global Tic Severity Scale (Leckman et al., 1989)	Current tic symptom rating scale	Assess presence and severity of tics in all groups	Motor Tic Score, Phonic Tic Score, Total Tic Score
Conners Parent Rating Scale-Revised (Conners et al., 1998)	Questionnaire-style assessment of ADHD and ODD traits	Assess presence and severity of ADHD and ODD traits in all groups	ADHD Index, Inattentive Score, Hyperactive-Impulsive Score, ODD Score

Assessment measure	Summary	Purpose of assessment	Indices employed in the current study
ADHD Rating Scale-IV (DuPaul et al., 1998)	Questionnaire-style rating scale for current ADHD symptoms	Assess severity of current ADHD symptoms in all groups	Total ADHD score
Strengths and Difficulties Questionnaire (SDQ)	Questionnaire-style rating scale for ADHD, Conduct (ODD), Emotional, and Peer problem behaviours	Included as part of the DAWBA. Hyperactivity and Conduct Scales used as measures of ADHD and ODD behaviours present in all groups	SDQ Hyperactivity and SDQ Conduct scores
Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Goodman et al., 1990)	Current OCD symptom rating scale	Assess presence and severity of OCD symptoms in all groups	Total CY-BOCS score
National Statistics Socio-economic Classification (NS-SEC)	Questionnaire to assess SES	Obtain SES estimate for all participants	NS-SEC score

peer problems, hyperactivity, and prosocial behaviour exhibited by the young person in the past six months are assessed with 5 items per symptom domain. Each 5-item set of scores are summed to produce Emotion, Conduct, Peer Problem, Hyperactivity and Prosocial Scales with scores of 0 (no symptoms) to 10 (high symptoms). The Hyperactivity and Conduct Scales were used as measures of ADHD and ODD traits in this study.

3.3.7 Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS)

The CY-BOCS (Goodman et al., 1990) is a rating scale used to assess the presence and severity of OCD symptoms in the past week. The scale is administered as an interview with the young person and parent/carer. An inventory is used to identify obsessions and compulsions present in the last week. Ten items (5 for obsessions, 5 for compulsions) assess the time occupied by symptoms, the distress associated with and the degree of control and resistance over symptoms. Sub-scores are produced for obsessions (0-20) and compulsions (0-20) as well as the total CY-BOCS score (0-40) calculated by summing the obsession and compulsion sub-scores. The total CY-BOCS score was used as a measure of OCD symptoms in the current study.

3.3.8 National Statistics Socio-economic Classification (NS-SEC)

The NS-SEC is a four-item paper-format questionnaire used to estimate socio-economic status. Scores resulting from responses to the four items fall within five SES classifications (1 = Managerial and Professional Occupations, 2 = Intermediate Occupations, 3 = Small Employers and Own Account Workers, 4 = Lower Supervisory and Technical Occupations, 5 = Semi-Routine and Routine Occupations). The scale was completed by each participant's parent/carer with reference to the main-earning individual in the family to assess SES.

3.3.9 Assessment procedure

The DAWBA, including the SDQ, was completed with the parent/carer on a different day from the participant's experimental testing session but within two weeks of the session taking place. The Conners, ADHD Rating Scale IV and NS-SEC were completed by the parent/carer while the participant took part

in the experimental session. Participants performed the WASI on the day of experimental testing, after the experimental tasks were completed. The YGTSS and CY-BOCS were administered to participant and parent/carer on the day of experimental testing, after the experimental tasks and WASI were completed.

3.3.10 Missing data

The full set of screening and symptom assessment measures was not completed for a minority of participants due to family time pressures. Participants with missing data were not excluded from the study providing at least one assessment of tic, ADHD, OCD and ODD severity was completed, a formal clinical diagnosis had been given by a clinician (clinical groups), and an IQ estimate was obtained. All study participants met this criterion. The number of participants in each group with missing data for each measure is summarised in table 3-3.

Table 3-3
Number of participants with missing data for each screening measure

	TS	TS+ADHD	ADHD	Control
DAWBA	0	0	3	0
WASI	0	0	0	0
YGTSS	0	0	0	0
CPRS-R	2	0	3	0
ADHD Rating Scale IV	2	0	2	0
SDQ	0	0	3	0
CYBOCS	0	0	0	0
NS-SEC	1	0	3	0

3.4 EXPERIMENTAL TESTING

Experimental testing consisted of a one-day session at the Division of Psychiatry, University of Nottingham. Experimental testing lasted

approximately 3 hours including rest and refreshment breaks. All participants first completed the tasks during which EEG was recorded (see chapters 4 and 6), followed by the behavioural task (see chapter 5) and the WASI, YGTSS and CY-BOCS. Further details of the tasks completed and testing procedures and analysis methods for each task are provided in the methods and results chapters 4, 5 and 6.

3.4.1 Electrophysiological recording

EEG was recorded continuously throughout performance of the two EEG tasks using a Biosemi Active II recording system (Biosemi, Amsterdam, The Netherlands) from 128 silver/silver chloride (Ag/AgCl) scalp electrodes placed according to the 5-20 system (Oostenveld & Praamstra, 2001). The data were referenced online to the Common Mode Sense (CMS) electrode located to the left of Cz on the scalp, and sampled at a rate of 512Hz. Extra flat-type Ag/AgCl electrodes were placed on the inner orbital ridge and outer canthus of each eye and the right and left mastoids to record eye movements and non-ocular artefacts. Electrode impedances were kept below 50KΩ throughout recording wherever possible. Participants were seated comfortably in a quiet, dimly lit room during EEG acquisition. Due to re-location of the Division of Psychiatry half-way through the study, the first 11 participants with TS, 1 participant with TS+ADHD and 4 controls were tested in a room without electrical shielding. The remaining participants in all groups were tested in a room protected by a Faraday cage in the new location. As a result, EEG recordings contained less 50Hz noise in participants tested in the new location. This was not considered as a confound in the study as 50Hz noise was filtered out of electrophysiological data during pre-processing.

4. METHODS AND RESULTS I: GOAL-DIRECTED LEARNING

4.1 METHODS AND HYPOTHESES

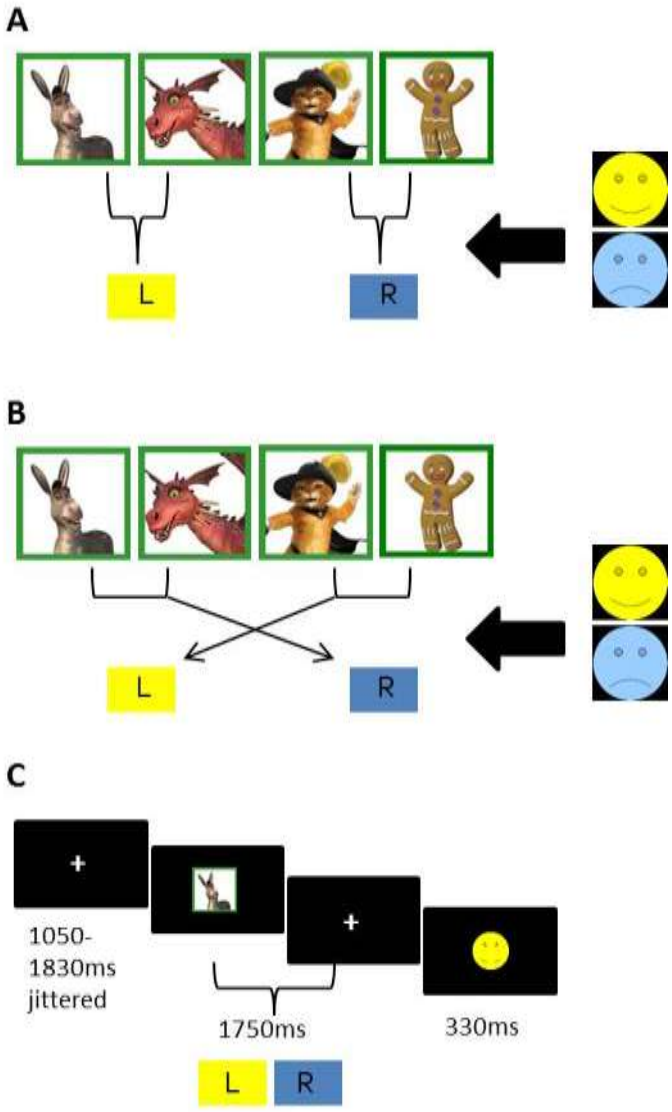
4.1.1 Goal-directed reinforcement learning paradigm

The goal-directed reinforcement learning task required participants to learn by trial-and-error, using positive and negative performance feedback, to associate two visual stimuli with a right hand button-press and another two stimuli with a left hand button-press (Figure 4-1). The allocation of stimuli to left/right responses was counterbalanced across participants. The task began with an acquisition phase in which three blocks of trials were presented for participants to learn the stimulus-response (S-R) associations. A reversal phase consisting of two trial blocks (blocks 4 and 5) followed the acquisition phase. In block 4, the S-R mappings reversed unexpectedly and participants had to re-learn which button-press to make for each stimulus. In block 5, the mappings remained reversed. Every block contained 48 trials, with each stimulus presented 12 times in random order in each block. The task was presented as a game in which the aim was to win as many points as possible by learning each character's preferred button-press. One point per correct response was awarded and the number of points won was displayed after each block. Participants were instructed to attend closely to the feedback to ensure they were aware of the change in response mappings but were not told when this would occur.

Stimuli were four cartoon characters from a popular animated film, presented in colour and surrounded by a rectangular 3mm thick green frame (see figure 4-1). Stimuli measured 60x57mm including the frame. Circular yellow happy-face images and blue sad-face images (both 60mm in diameter) were used as positive and negative feedback. The words 'Too slow!' (10x90mm) were displayed in green for late responses. On each trial, a white fixation cross (7x7mm) was presented for a jittered duration of 1050-1830ms followed by one of the four stimuli for a maximum duration of 1475ms.

Figure 4-1

Diagram of the goal-directed reinforcement learning task



A. Acquisition phase: task blocks 1-3
Participants learned which buttons (left/right) to press for each character stimulus. Two characters required right responses; two required left responses. Participants began the task by guessing which button to press for each character. Feedback was provided after each response to inform whether the response made was correct (happy face) or incorrect (sad face) for the character. Participants were instructed to remember (learn) which responses were correct for each character and produce those responses on all further trials. Feedback was provided on all trials to reinforce responses.

B. Reversal phase: task blocks 4-5
The required responses for each character reversed unexpectedly and participants had to re-acquire the correct S-R associations using feedback. For example, the two characters associated with a right response in blocks 1-3 required left responses in blocks 4-5 and were followed by incorrect feedback if right-hand responses were produced in blocks 4-5 but correct feedback when left-hand responses were produced. Participants learned to make the new correct responses for the characters by attending to and learning from the reinforcement feedback.

C. Trial structure
Every trial began with a fixation screen. Next, one of the stimuli was presented followed by a second fixation screen, during which time the participant responded. Every trial ended with a feedback display.

Stimulus presentation was terminated by the participant's response. A second white fixation cross was presented for a minimum of 275ms, followed by feedback for 330ms. Duration of the second fixation was dependent on the timing of the response, increasing with short latency responses and decreasing with long latency responses. This was done to fix the time period between when the stimulus appeared (stimulus-onset) and the second fixation cross disappeared (fixation offset) to 1750ms, thereby ensuring a sufficiently long period followed the stimulus before feedback was displayed to facilitate stimulus-locked epoching of the EEG data during analysis. Participants responded using the left/right buttons on a Cedrus RB-530 response button box (Cedrus Corporation, San Pedro, California). Correct/incorrect feedback was displayed if the participant responded within the stimulus onset - fixation offset time window; 'too slow' feedback was displayed otherwise to encourage prompt responding. All task objects were centrally presented on a black background on a Viglen computer (43cm monitor and 1024x768 pixels screen resolution). The task was programmed using E-Prime version 1.2 software (Psychology Software Tools Inc.).

After EEG set-up and task instructions, participants were seated in a dimly lit room at a viewing distance of 60cm from the monitor. Four practice trials (one per stimulus) were completed to ensure participants understood the task instructions, followed by the five task blocks separated by self-paced rest breaks.

4.1.2 Behavioural correlates of goal-directed learning

The measures selected as behavioural correlates of goal-directed reinforcement learning are summarised below. The measures were computed using Matlab R2011a (MathWorks, UK). Accuracy and RT in each block were used to establish how each group performed overall in the task. The accuracy and RT change (difference score) measures were calculated to establish how much learning-related change in performance occurred between task blocks in each group, and whether this differed between groups regardless of overall accuracy and RT differences. Within-block learning measures were used to examine group differences in the progression of learning within each block.

Participants with scores greater than 2.5 SD of their group mean on any behavioural correlate were excluded from analyses.

- Accuracy: % correct trials in each learning block (1-5)
- RT: the median RT (ms) for correct trials in each learning block. The first trial in every block was excluded to remove starting bias, that is, the tendency for longer RTs at the beginning of a block of trials.
- Accuracy and RT change: difference scores characterising the degree of change in accuracy (% correct trials) and median RT (ms) between successive learning blocks. Difference scores were calculated by subtracting the accuracy or median RT in one block from the accuracy or median RT in the next block in each participant. Thus, accuracy/RT in block 1 were subtracted from those values in block 2, values in block 2 were subtracted from those in block 3, values in block 3 were subtracted from those in block 4, and values in block 4 were subtracted from those in block 5.
- Within-block learning rate for accuracy and RT: these measures were computed by fitting a linear learning slope of the form $y = ax + b$ to accuracy and RT data separately within each learning block for each participant. The learning slopes were fitted after a moving 4-trial average of the accuracy and RT data had been computed to correct for the influence of auto-correlated data across trials. The slope values (a) were extracted for accuracy and RT within each block and standardised by z-transformation for analysis. Higher slope values indicate greater changes in accuracy and RT across trials in the block. Positive slope values indicate increases in accuracy and RT; negative slope values indicate decreases in these measures.

4.1.3 Electrophysiological correlates of goal-directed learning

Electrophysiological data were processed offline using EEGLab version 10.2.5.8b (Delorme & Makeig, 2004) within the Matlab environment (version R2011a, MathWorks, UK). Brain Vision Analyzer v.2.0 (Brain Products, Munich, Germany) was used to perform semi-automated peak detection

following data processing in EEGlab because this function is superior in Brain Vision Analyzer software.

Flat or noisy channels were removed prior to data processing. The data were re-referenced to the average reference and filtered with 0.5Hz high-pass, 30Hz low-pass, Butterworth 24dB slope filters. The data were segmented into learning blocks (1-5). Within these blocks, stimulus- and feedback- locked epochs were created by segmenting the data in time from -200ms to +1000ms around stimulus/feedback onset. Independent components analysis (ICA) was used to identify and remove artefacts resulting from eye movements, muscle movements and channel noise from the epoched data. ICA extracts individual components (signals) from the EEG data that are statistically independent from the overall mixture of EEG signals (Stone, 2000). The scalp topography, frequency (Hz), and presence across trials of extracted components are visually inspected to determine whether the components reflect artefact or brain activity. A component reflecting brain activity can be identified by a dipole-like topography and regular presence across trials. In contrast, a component reflecting ocular artefact for example can be identified by a maximally frontal negative topography, often without a corresponding positive dipole elsewhere on the scalp, restriction to high frequencies and less regular presence across trials (Delorme et al., 2006).

Following ICA, semi-automatic artefact rejection was performed to remove epochs containing data with extreme values (5 SD either side of the average for each channel per epoch) that had not been removed by the ICA. The cleaned epochs were baseline-corrected using a pre-stimulus/pre-feedback reference period of -200-0ms. Epochs were averaged within each block to create separate stimulus-locked and feedback-locked ERPs for blocks 1-5. Correct trials only (minimum of 15 trials) were included in the averages. Participants who did not meet this criterion were excluded from ERP analyses.

Differences in the number of trials included in averaged waveforms can result in differences in signal-to-noise ratio (SNR) between the averages, with those containing many trials having better SNR than those containing few trials (Luck, 2005). Amplitudes of averages with high SNR tend to be lower than those of averages with low SNR (Luck, 2005). To determine whether any group differences in ERP amplitudes found in this study might reflect group

differences in SNR of the averages due to unequal trial numbers between groups, the number of trials included in each participant's stimulus- and feedback-locked average in each learning block was measured and compared between participant groups. The results of this analysis are reported in section 4.2.4.4.

Electrophysiological correlates of goal-directed reinforcement learning were the stimulus-locked P3 and feedback-locked FRN ERP components. The P3 and FRN were selected for investigation based on previous research demonstrating that reliable learning-related changes occur in these components in reinforcement learning tasks (Eppinger et al., 2009; Holroyd & Coles, 2002; Rose et al., 2001; Shephard et al., *under review* (see appendix A); see chapter 2 section 2.2.4 for a full review of these findings). Based on parameters used in previous research and inspection of the grand and individual average waveforms, the components were defined as follows.

- Stimulus-locked P3: most positive peak in channel Pz (midline parietal scalp) in the time period 300-650ms post-stimulus in each learning block
- Feedback-locked FRN: most negative peak in channel FCz (midline frontal scalp) in the 200-400ms post-feedback period in each learning block.

Peak amplitudes of the P3 and FRN have traditionally been used in previous research in this area. However, because peak amplitudes can be influenced by group differences in SNR and latency jitter in event-related components between trials, some authors propose that mean amplitude, which is less sensitive to SNR differences, should be measured (Luck, 2005). Then again, the average amplitude in a large time-window (200ms+) may be insensitive to subtle, but genuine, amplitude differences between the participant groups in this study because a fixed time window may perfectly capture the relevant activity in one participant but not in another. Moreover, the use of mean rather than peak amplitude would complicate relating the results of this study to previous work using the P3 and FRN. Therefore, in the current study the peak amplitudes of the P3 and FRN in each learning block were taken and to address potentially confounding effects of SNR and inter-trial latency differences the mean amplitude in the 15 time-points (30ms) either side of the

peak were calculated. These mean-around-peak measures were used in analyses. The term 'peak amplitude' shall be used to refer to these measures in the remainder of this thesis.

The peak amplitudes in each learning block were used in group analyses, and additionally, change scores were created to represent the degree of learning-related change in amplitude from one learning block to the next. ERP change scores were computed in the same manner as difference scores for accuracy and RT; that is, block 2 P3/FRN minus block 1 P3/FRN, block 3 minus block 2, block 4 minus block 3, and block 5 minus block 4.

4.1.4 Hypotheses

The hypotheses for the acquisition and reversal phases of the goal-directed reinforcement learning task are as follows.

4.1.4.1 Acquisition phase (task blocks 1-3)

1. Based on the proposition that habit-learning and not goal-directed learning is affected in TS, it is predicted that the TS group will show comparable learning-related improvements in performance and changes in amplitude of the P3 and FRN as the Control group. In both groups, accuracy will increase and RT will decrease across and within blocks, P3 amplitude will increase and FRN amplitude will decrease across blocks.
2. The ADHD group will be impaired in goal-directed learning of the S-R associations compared with the TS and Control groups. This will manifest as lower accuracy and slower RT in blocks 1-3, smaller learning-related changes in accuracy and RT across these blocks, and lower within-block learning rate in the ADHD group compared with the TS and Control groups. Amplitude of the P3 will decrease less across blocks in ADHD than Controls and TS, reflecting weaker consolidation of the S-R associations. FRN amplitude will be smaller in ADHD than TS and Controls, indicating diminished positive prediction errors to positive reinforcement feedback following correct responses (incorrect trials were not analysed and thus no prediction is made concerning negative prediction errors and the FRN). Additionally, the FRN will

decrease less across blocks in ADHD than TS and Controls, reflecting a continuing reliance on feedback and lack of expectancy of positive feedback in young people with ADHD due to weaker learning of the S-R associations.

3. No specific hypotheses were made for performance and ERP amplitudes in the TS+ADHD group due to the lack of previous research in this area. However, if an additive model of comorbidity holds for TS+ADHD then the young people in this group should show the same pattern of impaired performance and ERP correlates of goal-directed learning as the ADHD group. Alternatively, if TS+ADHD is a symptomatic phenocopy of ADHD, then young people with TS+ADHD will show comparable performance and ERP changes as young people with TS. If TS+ADHD is an independent condition, young people in this group might differ from those with TS and ADHD alone.

4.1.4.2 Reversal phase (task blocks 4-5)

1. In block 4 of the task when participants must learn and implement the reversed S-R associations, accuracy will decrease, RT will increase, and within-block learning rate will be greater than in block 3. P3 amplitude should be smaller in block 4 than block 3, reflecting weaker associations between the newly reversed mappings in block 4 compared with the learned mappings in block 3. FRN amplitude will be larger in block 4 than block 3, reflecting greater reliance on feedback and reduced expectancy of positive reinforcement feedback (greater positive prediction errors) following correct production of the newly reversed associations in block 4. In block 5 of the task when the mappings remain reversed, accuracy will be greater, RT will be faster, and within-block learning rate will be smaller, P3 will be larger and FRN will be smaller than in block 4, reflecting the re-acquisition of the S-R associations.
2. It is hypothesised that the TS group will show comparable, or perhaps enhanced, reversal-related changes in performance and ERP amplitudes as Controls. The rationale for this prediction is that although the TS and Control groups will not differ in their ability to learn the reversed

mappings, the TS group might be better at suppressing the previously acquired associations and implementing the new reversed associations due to their enhanced ability to consciously control behaviours (see chapter 2, section 2.3.1 for a full discussion of enhanced cognitive control in TS).

3. Young people with ADHD will show greater reversal-related decrements in performance and ERP amplitudes in block 4 than the TS and Control groups. Further, the ADHD group will show smaller learning-related improvements in performance and ERP amplitudes in block 5 than TS and Controls. This pattern of findings would reflect impaired ability to learn and implement the reversed associations in young people with ADHD.
4. As with the acquisition phase, specific hypotheses were not formulated for performance and ERP amplitudes in the TS+ADHD group. If TS+ADHD reflects additive comorbidity then the young people in this group should produce similar behavioural performance and ERP impairments as young people with ADHD, while if this comorbidity reflects a symptomatic phenocopy then behavioural and ERP correlates of goal-directed learning will be comparable in young people with TS+ADHD and young people with TS. If TS+ADHD is an independent condition, these young people might differ from those with TS and ADHD.

4.1.4.3 Relationships between tic and ADHD symptoms and goal-directed learning

1. Consistent with the proposal that goal-directed reinforcement learning impairments are core to the pathology of ADHD, it is hypothesised that greater severity of ADHD symptoms will predict greater impairment in learning- and reversal- related changes in behavioural and ERP correlates of goal-directed learning.
2. In line with the hypothesis that goal-directed learning is not affected in TS, it is hypothesised that tic symptom severity will not be associated with learning-related changes in performance or electrophysiological activity in the acquisition phase of the task. In the reversal phase, tic

symptoms may be un-related to reversal- and re-learning- related changes in behavioural or ERP correlates. Alternatively, tic symptom severity might be associated with better performance and ERP changes during reversal, reflecting the involvement of cognitive control in this phase of the task and the enhancement of cognitive control in TS.

3. The extent to which comorbid symptoms of ODD and OCD modulate relationships between ADHD and tic severity and behavioural and ERP changes in goal-directed learning was explored. No specific hypotheses were formulated because this issue has not previously been examined in published research.

4.1.5 Analysis methods

4.1.5.1 Normality testing

All behavioural and electrophysiological correlates of goal-directed reinforcement learning were subjected to Shapiro-Wilk tests to check normality of distributions. Normally distributed variables were analysed with parametric ANCOVA tests and significant main effects and interactions were further investigated using univariate ANCOVAs and independent-samples t-tests. Due to the robustness of ANCOVA to violations of normality assumptions (Norman, 2010) and the limitations of non-parametric statistical tests, for example the preclusion of covariate or mixed-model analyses, variables that were not normally distributed were analysed with parametric ANCOVAs. However, non-parametric Mann-Whitney U tests were used in place of independent-samples t-tests to further investigate main effects and interactions revealed in the ANCOVA models.

4.1.5.2 Covariates

The variable age was included as a covariate in analyses of goal-directed reinforcement learning. Previous research indicates that goal-directed learning improves with age (Crone et al., 2004; Eppinger et al., 2009; Hämmerer et al., 2010) and that processing in fronto-striatal circuitry involved in goal-directed reinforcement learning changes with age (van Duijvenvoorde et al., 2008). In the pilot study of the current goal-directed learning task in typically developing 9-11 year olds and adults, there were no differences

between age groups in behavioural performance or P3 and FRN amplitudes during the acquisition phase, but there were significant age effects on both performance and P3 and FRN amplitudes during the reversal phase (Shephard et al., *under review* (see appendix A)). In light of these findings and due to the broader age-range (9-17 years) of participants included in the TS, TS+ADHD, ADHD and Control groups in this study, it was decided that age-related effects on goal-directed learning may have been present in each participant group in this study and that these effects may have moderated performance and ERP amplitudes. For these reasons, age was included as a covariate in analyses of the acquisition and reversal phase behavioural and ERP correlates to examine group differences in these measures while controlling for potentially confounding effects of age on these variables. However, in acknowledgement of the lack of age-effects found during the acquisition phase in the pilot study of this task, the analyses for the acquisition phase were also conducted without age included as a covariate and the results from these analyses are reported where they differed from those including age.

Other variables were also considered for inclusion as covariates. IQ was significantly lower in the ADHD group compared with the other groups despite attempts to match the groups on this variable. Common practice in cases where IQ differs between participant groups is to include this variable as a covariate in analyses. However, Dennis et al. (2009) point out that this approach is inappropriate. Individuals with ADHD frequently have lower IQ than unaffected individuals and individuals with TS. This close relationship between ADHD group membership and level of IQ mean that it is not possible to separate the effects of ADHD on cognitive function from the effects of IQ on cognitive function, and so covarying IQ is neither useful nor appropriate (Dennis et al., 2009). For these reasons IQ was not included as a covariate in the main analyses of goal-directed reinforcement learning in this thesis. However, to be consistent with previous research, additional analyses including IQ as a covariate were conducted and results are reported wherever they differed from those of the main analyses in which IQ was not covaried.

Finally, gender and SES were considered as covariates as it is conceivable that these factors could influence reinforcement learning. However, due to the male bias inherent in developmental disorders and the

tendency for individuals with ADHD to be from lower SES families, these variables were not deemed appropriate for inclusion as covariates.

4.1.5.3 Hypothesis testing

All statistical analyses were conducted using SPSS v.21 (IBM©). Performance and electrophysiological correlates of goal-directed reinforcement learning were analysed in the acquisition and reversal phases separately. To test the hypothesised group differences in the ability to learn the S-R associations in the acquisition phase, mixed-model ANCOVAs were conducted for each behavioural and ERP correlate from task blocks 1-3. ANCOVA models consisted of one within-subjects factor of block (3 levels: block 1, block 2, block 3), and one between-subjects factor of group (4 levels: TS, TS+ADHD, ADHD, Control). Age was included as a covariate. Significant main effects and interactions were further investigated with univariate ANCOVAs with age as the covariate and group (4 levels) as the between-subjects factor, and parametric (independent-samples t-tests) or non-parametric (Mann-Whitney U tests) planned contrasts between each pair of groups.

To test the hypothesised group differences in the ability to reverse the learned S-R associations, mixed-model ANCOVAs were conducted on the behavioural and ERP correlates from the reversal phase (blocks 4-5) and for comparison, block 3. The ANCOVA models consisted of one within-subjects factor of block (3 levels: block 3, block 4, block 5), one between-subjects factor of group (4 levels), and the covariate age. Significant main effects and interactions were further investigated with univariate ANCOVAs with the between-subjects factor group (4 levels) and age as a covariate, and parametric (independent-samples t-tests) or non-parametric (Mann-Whitney U tests) planned pairwise group contrasts.

Further details of the analyses conducted for each behavioural and ERP measure in the acquisition and reversal phases are provided in the appropriate section of the results (section 4.2). Greenhouse-Geisser corrections for violations of sphericity were used where appropriate. Due to the small sample sizes and consequent low power of this study in detecting effects, correction for multiple comparisons was not applied to the pairwise group contrasts in

either task phase. However, the effects that would not remain significant after correction are reported. .

To test the hypothesised predictive relationships between tic, ADHD, OCD and ODD symptom severity and learning-related changes in behavioural and ERP correlates of goal-directed learning, hierarchical multiple linear regression analyses were conducted. To limit the number of tests conducted regression analyses were only performed for behavioural and ERP change measures which differed significantly between groups. For each change measure, two separate hierarchical models were constructed.

Model A investigated whether tic and OCD severity predicted change measures in individuals with TS and TS+ADHD. Individuals with ADHD and unaffected controls were excluded from Model A analyses because they did not have tics and most individuals did not have OCD symptoms. The inclusion of ADHD and Control groups would not have been appropriate due to the non-linear distribution of tic and OCD scores. In block 1 of Model A, the variables age and total tic severity (YGTSS Total) were entered to assess how well tics predicted changes in goal-directed learning while accounting for the degree to which age predicted those changes. In block 2, OCD symptom scores on the CY-BOCS were entered to examine whether these commonly comorbid symptoms predicted learning-related changes and/or moderated relationships between tics and changes in learning. Scatterplots were produced to characterise significant relationships between tics/OCD and goal-directed learning change measures.

Model B tested relationships between ADHD and ODD symptomatology and change measures of goal-directed learning in the whole sample (TS, TS+ADHD, ADHD, Controls). In block 1, age and ADHD severity scores on the CPRS-R ADHD Index were entered to assess the extent to which ADHD severity predicted changes in goal-directed learning while accounting for the degree to which age predicted such changes. In block 2, ODD scores on the CPRS-R ODD scale were entered to explore whether these symptoms predicted changes in learning or moderated predictive relationships between ADHD symptoms and learning changes. Significant relationships were characterised using scatterplots. The CPRS-R measures were used rather

than the SDQ Hyperactivity and Conduct measures because the former scales provide a more thorough assessment of ADHD and ODD symptoms.

The Durbin-Watson statistic was computed for all models to check for autocorrelation among the residuals and test the assumption of independent errors. Multicollinearity among IVs in each block of the models was assessed with the VIF (variance inflation factor).

4.2 RESULTS

4.2.1 Participants

Table 4-1 presents a revised summary of the socio-demographic and clinical characteristics of each group following participant exclusions. One participant with TS and one participant with TS+ADHD were excluded from all analyses due to producing extreme scores (> 2.5 SD of group mean) on one or more behavioural correlates of goal-directed reinforcement learning. A further one participant with TS, two participants with TS+ADHD, three participants with ADHD and one Control were excluded from electrophysiological analyses due to having insufficient artefact-free trials (< 15 trials) for ERP averages. As table 4-1 shows, the clinical and socio-demographic characteristics in the reduced samples are comparable with those of the full sample (chapter 3, table 3-1), which indicates that group effects reported in the following sections are generalisable to the full sample.

Information not presented in table 4-1 concerns medication status. In the behavioural sample the following medications were being received. TS: Clonidine (2), Aripiprazole (2), Fluoxetine (1), Citalopram (1); TS+ADHD: Clonidine (1), methylphenidate (2 – withdrawn for 24 hours prior to testing), Aripiprazole (2), Fluoxetine (1); ADHD: methylphenidate (9 – withdrawn 24 hours prior to testing), Atomoxetine (2 - not withdrawn). In the ERP sample the medications received were as follows. TS: same as for behavioural sample; TS+ADHD: same as for behavioural sample; ADHD: methylphenidate (7 – withdrawn 24 hours prior to testing), Atomoxetine (2 - not withdrawn).

Table 4-1

Summary of clinical and socio-demographic characteristics for each participant group in the behavioural analysis sample (A) and ERP analysis sample (B). Group means are presented with standard deviations in parentheses.

(A) Behavioural sample	TS (n = 17)	TS+ADHD (n = 16)	ADHD (n = 13)	Control (n = 20)	Group differences
Age (months)	158.4 (34.3)	150.6 (33.4)	168.5 (32.9)	156.3 (34.8)	n/s
Gender (% males)	76.5	93.8	92.3	80.0	n/s
Handedness (% right handed)	82.4	87.5	92.3	85.0	n/s
SES	2.1 (1.4)	1.8 (1.2)	2.1 (1.5)	1.5 (1.1)	n/s
IQ	112.0 (11.7)	108.8 (11.2)	96.3 (15.6)	112.6 (11.2)	ADHD < TS/TS+ADHD/ Controls **
Motor tic severity (YGTSS Motor)	13.5 (7.7)	15.9 (4.5)	0 (0)	0 (0)	TS/TS+ADHD > ADHD/Controls***
Phonic tic severity (YGTSS Phonic)	5.8 (5.8)	12.1 (7.9)	0 (0)	0 (0)	TS > ADHD/Controls* TS+ADHD > TS/ADHD/Controls***
Total tic severity (YGTSS Total)	19.3 (12.1)	28.1 (11.3)	0 (0)	0 (0)	TS > ADHD/Controls*** TS+ADHD > TS*/ADHD***/Controls***

CPRS-R ADHD Index[a]	54.2 (9.3)	71.5 (9.4)	76.1 (16.0)	47.5 (6.9)	TS+ADHD/ADHD > TS/Controls***
CPRS-R Inattentive	50.7 (7.8)	73.0 (11.2)	72.8 (18.5)	47.3 (6.9)	TS+ADHD/ADHD > TS/Controls***
CPRS-R Hyper-Impulsive	57.3 (11.7)	69.0 (20.9)	81.1 (20.9)	48.5 (6.8)	TS+ADHD > Controls*** ADHD > TS/Controls***
CPRS-R ODD Index	51.9 (10.7)	33.1 (19.9)	76.0 (19.9)	47.2 (9.3)	ADHD > TS*/TS+ADHD***/Controls**
ADHD Rating Scale IV	55.2 (31.4)	85.1 (12.2)	97.1 (2.5)	38.4 (27.3)	TS+ADHD > TS**/Controls*** ADHD > TS/Controls***
SDQ Hyperactivity	4.5 (3.2)	5.9 (3.1)	8.3 (2.0)	2.6 (2.6)	TS+ADHD > Controls*** ADHD > TS**/Controls***
SDQ Conduct	1.6 (1.7)	9.0 (7.0)	7.1 (3.0)	.80 (1.2)	TS+ADHD > TS/Controls*** ADHD > TS**/Controls***
CY-BOCS	7.0 (9.9)	6.5 (5.5)	.62 (1.7)	.05 (.22)	TS > ADHD*/ Controls** TS+ADHD > ADHD*/Controls**

* = significant at the p < .05 level. ** = significant at the p < .01 level. *** = significant at the p < .001 level. [a] Scores above 60 on the CPRS-R ADHD and ODD scales are considered to be clinically significant

(B) ERP sample	TS (n = 16)	TS+ADHD (n = 14)	ADHD (n = 10)	Control (n = 19)	Group differences
Age (months)	161.4 (33.0)	156.1 (32.0)	174.8 (22.9)	156.7 (35.6)	n/s
Gender (% males)	75.0	92.9	100.0	78.9	n/s
Handedness (% right handed)	81.3	85.7	90.0	84.2	n/s
SES	2.1 (1.4)	1.9 (1.3)	2.3 (1.6)	1.3 (.65)	n/s
IQ	111.9 (12.0)	107.3 (11.2)	95.5 (14.1)	113.3 (11.0)	ADHD < TS/Controls **
Motor tic severity (YGTSS Motor)	13.7 (7.9)	15.6 (4.8)	0 (0)	0 (0)	TS/TS+ADHD > ADHD/Controls***
Phonic tic severity (YGTSS Phonic)	6.2 (5.8)	11.5 (8.5)	0 (0)	0 (0)	TS > ADHD*/Controls** TS+ADHD > TS*/ADHD***/Controls***
Total tic severity (YGTSS Total)	19.9 (12.3)	27.1 (12.2)	0 (0)	0 (0)	TS/TS+ADHD > ADHD/Controls***
CPRS-R ADHD Index[a]	54.1 (9.6)	73.7 (10.1)	73.9 (17.2)	47.8 (6.6)	TS+ADHD/ADHD > TS/Controls***
CPRS-R Inattentive	50.6 (8.0)	71.1 (9.1)	70.3 (19.8)	47.4 (7.1)	TS+ADHD/ADHD > TS/Controls***

CPRS-R Hyper-Impulsive	56.5 (11.7)	74.9 (11.7)	78.9 (23.1)	48.6 (7.0)	TS+ADHD > TS**/Controls*** ADHD > TS/Controls***
CPRS-R ODD Index	51.4 (10.9)	66.9 (12.7)	75.4 (22.5)	47.5 (9.5)	TS+ADHD > TS*/Controls*** ADHD > TS/Controls**
ADHD Rating Scale IV	53.4 (31.8)	95.1 (4.8)	97.4 (1.5)	37.7 (27.9)	TS+ADHD > TS*/Controls*** ADHD > TS/Controls***
SDQ Hyperactivity	4.4 (3.3)	8.0 (2.2)	8.3 (2.1)	2.4 (2.6)	TS+ADHD > TS**/Controls*** ADHD > TS**/Controls***
SDQ Conduct	1.6 (1.7)	3.6 (2.3)	7.6 (2.6)	.79 (1.2)	TS+ADHD > TS*/Controls*** ADHD > TS/TS+ADHD/Controls***
CY-BOCS	7.4 (10.1)	2.2 (5.7)	.80 (1.9)	.05 (.23)	TS > ADHD*/Controls**

* = significant at the $p < .05$ level. ** = significant at the $p < .01$ level. *** = significant at the $p < .001$ level. [a] Scores above 60 on the CPRS-R ADHD and ODD scales are considered to be clinically significant.

4.2.2 Group differences in behavioural correlates of goal-directed learning

The variables accuracy, RT, and within-block learning rate were compared between groups and learning blocks in the acquisition and reversal phases separately using 3 (block) x 4 (group) ANCOVAs with age as the covariate. Blocks 1-3 were analysed in the acquisition phase and blocks 3-5 were examined in the reversal phase. The difference score measures characterising learning-related changes in accuracy and RT were compared between groups using separate univariate ANCOVAs with group (4) as the between-subjects factor and age as the covariate. The variables RT and within-block accuracy/RT learning rates were normally distributed (Shapiro Wilk $p > .05$), while the remaining variables were not normally distributed (Shapiro Wilk $p < .05$). Therefore, further investigation of significant main effects and interactions was conducted using independent-samples t-tests for RT and within-block learning rates, and using Mann-Whitney U tests for accuracy, and accuracy and RT change measures.

4.2.2.1 Accuracy

Figure 4-2 displays the mean accuracy achieved by each participant group in each learning task block.

4.2.2.1.1 Accuracy in the acquisition phase

The 3 x 4 ANCOVA revealed that accuracy in the acquisition phase differed at trend-level between blocks ($F (1.7, 103.2) = 2.8$, $p = .07$, $\eta^2 = .044$), and significantly between groups ($F (3, 61) = 3.0$, $p = .04$, $\eta^2 = .127$), but there was no interaction between block and group ($F (1.7, 103.2) = 1.3$, $p = .25$, $\eta^2 = .061$). Sign tests comparing accuracy between successive blocks showed that, across all participants, accuracy significantly increased from block 1 to 2 ($z = 5.2$, $p < .001$) and from block 2 to 3 ($z = 2.6$, $p = .009$).

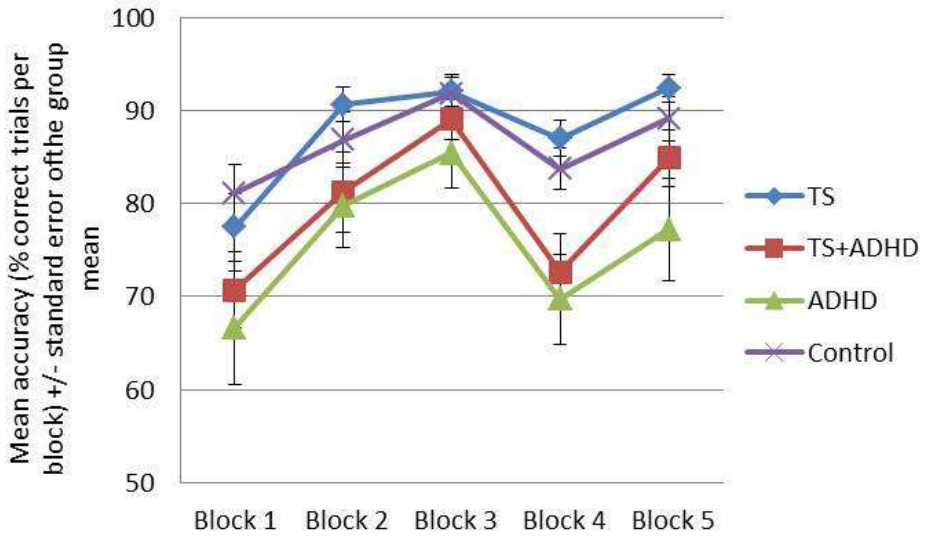
Further investigation of the significant main effect of group using Mann-Whitney U tests revealed that, across blocks 1-3, accuracy was significantly lower in the ADHD group than the Control group ($U = 184.0$, $p = .02$ (1-tailed), $d = .57$), and lower at trend-level in the ADHD group than the TS group ($U = 72.5$, $p = .06$ (1-tailed), $d = .59$). The TS+ADHD group also produced trend-level lower accuracy than Controls (U = 216.0. p = .08 (2-

tailed), *d* = .43) and TS (U = 85.0, p = .07 (2-tailed), *d* = .44). The TS+ADHD and ADHD groups did not differ in accuracy, nor did the TS and Control groups (all p > .10).

The significant main effect of group on accuracy remained at trend-level when age was not included as a covariate (F (3, 62) = 2.5, p = .07, η^2 = .108), but did not remain when IQ was included as a covariate (F (3, 60) = 1.6, p = .20, η^2 = .07). The pairwise group differences between ADHD and TS+ADHD groups and the TS and Control groups would not remain significant after correcting for multiple comparisons.

Figure 4-2

Group means for accuracy (% correct trials) in each learning block plotted by group (TS, TS+ADHD, ADHD, Controls). Error bars represent the standard error of the group mean.



4.2.2.1.2 Accuracy in the reversal phase

Accuracy in the reversal phase differed significantly between blocks (F (1.7, 105.1) = 4.4, p = .02, η^2 = .067) and between groups (F (3, 61) = 6.5, p = .001, η^2 = .243), and there was a significant interaction between block and group (F (5.2, 105.1) = 2.8, p = .02, η^2 = .122). Sign tests comparing accuracy between successive blocks showed that accuracy significantly decreased from block 3 to 4 (z = -6.0, p < .001) and increased significantly from block 4 to 5 (z = 4.9, p < .001). The main effect of group was further investigated with Mann-

Whitney U tests comparing accuracy between each pair of groups. Across blocks 3-5, accuracy was significantly lower in ADHD than Controls (U = 192.5, p = .01 (1-tailed), *d* = -.74) and TS (U = 52.5, p = .007 (1-tailed), *d* = -.95), and in TS+ADHD than Controls (U = 227.5, p = .03 (2-tailed), *d* = -.49) and TS (U = 58.5, p = .004 (2-tailed), *d* = -.73). The TS and Control groups did not differ in accuracy, nor did the ADHD and TS+ADHD groups (all p > .10).

The significant interaction between block and group was investigated using univariate ANCOVAs to compare accuracy between the groups in blocks 3, 4 and 5 separately. Accuracy differed at trend-level between groups in block 3 (F (3, 61) = 2.3, p = .09, η^2 = .102), and significantly between groups in blocks 4 (F (3, 61) = 7.6, p < .001, η^2 = .273) and 5 (F (3, 61) = .5.0, p = .004, η^2 = .198). In block 3, accuracy was lower at trend-level in ADHD than Controls (U = 168.5, p = .08 (1-tailed), *d* = -.57), but did not differ between the remaining group pairs (all p > .10). In block 4, accuracy was significantly lower in ADHD than Controls (U = 201.0, p = .004 (1-tailed), *d* = -.97) and TS (U = 32.5, p < .001 (1-tailed), *d*= -1.3). Likewise, accuracy was significantly lower in TS+ADHD than Controls (U = 228.5, p = .03 (2-tailed), *d* = -.83) and TS (U = 60, p = .005 (2-tailed), *d* = -1.1). TS and Controls did not differ from one another in block 4, nor did the ADHD and TS+ADHD groups (all p > .10). In block 5, accuracy was significantly lower in the ADHD than Control (U = 181.5, p = .03 (1-tailed), *d* = -.74) and TS (U = 55.5, p = .01 (1-tailed), *d* = -1.0) groups, but did not differ between the remaining group pairs (all p > .10).

If correction for multiple comparisons was applied to these data, the following group differences would not remain significant. Block 3: ADHD < Controls; block 4: TS+ADHD < Controls; block 5: ADHD < Controls; ADHD < TS. The main effect of group and the interaction between block and group remained significant when IQ was included as a covariate, but the main effect of block remained only at trend-level (F (1.7, 103.7) = 2.4, p = .11, η^2 = .038).

4.2.2.2 RT

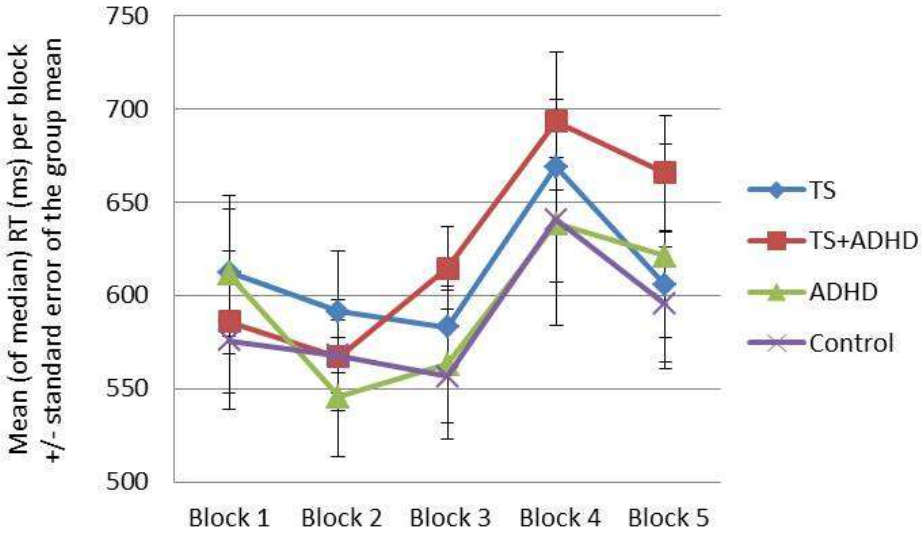
Figure 4-3 displays the mean of median RT for correct trials in each participant group in each learning block.

4.2.2.2.1 RT in the acquisition phase

The 3 x 4 ANCOVA on correct trial median RT in blocks 1-3 revealed no significant main effects of block ($F(1.6, 96.7) = .37$, $p = .64$, $\eta^2 = .006$) or group ($F(3, 61) = .24$, $p = .87$, $\eta^2 = .011$) and no interaction between block and group ($F(4.8, 96.7) = 1.1$, $p = .37$, $\eta^2 = .051$). These results did not change when age was not included as a covariate, or when IQ was covaried.

Figure 4-3

Group means of median RT (ms) for correct trials in each learning block. Error bars represent the standard error of the group mean.



4.2.2.2.1 RT in the reversal phase

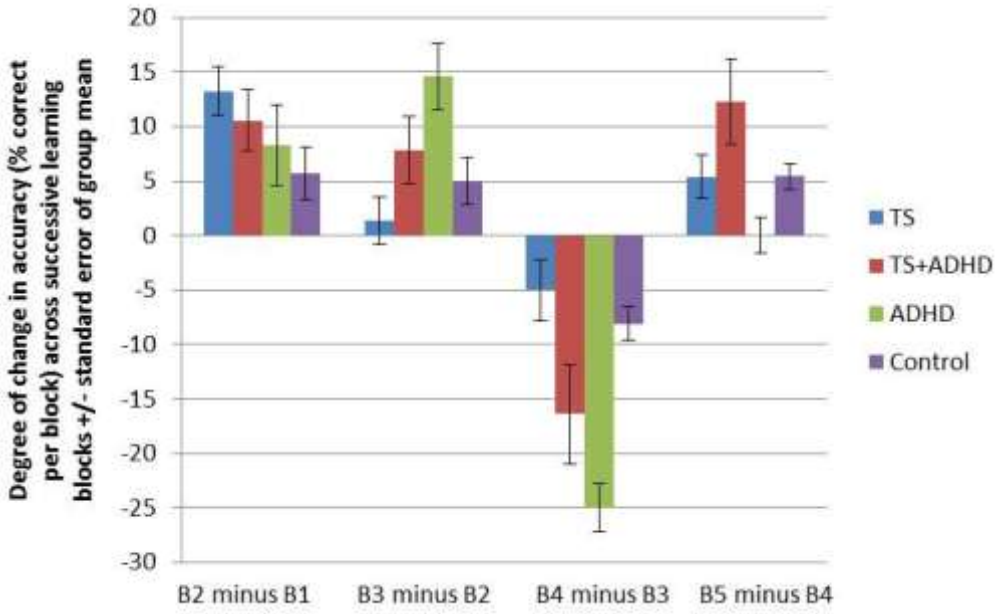
In the reversal phase, RT for correct trials differed significantly between blocks ($F(2, 122) = 7.1$, $p = .001$, $\eta^2 = .104$), but not between groups ($F(3, 61) = .53$, $p = .66$, $\eta^2 = .026$), and the interaction between block and group was not significant ($F(6, 122) = .57$, $p = .76$, $\eta^2 = .027$). Paired-samples t-tests revealed that, across groups, RT significantly increased from block 3 to block 4 ($t(65) = -7.5$, $p < .001$, 1-tailed), and significantly decreased from block 4 to block 5 ($t(65) = 3.8$, $p < .001$, 1-tailed). When IQ was included as a covariate the main effect of block did not remain ($F(2, 120) = .26$, $p = .78$, $\eta^2 = .004$) but the group and group*block interaction results were unchanged.

4.2.2.3 Accuracy and RT learning change measures

The difference scores characterising the degree of learning-related change in accuracy and correct trial RT across successive task blocks in each group are presented in figure 4-4 (accuracy) and figure 4-5 (RT). Each difference score was compared between the four participant groups using univariate ANCOVAs with age as a covariate.

Figure 4-4

Difference scores characterising the degree of learning-related change in accuracy (% correct trials) across successive task blocks plotted by participant group. Error bars represent the standard error of the group mean.



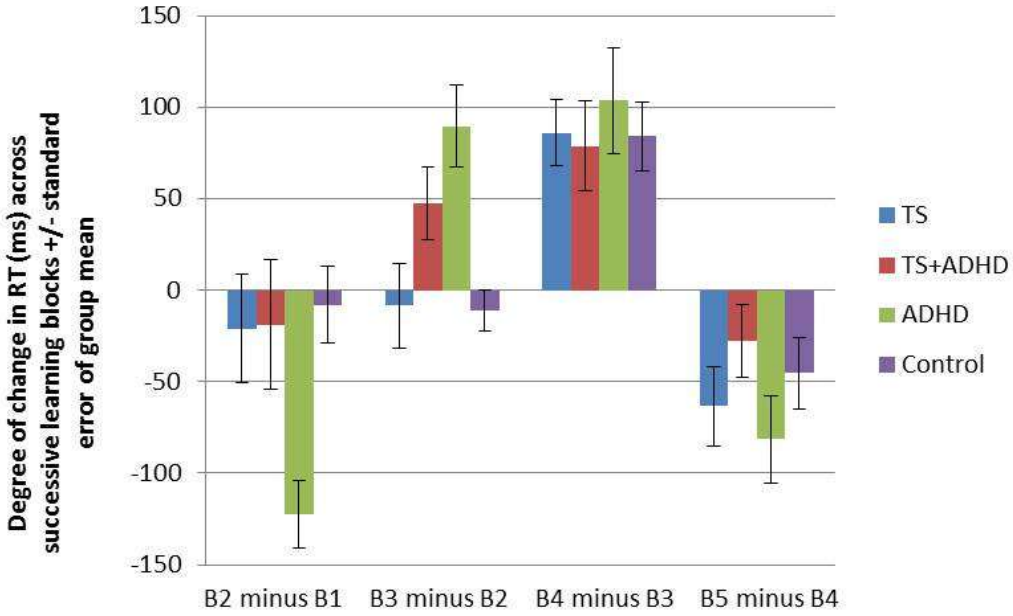
4.2.2.3.1 Changes in accuracy with learning

The groups did not differ significantly in the degree to which accuracy increased from block 1 to 2 ($F (3, 61) = 1.9$, $p = .15$, $\eta^2 = .083$), block 2 to 3 ($F (3, 61) = 1.1$, $p = .36$, $\eta^2 = .051$), or block 4 to 5 ($F (3, 61) = 1.8$, $p = .16$, $\eta^2 = .080$). However, the extent to which accuracy decreased from block 3 to the reversal block 4 differed significantly between groups ($F (3, 61) = 3.6$, $p = .02$, $\eta^2 = .151$). Mann-Whitney U tests comparing the change in accuracy from block 3 to 4 between each pair of groups revealed that the ADHD group showed a significantly greater decrease in accuracy than the TS ($U = 42.0$, $p = .002$ (1-tailed), $d = 1.1$) and Control ($U = 201.0$, $p = .004$ (1-tailed), $d = 1.0$)

groups. Similarly, accuracy decreased significantly more across blocks 3 to 4 in the TS+ADHD group compared with the TS (U = 74.5, p = .03 (2-tailed), *d* = .75) and Control (U = 220.5, p = .05 (2-tailed), *d* = .60) groups. TS and Controls showed a comparable decrease in accuracy, as did the TS+ADHD and ADHD groups (all p > .10).

Figure 4-5

Difference scores characterising the degree of learning-related change in correct trial RT (ms) across successive task blocks plotted by participant group. Error bars represent the standard error of the group mean.



4.2.2.3.1 Changes in RT with learning

No significant group differences were revealed in the degree of learning-related change in RT from block 1 to 2 (F (3, 61) = .79, p = .51, η^2 = .037), block 2 to 3 (F (3, 61) = 2.1, p = .12, η^2 = .092), block 3 to 4 (F (3, 61) = .05, p = .99, η^2 = .002), or block 4 to 5 (F (3, 61) = .92, p = .44, η^2 = .043). However, it is interesting to note that the data in figure 4-5 indicate that the ADHD group produced an atypical pattern of RT changes in the acquisition phase of the task, with a large initial decrease from block 1 to 2, and then a large increase from block 2 to 3. The TS+ADHD group also showed a marked increase in RT from block 2 to3. These results were unchanged when IQ was

included as a covariate, or for the acquisition phase change measures (block 2-1 and block 3-2) when the covariate age was removed.

4.2.2.4 Within-block learning rate: accuracy

Figure 4-6 presents the within-block learning slopes for accuracy in each task block during the acquisition phase (A) and during the reversal phase (B).

4.2.2.4.1 Acquisition phase

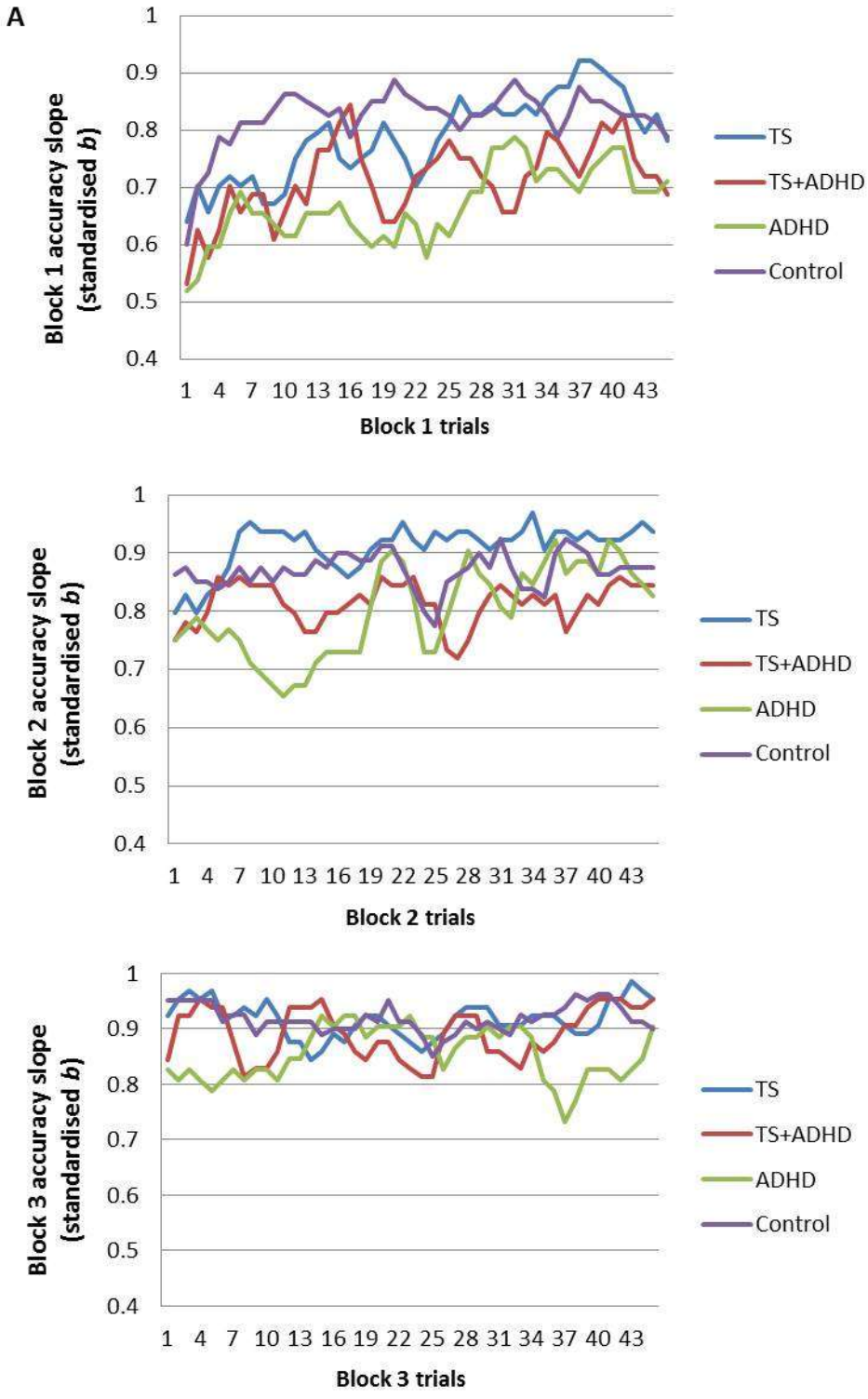
The 3 x 4 ANCOVA revealed that the within-block learning rate for accuracy in the acquisition phase did not differ between blocks ($F (2, 122) = .46$, $p = .63$, $\eta^2 = .008$) or between participant groups ($F (3, 61) = 2.0$, $p = .12$, $\eta^2 = .091$), and there was no significant interaction between block and group ($F (6, 122) = .52$, $p = .78$, $\eta^2 = .025$). However, inspection of the plots in figure 4-6 indicates that learning rate was greater in block 1 compared with blocks 2 and 3 (steeper slopes), suggesting that learning of the S-R associations proceeded more rapidly in the initial learning block and tapered off to asymptote in following two blocks. The large degree of variability in the slopes, also evident from figure 4-6, may have obscured these differences in learning rate. When the covariate age was removed from the model the results were unchanged. Similarly, when IQ was included as a covariate the results were unaltered.

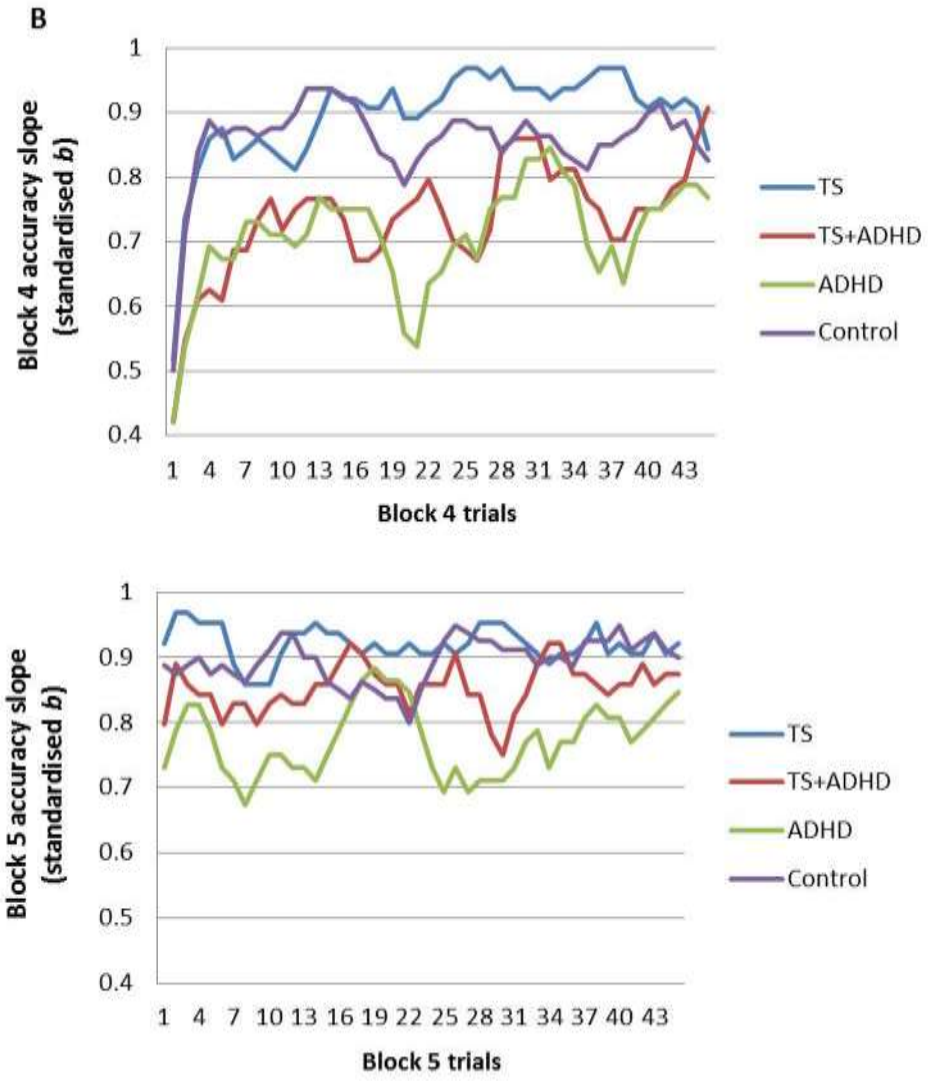
4.2.2.4.2 Reversal phase

Within-block accuracy learning rate during the reversal phase did not differ significantly between blocks ($F (1, 122) = .16$, $p = .86$, $\eta^2 = .003$) or groups ($F (3, 61) = .26$, $p = .85$, $\eta^2 = .013$), and the interaction between these factors was not significant ($F (6, 122) = .94$, $p = .47$, $\eta^2 = .044$). Nevertheless, it is clear from figure 4-6 that learning rate was more rapid in the reversal block 4 than block 5, which is consistent with a greater amount of learning of the S-R associations immediately after the reversal than in the following block. The large variability of slope values may have obscured these differences between blocks 4 and 5. The inclusion of IQ as a covariate did not alter these results.

Figure 4-6

Learning slopes fitted to the accuracy data in each block in the acquisition phase (A) and reversal phase (B). The average slope values are plotted for each participant group.





4.2.2.5 Within-block learning rate: RT

Table 4-2 presents the group means for within-block learning rate for correct trial RT in each task block.

4.2.2.5.1 Acquisition phase

The 3 x 4 ANCOVA examining the rate at which RT for correct trials changed within each learning block in the acquisition phase revealed a trend-level effect of block ($F (2, 122) = 1.7$, $p = .07$, $\eta^2 = .043$) but no main effect of group ($F (3, 61) = .23$, $p = .88$, $\eta^2 = .011$) or interaction between block and group ($F (6, 122) = .46$, $p = .84$, $\eta^2 = .022$). Paired-samples t-tests comparing RT learning rate between successive task blocks revealed that, across all participants, RT learning rates did not differ between blocks 1 and 2 (t (65) =

0.0, p = 1.0, 2-tailed) or between blocks 2 and 3 (t (65) = 0.0, p = 1.0, 2-tailed). The trend-level effect of block did not remain when age was removed as a covariate (F (2, 122) = .001, p = .10, η^2 = .000), while the non-significant results for group and the block*group interaction did not change. The inclusion of IQ as a covariate did not alter these results.

Table 4-2

Summary of learning rate (standardised *b* coefficients) values from the learning slopes fitted to the correct trial RT data in blocks 1-5. Group means are presented with standard deviations in parentheses.

	TS	**TS+ADHD**	**ADHD**	**Control**
Block 1	-.041 (.996)	.134 (1.18)	-.104 (1.05)	-.004 (.878)
Block 2	.056 (1.15)	-.164 (.743)	-.060 (1.06)	.123 (1.05)
Block 3	-.199 (.917)	-.044 (.849)	-.057(1.31)	.168 (.999)
Block 4	.288 (.867)	-.133 (.752)	.256 (1.10)	-.304 (1.16)
Block 5	-.481 (.748)	.015 (1.21)	.566 (1.14)	.029 (.739)

4.2.2.5.2 Reversal phase: learning rate

The rate at which RT for correct trials changed within blocks in the reversal phase did not differ between blocks (F (1, 122) = .36, p = .70, η^2 = .006) or groups (F (3, 61) = 1.7, p = .17, η^2 = .079), and there was no block*group interaction (F (6, 122) = 1.5, p = .18, η^2 = .069). These results did not change when IQ was included as a covariate.

4.2.3 Summary of group differences in behavioural correlates of goal-directed reinforcement learning

To summarise, the groups differed significantly in the total percentage of correct trials (accuracy) obtained during the acquisition and reversal phases, and the extent to which accuracy decreased in the reversal block compared with the previous learning block. The groups did not differ in RTs for blocks during acquisition and reversal phases, the extent to which RT changed with learning across task blocks, or the degree to which accuracy and RT increased or decreased within learning blocks in the acquisition and reversal phases.

Concerning the group differences in accuracy, the ADHD group was significantly less accurate than the Control group during the acquisition phase (average accuracy across blocks 1-3) and tended to be less accurate than the TS group during this phase. The TS+ADHD group also tended to be less accurate during the acquisition phase than the TS and Control groups. In the reversal phase (average accuracy across blocks 3-5), the ADHD and TS+ADHD groups produced significantly poorer accuracy than the TS and Control groups. These findings indicate that the young people with ADHD symptoms, with or without tics, were generally less successful at learning and reversing the S-R associations than young people without ADHD, with or without tics. However, young people with TS+ADHD were marginally less impaired than young people with ADHD in acquiring the S-R associations.

This overall difference in accuracy was qualified by a significant block by group interaction in the reversal phase. Further investigation of this interaction revealed that the ADHD group was significantly less accurate than TS and Controls in the reversal block 4 and the following block 5, but were only marginally less accurate in block 3, the point in the task at which the S-R associations would have been consolidated prior to the reversal. Similarly, the TS+ADHD group was significantly less accurate than TS and Controls during the reversal block 4 but not during the preceding block 3 or following block 5. These findings indicate that, in addition to performing more poorly than TS and Controls in general, the ADHD and TS+ADHD groups were specifically impaired when they were required to reverse the S-R associations. This was further demonstrated by the finding that the degree of decrease in accuracy from block 3 to the reversal block 4 was significantly greater in ADHD and TS+ADHD than TS and Controls, while the degree to which accuracy increased from blocks 1-2, 2-3 and 4-5 did not differ between the groups. As hypothesised, the TS group did not differ in accuracy from the Control group in the acquisition or reversal phases of the task.

4.2.4 Group differences in electrophysiological correlates of goal-directed learning

Peak amplitudes of the P3 and FRN were analysed using 3 (block) x 4 (group) ANCOVAs with age as a covariate in the acquisition phase (blocks 1-

3) and reversal phase (blocks 3-5) separately. The difference scores characterising the degree of learning-related change in P3 and FRN amplitudes from one task block to the next were analysed using univariate ANCOVAs with group (4) as the between-subjects factor and age as the covariate. FRN amplitudes in blocks 1-5 were normally distributed (Shapiro Wilk $p > .05$); therefore, significant main effects and interactions in FRN amplitude were further investigated using parametric independent-samples t-tests. P3 amplitude in blocks 1-5 and FRN and P3 change scores were not normally distributed (Shapiro Wilk $p < .05$); further investigation of significant main effects and interactions in these variables was conducted using non-parametric Mann-Whitney U tests.

4.2.4.1 P3 amplitude

Figure 4-7 presents the group means, plotted by learning block, for peak P3 amplitude. The grand average stimulus-locked waveforms and topographical plots for the P3 are presented in figure 4-8.

Figure 4-7

Group mean peak amplitudes for the P3 at Pz plotted by learning block (1-5). Error bars represent the standard error of the group mean.

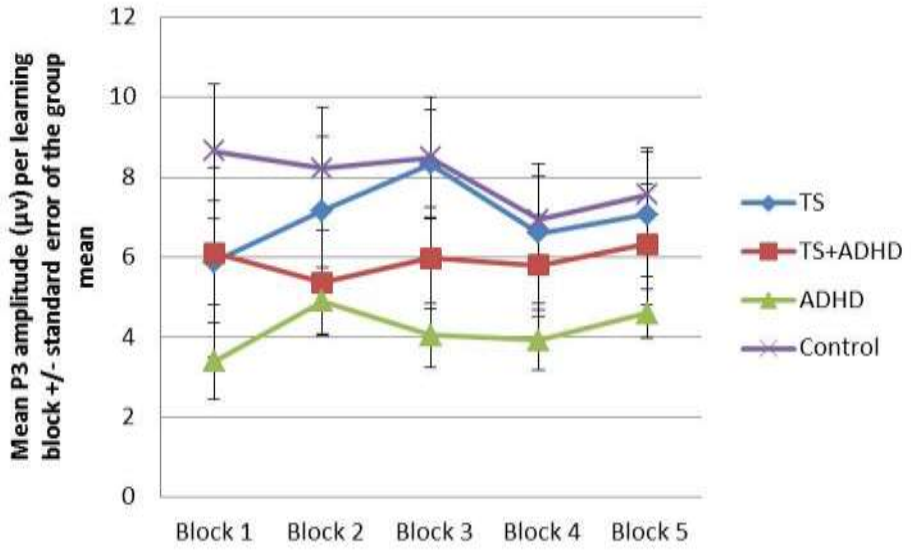
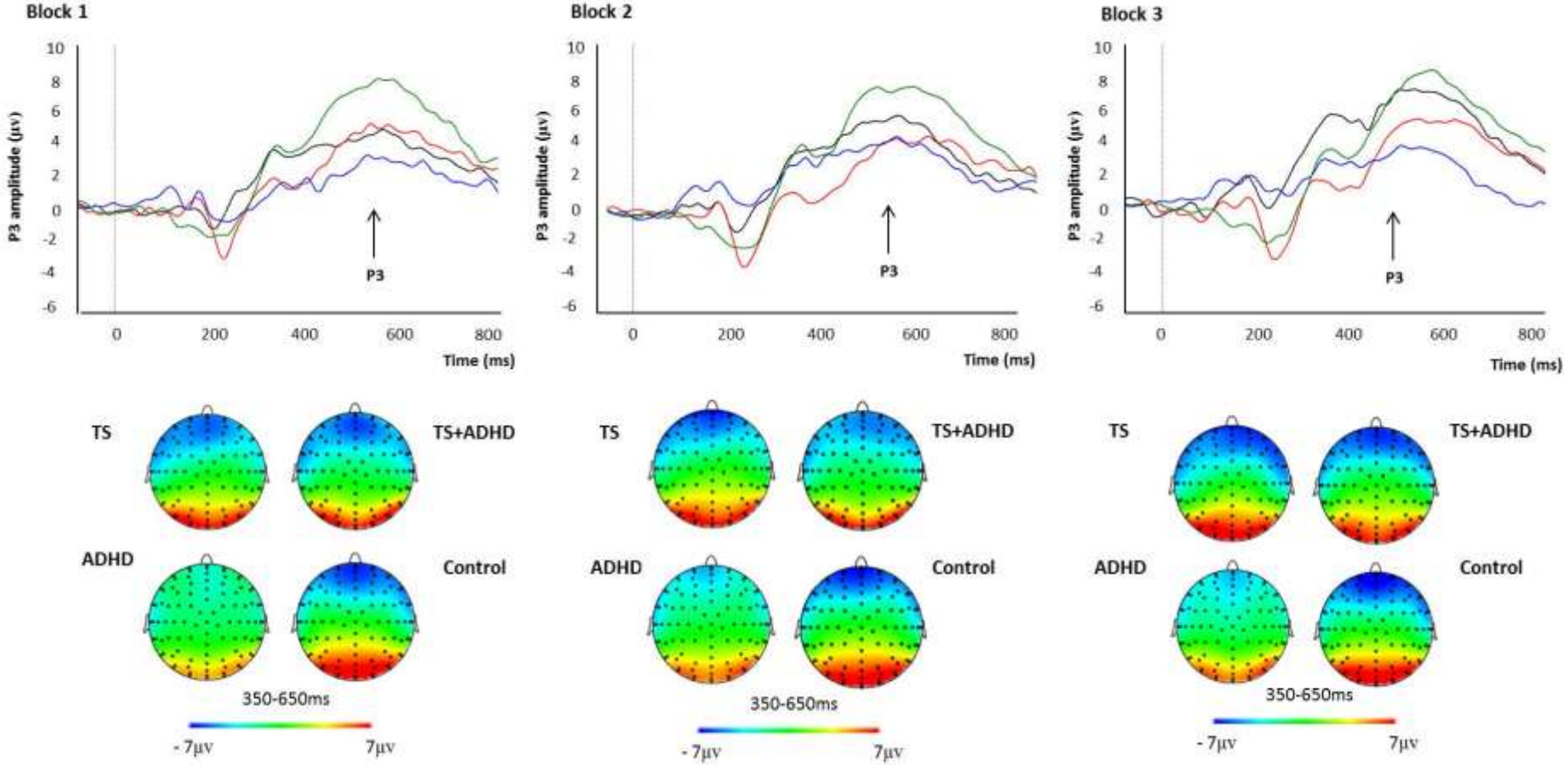
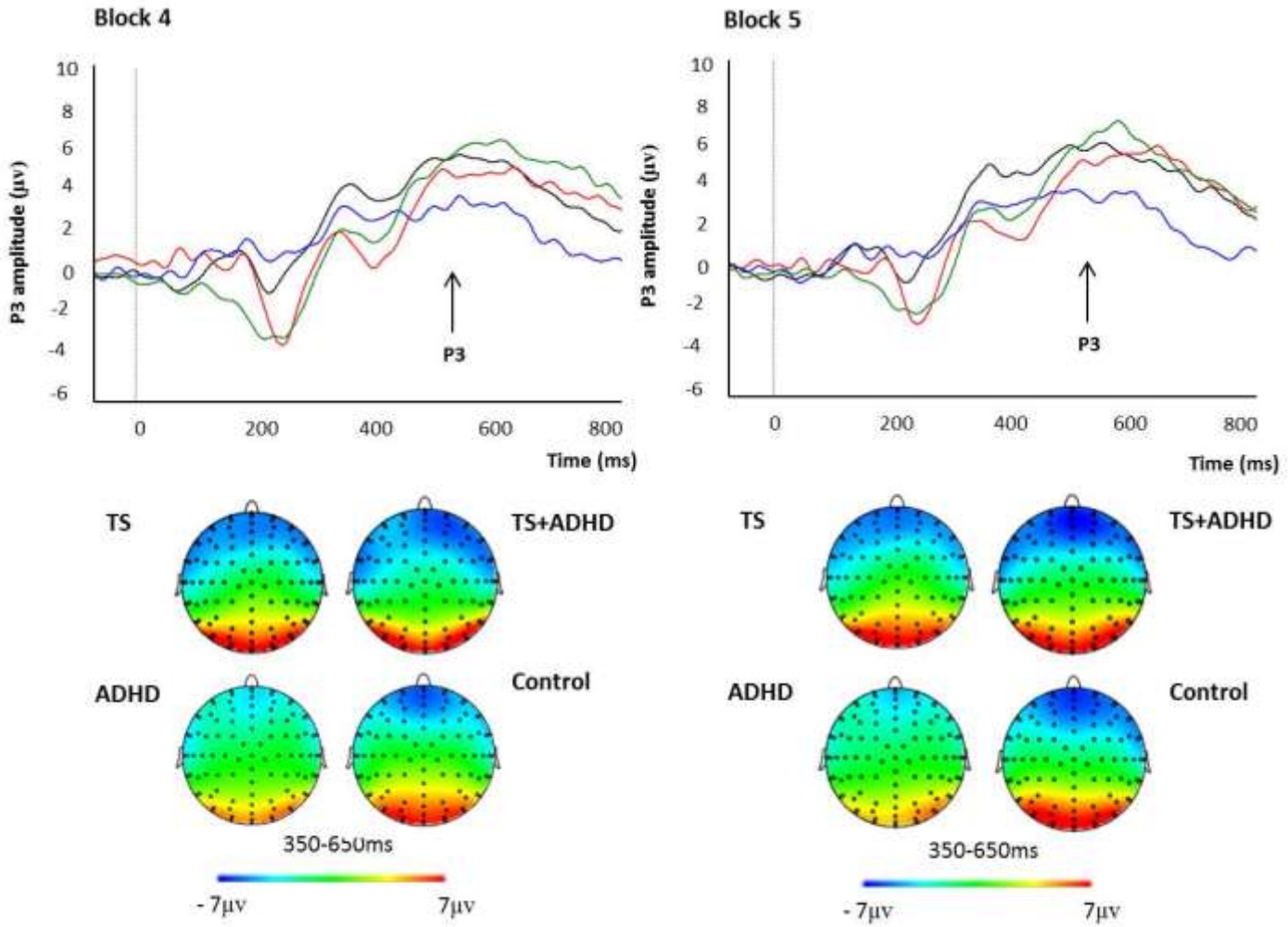


Figure 4-8. Stimulus-locked grand average waveforms plotted by participant group (TS = black line, TS+ADHD = red line, ADHD = blue line, Controls = green line) and scalp topographies for each group in each learning block




Block 4
P3 amplitude (µv)
10
8
6
4
2
0
-2
-4
-6
0
200
400
600
800
Time (ms)
P3
TS
TS+ADHD
ADHD
Control
350-650ms
- 7µv
7µv
Block 5
P3 amplitude (µv)
10
8
6
4
2
0
-2
-4
-6
0
200
400
600
800
Time (ms)
P3
TS
TS+ADHD
ADHD
Control
350-650ms
- 7µv
7µv

4.2.4.1.1 P3 amplitude in the acquisition phase

As figures 4-7 and 4-8 demonstrate, amplitude of the P3 increased across blocks in the acquisition phase in the TS and ADHD groups, but not in the Control and TS+ADHD groups. The 3 x 4 ANCOVA on these data revealed that P3 amplitude did not differ significantly between blocks 1 to 3 ($F(1.7, 90.5) = .76$, $p = .47$, $\eta^2 = .014$) or between groups ($F(3, 54) = 1.5$, $p = .23$, $\eta^2 = .076$), and there was no significant interaction between these factors ($F(5.0, 90.5) = 1.9$, $p = .10$, $\eta^2 = .095$). Removing age as a covariate did not alter these results. Including IQ as a covariate did not change these results.

4.2.4.1.2 P3 amplitude in the reversal phase

Figures 4-7 and 4-8 indicate that P3 amplitude in the reversal phase showed the expected decrease during the reversal block 4 in the TS and Control groups, but not in the ADHD and TS+ADHD groups. The 3 x 4 ANCOVA showed that P3 amplitude did not differ between blocks 3 to 5 ($F(1.7, 94.0) = 1.3$, $p = .32$, $\eta^2 = .020$) or groups ($F(3, 54) = 1.1$, $p = .37$, $\eta^2 = .056$) and the interaction between these factors was non-significant ($F(5.2, 94.0) = .97$, $p = .44$, $\eta^2 = .051$). These results did not change when IQ was included as a covariate.

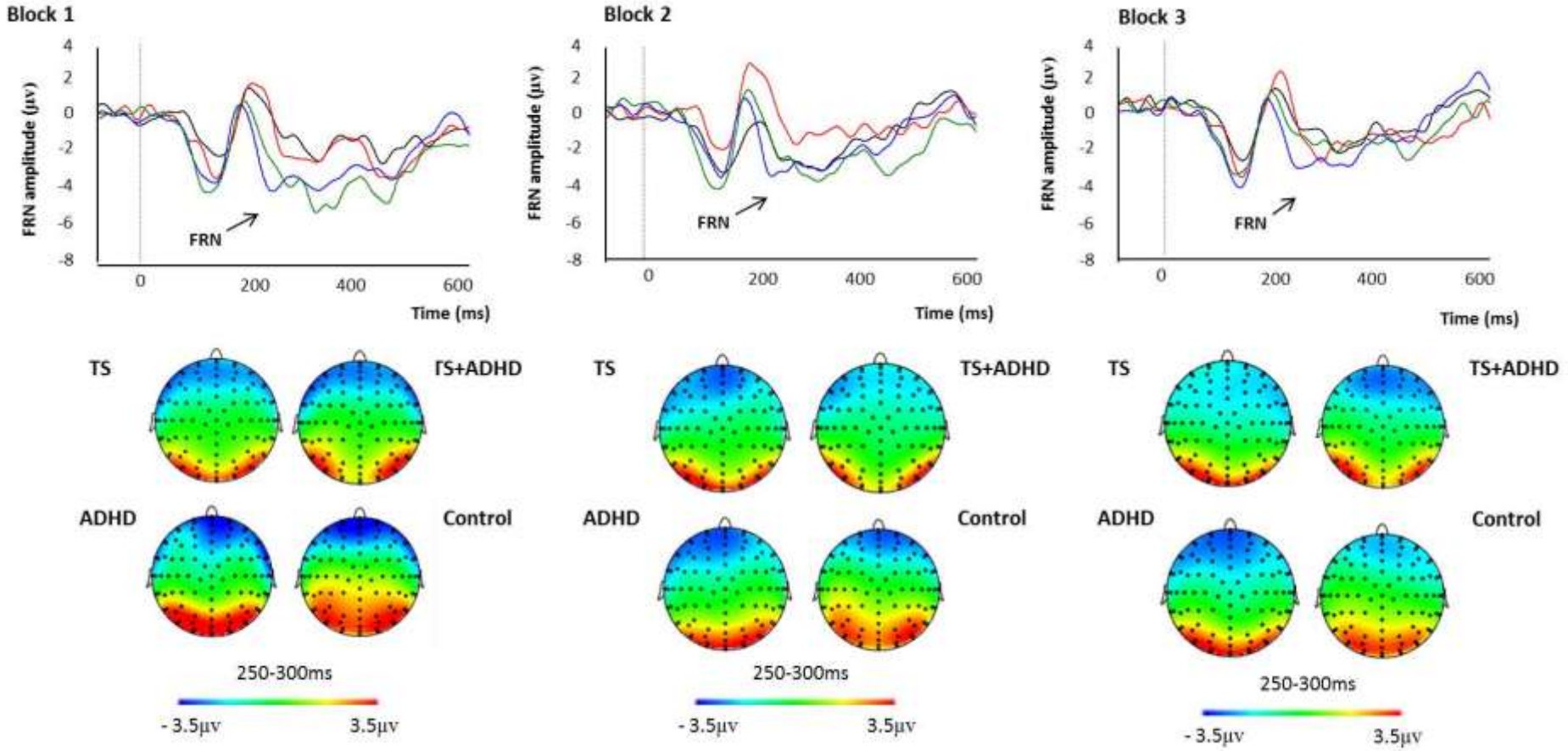
4.2.4.2 FRN amplitude

Figure 4-9 presents the grand average feedback-locked waveforms and the topographical plots for the FRN. The group means for peak FRN amplitude in each learning block are presented in figure 4-10.

4.2.4.2.1 FRN amplitude in the acquisition phase

Figures 4-9 and 4-10 indicate that amplitude of the FRN showed the expected decrease across blocks 1 to 3 in the Control group, but not in the other groups. The 3 x 4 ANCOVA showed that FRN amplitude did not differ significantly between blocks ($F(1.6, 87.3) = .79$, $p = .43$, $\eta^2 = .014$) or groups ($F(3, 54) = 1.5$, $p = .23$, $\eta^2 = .076$) and there was no interaction between block and group ($F(4.9, 87.3) = 1.8$, $p = .13$, $\eta^2 = .089$). These results were unchanged when the covariate age was removed or IQ was covaried.

Figure 4-9. Feedback-locked grand average waveforms plotted by participant group (TS = black line, TS+ADHD = red line, ADHD = blue line, Controls = green line) and scalp topographies for each group in each learning block



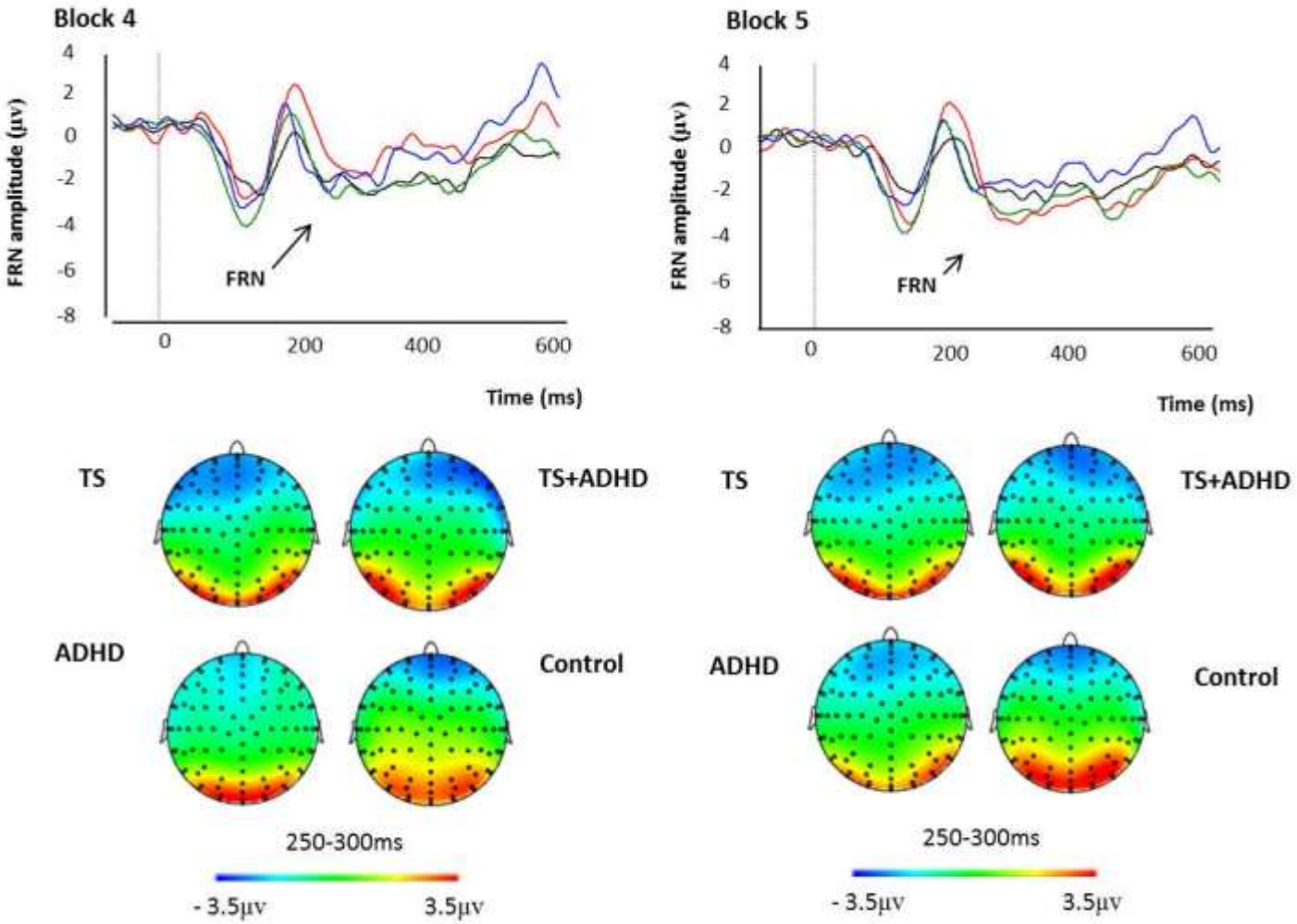
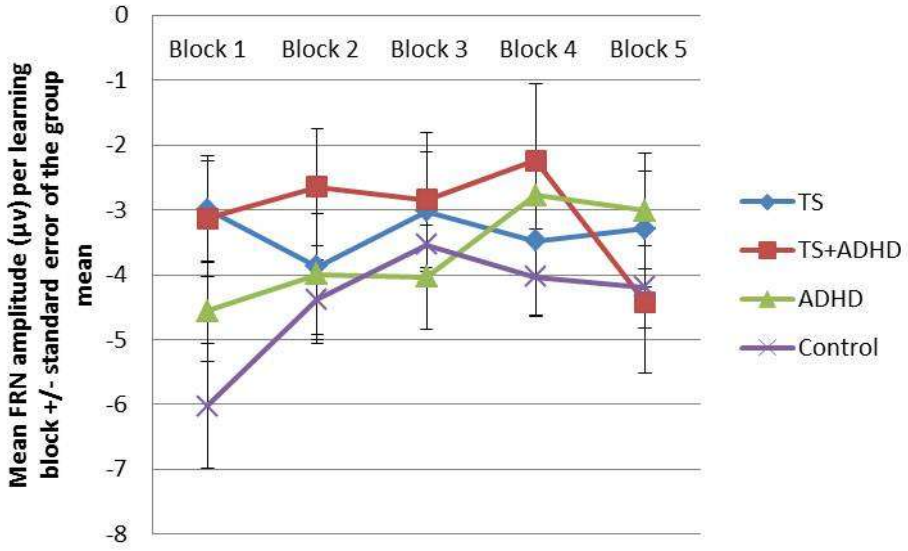

Block 4
FRN amplitude (μv)
4
2
0
-2
-4
-6
-8
FRN
0
200
400
600
Time (ms)
Block 5
FRN amplitude (μv)
4
2
0
-2
-4
-6
-8
FRN
0
200
400
600
Time (ms)
TS
TS+ADHD
ADHD
Control
250-300ms
- 3.5μv
3.5μv
TS
TS+ADHD
ADHD
Control
250-300ms
- 3.5μv
3.5μv

Figure 4-10

Group mean peak amplitudes for the FRN at FCz plotted by learning block (1-5). Error bars represent the standard error of the group mean.



4.2.4.2.2 FRN amplitude in the reversal phase

Figures 4-9 and 4-10 show that FRN amplitude showed little variation during the reversal phase in the TS and Control groups. However, FRN amplitude decreased during the reversal block 4 in the ADHD group, which was in contrast to the expected increase in this component at this stage in the task. In the TS+ADHD group, FRN amplitude increased in block 5, which was in contrast to the expected decrease in this component with the re-acquisition of the reversed associations. However, the 3 x 4 ANCOVA on these data revealed that FRN amplitude did not differ significantly between blocks 3 to 5 ($F (2, 108) = 1.5$, $p = .22$, $\eta^2 = .027$) or groups ($F (3, 54) = .23$, $p = 87$, $\eta^2 = .013$). There was no interaction between block and group ($F (6, 108) = 1.7$, $p = .12$, $\eta^2 = .087$). These results did not change when IQ was included as a covariate.

4.2.4.3 Learning-related changes in P3 and FRN amplitude

The difference scores characterising the degree of learning-related change in P3 and FRN amplitudes across successive task blocks in each group are presented in figure 4-11 (P3) and figure 4-12 (FRN). Each difference score

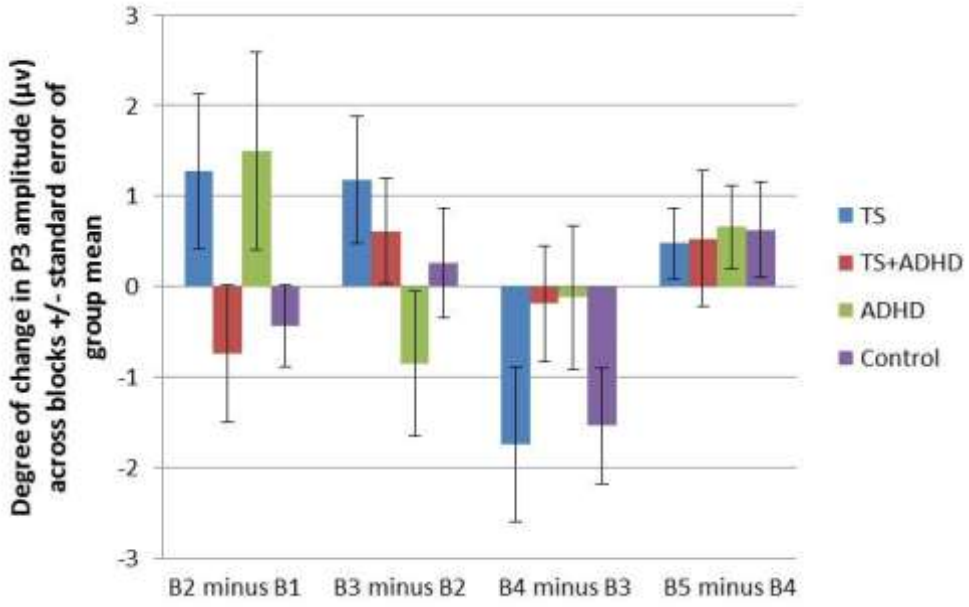
was compared between the four participant groups using univariate ANCOVAs with age as a covariate.

4.2.4.3.1 P3 amplitude changes

The extent to which P3 amplitude changed from block 1 to block 2 differed at trend-level between groups (F (3, 54) = 2.5, p = .07, η^2 = .120). Further investigation of this group difference with planned pairwise group contrasts revealed that the TS group showed a significantly greater increase in P3 amplitude from block 1 to 2 than Controls (U = 100.0, p = .05 (1-tailed), *d* = .31), and there was a trend for the same difference between TS and TS+ADHD (U = 70.0, p = .09 (2-tailed), *d* = .18). The ADHD group showed a trend-level greater increase in P3 than Controls (U = 63.0, p = .08 (1-tailed), *d* = .37). The remaining pairwise group contrasts for block 1 to 2 were not significant (all p > .10). The changes in P3 amplitude from block 2 to block 3 (F (3, 54) = 1.3, p = .28, η^2 = .069), block 3 to 4 (F (3, 54) = 1.2, p = .32, η^2 = .062), and block 4 to 5 (F (3, 54) = .06, p = .98, η^2 = .004) did not differ significantly between groups.

Figure 4-11

Difference scores characterising the degree of learning-related change in P3 amplitude across successive task blocks plotted by participant group. Error bars represent the standard error of the group mean.



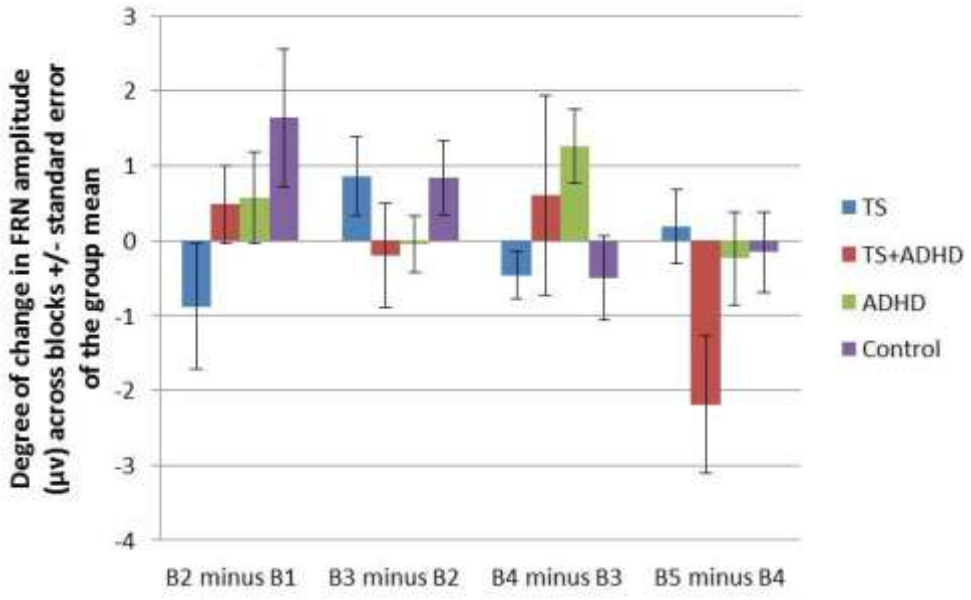
When age was removed as a covariate in the analysis of the P3 change scores from the acquisition phase (blocks 1 to 2 and blocks 2 to 3) the results were unchanged. Likewise, when IQ was included as a covariate in analysis of all change scores the results did not change. The pairwise group differences in the block 1 to 2 P3 change score would not remain significant if correction for multiple comparisons was applied.

4.2.4.3.2 FRN amplitude changes

Changes in FRN amplitude between blocks 1 and 2 ($F(3, 54) = 1.9$, $p = .14$, $\eta^2 = .096$), 2 and 3 ($F(3, 54) = .96$, $p = .42$, $\eta^2 = .051$), and 3 and 4 ($F(3, 54) = 1.1$, $p = .37$, $\eta^2 = .056$) did not differ significantly between groups. However, the change in FRN amplitude between blocks 4 and 5 differed at trend-level between the groups ($F(3, 54) = 2.5$, $p = .07$, $\eta^2 = .122$).

Figure 4-12

Difference scores characterising the degree of learning-related change in FRN amplitude across successive task blocks plotted by participant group. Error bars represent the standard error of the group mean. Positive scores reflect decreases in FRN amplitude (the component becoming less negative). Negative scores reflect increases in FRN amplitude (the component becomes more negative).



Further investigation of this group difference with planned pairwise contrasts revealed that the TS+ADHD group showed a significantly greater increase in FRN amplitude, that is, amplitude became more negative, from block 4 to 5 than the TS group (U = 57.0, p = .02 (2-tailed), *d* = -.84), and there was a trend for the same difference comparing the TS+ADHD group with the ADHD group (U = 103.0, p = .06 (2-tailed), *d* = -.69). The remaining pairwise contrasts were non-significant (all p > .10). The differences between TS+ADHD and TS and ADHD would not remain significant after correcting for multiple comparisons.

These results did not change when age was removed as a covariate in the acquisition phase (blocks 1 to 2 and blocks 2 to 3), and when IQ was included as a covariate of all block change scores.

4.2.4.4 Group differences in signal-noise-ratio

Kruskal-Wallis tests were conducted to assess whether the number of trials included in each participant's ERP average differed between groups. This was done to examine whether ERP waveforms may have differed in SNR between groups, which might have influenced group differences in peak P3 and FRN amplitudes. The number of trials included in stimulus-locked averages for the P3 and feedback-locked averages for the FRN did not differ between groups in blocks 1, 2, 3 and 5. However, the groups differed significantly in trial numbers included in the stimulus-locked P3 (χ^2 (3) = 7.9, p = .05) and feedback-locked FRN (χ^2 (3) = 11.3, p = .01) averages in block 4. These effects reflected significantly greater numbers of trials for the P3 and FRN in the TS group (P3: 38 trials; FRN: 37 trials) compared with the TS+ADHD group (P3: 33 trials, U = 57.0, p = .02; FRN: 31 trials, U = 52.5, p = .01) and ADHD group (P3: 32 trials, U = 37.0, p = .02; FRN 31 trials, U = 26.0, p = .003). Since the group differences in P3 amplitude were between blocks 1 and 2, the difference in trial numbers for the P3 in block 4 was not problematic. The group difference in trial numbers for the FRN in block 4 was of more concern and should be considered when interpreting the difference between the TS+ADHD and TS groups in FRN amplitude change from blocks 4 to 5.

4.2.5 Summary of group differences in electrophysiological correlates of goal-directed reinforcement learning

The groups did not differ in the overall magnitude of P3 and FRN amplitudes in blocks 1 to 5 of the task. However, examination of learning-related changes in P3 amplitude across successive task blocks showed that P3 amplitude increased significantly more during the initial acquisition phase (blocks 1 to 2) in young people with TS than unaffected young people. There were also trends for the P3 to increase more across blocks 1 to 2 in the TS group than the TS+ADHD group, and in the ADHD group than the Control group. These findings were unexpected. It is possible that the greater increase in the P3 in the TS group reflected stronger consolidation of the S-R associations in the young people with TS at this stage of the task. However, it is unlikely that the trend-level difference between ADHD and Controls reflected better consolidation of the S-R associations in the young people with ADHD, since this group was significantly less accurate in executing the S-R behaviours than the Controls, as reported in section 4.2.2.1. Instead, the larger increase in P3 amplitude in ADHD might reflect greater effort in these young people in processing to the to-be-learned stimuli in block 2, perhaps because these young people were finding it difficult to learn the S-R associations. These findings will be discussed further in chapter 7 (section 7.1.3).

The investigation of learning-related changes in FRN amplitude across task blocks revealed that the FRN became significantly more negative (larger) in block 5 versus block 4 in the TS+ADHD group than in the TS group. There was also a trend for the increase in FRN amplitude from block 4 to 5 to be larger in the TS+ADHD group than the ADHD group. These results are in contrast to the expectation that the FRN would decrease (become less negative) in the final task block. A decrease in FRN amplitude would reflect increasing learning of the reversed S-R associations and corresponding reductions in dopaminergic prediction errors, which are thought to underlie the FRN. The finding that the FRN increased in the TS+ADHD group suggests that the outcome of producing the correct S-R behaviours in the final task block was more unexpected than the outcome of producing those behaviours in the reversal block 4 in these young people. Therefore, larger dopaminergic prediction errors were elicited by feedback in block 5 than block 4 in

TS+ADHD. However, this interpretation makes little sense considering the participants had less knowledge (and less expectation) of the reversed S-R associations in the reversal block 4 than block 5. An alternative explanation is that the increase in FRN amplitude in the final task block reflected enhanced processing of the feedback information in the TS+ADHD group, possibly to assist with re-learning the reversed associations. The lower number of trials in the TS+ADHD group compared with the TS group in block 4 FRN averages should be considered when interpreting this finding.

4.2.6 Relationships between symptomatology and goal-directed reinforcement learning

The extent to which tic, ADHD and ODD symptom severity predicted learning-related changes in accuracy and P3 and FRN amplitudes that were shown to differ significantly between groups was examined using hierarchical regression analyses. To be clear, the following behavioural and electrophysiological correlates of goal-directed learning were examined: difference scores characterising the degree of decrease in accuracy in the reversal block 4 compared with the previous block 3, the increase in P3 amplitude from block 1 to block 2, and the increase in FRN amplitude from the reversal block 4 to the following block 5. Separate regression models were conducted for each of these behavioural and ERP measures and were constructed thus: Model A: age and total tic severity were entered in block 1. Model B: age and ADHD severity were entered in block 1; ODD severity was entered in block 2. Model A was conducted in participants with TS and TS+ADHD only, while Model B was performed in the whole sample.

A large proportion of the TS and TS+ADHD groups combined did not have OCD symptoms and produced zero scores on the CY-BOCS measure of OCD symptomatology (43% of with TS or TS+ADHD in the behavioural sample, and 66.7% of young people in the ERP sample). Consequently, OCD symptom scores were non-linearly distributed. Therefore, it was not possible to examine relationships between OCD symptomatology and goal-directed reinforcement learning in regression analyses.

4.2.6.1 Accuracy difference between blocks 3 and 4

Table 4-3 presents the regression model statistics for the difference in accuracy between blocks 3 and 4. In Model A, the combined variables of age and total tic severity entered in block 1 did not significantly predict the accuracy change between blocks 3-4 (F (2, 30) = .18, p = .83). Inspection of the individual regression coefficients for age and tic severity demonstrated that neither of these IVs were significant individual predictors of accuracy change (age: p .60; tic severity: p = .76). The Durbin-Watson statistic indicated the assumption of independent errors was met in Model A (DW = 1.99), and the VIF value (1.0) indicated the IVs tics and age were not correlated.

Table 4-3

Summary of regression model statistics in the prediction of the accuracy decrease from block 3 to block 4

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.01	-.05	.28				
Constant				-15.9	14.6		-1.1
Age				.05	.09	.10	.53
Tics				-.07	.23	-.06	-.32
Model B							
Block 1	.05	.02	1.5				
Constant				-4.4	9.2		-.48
Age				.03	.05	.07	.55
ADHD				-.18	.11	-.22	-1.7
Block 2	.10	.05	2.0				
Constant				-3.1	9.1		-.34
Age				.04	.05	.10	.77
ADHD				-.14	.11	-.17	-1.3
ODD				-.12	.07	-.23	-1.7

In Model B, the combined variables of age and ADHD severity entered in block 1 did not significantly predict the decrease in accuracy from block 3 to

block 4 (F (2, 58) = 1.5, p = .23). The variables age and ADHD severity were not significant individual predictors of accuracy change (age: p = .58; ADHD severity: p = .09). In block 2, the combined variables age, ADHD and ODD severity did not predict accuracy change (F (3, 57) = 2.0, p = .12). Again, the change in accuracy was not significantly predicted by age (p = .44), ADHD severity (p = .21) or ODD severity (p = .09). The assumption of independent errors was met in Model B (DW = 2.4). The IVs age and ADHD severity in block 1 were not correlated (VIF = 1.04), nor were the IVS age (VIF = 1.05), ADHD (VIF = 1.11) and ODD (VIF = 1.10) severity in block 2.

4.2.6.2 P3 amplitude difference between blocks 1 and 2

Table 4-4 presents the regression model statistics for the difference in P3 amplitude between blocks 1 and 2.

Table 4-4

Summary of regression model statistics in the prediction of the P3 amplitude increase from block 1 to block 2

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.05	-.01	.74				
Constant				1.8	3.2		.57
Age				-.02	.02	-.16	-.84
Tics				.05	.05	.17	.93
Model B							
Block 1	.01	-.03	.30				
Constant				2.2	2.5		.86
Age				-.008	.01	-.08	-.58
ADHD				-.01	.03	-.06	-.39
Block 2	.07	.01	1.3				
Constant				1.9	2.5		.77
Age				-.005	.01	-.05	-.36
ADHD				.07	.05	.35	1.3
ODD				-.09	.05	-.48	-1.8

In Model A, the combined variables age and total tic severity entered in block 1 did not significantly predict the increase in P3 amplitude from block 1 to 2 ($F (2, 27) = .74$, $p = .49$). Age and tic severity were not significant individual predictors of P3 increase (age: $p = .41$; tic severity: $p = .93$). The assumption of independent errors was met (DW = 1.9). Age and tic severity were not correlated (VIF = 1.00).

The combined variables entered in block 1 of Model B (age, ADHD severity) did not predict P3 amplitude increase ($F (2, 52) = .30$, $p = .74$). Age and ADHD severity did not individually predict P3 amplitude change (age: $p = .56$; ADHD severity: $p = .70$). Similarly, the combined variables of age, ADHD and ODD severity entered in block 2 did not predict the change in P3 amplitude ($F (3, 51) = 1.3$, $p = .30$). The variables age, ADHD and ODD severity did not predict P3 change individually (age: $p = .72$; ADHD severity: $p = .19$; ODD severity: $p = .08$). Model B met the assumption of independent errors (DW = 1.8). The IVs age and ADHD severity in block 1 were not correlated (VIF = 1.04), nor were the variables age (VIF = 1.06), ADHD severity (VIF = 3.9), and ODD severity (VIF = 4.0) in block 2.

4.2.6.3 FRN amplitude difference between blocks 4 and 5

Table 4-5 presents the regression model statistics for the difference in FRN amplitude between blocks 4 and 5. The combined variables of age and total tic severity entered in block 1 of Model A did not significantly predict the increase in FRN amplitude from block 4 to 5 ($F (2, 27) = 1.0$, $p = .38$), and the individual variables were not significant predictors (age: $p = .58$; tic severity: $p = .19$). The assumption of independent errors was met in Model A (DW = 1.6) and the IVs age and tic severity were uncorrelated (VIF = 1.03).

In Model B, the combined variables of age and ADHD severity predicted the increase in FRN amplitude from block 4 to 5 at trend-level ($F (2, 52) = 2.9$, $p = .06$). ADHD severity, but not age, was a significant individual predictor of FRN amplitude increase (ADHD severity: $p = .05$; age: $p = .10$). Higher ADHD severity predicted smaller amplitude increases in the FRN. When ODD symptom severity was added in block 2, the model became non-significant ($F (3, 51) = 1.9$, $p = .14$). Examination of the regression coefficients indicated that ODD symptomatology suppressed the relationship between

ADHD severity, since ADHD symptoms did not significantly predict FRN amplitude increases in block 2 (p = .30). ODD severity and age were also not significant predictors of FRN change (age: p = .11; ODD severity: p = .99). The assumption of independent errors was met in Model B (DW = 1.9). The IVs age and ADHD severity in block 1 were not correlated (VIF = 1.04), nor were the IVs age (VIF = 1.06), ADHD severity (VIF = 3.9) and ODD severity (VIF = 4.0) in block 2.

Table 4-5

Summary of regression model statistics in the prediction of the FRN amplitude increase from block 4 to block 5

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.07	.00	1.0				
Constant				-1.1	2.9		-.38
Age				.01	.02	.10	.56
Tics				-.06	.04	-.25	-1.3
Model B							
Block 1	.10	.07	.06*				
Constant				-.80	2.1		-.38
Age				.02	.01	.23	1.7
ADHD				-.05	.02	-.27	-2.0**
Block 2	.10	.05	.14				
Constant				-.80	2.1		-.38
Age				.02	.01	.23	1.7
ADHD				-.05	.05	-.27	-1.0
ODD				.00	.04	.00	.99

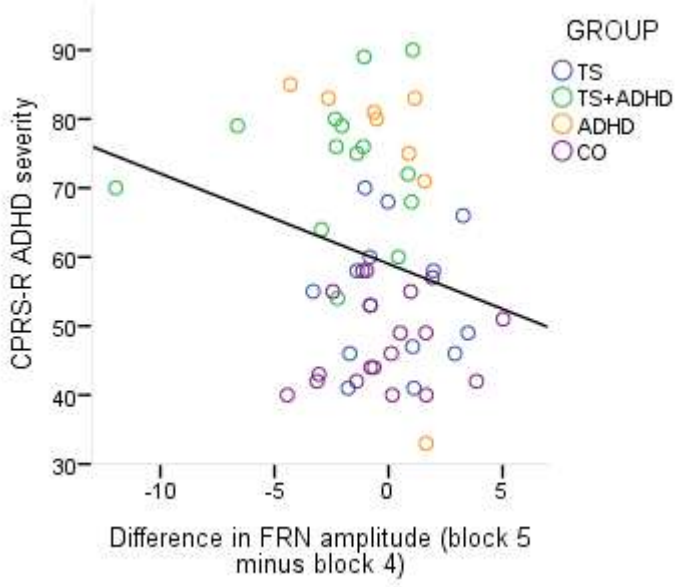
* = p < .10; ** = p < .05

The significant relationship between ADHD severity and FRN amplitude difference between blocks 4 and 5 is plotted in figure 4-13. Positive values for the FRN difference score reflect a decrease in amplitude from blocks 4 to 5 (the component becoming less negative), while negative difference scores reflect an increase in amplitude from blocks 4 to 5 (the component

becoming more negative). Thus, greater ADHD severity was associated with less negative difference scores, reflecting smaller increases in amplitude. Following the interpretation given in section 4.2.6 that increasing FRN amplitudes from block 4 to block 5 reflect enhanced processing of the feedback information, the relationship with ADHD severity suggests that young people with greater ADHD severity were showing less enhanced processing of the feedback information than young people with less severe symptoms. This might indicate that young people with severe ADHD were utilising the feedback information to a lesser degree to improve their learning of the reversed associations than young people with less severe ADHD. Inspection of the scatterplot demonstrates that the negative relationship between ADHD severity and FRN amplitude difference is present in all groups.

Figure 4-13

Scatterplot displaying the relationship between ADHD symptom severity and the difference score characterising the extent to which FRN amplitude changed across blocks 4 to 5. Positive difference score values reflect decreases in amplitude (the component becoming less negative). Negative difference scores reflect increases in amplitude (the component becoming more negative)



4.3 CHAPTER SUMMARY

The aim of the research presented in this chapter was to explore the basis of TS+ADHD by examining goal-directed reinforcement learning in young people with this comorbidity compared with young people with ADHD and TS and unaffected young people. Impairments in behavioural and electrophysiological signatures of goal-directed learning were expected in the ADHD group, but goal-directed learning in the TS group was predicted to be comparable with that of Controls. It was predicted that if TS+ADHD reflects additive comorbidity, then young people with TS+ADHD should show impaired goal-directed learning in a similar manner to the ADHD group. On the other hand, if TS+ADHD is a symptomatic phenocopy of ADHD, then no impairment should be present and the TS+ADHD group should perform as well as TS and Controls. Alternatively, if TS+ADHD is an independent condition from TS and ADHD, young people in this group might show differences in performance and electrophysiological activity from individuals in the TS and ADHD groups.

Analysis of behavioural correlates of goal-directed learning revealed the following group differences. During the initial acquisition of the S-R associations (blocks 1-3), the ADHD group was significantly less accurate than the Control group, and tended to be less accurate than the TS group (average accuracy in blocks 1-3). The TS+ADHD group also showed a tendency for poorer accuracy during the acquisition phase (averaged across blocks 1-3) than the TS and Control groups. In the reversal phase when participants were required to reverse (block 4) and re-learn the reversed associations (block 5), both the ADHD and TS+ADHD groups were significantly less accurate than the TS and Control groups (accuracy averaged across blocks 3-5). Furthermore, investigation of a significant block by group interaction during the reversal phase showed that the ADHD group was significantly less accurate than TS and Controls in blocks 4 and 5, but only marginally less accurate than TS and Controls in block 3 (the block prior to reversal). The TS+ADHD group was significantly less accurate than TS and Control groups in block 4, but not in blocks 3 or 5. Finally, the degree to which accuracy decreased in the reversal

block 4 compared with the previous block 3 was significantly greater in the ADHD and TS+ADHD groups than in the TS and Control groups.

Analysis of electrophysiological correlates of goal-directed learning revealed that the groups differed in the increase in amplitude of the stimulus-locked P3 across blocks 1 to 2 during the acquisition phase. The increase in P3 amplitude was significantly greater in the TS group than the Control group, and tended to be greater in TS than ADHD, and in ADHD than Controls. The extent to which FRN amplitude changed between the reversal block 4 and the final task block 5 differed at trend-level between groups. This was shown to reflect greater increases in amplitude from block 4 to block 5 in the TS+ADHD group compared with the TS group. There was also a trend for the increase in FRN amplitude to be greater in the TS+ADHD than ADHD group. Regression analyses examining the extent to which severity of tics, ADHD and ODD symptoms predicted changes in accuracy, P3 amplitude, and FRN amplitude revealed that more severe ADHD symptoms significantly predicted smaller increases in FRN amplitudes. These behavioural and electrophysiological findings will be discussed in full in chapter 7.

5. METHODS AND RESULTS II: HABIT-LEARNING

5.1 METHODS AND HYPOTHESES

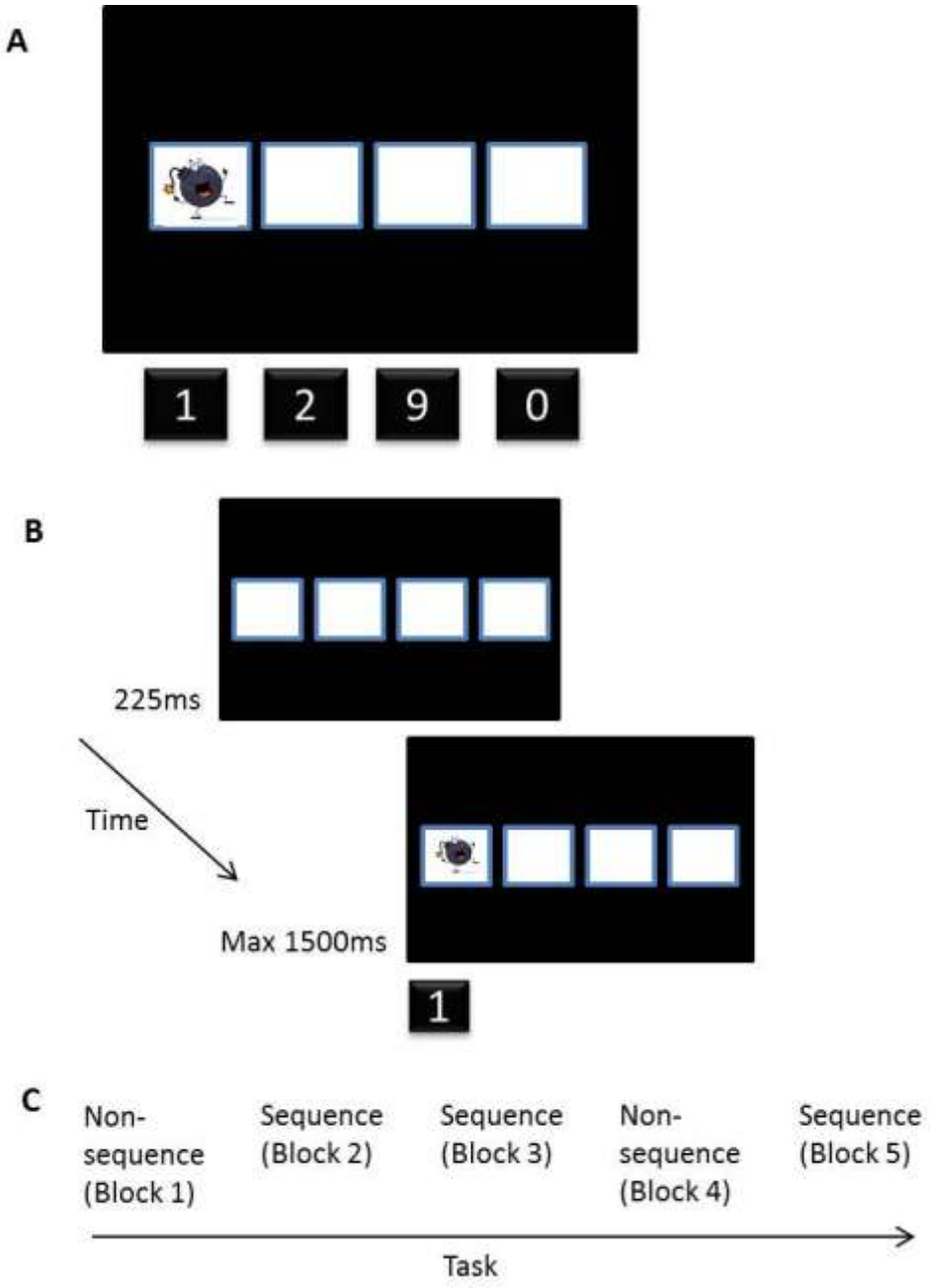
5.1.1 Habit-learning paradigm: the serial reaction time (SRT) task

An engaging, child-friendly version of the SRT task was used to assess habit-learning. The SRT paradigm (Nissen & Bullemer, 1987) involves producing rapid button presses according to the spatial locations of an on-screen stimulus. A different, spatially corresponding button is used for each screen location. In some task blocks, unknown to participants the stimulus samples the screen locations in a repeating sequence of 8 to 12 items and this sequence is repeated throughout the block. In other task blocks the stimulus samples the locations pseudorandomly, that is, sampling is random apart from the requirement that no one screen location is visited on successive trials. In sequence blocks, participants' RTs speed up and this is thought to reflect non-conscious learning of the repeating sequence. In pseudorandom blocks presented after sequence blocks, RTs decrease markedly which indicates that performance was disrupted due to the non-presentation of the learned sequence.

The current SRT task (figure 5-1) was presented to participants as a game in which the aim was to stop a cartoon bomb character 'Bob the bomb' from exploding by pressing appropriate 'extinguish buttons'. On every trial, a screen was presented displaying four white boxes (40x40mm) arranged in a horizontal line across the centre of the screen. The box screen was displayed for 225ms after which Bob the bomb (a 33x33mm square colour image of a cartoon smiling bomb) appeared in one of the boxes. The participant was required to press one of the keyboard 'extinguish' buttons (keys 1, 2, 9, 0) corresponding to the box (far left, centre-left, centre-right, far right respectively) Bob had appeared in. To encourage accuracy and prompt responding, participants were instructed to press the correct extinguish buttons very quickly to prevent Bob exploding. The stimulus screen terminated with

Figure 5-1

Diagram of the SRT task



A. Stimulus, screen set-up and response buttons
The cartoon bomb stimulus sampled one of four box locations arranged horizontally across the screen. Participants responded to the stimulus using the keyboard keys 1, 2, 9 and 0.

B. Trial structure
Every trial began with a screen displaying the four boxes for 225ms. Next, the cartoon bomb stimulus appeared in one of the four boxes and participants pressed the corresponding button on the keyboard. The trial ended when the participant pressed a button or after 1500ms had elapsed.

C. Task structure
Five blocks of 120 trials were completed. Block 1 was a non-sequence block, blocks 2 and 3 were sequence blocks, block 4 was the disruption (non-sequence) block, block 5 was a sequence block.

the participant's response or after 1500ms had elapsed, after which the trial ended.

Five blocks of 120 trials were completed. In blocks 2, 3 and 5 (sequence blocks) the stimulus sampled the boxes in a sequence of 12 locations that repeated ten times. Blocks 1 and 4 were the non-sequence blocks. The repeating sequence was carefully constructed so that it was fully balanced. A balanced sequence is one in which the probability of each location following each other location is matched. For example, location 1 does not follow location 2 any more frequently than location 1 follows location 3, which is the case in an unbalanced sequence. This structuring of the sequence is important in assessing habit-learning because if an unbalanced sequence is employed, it might be possible for participants to notice that one location more frequently follows another and consciously learn that pairwise association in a goal-directed manner, which would result in decreased RTs for sequence blocks but might not reflect non-conscious habit-learning (Jackson et al., 1995).

Furthermore, ensuring the repeating sequence was balanced was particularly important in this study because it afforded a method of testing Marsh et al.'s (2004) hypothesis that the basal ganglia concatenation mechanism is impaired in TS (see chapter 2, section 2.2.1 for a full explanation of this hypothesis). If this hypothesis is accurate, children with TS would be unable to learn a sequence of motor responses, such as those constituting a balanced repeating sequence in the SRT task. However, they may be able to learn smaller pairwise associations, such as is the case in an unbalanced sequence of the SRT task, and also in the Weather task from which Marsh et al. (2004) derived their hypothesis. For these reasons, the current study employed a balanced repeating sequence of locations of the form 0-1-9-2-1-0-9-0-2-9-1-2, where the numbers correspond to the keyboard buttons arranged horizontally from left to right (1-2-9-0). To ensure any habit-learning effects found could not be attributed to properties of this particular sequence, a second balanced sequence was created of the form 1-2-0-9-2-9-0-1-0-2-1-9 and the sequence employed was counterbalanced across participants.

Consideration was also given to the structure of the non-sequence blocks in the current version of the SRT. Traditionally, non-sequence blocks are constructed such that the stimulus samples locations in a random manner

with the constraint that a location must not be sampled on two successive trials. This pseudorandom method was used in the previous SRT studies in children with ADHD and TS+ADHD (Channon et al., 2003; Karatekin et al., 2009). Pseudorandom sampling is problematic because it does not match the highly structured sampling of the sequence blocks, which a non-learning control condition ought to (Jackson et al., 1995). Therefore, in this study the non-sequence blocks were each constructed to consist of ten different 12-item balanced sequences of locations (different from the repeating sequences used in the sequence blocks). This ensured that the structure of the sequence and non-sequence blocks was matched, and the only difference between the conditions was in the particular locations sampled and the repetition or non-repetition of the sequences. Pilot data from typically developing adults confirmed that this version of the SRT paradigm produced the typical learning effects, that is, faster RTs for sequence versus non-sequence blocks (see appendix B).

Following task instructions participants completed four practice trials, one trial for each box the stimulus could appear in, to familiarise them with the task. The five blocks of experimental trials were then completed separated by self-paced rest breaks. The task was performed on a Samsung P510 laptop (screen size 20x34cm, resolution 1280x800 pixels). The task was programmed and presented using E-Prime version 1.2 (Psychology Software Tools Inc.).

5.1.2 Assessment of conscious learning of the sequence: the Generate task

To assess whether participants had been aware of the repeating sequence and might have consciously learned all or part of the sequence, after completion of the SRT task participants were asked if they had noticed anything about the way Bob had moved between the boxes. Next, participants completed the Generate task (Nissen & Bullemer, 1987) which involved cued reproduction of the repeating sequence they had been exposed to. On each Generate trial, the screen of boxes was presented (as described for the SRT task in 5.2.1) with the stimulus in one of the box locations. Participants used the 1, 2, 9, 0 keys to indicate which box the stimulus would appear in next. The box screen was displayed until the participant responded, after which the trial ended and the bomb character appeared in the next location in the sequence. The 12-item sequence was repeated twice across the Generate task. Conscious

awareness of the sequence was defined by correct responses to four or more consecutive trials of the Generate task. Participants meeting this criterion were excluded from analysis of the SRT task data to ensure that group differences in task performance reflected differences in habit-learning rather than conscious, goal-directed learning as much as possible.

5.1.3 Behavioural correlates of habit-learning

The measures selected as behavioural correlates of habit-learning in the SRT task are summarised below. The measures were computed using Matlab R2011a (MathWorks, UK). RT in each block was measured to establish how each group performed overall in the task. The RT change (difference score) measures were calculated to establish how much learning-related change in performance occurred between task blocks in each group, and whether this differed between groups regardless of overall RT differences. Of particular interest were the difference scores between blocks 2 to 3, 3 to 4 and 4 to 5 (see figure 4-1). The difference in RT between blocks 2 and 3 reflected how much RT improved (decreased) with presentation of the repeating sequence. The difference between blocks 3 to 4 indexed how much performance was disrupted (increase in RT) by the absence of the learned sequence and the ability of participants to modify habitual behaviours. The difference between blocks 4 and 5 characterised the improvement in performance (decreased RT) with re-presentation of the repeating sequence. Within-block learning measures were used to examine group differences in the progression of sequence learning (sequence blocks) compared with non-learning improvement in performance (non-sequence blocks) within each block. Participants with scores greater than 2.5 SD of their group mean on any behavioural correlate were excluded from analyses.

- RT: median RT (ms) for correct trials in each task block. The median RT for trials of each 12-location sequence in each block (the repeating sequence in sequence blocks or each individual unique sequence in non-sequence blocks) was taken and the average of the resulting ten sequence medians was calculated. This was done rather than taking the median of the entire block to provide a more sensitive measure of RT performance in repeating or non-repeating sequences. The first block in

every trial was excluded to reduce the influence of starting bias, that is, the tendency for slower RTs at the beginning of a block of trials.

- RT change: difference scores characterising the degree of change in RT (mean of ten medians, ms) for correct trials between successive task blocks. The mean of median RT in one block was subtracted from the mean of median RT in the following block (block 2 values minus block 1 values, block 3 minus block 2, block 4 minus block 3, block 5 minus block 4).
- Within-block learning rate for RT: these measures were computed by fitting a linear learning slope of the form $y = ax + b$ to the ten 12-location sequence averages for the correct trial RT data within each block for each participant. The slope values (a) were extracted within each block and standardised by z-transformation for analysis. Higher slope values indicate greater changes in RT across sequences in the block. Positive slope values indicate increases in RT; negative slope values indicate decreases in RT.

5.1.4 Hypotheses

The hypotheses for habit-learning during initial learning of the sequence in blocks 1 to 3 (acquisition phase) and the disruption to sequence learning in blocks 4 and 5 (disruption phase) are as follows.

5.1.4.1 Acquisition phase

- In line with the hypothesis that habit-learning is hyperactive in TS due to excessive dopamine activity, it is predicted that the TS group will show faster acquisition of the sequence than the Control and ADHD groups. This will be evidenced by faster RTs in blocks 2 and 3, and a greater decrease in RT from blocks 2 to 3 in young people with TS compared with young people with ADHD or unaffected young people. The rate of learning within blocks 2 and 3 will also be greater (more negative slopes) in the TS group than ADHD or Control groups.
- Consistent with the proposal that dopamine-related deficits in reinforcement learning are restricted to goal-directed learning in

ADHD, it is predicted that the ADHD group will perform as well as the Control group in habit-learning during the acquisition phase.

- Due to the scarcity of previous research in this area, no specific hypotheses were formulated concerning habit-learning in the TS+ADHD group. However, it can be expected that if TS+ADHD reflects additive comorbidity or is a symptomatic phenocopy of ADHD, then young people with TS+ADHD should show hyper-learning of the sequence in a similar manner to the TS group. If TS+ADHD is an independent condition, young people with TS+ADHD will perform dissimilarly to the TS group.

5.1.4.2 Disruption phase

- It is hypothesised that the TS group will experience greater disruption to performance in block 4 as a result of difficulty in modifying the hyper-learned sequence. This hypothesis is in line with the intractable nature of habitual behaviours. Thus, RT will be slower in block 4 and the degree of increase in RT from blocks 3 to 4 will be larger in the TS group than the Control and ADHD groups. In block 5, the TS group will show greater facilitation of performance (decreased RT, greater decrease in RT from blocks 4 to 5) by the re-presentation of the repeating sequence than the ADHD and Control groups.
- The Control and ADHD groups will show a similar level of disruption to performance by the non-presentation of the repeating sequence in block 4 and facilitation of performance by the re-presentation of the sequence in block 5.
- As with the acquisition phase, no specific hypothesis was produced for the TS+ADHD group. Performance in this group was expected to be similarly disrupted in block 4 and facilitated in block 5 as in the TS group if this comorbidity reflects additive or phenocopy effects. If TS+ADHD is an independent condition, young people with TS+ADHD would perform differently to the TS group.

5.1.4.3 Relationships between symptomatology and habit-learning

- Consistent with the hypothesis that tics are hyper-learned habitual behaviours, higher tic severity will predict greater hyper-learning during the acquisition phase and greater impairment in performance in the disruption phase.
- In line with the proposal that ADHD is not associated with habit-learning impairments, ADHD symptom severity will not be predictive of performance during the acquisition or disruption phases.
- The extent to which OCD and ODD symptoms modulate relationships between tic and ADHD severity and task performance will be examined. This has not been conducted previously and hence no specific hypotheses are formulated.

5.1.5 Analysis methods

5.1.5.1 Normality testing

All behavioural correlates of habit-learning were subjected to Shapiro-Wilk tests to check normality of distributions. Normally distributed variables were analysed with parametric ANOVA tests and significant main effects and interactions were further investigated using univariate ANOVAs and independent-samples t-tests. Variables that were not normally distributed were analysed with ANOVA tests in cases where mixed-model designs were required (described in 5.1.5.3 below) and non-parametric Kruskal-Wallis tests in cases where univariate analyses were sufficient (see 5.1.5.3). The use of ANOVAs for non-normal variables was justified by the robustness of ANOVA to violations of normality assumptions (Norman, 2010) and the inability to produce mixed-model designs in non-parametric equivalent tests. Mann-Whitney U tests were used to further investigate significant main effects and interactions for non-normal variables.

5.1.5.2 Covariates

The variables age, IQ, gender and SES were considered as covariates in analyses of habit-learning. Habit-learning, and more specifically SRT task performance, has been found to be invariant to age, with children performing as well as adults (Meulemans et al., 1998). Therefore, age-related effects on

habit-learning were not expected to be present in the current study and hence age was not included as a covariate in analyses. IQ differed significantly between groups but was not included as a covariate in the main analyses of behavioural correlates for reasons explained in chapter 4 (section 4.1.5.2). However, the main analyses were repeated with IQ included as a covariate and the results are reported wherever they differ from those of the main analyses. Gender and SES were not included as covariates for reasons explained in chapter 4, section 4.1.5.2.

5.1.5.3 Hypothesis testing

All statistical analyses were conducted using SPSS v.21 (IBM©). Behavioural correlates of habit-learning were analysed in the acquisition and disruption phases separately. To test the hypothesised group differences in initial learning of the sequence in the acquisition phase, the variables RT and within-block learning rate were analysed using mixed-model ANOVAs with block (3 levels: 1, 2, 3) as the within-subjects factor and group (4 levels: TS, TS+ADHD, ADHD, Control) as the between-subjects factor. Significant main effects and interactions were further investigated using univariate ANOVA or Kruskal-Wallis tests with group (4) as the between-subjects factor, and parametric (independent-samples t-tests) or non-parametric (Mann-Whitney U tests) planned contrasts between each pair of groups. The measures characterising the degree of change in RT from blocks 1 to 2 and 2 to 3 were analysed using univariate ANOVA or Kruskal-Wallis tests with group (4) as the between subjects factor and parametric or non-parametric planned pairwise contrasts.

To test the hypothesised group differences in the ability to modify the learned sequence in the disruption phase, the RT and within-block learning data from blocks 3, 4 and 5 were analysed using 3 x 4 mixed-model ANOVAs as described for the acquisition phase. Univariate ANOVAs or Kruskal-Wallis tests (one between-subjects factor of group with 4 levels) and planned parametric or non-parametric pairwise group contrasts were used to further investigate significant main effects and interactions from the mixed-model analyses. The difference scores representing the degree of disruption in performance in the non-sequence block 4 compared with previous sequence

block 3 and the degree of facilitation in performance by the re-presentation of the sequence in block 5 compared with block 4 were analysed using univariate ANOVAs or Kruskal-Wallis tests (group (4) as the between-subjects factor). Significant effects of group were further investigated using parametric independent-samples t-tests or Mann-Whitney U tests between each pair of groups.

Further details of the analyses conducted for each behavioural correlate of habit-learning are presented in the corresponding section of the results (section 5.2 below). Greenhouse-Geisser corrections for violations of sphericity were used where appropriate. Due to the small sample sizes and consequent low power of this study in detecting effects, correction for multiple comparisons was not applied to the pairwise group contrasts in the acquisition or disruption phases. The effects that would not remain significant after correction are reported.

To test the hypothesised predictive relationships between tic, ADHD, OCD and ODD symptom severity and habit-learning, hierarchical multiple linear regression analyses were conducted. To restrict the number of tests conducted, regression analyses were only performed for variables characterising the degree of change in RT performance within or between blocks that differed significantly between groups. Two separate models were constructed for each measure of habit-learning. Model A investigated whether tic and OCD severity predicted habit-learning in the TS and TS+ADHD groups. The ADHD and Control groups were excluded from Model A due to the absence of tic symptoms, and largely absent OCD symptoms, in these individuals and the consequent non-linear distribution of tic and OCD scores. In the first block of Model A, the variable total tic severity (YGTSS Total) was entered to examine how well tics predicted acquisition of the repeating sequence and disruption to sequence learning. In the second block of Model A, OCD symptom scores on the CY-BOCS were entered to examine whether these symptoms predicted changes in acquisition and disruption to performance and/or moderated relationships between tics and habit-learning performance. Significant relationships between tics or OCD symptoms and performance were characterised using scatterplots.

Model B examined whether ADHD and ODD symptom severity predicted habit-learning in the whole participant sample (TS, TS+ADHD, ADHD and Controls). In block 1, ADHD symptom severity scores on the CPRS-R ADHD Index were entered to assess how well ADHD severity predicted sequence-learning and disruption to sequence-learning. In block 2, scores on the CPRS-R ODD scale were entered to assess whether ODD symptomatology predicted habit-learning or moderated relationships between ADHD severity and habit-learning.

The Durbin-Watson statistic was computed for all models to check for autocorrelation among the residuals and test the assumption of independent errors. Multicollinearity among IVs in each block of the models was assessed with the VIF (variance inflation factor).

5.2 RESULTS

5.2.1 Participants and Generate task performance

Four participants with TS+ADHD and two participants with ADHD did not complete the SRT task. A further 6 participants with TS, 1 participant with TS+ADHD, 2 participants with ADHD, and 9 Controls showed evidence of conscious awareness of the repeating sequence in the Generate task and were excluded from analysis of the SRT data. Table 5-1 presents a summary of the revised group characteristics for the clinical and socio-demographic variables following these participant exclusions. Information concerning medication is not provided in table 5-1 but was as follows. TS: Clonidine (3), Aripiprazole (2), Fluoxetine (1); TS+ADHD: methylphenidate (2 – withdrawn 24 hours prior to testing), Aripiprazole (1), Fluoxetine (1); ADHD: methylphenidate (4 – withdrawn 24 hours prior to testing); Atomoxetine (1 – not withdrawn). Inspection of table 5-1 indicates that the clinical and socio-demographic characteristics in the sample following participant exclusions are comparable with those of the full sample (chapter 3, table 3-1). This indicates that the habit-learning findings reported below are representative of the full participant sample.

Table 5-1

Summary of clinical and socio-demographic characteristics for each participant group included in the analysis of the SRT data. Group means are presented with standard deviations in parentheses.

	TS (n = 12)	TS+ADHD (n = 12)	ADHD (n = 9)	Control (n = 11)	Group differences
Age (months)	156.3 (28.9)	157.3 (34.6)	169.9 (30.9)	145.7 (31.8)	n/s
Gender (% males)	66.7	91.7	88.9	81.8	n/s
Handedness (% right handed)	83.3	91.7	100.0	72.7	n/s
SES	2.3 (1.2)	2.0 (1.3)	1.7 (1.6)	1.6 (1.3)	n/s
IQ	108.7 (10.0)	109.3 (10.6)	98.8 (16.4)	112.9 (10.8)	ADHD < Controls*
Motor tic severity (YGTSS Motor)	11.8 (6.8)	16.8 (3.8)	0 (0)	0 (0)	TS/TS+ADHD > ADHD/Controls*** TS+ADHD > TS**
Phonic tic severity (YGTSS Phonic)	5.3 (5.3)	12.4 (8.6)	0 (0)	0 (0)	TS > ADHD/Controls* TS+ADHD > TS*/ADHD***/Controls***
Total tic severity (YGTSS Total)	17.2 (10.8)	29.1 (11.3)	0 (0)	0 (0)	TS > ADHD/Controls*** TS+ADHD > TS/ADHD/Controls***

CPRS-R ADHD Index[a]	53.1 (7.2)	73.0 (10.8)	71.7 (20.0)	45.6 (6.6)	TS+ADHD > TS/Controls*** ADHD > TS**/Controls***
CPRS-R Inattentive	48.9 (5.3)	70.3 (9.6)	67.5 (23.0)	45.6 (6.3)	TS+ADHD > TS/Controls*** ADHD > TS**/Controls***
CPRS-R Hyper-Impulsive	53.6 (6.0)	75.3 (12.5)	75.2 (26.1)	48.3 (7.0)	TS+ADHD > TS/Controls*** ADHD > TS**/Controls***
CPRS-R ODD Index	51.6 (11.2)	66.3 (11.1)	68.8 (23.1)	46.5 (9.4)	ADHD/TS+ADHD > TS*/Controls***
ADHD Rating Scale IV	53.6 (25.9)	94.8 (5.1)	96.1 (2.8)	34.6 (26.7)	TS+ADHDADHD > TS/Controls*** TS > Controls*
SDQ Hyperactivity	4.6 (2.6)	7.9 (2.4)	7.9 (2.0)	2.6 (2.4)	TS+ADHD > TS**/Controls*** ADHD > TS**/Controls***
SDQ Conduct	1.6 (1.2)	3.5 (2.0)	6.8 (3.2)	.55 (1.0)	TS+ADHD > TS**/Controls*** ADHD > TS/Controls***
CY-BOCS	5.8 (9.9)	2.6 (6.1)	.67 (2.0)	.09 (.30)	TS > Controls*

* = significant at the $p < .05$ level. ** = significant at the $p < .01$ level. *** = significant at the $p < .001$ level. [a] Scores above 60 on the CPRS-R ADHD and ODD scales are considered to be clinically significant

5.2.2 Group differences in behavioural correlates of habit-learning

The variables RT and within-block learning rate were analysed using 3 (block) x 4 (group) mixed-model ANOVAs. In the acquisition phase blocks 1, 2 and 3 were analysed; in the disruption phase blocks 3 (for comparison with block 4) 4, 5 were analysed. RT and within-block learning rate were normally distributed (Shapiro Wilk $p > .05$); significant main effects and interactions in these variables were further investigated using univariate ANOVAs and independent-samples t-tests. The difference scores characterising the degree to which RT changed across successive blocks were not normally distributed (Shapiro Wilk $p < .05$) and were compared between the four groups using Kruskal-Wallis tests with group (4) as the between-subjects factor and Mann-Whitney U tests for pairwise group contrasts.

5.2.2.1 RT

Figure 5-2 presents the group means (of medians) RT (ms) for correct trials in each SRT task block. Inspection of the plot shows that the ADHD, TS+ADHD and Control groups produced the typical SRT RT effects, that is, initial decrease in RT during sequence blocks, followed by an increase in RT when the repeating sequence was no longer presented in block 4, and a final decrease in RT with the presentation of the repeating sequence again in block 5. In contrast, variations in RT by sequence and non-sequence blocks were largely absent in the TS group.

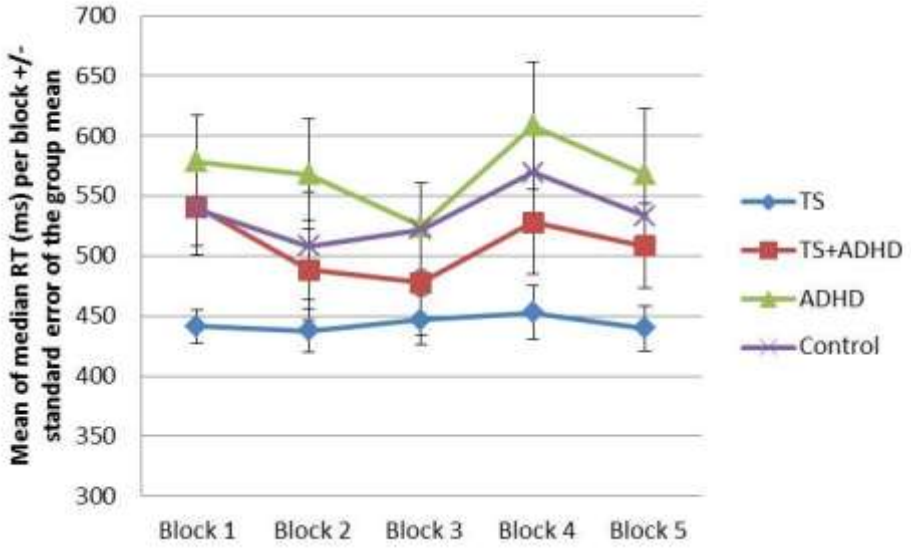
5.2.2.1.1 RT in the acquisition phase

The 3 x 4 ANOVA comparing RT between blocks and groups in the acquisition phase revealed a significant main effect of block ($F (2, 80) = 3.7$, $p = .03$, $\eta^2 = .084$) but no main effect of group ($F (3, 40) = 2.2$, $p = .10$, $\eta^2 = .141$) and no interaction between these factors ($F (6, 80) = 1.2$, $p = .32$, $\eta^2 = .082$). Further investigation of the difference in RT between blocks with paired-samples t-tests showed that, across all participants, RT significantly decreased from the first task block (non-sequence block, mean 521.1ms) to the second task block (first sequence block, mean 496.0ms) ($t (43) = 2.3$, $p = .02$, 1-tailed) but did not decrease significantly from block 2 to 3 (the first to second sequence blocks, block 2 mean 490.1ms) ($t (43) = .47$, $p = .32$, 1-tailed).

When IQ was included as a covariate in the model the main effect of block remained significant, and further, the effect of group reached significance (F (3, 39) = 3.7, p = .02, η^2 = .220). Planned pairwise contrasts showed that this group effect reflected significantly faster RTs (averaged across blocks 1 to 3) in TS (mean 442.1ms) compared with ADHD (mean 557.1ms) (t (19) = -3.1, p = .003 (1-tailed), *d* = -1.3) and Controls (mean 523.3ms) (t (21) = -2.1, p = .03 (1-tailed), *d* = -.84). The remaining pairwise group contrasts were not significant (TS+ADHD mean 502.5ms. All p > .10).

Figure 5-2

Group means for median RT (ms) in each SRT block plotted by group (TS, TS+ADHD, ADHD, Controls). Error bars represent the standard error of the group mean. Blocks 1 and 4 are non-sequence blocks; blocks 2, 3 and 5 are sequence blocks.



5.2.2.1.2 RT in the disruption phase

RT differed significantly between blocks in the disruption phase (F (2, 80) = 10.9, p < .001, η^2 = .214) and at trend-level between groups (F (3, 40) = 2.3, p = .09, η^2 = .145), but the interaction between block and group was not significant (F (6, 80) = 1.3, p = .25, η^2 = .091). Paired-samples t-tests showed that, across all participants, RT significantly increased from block 3 (second sequence block, mean 490.1ms) to the disruption block 4 (non-sequence block, mean 534.4ms) (t (43) = -4.0, p < .001, 1-tailed), and decreased from block 4 to

block 5 when the sequence was presented once more (block 5 mean 508.1) (t (43) = 3.3, p = .001, 1-tailed). The trend-level group effect reflected significantly shorter RTs (averaged across blocks 3 to 5) in TS (mean 446.6ms) than ADHD (mean 567.0ms) (t (19) = -2.7, p = .005 (1-tailed), *d* = -1.1) and Controls (mean 541.6ms) (t (21) = -2.4, p = .01 (1-tailed), *d* = -1.0). No other pairwise group comparisons were significant (TS+ADHD mean 541.6. All p > .10). The difference in RT between TS and ADHD groups would remain significant following correction for multiple comparisons, while the difference between TS and Controls would not remain.

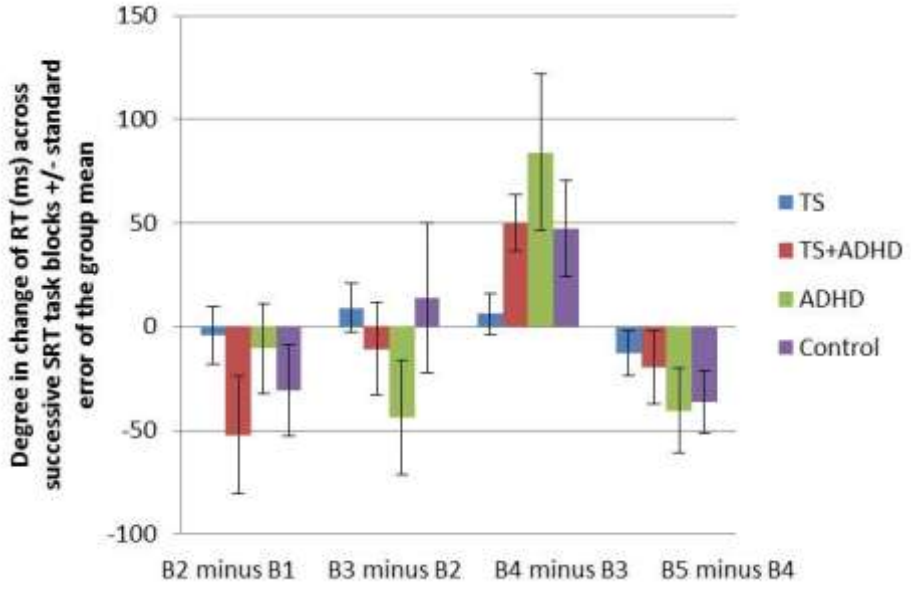
The main effect of block did not remain when IQ was included as a covariate (F (2, 78) = .11, p = .90, η^2 = .003) but the trend-level effect of group reached significance (F (3, 39) = 3.4, p = .03, η^2 = .208).

5.2.2.3 Difference scores characterising changes in RT

The difference scores characterising the degree of change in correct trial RT across successive task blocks in each group are presented in figure 5-3.

Figure 5-3

Difference scores characterising the degree of change in correct trial RT (ms) across successive task blocks plotted by participant group. Error bars represent the standard error of the group mean. Blocks 1 and 4 are non-sequence blocks; blocks 2, 3 and 5 are sequence blocks.



Each difference score was compared between the four participant groups using Kruskal-Wallis tests. The changes in RT for correct trials across successive SRT task blocks did not differ significantly between groups for blocks 1 to 2 (χ^2 (3) = .62, p = .89), blocks 2 to 3 (χ^2 (3) = 2.4, p = .50), blocks 3 to 4 (χ^2 (3) = 5.1, p = .17), or blocks 4 to 5 (χ^2 (3) = .95, p = .81). However, inspection of figure 5-3 demonstrates that the increases and decreases in RT across successive SRT task blocks are markedly smaller in the TS group compared with the other groups.

5.2.2.4 Within-block learning rate

Table 5-2 presents the group means for the degree to which RT increased or decreased within each SRT task block.

5.2.2.4.1 Acquisition phase

The 3 x 4 ANOVA examining the within-block changes in RT during the acquisition phase revealed no significant main effects of block (F (2, 80) = .24, p = .79, η^2 = .006) or group (F (3, 40) = .26, p = .85, η^2 = .019), and no interaction between block and group (F (6, 80) = .99, p = .44, η^2 = .069). These results did not change when IQ was included as a covariate.

Table 5-2

Summary of learning rate (standardised *b* coefficients) values from the learning slopes fitted to the correct trial RT data in blocks 1-5. Group means are presented with standard deviations in parentheses.

Learning rate	TS	TS+ADHD	ADHD	Control
Block 1	-.14 (1.0)	.05 (1.1)	.40 (.82)	.27 (.72)
Block 2	.29 (1.0)	.04 (1.2)	-.15 (.95)	-.14 (.90)
Block 3	.28 (.96)	-.32 (1.2)	-.004 (1.1)	.24 (.79)
Block 4	-.11 (1.1)	.06 (.99)	-.06 (.96)	.29 (.94)
Block 5	-.16 (1.0)	-.07 (.90)	-.19 (1.2)	.37 (.99)

5.2.2.4.2 Disruption phase

The degree to which RT changed within blocks in the disruption phase did not differ between blocks 3 to 5 ($F (2, 80) = .06$, $p = .94$, $\eta^2 = .001$) or groups ($F (3, 40) = .84$, $p = .48$, $\eta^2 = .059$), and there was no interaction between these factors ($F (6, 80) = .50$, $p = .81$, $\eta^2 = .036$). These results were unaltered by the inclusion of IQ as a covariate.

5.3 CHAPTER SUMMARY

The research presented in this chapter was conducted to investigate the basis of TS+ADHD. The TS group was expected to show hyper-learning of the repeating sequence and difficulty in modifying the learned sequence. In contrast, the ADHD group was predicted to show comparable habit-learning as the Control group. It was hypothesised that if additive or symptomatic phenocopy comorbidity models hold for TS+ADHD, then young people in this group should show evidence of hyper-learning like the TS group. Alternatively, if TS+ADHD is an independent condition from TS and ADHD, then habit-learning in this group would be different from the TS and ADHD groups.

In contrast to these predictions, the analysis of behavioural correlates of habit-learning revealed no significant differences between the groups in the degree to which RT changed between or within blocks. This indicates that the groups did not differ in the degree to which they learned and modified the repeating sequence. The one significant group difference in the analyses was that the TS group produced significantly faster RTs than ADHD and Controls in the disruption phase, averaged across blocks 3-5. Collapsing across all groups, RTs showed the typical decrease at the beginning of the task, increase during the disruption block 4 when the repeating sequence was no longer presented, and decrease in the final task block when the repeating sequence was repeated once more. Due to the absence of significant group differences in RT change measures of habit-learning, relationships between tic, ADHD, OCD and ODD symptomatology and habit-learning were not examined. These findings shall be discussed in full in chapter 7.

6. METHODS AND RESULTS III: COGNITIVE CONTROL

6.1 METHODS AND HYPOTHESES

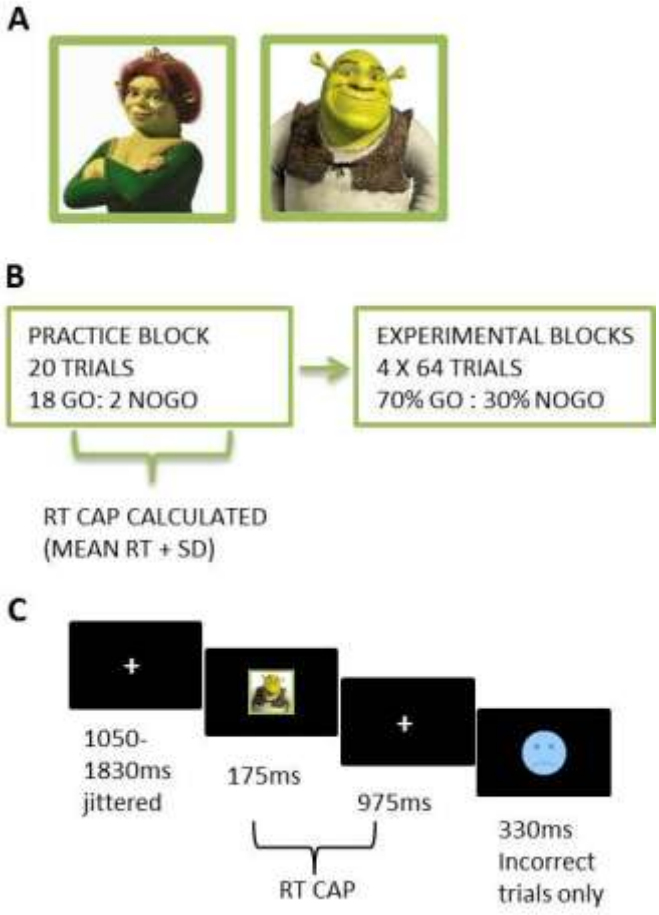
6.1.1 Cognitive control paradigm: the Go/Nogo task

The Go/Nogo task (figure 6-1) was presented to participants as a game in which they would be playing with two cartoon characters and the aim was to try and reach a top game-score of 40 points in each chance (trial block) they had at playing. The task was explained such that one of the characters (the Go stimulus) wanted the participants to win and would give them points if they 'caught' the character very quickly by pressing a button every time it appeared on screen. The other character was mean and would steal points if the participant caught them (the Nogo stimulus) and so young people were to ensure they did not press the button when this character appeared. The two character stimuli were visually similar creatures from an animated film. The allocation of characters to Go and Nogo conditions was counterbalanced across participants. The film theme was the same as in the reinforcement learning task but different characters from the film were used in the Go/Nogo task.

The task consisted of a block of 20 practice trials (18 Go trials) followed by four blocks of 52 experimental trials. The ratio of Go to Nogo trials in each block was 70:30 to encourage a prepotent response tendency and enhance the difficulty of withholding responses on infrequent Nogo trials. A RT cap was used to limit the length of time available for participants to respond to the Go stimulus on experimental trials. The length of the cap was set for each participant individually and calculated as the mean plus one standard deviation of the participant's reaction times in the practice block. The purpose of the RT cap was to encourage a prepotent response tendency on Go trials by preventing the participant from simply waiting to prepare responses until after the type of stimulus had been determined on each trial. This also served to increase the difficulty of the Go condition and thereby reduce boredom effects.

Figure 6-1

Diagram of the Go/Nogo task



A. Task stimuli
One character was allocated the Go stimulus to which prompt button-press responses were required. The other was allocated the Nogo stimulus to which responses were to be withheld. Allocation to Go and Nogo conditions was counterbalanced across participants.

B. Task design
Participants performed one block of practice trials consisting of 18 Go trials and 2 Nogo trials, followed by four blocks of 64 experimental trials separated by rest breaks. Each participant's mean RT plus one standard deviation for Go trials (correct and incorrect) in the practice block were used as a RT cap in the experimental trials.

C. Experimental trial Structure (see text below)

Every trial began with a white fixation cross (7x7mm) presented for a jittered duration of 1050-1830ms. The Go or Nogo stimulus (the character surrounded by a rectangular 3mm green frame, measuring 60x57mm including the frame) followed for 175ms and was replaced by a second white fixation cross for 975ms. Participants responded to Go stimuli with their right hand using the middle button of a Cedrus RB-530 response button box (Cedrus Corporation, San Pedro, California). If the response was incorrect, (i.e. if the participant responded to a Nogo stimulus or did not respond to a Go stimulus) a

blue sad-face (60mm diameter) was displayed for 330ms after which the trial ended. On correct trials no feedback was provided and the trial ended after the second fixation cross. Task objects were centrally presented on a black background on a Viglen computer (43cm monitor, 1024x768 pixels screen resolution). The task was performed in a dimly lit room at a viewing distance of 60cm from the monitor. Task programming was carried out in E-Prime version 1.2 (Psychology Software Tools Inc.).

6.1.2 Behavioural correlates of cognitive control

The measures selected as behavioural correlates of cognitive control are summarised below. Go/Nogo accuracy, D-prime and Go RT are standard measures of cognitive control performance in the Go/Nogo task. Go RT variability was selected as a measure of IIV due to its robust association with ADHD (see 2.3.2). Post-error slowing (PES) was selected as a correlate of error monitoring and adjustment due to the proposal that this capacity might be important in tic control in TS (discussed in 2.3.4). The measures were computed using Matlab R2011a (MathWorks, UK). Participants with scores greater than 2.5 SD of their group mean on any behavioural correlate were excluded from analyses.

- Go and Nogo accuracy: % correct trials per condition. For the Go condition, only trials on which timely responses were made (</= 1000ms post-stimulus) were considered correct.
- D-prime: sensitivity to target. Z-transformed probability of hits (correct Go trials) minus z-transformed probability of false-alarms (incorrect Nogo trials) (zH-zFA). D-prime provides a measure of performance accuracy while controlling for response bias (e.g. responding correctly to Go trials at the expense of few correct Nogo trials). Larger D-prime scores indicate better performance (greater sensitivity to target e.g. high % of correct Go and low % of incorrect Nogo.
- Go RT: median RT for correct Go trials (ms)
- Go RT variability: the coefficient of variation (CV) was computed as a measure of RT variability by taking each individual's standard

deviation of RT for correct Go trials and dividing by the individual's mean RT for correct Go trials (RTSD/meanRT)

- Post-error slowing: the difference in median RT (ms) between correct Go trials following erroneous Nogo trials and correct Go trials following correct Go trials (PostErrorRT - PostCorrectRT)

6.1.3 Electrophysiological correlates of cognitive control

EEG data were processed offline as described for the goal-directed reinforcement learning task in chapter 4 (section 4.1.3). The data were segmented into stimulus-locked epochs beginning -200ms and ending +1000ms around stimulus onset and response-locked epochs beginning -250ms and ending +1000ms surrounding the response. Stimulus-locked epochs were baseline-corrected using the -200–0ms baseline period. Baseline-correction for response-locked epochs was achieved using the -250 to -50ms baseline period to facilitate measurement of the ERN in the -50 to 100ms time-range. Epochs were averaged by condition to create correct Go and correct Nogo stimulus-locked ERPs and incorrect Nogo (Nogo Error) response-locked ERPs. A minimum of 15 trials was included in each average. Participants with fewer than 15 trials per average were excluded from component analyses. To check whether differences in SNR of averaged waveforms may have contributed to group differences in ERP measures in this study (see chapter 4 section 4.1.3 for full explanation), the number of trials included in each participant's stimulus and response-locked waveforms were computed and compared between groups. The results of this analysis are reported in section 6.2.3.

Electrophysiological correlates of cognitive control were peak amplitudes, that is the mean of +/- 15 time-points around the peak amplitude (see chapter 4 section 4.1.3 for the rationale for this approach), of the stimulus-locked N2 and P3 and response-locked ERN and Pe ERP components. These components were selected due to their robust association with cognitive control and sensitivity to ADHD and TS in previous research (discussed in 2.3.4). Based on parameters used in previous research and inspection of the individual and grand average waveforms, the components were defined as follows:

- N2: most negative peak within 200-400ms post-stimulus at Fz (midline frontal scalp), Cz (midline central scalp), Pz (midline parietal scalp)

- P3: most positive peak within 300-650ms post-stimulus at Fz, Cz, Pz
- ERN: most negative peak within -50 to 100ms surrounding response at FCz (midline frontal scalp, anterior to Fz) and Fz
- Pe: most positive peak within 100-350ms post-response at Cz

6.1.4 Hypotheses

The hypotheses for the investigation of cognitive control section in this thesis are as follows:

1. The TS group will show enhanced behavioural performance compared with ADHD and Control groups on cognitive control measures that can be conceived to be involved in tic control. These measures are Nogo accuracy and D-prime, relating to the ability to withhold inappropriate prepotent responses while maintaining adequate on-going performance, and PES, relating to the ability to adjust on-going performance following errors (e.g. tics) in behaviour. Behavioural cognitive control measures that are not proposed to be related to tic control, Go accuracy, Go RT and Go RT variability, will be comparable to the Control group. Amplitudes of the N2 and P3 at frontal scalp, ERN, and Pe are hypothesised to be enhanced in TS compared with Controls and ADHD, reflecting enhanced engagement of frontal control regions (N2, P3) and superior monitoring and adjustment for errors (ERN, Pe).
2. The ADHD group will show impaired behavioural performance compared with Control and TS groups on measures that are sensitive to ADHD. These are Nogo accuracy, D-prime and Go RT variability. Go RT and PES are predicted to be comparable to Controls as these measures have not been so robustly linked with ADHD. N2 and P3 amplitudes at frontal scalp will be reduced in ADHD compared with Controls and TS, reflecting impaired frontal control networks. ERN and Pe amplitudes are predicted to be comparable to Controls.
3. The TS+ADHD group will show a pattern of impaired performance and ERP amplitudes relative to the TS and Control groups for measures related to ADHD (Nogo accuracy, D-prime, Go RT variability, N2 and P3 amplitudes at frontal scalp) due to the impairing effect of ADHD symptoms. However, due to ameliorating effects of TS-related

enhancements in cognitive control processes due to their repeated engagement in tic control, TS+ADHD will show better performance and larger ERP amplitudes compared with ADHD for measures that are proposed to be involved in tic control. These are Nogo accuracy, D-prime, PES, and amplitudes of the N2 and P3 at frontal scalp, ERN and Pe ERPs. Therefore, for some correlates of cognitive control which are related to tic control and ADHD (Nogo accuracy, D-prime, N2/P3 ERPs) in opposite ways (enhanced in TS and impaired in ADHD), the TS+ADHD group will fall in between the TS and ADHD groups. For example, D-prime scores will be lowest in ADHD, then higher in TS+ADHD, and highest in TS. To clarify whether such group differences truly reflect the presence of both TS-related enhancements and ADHD-related impairments in individuals with TS+ADHD, relationships between tic and ADHD severity and correlates of cognitive control will be examined.

4. Higher tic severity will predict better behavioural performance and larger ERP amplitudes of measures that are proposed to be involved in tic control, namely Nogo accuracy, D-prime, PES, and N2 and P3 (at Fz), ERN and Pe ERPs. The rationale for this prediction is that young people with more severe tics may have to engage cognitive control more frequently in tic control than young people with less severe tics. This might lead to greater enhancement of cognitive control in more severely affected individuals. Higher ADHD symptom severity will predict poorer behavioural performance and smaller ERP amplitudes of measures associated with ADHD, which are Nogo accuracy, D-prime, Go RT variability, and N2 and P3 ERPs at Fz. The presence of both of these associations in the TS+ADHD group would be consistent with an additive model of comorbidity and, for those correlates which are expected to be better in TS+ADHD relative to ADHD but impaired in TS+ADHD relative to TS, would support the hypothesis that this mixture of enhancement and impairment occurs in TS+ADHD.
5. Symptom severity of other comorbid conditions that frequently occur with TS and ADHD, that is, OCD and ODD, are expected to modulate relationships between tic and ADHD symptoms and cognitive control.

However, due to the lack of previous research addressing this question no directional hypothesis concerning such modulation was formulated.

6.1.5 Analysis methods

6.1.5.1 Normality testing

All behavioural and electrophysiological correlates of cognitive control were subjected to Shapiro-Wilk tests to check normality of distributions. Variables that were normally distributed were analysed with parametric ANCOVA tests and significant main effects and interactions were further investigated using independent-samples t-tests. Variables that were not normally distributed were analysed, in the first instance, with parametric ANCOVA tests for reasons explained in chapter 4 (see section 4.1.5.1). Non-parametric Mann-Whitney U tests were used in place of independent-samples t-tests to further investigate main effects and interactions revealed in ANCOVA models for non-normal variables.

6.1.5.2 Covariates

The variable age was included as a covariate in analyses of cognitive control. The reason for this is that there are known robust age effects on behavioural performance and ERP correlates of cognitive control. Performance improves with increasing age, while ERP amplitudes decrease or increase depending on the component examined (Bunge et al., 2002; Dimoska et al., 2007; Hogan et al., 2005; Johnstone et al., 2005; Jonkman, 2006; Ladouceur et al., 2007). The age range for participants in this research was large at 9-17 years, and it is likely that age-related effects on cognitive control were present in each participant group and moderated performance. To isolate the group effects on cognitive control without confounding effects of age, group differences were examined after the proportion of variance in analyses accounted for by age had been removed. The variables IQ, SES and gender were also considered as covariates but were not included for reasons explained in chapter 4, section 4.1.5.2. To be consistent with previous research, additional analyses were conducted with IQ included as a covariate because this variable differed between participant groups, and the results of these

additional analyses are reported where they differed from the main analyses without IQ as a covariate.

6.1.5.3 Hypothesis testing

All statistical analyses were conducted using SPSS v.21 (IBM©). To test the hypothesised group differences in behavioural performance and ERP correlates of cognitive control, each behavioural and ERP amplitude measure was entered into a separate ANCOVA model with group as a 4-level between-subjects factor and age as a covariate. Further details of particular ANCOVA models used are given in the appropriate section of the results (6.2). Significant main effects and interactions were further investigated with parametric (independent-samples t-tests) or non-parametric (Mann-Whitney U tests) planned contrasts between each pair of groups. Due to the small sample sizes and consequent low power of this study in detecting effects, correction for multiple comparisons was not applied in the main analyses but the effects that would not remain significant after correction are reported. Greenhouse-Geisser corrections for violations of sphericity were used where appropriate.

To test the hypothesised relationships between symptom severity and cognitive control, hierarchical multiple linear regression analyses were performed. These analyses aimed to establish the extent to which tic, ADHD, OCD and ODD symptom severity predicted behavioural and electrophysiological correlates of cognitive control. To limit the number of tests conducted, regression analyses were only performed on correlates for which there were hypothesised group differences (Nogo accuracy, D-prime, Go RT variability, PES, Nogo N2 and P3 at frontal scalp (site Fz), and ERN and Pe). For each dependent variable, two separate hierarchical models were constructed.

Model A examined the extent to which tic and OCD symptom severity predicted cognitive control in individuals with TS and TS+ADHD. ADHD and Controls scored zero on the tic scales and OCD measure (majority of participants) and were excluded from Model A. The inclusion of these groups would not have been appropriate due to the non-linear distribution of tic and OCD scores. In block 1 of Model A, the variables age and total tic severity (YGTSS Total) were entered to assess how well tics predicted behavioural and

ERP correlates while accounting for the degree to which age predicted those DVs. OCD symptom scores on the CY-BOCS were entered in a second block to assess whether these commonly comorbid symptoms predicted DVs and/or moderated relationships between tics and DVs. Scatterplots were produced to characterise the relationships between tics/OCD and cognitive control measures. Similar relationships in the TS and TS+ADHD groups would indicate that tics (and OCD) contributed to performance comparably in these two groups.

Model B tested relationships between ADHD and ODD symptomatology and cognitive control measures in the whole sample (TS, TS+ADHD, ADHD, Controls). In block 1, age and ADHD severity scores on the CPRS-R ADHD Index were entered to assess the extent to which ADHD severity predicted cognitive control correlates while accounting for the degree to which age predicted those DVs. In block 2, ODD scores on the CPRS-R ODD scale were entered to explore predictive relationships between these symptoms and cognitive control, and to assess whether ODD symptomatology moderated associations between ADHD symptoms and DVs. Relationships were characterised using scatterplots to examine similarities between the TS+ADHD and ADHD groups.

6.2 RESULTS

6.2.1 Participants

Table 6-1 presents a revised summary of the socio-demographic and clinical characteristics of each group following participant exclusions. Two participants with ADHD did not complete the Go/Nogo task and therefore could not be included in the analysis of cognitive control. In addition, the following exclusions were made. One participant with TS and two Controls were excluded from all analyses due to extreme scores (>2.5 SD of group mean) on behavioural Go/Nogo variables. A further five participants with TS, two participants with TS+ADHD, two participants with ADHD and six Controls had too few artefact-free epochs (<15) in the waveform averages for

Table 6-1

Summary of clinical and socio-demographic characteristics for each participant group in the behavioural analysis sample (A) and ERP analysis sample (B). Group means are presented with standard deviations in parentheses.

(A) Behavioural sample	TS (n = 17)	TS+ADHD (n = 17)	ADHD (n = 11)	Control (n = 18)	Group differences
Age (months)	158.4 (34.3)	148.2 (33.9)	174.9 (29.9)	161.4 (32.6)	n/s Kruskal-Wallis but pairwise contrasts (Mann-Whitney U) showed ADHD > TS+ADHD*
Gender (% males)	76.5	94.1	90.9	77.8	n/s
Handedness (% right handed)	82.4	88.2	90.9	77.8	n/s
SES	2.1 (1.4)	1.8 (1.2)	2.1 (1.6)	1.5 (1.1)	n/s
IQ	112.0 (11.7)	110.1 (10.2)	96.5 (16.6)	112.4 (11.6)	ADHD < TS/TS+ADHD/ Controls **
Motor tic severity (YGTSS Motor)	13.5 (7.7)	15.9 (4.5)	0 (0)	0 (0)	TS/TS+ADHD > ADHD/Controls***
Phonic tic severity (YGTSS Phonic)	5.8 (5.8)	12.1 (7.9)	0 (0)	0 (0)	TS > ADHD/Controls** TS+ADHD > TS**/ADHD***/Controls***

Total tic severity (YGTSS Total)	19.3 (12.1)	28.1 (11.3)	0 (0)	0 (0)	TS > ADHD/Controls*** TS+ADHD > TS**/ADHD***/Controls***
CPRS-R ADHD Index[a]	54.2 (9.3)	72.8 (9.3)	74.8 (17.8)	48.2 (6.5)	TS+ADHD/ADHD > TS/Controls***
CPRS-R Inattentive	50.7 (7.8)	70.5 (8.6)	71.3 (20.6)	47.7 (7.1)	TS+ADHD/ADHD > TS/Controls***
CPRS-R Hyper-Impulsive	57.3 (11.7)	74.7 (11.2)	78.9 (23.1)	49.1 (7.0)	TS+ADHD/ADHD > TS/Controls***
CPRS-R ODD Index	51.9 (10.7)	65.4 (13.0)	74.0 (21.8)	47.8 (9.7)	TS+ADHD/ADHD > TS/Controls**
ADHD Rating Scale IV	55.2 (31.4)	95.2 (4.4)	96.8 (2.6)	41.5 (27.0)	TS+ADHD/ADHD > TS/Controls***
SDQ Hyperactivity	4.5 (3.2)	8.1 (2.0)	8.1 (2.0)	2.4 (2.7)	TS+ADHD/ADHD > TS/Controls*** TS > Controls*
SDQ Conduct	1.6 (1.7)	3.6 (2.1)	6.8 (3.0)	.89 (1.2)	ADHD/TS+ADHD > TS/Controls*** ADHD > TS+ADHD**
CY-BOCS	7.0 (9.9)	2.1 (5.3)	.55 (1.8)	.06 (.24)	TS > TS+ADHD*/ ADHD**/ Controls**

* = significant at the $p < .05$ level. ** = significant at the $p < .01$ level. *** = significant at the $p < .001$ level. [a] Scores above 60 on the CPRS-R ADHD and ODD scales are considered to be clinically significant.

(B) ERP sample	TS (n = 13)	TS+ADHD (n = 15)	ADHD (n = 9)	Control (n = 12)	Group differences
Age (months)	158.4 (34.9)	153.3 (32.8)	170.2 (31.2)	162.3 (27.5)	n/s
Gender (% males)	76.9	93.3	88.9	83.3	n/s
Handedness (% right handed)	92.3	86.7	88.9	75.0	n/s
SES	2.2 (1.5)	1.9 (1.2)	2.2 (1.8)	1.6 (1.2)	n/s
IQ	112.8 (11.4)	107.3 (10.0)	96.4 (14.4)	114.4 (12.3)	ADHD < TS/Controls ** ADHD < TS+ADHD*
Motor tic severity (YGTSS Motor)	14.0 (7.9)	16.0 (4.8)	0 (0)	0 (0)	TS/TS+ADHD > ADHD/Controls***
Phonic tic severity (YGTSS Phonic)	5.5 (6.3)	11.4 (8.2)	0 (0)	0 (0)	TS > ADHD/Controls* TS+ADHD > TS**/ADHD***/Controls***
Total tic severity (YGTSS Total)	19.5 (12.5)	27.4 (11.9)	0 (0)	0 (0)	TS > ADHD/Controls*** TS+ADHD > TS*/ADHD***/Controls***
CPRS-R ADHD Index[a]	54.2 (10.4)	73.6 (9.6)	72.3 (20.4)	45.6 (4.5)	TS+ADHD > TS/Controls*** ADHD > TS**/Controls***

CPRS-R Inattentive	51.5 (8.3)	71.9 (8.2)	67.7 (23.1)	45.2 (4.6)	TS+ADHD > TS/Controls*** ADHD > TS**/Controls***
CPRS-R Hyper-Impulsive	57.9 (13.3)	75.1 (11.9)	75.2 (26.1)	47.5 (4.3)	TS+ADHD > TS**/Controls*** ADHD > TS*/Controls***
CPRS-R ODD Index	51.6 (12.0)	65.7 (13.8)	71.7 (24.7)	45.8 (7.4)	TS+ADHD > TS*/Controls*** ADHD > TS/Controls**
ADHD Rating Scale IV	46.4 (34.3)	95.4 (4.7)	96.3 (2.8)	31.5 (21.3)	TS+ADHD/ADHD > TS/Controls*** TS > Controls*
SDQ Hyperactivity	4.6 (3.6)	8.5 (1.6)	7.6 (2.0)	2.2 (2.8)	TS+ADHD > TS/Controls*** ADHD > TS*/Controls***
SDQ Conduct	1.5 (1.9)	3.6 (2.3)	7.3 (3.1)	.83 (1.3)	TS+ADHD > TS*/Controls** ADHD > TS/TS+ADHD/Controls***
CY-BOCS	7.4 (9.9)	1.2 (3.5)	.67 (2.0)	.08 (.29)	TS > TS+ADHD/ADHD/ Controls**

* = significant at the p < .05 level. ** = significant at the p < .01 level. *** = significant at the p < .001 level. [a] Scores above 60 on the CPRS-R ADHD and ODD scales are considered to be clinically significant.

at least one of the task conditions (correct Go, correct Nogo, Error Nogo) and were excluded from the ERP analysis. Inspection of the group characteristics in table 6-1 demonstrates that symptom severity, age, IQ and other socio-demographic characteristics in the reduced samples are comparable with those of the full sample (chapter 3, table 3-1). It is therefore likely that effects reported below in the reduced behavioural and ERP samples are representative of the full sample.

Information concerning medication use in the reduced behavioural and ERP samples is not provided in table 6-1. In the behavioural sample the medications received were as follows. TS: Clonidine (2), Aripiprazole (2), Fluoxetine (1), Citalopram (1); TS+ADHD: Clonidine (1), methylphenidate (2 – withdrawn for 24 hours prior to testing), Aripiprazole (2), Fluoxetine (1); ADHD: methylphenidate (7 – withdrawn 24 hours prior to testing), Atomoxetine (2 – not withdrawn). In the ERP sample the medications received were as follows. TS: Clonidine (2), Aripiprazole (2), Citalopram (1), Fluoxetine (1); TS+ADHD: Clonidine (1), methylphenidate (1 – withdrawn 24 hours prior to testing), Aripiprazole (2); ADHD: methylphenidate (6 – withdrawn 24 hours prior to testing).

6.2.2 Group differences in behavioural correlates of cognitive control

Table 6-2 presents the group means for each behavioural correlate of cognitive control. Each behavioural correlate was compared between the four groups using univariate ANCOVAs with group (4 levels) as a between-subjects factor and age as a covariate. The variables Go accuracy and Go RT variability were not normally distributed; therefore, Mann-Whitney U tests were used to further investigate significant main effects for these variables. The remaining variables Nogo accuracy, D-prime, Go RT and PES were normally distributed and significant main effects for these variables were further examined using independent-samples t-tests.

6.2.2.1 Go and Nogo accuracy

The groups differed significantly in Go accuracy ($F (3, 58) = 2.9$, $p = .05$, $\eta^2 = .129$) and Nogo accuracy ($F (3, 58) = 3.1$, $p = .03$, $\eta^2 = .137$). Further investigation of the group difference in Go accuracy revealed that the

TS+ADHD group produced significantly poorer Go accuracy than the TS group (U = 86.0, p = .05 (2-tailed), *d*= .54) and Control group (U = 218.5, p = .03 (2-tailed), *d* = .76). There was a trend for the ADHD group to show poorer Go accuracy the Controls (U = 136.5, p = .09 (2-tailed), *d* = .75). There were no other significant differences between pairs of groups (all p > .10).

Table 6-2

Summary of behavioural performance in the Go/Nogo task. Group means are presented with standard deviations in parentheses.

	TS	**TS+ADHD**	**ADHD**	**Controls**
Go accuracy (% correct)	94.9 (5.9) [a]	91.3 (7.3)[ab]	89.7 (10.6)[c]	95.8 (3.7)[bc]
Nogo accuracy (% correct)	54.7 (16.4)[a]	49.5 (15.1)[b]	40.5 (11.9)[abc]	48.8 (17.8)[c]
D-prime	.631 (1.5) [ad]	-.156 (1.2)[bd]	-.928 (1.7) [abc]	.374 (1.3) [c]
Go RT (ms)	297.6 (56.1)	291.8 (46.9)	270.0 (46.9)	265.4 (39.4)
Go RT variability (CV)	.213 (.05) [ac]	.272 (.08) [ab]	.264 (.06) [cd]	.210 (.05) [bd]
PES (ms)	31.3 (79.9)[abc]	-15.4 (49.6)[a]	-2.6 (16.9)[b]	.722 (13.1)[c]

Superscript letters ([abcd]) are placed to mark pairwise group differences. For example, for the measure Go accuracy the TS+ADHD and Control groups differed significantly, hence they are marked with a matching superscript letter ([a])

Independent-samples t-tests exploring the group difference in Nogo accuracy showed that young people with ADHD produced significantly poorer accuracy than young people with TS (t (26) = 2.5, p = .01 (1-tailed), *d* = 1.0) and young people with TS+ADHD (t (26) = 1.7, p = .05 (1-tailed), *d* = .69). There was also a trend for the ADHD group to exhibit lower Nogo accuracy than the Control group (t (27) = -1.4, p = .09 (1-tailed), *d* = .57). There were no other significant pairwise group differences for Nogo accuracy (all p > .10).

Group differences in Go accuracy between the ADHD and Control groups and between the TS+ADHD and TS and Control groups would not remain after correcting for multiple comparisons. The difference in Nogo accuracy between the TS and ADHD groups would remain significant after

correcting for multiple comparisons, while the differences between TS+ADHD and ADHD, and ADHD and Controls would not remain. The overall group differences in Go and Nogo accuracy became non-significant when IQ was included as a covariate: Go accuracy ($F (3, 58) = 1.9$, $p = .14$, $\eta^2 = .091$); Nogo accuracy ($F (3, 58) = 2.1$, $p = .12$, $\eta^2 = .098$).

6.2.2.2 D-prime

There was a significant group difference for D-prime scores ($F (3, 58) = 4.8$, $p = .005$, $\eta^2 = .196$). Further investigation with planned pairwise contrasts showed that the ADHD group produced significantly lower D-prime scores, indicating poorer sensitivity to the Go/Nogo stimuli, than the TS group ($t (26) = 2.6$ $p = .008$ (1-tailed), $d = -.97$) and the Control group ($t (27) = -2.3$, $p = .01$ (1-tailed), $d = -.86$). The ADHD group also tended to have lower D-prime scores than the TS+ADHD group ($t (26) = 1.4$, $p = .08$ (1-tailed), $d = -.52$). The TS+ADHD group also produced significantly lower D-prime scores than the TS group ($t (32) = 1.7$, $p = .05$ (1-tailed), $d = .58$). There were no differences between the TS and Control groups ($p > .10$), or the TS+ADHD and Control groups ($p > .10$). The differences between ADHD and TS, and ADHD and Controls would remain significant if controlling for multiple comparisons, while the differences between TS+ADHD and ADHD, and TS+ADHD and TS would not remain. The inclusion of IQ as a covariate did not alter the results.

6.2.2.3 Go RT and Go RT variability

Go RT did not differ significantly between the four groups ($F (3, 58) = 1.8$, $p = .15$, $\eta^2 = .087$) and this did not change when IQ was included as a covariate. However, there was a highly significant group difference in Go RT variability ($F (3, 58) = 4.9$, $p = .004$, $\eta^2 = .203$). Planned pairwise contrasts showed that Go RT variability was significantly higher in the ADHD than TS ($U = 139.0$, $p = .02$ (1-tailed), $d = .92$) and Control ($U = 45.0$, $p = .007$ (1-tailed), $d = .98$) groups. Likewise, Go RT variability was significantly greater in the TS+ADHD group compared with the TS ($U = 210.0$, $p = .01$ (1-tailed), $d = .88$) and Control ($U = 76.0$, $p = .005$ (1-tailed), $d = .93$) groups. TS and Controls did not differ from one another, nor did the TS+ADHD and ADHD groups (all $p > .10$). The differences between ADHD and Controls, and

TS+ADHD and Controls would remain significant after controlling for multiple comparisons, while the differences between TS and ADHD/TS+ADHD would not remain. The group difference in Go RT variability remained significant when IQ was included as a covariate.

6.2.2.4 Post-error slowing (PES)

PES differed at trend-level between the four groups ($F (3, 58) = 2.6$, $p = .06$, $\eta^2 = .117$). This trend remained when IQ was included as a covariate. Further investigation of this group difference revealed that the TS group exhibited significantly greater PES than TS+ADHD ($t (32) = 2.1$, $p = .05$ (2-tailed), $d = .70$), and trend-level PES than ADHD ($t (26) = 1.4$, $p = .09$ (1-tailed), $d = .59$) and Control ($t (33) = 1.6$, $p = .06$ (1-tailed), $d = .53$) groups. There were no other significant group differences (all $p > .10$). These differences between TS and the other groups in PES would not remain significant after correction for multiple comparisons.

6.2.3 Group differences in electrophysiological correlates of cognitive control

Go and Nogo N2 and P3 amplitudes were subjected to separate 3 (electrode: Fz, Cz, Pz) x 4 (group) mixed-model ANCOVAs to examine differences between electrode sites and groups while covarying age. ERN amplitude at Fz and FCz and Pe amplitude were analysed using separate univariate ANCOVAs with group (4) as the between-subjects factor and age as a covariate. Amplitudes of the Go P3 at Cz, Nogo P3 at Cz and Pz, Nogo N2 at Cz, and the ERN at FCz and Fz were not normally distributed (Shapiro-Wilk $p < .05$) and hence Mann-Whitney U tests were used to investigate significant main effects and interactions for these variables. The remaining variables were normally distributed and significant main effects and interactions were followed up with independent-samples t-tests.

6.2.3.1 Go and Nogo N2

Table 6-3 presents the mean amplitudes for the Go and Nogo N2 for each participant group at each electrode site. Figures 6-2 and 6-3 present the grand averages and topographical plots for the Go and Nogo N2 respectively.

The 3 x 4 ANCOVA for Go N2 amplitude revealed a significant interaction between electrode site and the covariate age (F (1.5, 67.6) = 1.39, p .049, η_p^2 = .073); therefore, univariate ANCOVAs were conducted to examine group differences in amplitude at each electrode site separately. The groups differed significantly in Go N2 amplitude at site Pz (F (3, 44) = 4.94, p = .005, η_p^2 = .252), but not at Cz (F (3, 44) = 1.90, p = .14, η_p^2 = .115) or Fz (F (3, 44) = .144, p = .93, η_p^2 = .010).

Table 6-3

Summary of group mean amplitudes for the Go and Nogo N2 at sites Cz, Pz and Fz. Standard deviations are presented in parentheses.

	TS	TS+ADHD	ADHD	Control
Go N2 amplitude (μv)				
Fz	-6.92 (4.5)	-6.95 (2.7)	-6.49 (4.1)	-7.57 (4.2)
Cz	-2.12 (2.6)	-3.55 (3.0)	-4.23 (3.3)	-4.90 (4.1)
Pz	.938 (2.8)^{ab}	-.453 (3.1)^{c}	-2.02 (4.2)^{a}	-3.00 (3.3)^{bc}
Nogo N2 amplitude (μv)				
Fz	-6.81 (4.0)	-6.63 (3.7)	-6.85 (5.3)	-6.38 (3.8)
Cz	-3.12 (2.9)	-4.10 (3.7)	-5.91 (4.2)	-6.49 (3.8)
Pz	-.434 (3.4)^{a}	-1.12 (4.4)^{b}	-2.73 (4.3)	-4.71 (4.1)^{ab}

Superscript letters (^{abcd}) mark significant or trend-level pairwise group differences. Groups marked with the same letter differed from one another.

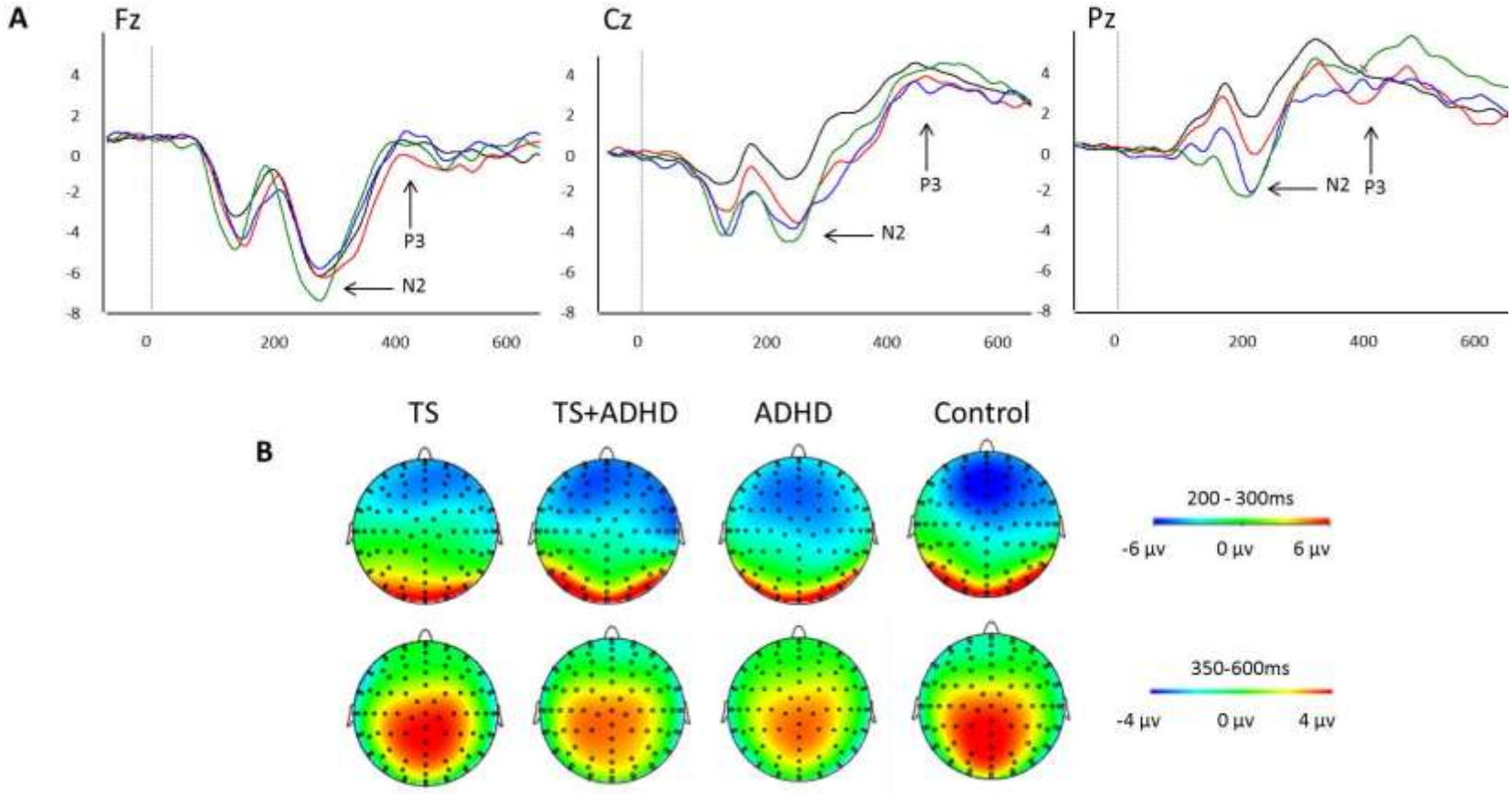
Further investigation of the group difference at Pz revealed that the TS group exhibited significantly less negative Go N2 amplitudes at Pz than Controls (t (23) = 3.23, p = .004 (2-tailed), *d* = 1.3). There were trends for less negative Go N2 amplitudes in TS than ADHD (t (20) = 2.02, p = .06 (2-tailed), *d* = .82) and in TS+ADHD than Controls (t (25) = 2.04, p = .05 (2-tailed), *d* = .80). There were no other significant pairwise group differences (all p > .10). The smaller Go N2 amplitude in TS compared with Controls remained significant after correcting for multiple comparisons while the other trend-level effects did not remain. These results were unchanged when IQ was included as a covariate.

There was also a significant interaction between the covariate age and electrode in the 3 x 4 ANCOVA examining Nogo N2 amplitude (F (1.6, 71.1) = 5.13, p = .013, η_p^2 = .104). Therefore, a repeated-measures ANOVA with one within-subjects factor of electrode site (3 levels: Fz, Cz, Pz) was conducted to check whether the N2 showed the expected cognitive control related enhancement at frontal sites relative to centro-posterior sites. Group differences in N2 amplitude were examined using univariate ANCOVAs with one between-subjects factor (group: 4 levels) at each electrode site separately. The repeated-measures ANOVA confirmed that Nogo N2 amplitude differed significantly between electrode sites in the whole participant sample (F (1.5, 72.4) = 23.0, p < .001, η_p^2 = .324). Paired-sample t-tests revealed that N2 amplitude was significantly larger at Fz (mean: -6.66μv) than Pz (mean: -1.88 μv) (t (48) = -5.37, p < .001, 1-tailed) and Cz (mean: -4.76μv) (t (48) = -3.12, p = .002, 1-tailed). Additionally, Nogo N2 was significantly larger at Cz than Pz (t (48) = -4.87, p < .001, 2-tailed).

Univariate ANCOVAs revealed that the groups did not differ significantly in Nogo N2 amplitude at site Fz (F (3, 44) = .030, p = .99, η_p^2 = .002), but there was a trend for group differences at site Cz (F (3, 44) = 2.70, p = .06, η_p^2 = .155) and a significant group difference at Pz (F (3, 44) = 6.18, p = .001, η_p^2 = .297). Further investigation of the effect at Pz showed that the N2 amplitudes were significantly less negative in TS and Controls (t (23) = 3.43, p = .002 (2-tailed), *d* = 1.1), and there was a trend for the same group difference between TS and ADHD (t (20) = 1.93, p = .07 (2-tailed), *d* = .59). The TS+ADHD group also displayed significantly less negative N2 amplitudes than Controls (t (25) = 2.16, p = .04 (2-tailed), *d* = .85). There were no other significant group differences at Pz (all p > .10). The pairwise group differences between TS and Controls would remain significant when controlling for multiple comparisons while the other effects would not remain. Covarying IQ did not alter these results.

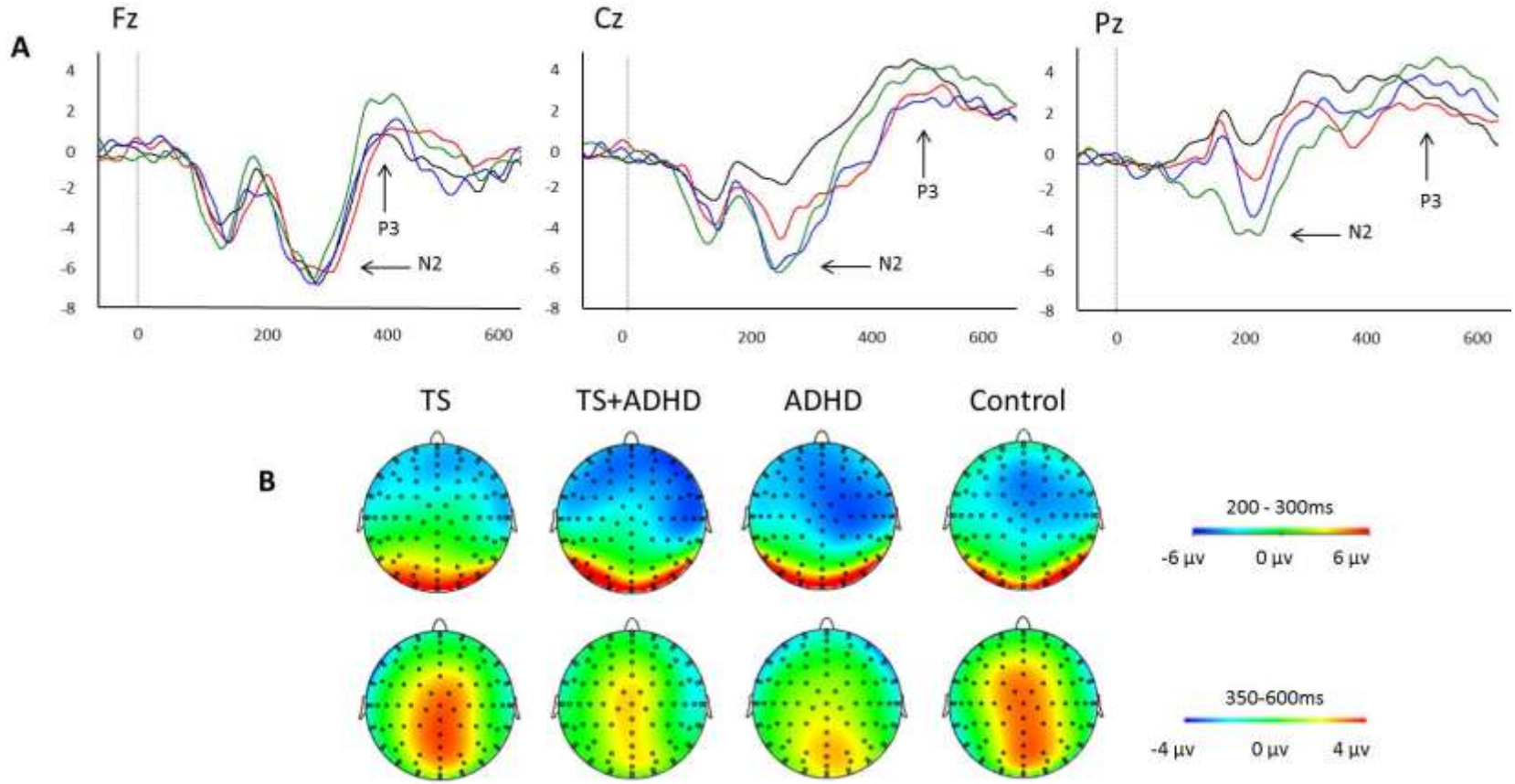
Follow-up planned comparisons of the trend-level group difference in Nogo N2 amplitude at site Cz revealed that the TS group had significantly less negative amplitudes than Controls (U = 34.0, p = .02 (2-tailed), *d* = 1.0). There was a trend for less negative amplitudes in TS+ADHD than Controls (U =

Figure 6-2. The N2 and P3 ERP components in the Go condition.



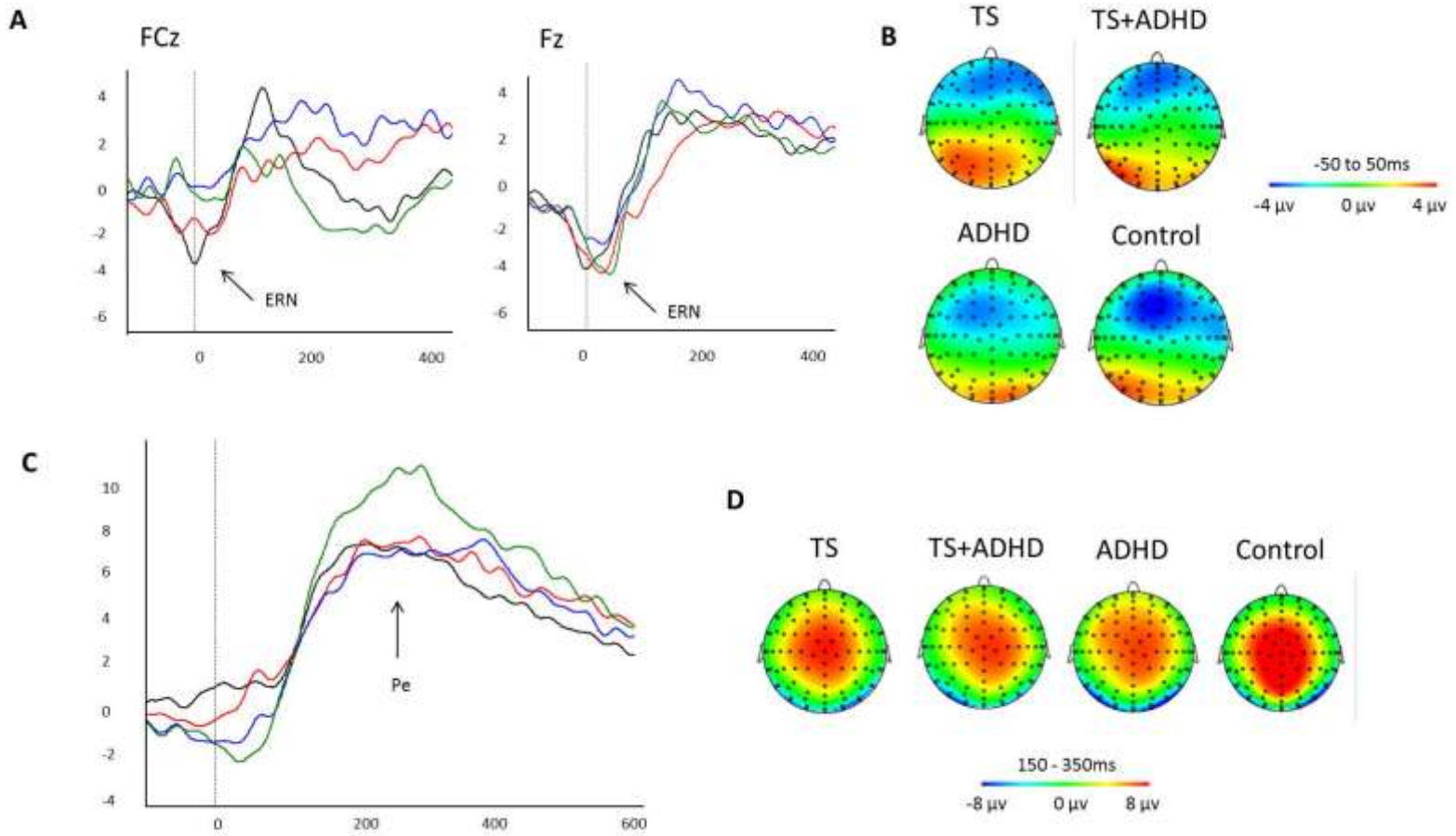
Panel A: stimulus-locked grand average waveforms plotted by participant group (TS = black line, TS+ADHD = red line, ADHD = blue line, Controls = green line).
Panel B: topographies for the Go N2 (top line) and P3 (bottom line) for each participant group.

Figure 6-3. The N2 and P3 ERP components in the Nogo condition.



Panel A: stimulus-locked grand average waveforms plotted by participant group (TS = black line, TS+ADHD = red line, ADHD = blue line, Controls = green line).
Panel B: topographies for the Nogo N2 (top line) and P3 (bottom line) for each participant group.

Figure 6-4. The ERN and Pe ERP components following erroneous Nogo responses.



A: Response-locked ERN grand averages by participant group (TS = black line, TS+ADHD = red line, ADHD = blue line, Controls = green line). **B:** Topography of the ERN by participant group. **C:** Response-locked Pe grand averages (colour-group denotation as in A.). **D:** Topography of the Pe by participant group.

54.0, p = .08 (2-tailed), *d* = .64). No other significant pairwise group differences were found at Cz (all p > .10). The differences between TS and Controls and TS+ADHD and controls would become non-significant after controlling for multiple comparisons. These effects were unchanged when IQ was included as a covariate.

6.2.3.2 Go and Nogo P3

The group mean amplitudes for the Go and Nogo P3 are presented in table 6-4. Grand average waveforms and topographical plots for the Go and Nogo P3 are presented in figures 6-2 and 6-3 respectively.

Table 6-4

Group mean amplitudes for the Go and Nogo P3 at sites Cz, Pz and Fz. Standard deviations are presented in parentheses.

	TS	**TS+ADHD**	**ADHD**	**Control**
Go P3 amplitude (μv)				
Fz	1.47 (2.5)	.613 (2.6)	1.30 (2.0)	1.59 (3.0)
Cz	5.53 (4.8)	5.15 (3.5)	3.93 (2.6)	5.40 (1.7)
Pz	6.18 (4.7)	4.66 (3.0)	4.00 (3.4)	6.38 (3.6)
Nogo P3 amplitude (μv)				
Fz	1.90 (3.9)	2.31 (3.1)	2.05 (2.8)	3.67 (4.1)
Cz	5.72 (3.5)	3.89 (3.3)	4.21 (2.8)	5.73 (3.2)
Pz	6.30 (3.2)	4.33 (2.3)	4.95 (3.5)	5.59 (3.5)

The 3x4 ANCOVA for Go P3 amplitude revealed a significant main effect of electrode site (F (1.5, 66.8) = 7.04, p = .004, η_p^2 = .138), but no main effect of group (F (3,44) = .811, p = .50, η_p^2 = .052) and no interaction between site and group (F (1.5, 66.8) = .260, p = .92, η_p^2 = .050). Further investigation of the significant effect of site revealed that Go P3 amplitude was significantly smaller at Fz than Cz (t (48) = -6.96, p < .001, 2-tailed) and Pz (t (48) = 6.87, p < .001, 2-tailed). Amplitudes did not differ significantly between Pz and Cz (t (48) = -1.65, p = .11, 2-tailed). This posterior maximum of the P3 is typical for the Go condition of the Go/Nogo task. These results did not change when IQ was covaried.

In the Nogo condition, there was a significant main effect of electrode on P3 amplitude (F (4.4, 64.5) = 4.01, p = .03, η_p^2 = .085), but no effect of group (F (3, 44) = .986, p = .41, η_p^2 = .063) and no interaction between group and site (F (4.4, 64.5) = .825, p = .52, η_p^2 = .053). Planned comparison of amplitudes at each pair of electrodes sites from all participants with related-samples sign tests showed that Nogo P3 amplitude was significantly smaller at Fz than Cz (z = -3.7, p < .001) and Pz (z = 2.6, p < .001) but did not differ between Cz and Pz (z = 0, p = .10). As discussed in chapter 2 (section 2.3.1) the P3 is typically larger at frontal than posterior sites in Nogo conditions (the NGA effect), which suggests that the P3 in the Nogo condition in this study did not reflect cognitive control, but more likely indexed attentional processes or stimulus-processing associated with the posterior P3. The main effect of electrode site did not remain when IQ was included as a covariate (F (1.5, 63.4) = .169, p = .85, η_p^2 = .004).

6.2.3.3 ERN and Pe

Table 6-5 presents the group mean amplitudes for the ERN and Pe. The grand average waveforms and topographical plots for the ERN and Pe are presented in figure 6-4. Amplitude of the ERN differed at trend-level between groups at FCz (F (3, 44) = 2.47, p = .07, η_p^2 = .144) but not at Fz (F (3, 44) = .393, p = .78, η_p^2 = .026). Further investigation of the group difference at FCz showed that the TS+ADHD group produced significantly larger (more negative) ERN amplitudes than the ADHD group (U = 100.0, p = .03 (1-tailed), *d* = -.37) and there was a trend for larger ERN amplitudes in the TS group compared with the ADHD group (U = 80.0, p = .08 (1-tailed), *d* = -.24). The remaining group pairings did not differ significantly (all p > .10). None of these group differences would remain significant after correction for multiple comparisons. These results were unchanged when IQ was included as a covariate.

Pe amplitude did not differ significantly between the groups (F (3, 44) = 1.38, p = .26, η_p^2 = .086). This result was unaltered when IQ was included as a covariate.

Table 6-5

Group mean amplitudes for the ERN and Pe. Standard deviations are presented in parentheses.

	TS	TS+ADHD	ADHD	Control
ERN amplitude (μv)				
FCz	-4.28 (4.1)[a]	-4.59 (3.2)[b]	-3.42 (3.2)[ab]	-4.42 (3.2)
Fz	-3.54 (4.4)	-3.20 (3.2)	-.912 (2.4)	-1.62 (2.9)
Pe amplitude (μv)				
Pz	8.46 (5.2)	8.18 (4.1)	7.98 (5.7)	11.36 (3.8)

Superscript letters ([abcd]) mark significant or trend-level pairwise group differences. Groups marked with the same letter differed from one another.

6.2.3.4 Group differences in signal-noise-ratio

One-way ANOVA tests were conducted to assess whether the number of trials included in each participant's stimulus-locked and response-locked ERP average differed between groups. This was done to examine whether ERP waveforms may have differed in SNR between groups, which might have influenced group differences in peak N2, P3, ERN and P3 amplitudes. The groups did not differ significantly in the number of trials included in stimulus-locked waveforms for the correct Go ($F (3, 45) = .26$, $p = .85$) or correct Nogo ($F (3, 45) = 1.6$, $p = .20$) conditions. However, the number of trials included in response-locked averages for the error Nogo condition differed at trend-level between groups ($F (3, 45) = 2.4$, $p = .08$). Further investigation of this difference showed that significantly fewer trials were included in the TS group averages (mean 26) than the ADHD group averages (mean 33) ($t (20) = -2.3$, $p = .03$ (2-tailed), $d = -.93$). Similarly, significantly more trials were included in the ADHD group averages than the Control group averages (mean 27) ($t (19) = -2.3$, $p = .03$ (2-tailed), $d = -1.0$).

In light of the difference in trial numbers between TS and ADHD groups, it is possible that lower SNR of the response-locked averages contributed to the greater amplitude of the ERN at FCz in the TS than ADHD group. However, since the same amplitude difference was found between the TS+ADHD and ADHD groups, and there were no amplitude differences

between TS and ADHD in the other response-locked components (Pe and ERN at Fz) which also differed in SNR between these two groups, it is unlikely that differences in SNR can fully explain the ERN amplitude difference between TS and ADHD. Nevertheless, this should be considered when interpreting the response-locked ERP findings in these group comparisons.

6.2.4 Summary of group differences in cognitive control

Group differences in behavioural and ERP amplitude correlates of cognitive control in the Go/Nogo task are summarised in table 6-6 and in the following sections.

Table 6-6

Summary of group differences in cognitive control

Cognitive control measure	Group differences
Go accuracy	TS+ADHD < TS**/Controls**. ADHD < Controls*
Nogo accuracy	ADHD < TS**/TS+ADHD**/Controls*
D-prime	ADHD < TS**/Controls**/TS+ADHD*. TS+ADHD < TS**
Go RT	n/s
Go RT variability	ADHD > TS**/Controls**. TS+ADHD > TS**/Controls**
Post-error slowing	TS > TS+ADHD**/ADHD*/Controls*
Go and Nogo N2	Go: Pz TS < Controls**/ADHD*. TS+ADHD < Controls* Cz n/s Fz n/s Nogo: Pz TS < Controls**. TS+ADHD < ADHD* Cz TS < Controls**. TS+ADHD < Controls* Fz n/s
Go and Nogo P3	n/s
ERN	FCz TS > ADHD*. TS+ADHD > ADHD**. Fz n/s
Pe	n/s

* $p < .10$. ** $p < .05$

6.2.4.1 TS vs. Controls

Compared with the Control group, young people with TS produced comparable Nogo accuracy and D-prime scores, but greater post-error slowing. These findings indicate that in contrast to hypotheses, the TS group were no better at withholding inappropriate prepotent behaviours than Controls; however, as predicted the young people with TS exhibited enhanced ability to adjust performance following errors compared with unaffected individuals. Other behavioural measures of cognitive control which were not hypothesised to be enhanced in TS, namely Go accuracy, Go RT, and Go RT variability, did not differ between the TS and Control groups.

Unexpectedly, the N2 ERP at posterior and central scalp was smaller, that is, less negative, in TS compared with Controls in the Go and Nogo conditions. However, it is likely that this reduction was unrelated to cognitive control because of the posterior topographical location of amplitude differences. At frontal scalp where the N2 is thought to index neural cognitive control mechanisms, the TS and Control groups showed comparable enhancement of amplitude on Nogo trials. This indicates that neural processing underlying withholding responses on Nogo trials was unimpaired, but also not enhanced, in TS compared with unaffected individuals. The difference in N2 amplitude might reflect a difference in the positivity of the waveforms in TS and Controls in the pre-N2 time-period. Figure 6-3 demonstrates that from approximately 100ms onwards, up to and including the N2 time-range, the waveforms showed a positive shift in the TS group and negative shift in the Control group. This was the case for the Cz and Pz sites, but not the Fz site. This baseline difference may explain the less negative N2 amplitudes in the TS than Control group at Cz and Pz. Analysis of the N2 with reference to the preceding positive peak, i.e. taking a peak-to-peak measure of the N2, would have clarified this possibility, but since this amplitude difference likely did not reflect a cognitive control effect and was therefore not of relevance to the main aims of this study, it was not investigated further. The ERN correlate for error-monitoring on erroneous Nogo trials did not differ between TS and Controls, but was larger at fronto-central scalp in TS than ADHD. The P3 and Pe ERPs did not differ between groups.

6.2.4.2 ADHD vs. Controls and TS

The ADHD group produced significantly lower Nogo accuracy and D-prime scores and larger Go RT variability than TS and Controls. These findings indicate that, as predicted, young people with ADHD were impaired at withholding inappropriate responses and exhibited increase IIV compared with unaffected young people and young people with TS. Additionally, the ADHD group produced poorer Go accuracy than Controls and less post-error slowing than TS, suggesting a difficulty with responding timely and accurately to the Go stimuli compared with unaffected individuals, and poorer adjustment for errors compared with TS. In contrast to hypotheses, the ADHD group did not show reduced frontal amplitudes of the N2 or P3 compared with Controls or TS. ADHD produced larger N2 amplitudes at posterior scalp for the Go condition compared with TS, which might reflect increased attention to or processing of the Go stimuli. In line with predictions the ERN at fronto-central scalp was smaller in ADHD than TS, indicating less efficient error-monitoring in ADHD than TS.

6.2.4.3 TS+ADHD vs. TS, ADHD and Controls

The pattern of findings in the TS+ADHD group showed some similarities to the TS group and some to the ADHD group. Like TS, young people with TS+ADHD produced better Nogo accuracy and higher D-prime scores than the ADHD group, smaller N2 amplitudes at centro-posterior scalp for Go and Nogo conditions than Controls, and greater ERN amplitudes at fronto-central scalp than ADHD. Similar to the ADHD group, the TS+ADHD group showed poorer Go accuracy and greater Go RT variability than TS and Controls, and less post-error slowing and lower D-prime scores than TS. These findings present a mixed pattern of apparent enhancements in TS+ADHD relative to ADHD, specifically in the ability to withhold inappropriate responses and in neural activity associated with error-monitoring, and impairments relative to TS in IIV and responding to Go stimuli while withholding responses to Nogo stimuli.

6.2.5 Symptom severity and behavioural and electrophysiological correlates of cognitive control

The results of multiple linear regression analyses investigating the extent to which tic, ADHD and ODD symptomatology predicted Nogo accuracy, D-prime, Go RT variability, PES, Nogo N2 amplitude at Fz, ERN amplitude at FCz (since this site, rather than Fz, was where group differences were found), and Pe amplitude are presented in the following sections. Nogo P3 amplitude was not investigated in regression analyses because unlike the N2, this component did not show the typical frontal enhancement for Nogo trials, and therefore it is unclear the extent to which the P3 in this study reflected cognitive control as opposed to more attentional processes associated with a posterior topography of the P3. OCD symptoms were only present in a small sub-set of the TS and TS+ADHD groups combined (11 in the behavioural sample, 9 in the ERP sample). Due to the consequent non-linear distribution of scores on the CY-BOCS OCD measure, with the majority of participants with TS and TS+ADHD scoring zero, it was not possible to examine relationships between OCD symptomatology and cognitive control.

Regression models were constructed hierarchically as follows. Model A: age and total tic severity were entered in block 1. Model B: age and ADHD severity were entered in block 1; ODD severity was entered in block 2. Model A was conducted in participants with TS and TS+ADHD only, while Model B was performed in the whole sample.

6.2.5.1 Nogo accuracy

Table 6-7 presents the regression model statistics for Nogo accuracy. In Model A, the combined variables of age and total tic severity entered into block 1 of the model significantly predicted Nogo accuracy ($F(2, 31) = 8.0$, $p = .002$). Examination of the regression coefficients for each IV in block 1 showed that age, but not tic severity, was a significant predictor of Nogo accuracy (age: $p = .001$; tics: $p = .19$). The Durbin-Watson statistic indicated the assumption of independent errors was met in Model A ($DW = 2.7$), and the VIF value (1.0) indicated the IVs tic severity and age were not correlated.

In Model B, block 1 variables (age, ADHD severity) predicted Nogo accuracy at trend-level (F (2, 55) = 3.0, p = .06). Age significantly predicted Nogo accuracy (p = .02) but ADHD symptoms did not (p = .37). The inclusion of ODD severity as an IV in block 2 reduced the trend-level predictive ability of the model (F (3, 54) = 2.1, p = .11). Age remained a significant predictor of Nogo accuracy (p = .03). ADHD and ODD symptoms did not predict Nogo accuracy (p = .29 and p = .49 respectively). The assumption of independent errors was met in Model B (DW = 2.1). The IVs age and ADHD severity in block 1 were not correlated (VIF = 1.02), nor were the IVS age (VIF = 1.05), ADHD (VIF = 3.40) and ODD (VIF = 3.51) severity in block 2. In Models A and B, older age was associated with higher Nogo accuracy.

Table 6-7

Summary of regression model statistics in the prediction of Nogo accuracy

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.34	.30	8.0***				
Constant				19.0	11.5		1.7
Age				.26	.07	.55	3.8****
Tics				-.25	.19	-.20	-1.3
Model B							
Block 1	.10	.07	3.0*				
Constant				32.3	12.3		2.6**
Age				.15	.06	.29	2.2**
ADHD				-.12	.14	-.12	-.90
Block 2	.11	.06	2.1				
Constant				32.7	12.4		2.6**
Age				.15	.07	.29	2.2**
ADHD				-.27	.26	-.26	-1.1
ODD				.17	.24	.17	.69

* = p < .10; ** = p < .05; *** = p <.01; **** = p < .001

6.2.5.2 D-prime

The regression model statistics for D-prime are presented in table 6-8. The combined variables age and total tics significantly predicted D-prime scores in block 1 of Model A (F (2, 31) = 12.8, p < .001). Age and tic severity were significant individual predictors (p < .001 and p = .02 respectively). Older age and less severe tics were associated with higher scores. The assumption of independent errors was met (DW = 2.6) and the variables age and tic severity were not correlated (VIF = 1.00).

Table 6-8

Summary of regression model statistics in the prediction of D-prime scores

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.45	.42	12.8****				
Constant				-2.6	.92		-2.9***
Age				.02	.005	.60	4.5****
Tics				-.04	.02	-.32	-2.4**
Model B							
Block 1	.13	.10	4.2**				
Constant				-1.1	1.1		-.95
Age				.02	.006	.33	2.6**
ADHD				-.02	.01	-.21	.27
Block 2	.24	.20	5.8***				
Constant				-.93	1.0		-.89
Age				.01	.005	.27	2.3**
ADHD				-.07	.02	-.73	-3.3***
ODD				.06	.02	.63	2.8***

* = p < .10; ** = p < .05; *** = p <.01; **** = p < .001

In Model B the combined block 1 variables of age and ADHD severity significantly predicted D-prime scores (F (2, 55) = 4.2, p = .02). Significant individual predictors were age (p = .01), but not ADHD severity (p = .10), with older age associated with higher scores. When ODD symptom severity was added in block 2, the predictive power of the combined variables in the model

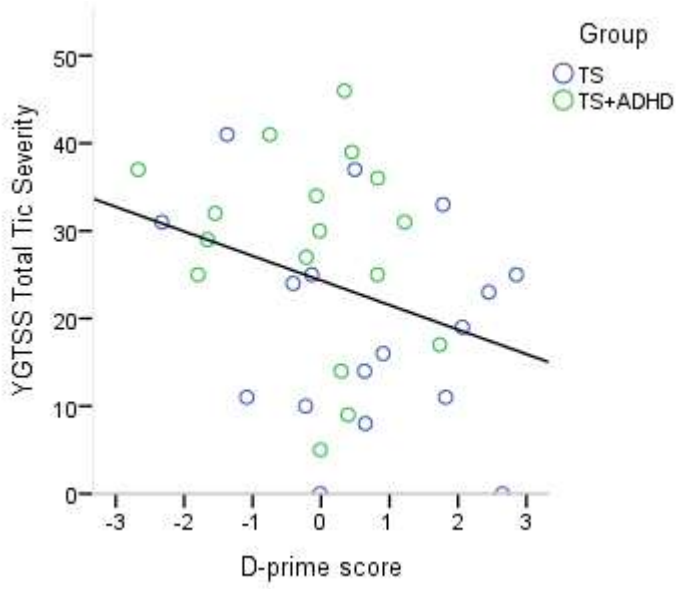
improved markedly (F (3, 54) = 5.8, p = .002). Age remained a significant predictor (p = .03). Additionally, ADHD severity became a highly significant predictor (p = .002) after controlling for the relationship between ODD severity and D-prime scores. ODD was also a significant predictor (p = .006). Interestingly, the relationships between ADHD and ODD severity and D-prime scores were opposite. Higher D-prime was associated with less severe ADHD but more severe ODD. The assumption of independent errors was met in Model B (DW = 2.2), and the IVs in block 1 were not correlated (age and ADHD severity VIF = 1.02), nor were the IVs in block 2 (age VIF = 1.05; ADHD VIF = 3.40; ODD VIF = 3.51).

Scatterplots depicting the relationships between tics, ADHD, ODD and D-prime scores are presented in figure 6-5. Plot A demonstrates that the negative association between tic severity and D-prime scores was present in both TS and TS+ADHD groups. Plots B and C highlight the similarity in ADHD/ODD relationships with D-prime in the ADHD and TS+ADHD groups.

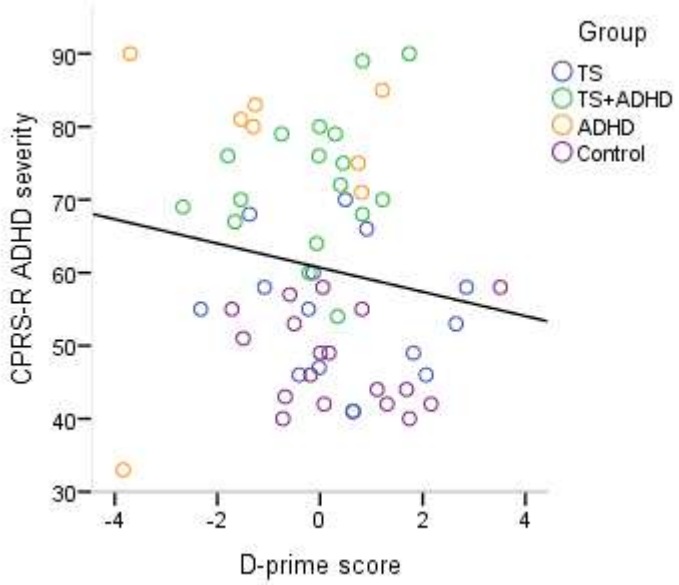
Figure 6-5.

Scatterplots displaying the relationships between D-prime scores and motor tic severity (**A**), ADHD symptom severity (**B**), and ODD severity (**C**)

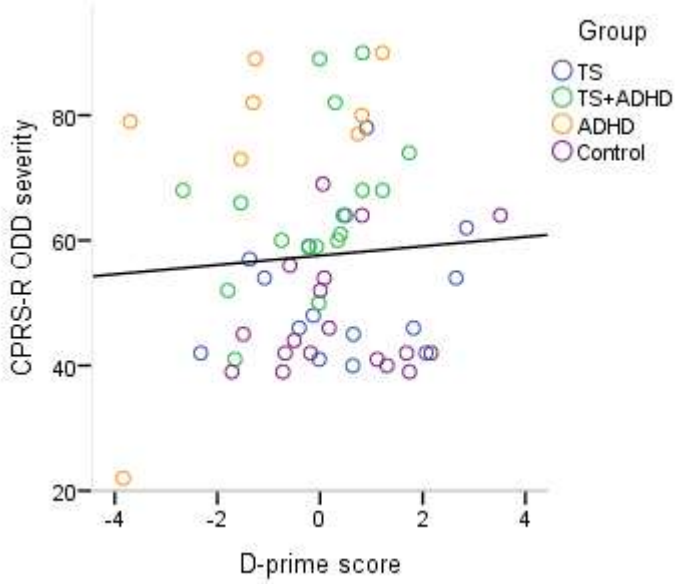
A



B



C



6.2.5.3 Go RT variability

The regression model statistics are presented in table 6-9. The combined variables in block 1 of Model A significantly predicted Go RT variability (F (2, 31) = 6.3, p = .002). Examination of the beta coefficients revealed that total tic severity was a significant predictor of variability (p = .002), with greater tic severity associated with greater variability. Age did not

significantly predict variability (p = .26). The assumption of independent errors was met (DW = 1.9) and the variables age and tic severity were not correlated (VIF = 1.00).

Table 6-9

Summary of regression model statistics in the prediction of Go RT variability

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.29	.24	6.3***				
Constant				.23	.05		4.3****
Age				.00	.00	-.17	-1.1
Tics				.003	.001	.51	3.4***
Model B							
Block 1	.17	.14	5.6***				
Constant				.21	.05		4.5****
Age				.00	.00	-.23	-1.9*
ADHD				.002	.001	.38	3.0***
Block 2	.32	.28	8.4****				
Constant				.21	.04		4.8****
Age				.00	.00	-.17	-1.5
ADHD				.004	.001	.97	4.7****
ODD				-.003	.001	-.72	-3.4****

* = p < .10; ** = p < .05; *** = p <.01; **** = p < .001

In Model B, block 1 variables (age, ADHD severity) significantly predicted Go RT variability (F (2, 55) = 5.6, p = .006). Age was a trend-level predictor of variability (p = .07) while ADHD severity was a highly significant predictor (p = .004). Greater Go RT variability was associated with younger age and more severe ADHD symptoms. The addition of ODD severity in block 2 of the model improved the prediction of the combined variables (age, ADHD, ODD) in Go RT variability (F (3, 54) = 8.5, p < .001). Age did not remain as a predictor (p = .14) but ADHD and ODD severity were highly significant predictors (both p < .001). As with the opposing relationships between these

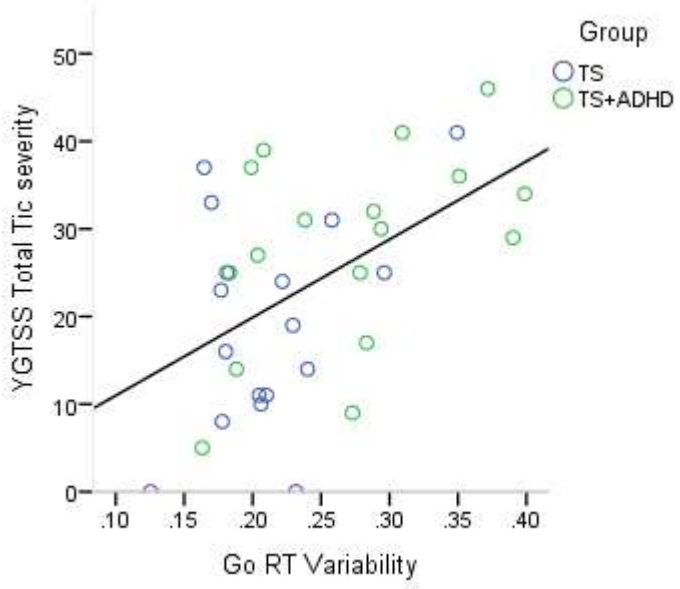
variables and D-prime scores, greater Go RT variability was associated with more severe ADHD symptoms but less severe ODD symptoms. Moreover, it is clear that ODD symptomatology enhanced the relationship between ADHD and variability. The assumption of independent errors was met for Model B (DW = 1.6). The IVs age and ADHD severity were not correlated in block 1 (VIF = 1.02), nor were the variables age (VIF = 1.05), ADHD severity (3.40) and ODD severity (3.51) in block 2.

Figure 6-6 presents scatterplots displaying the relationships between Go RT variability and tic, ADHD and ODD symptom severity. The positive relationships between tic and ADHD severity and Go RT variability are clearly observed in all groups (plots A and B), with the TS+ADHD group showing comparable relationships for tic severity as the TS group and for ADHD severity as the ADHD group. However, inspection of plot C indicates that the negative relationship between ODD severity and variability is most clearly present in the two ADHD groups, and less strong in the TS and Control groups.

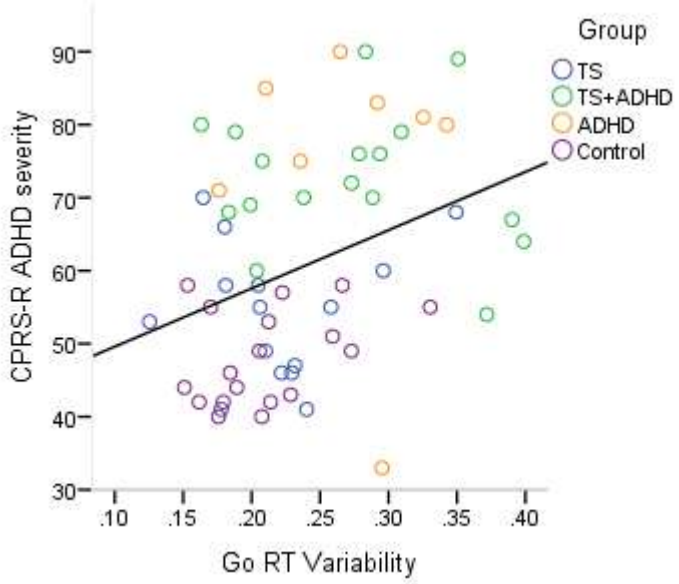
Figure 6-6

Scatterplots displaying the relationships between Go RT variability and tic severity (**A**), ADHD severity (**B**) and ODD severity (**C**)

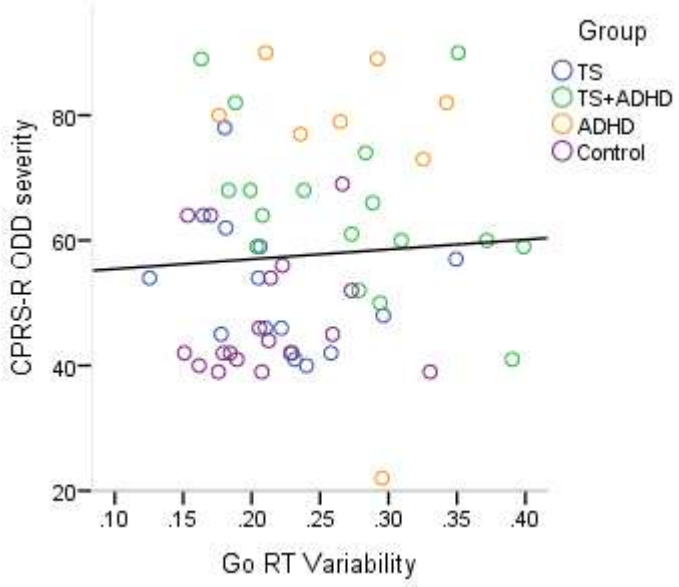
A



B



C



6.2.5.4 Post-error slowing

Table 6-10 presents the regression model statistics for PES. In Model A, the combined IVs in block 1 (age, tics) did not significantly predict PES ($F(2, 31) = .57$, $p = .37$). Furthermore, inspection of the regression coefficients for each IV revealed that no individual variable was a predictor of PES in

Model A (all p > .10). The assumption of independent errors was met (DW = 2.0). The IVs age and tic severity were not correlated (VIF = 1.00).

Block 1 variables in Model B did not predict PES (age, ADHD: F (2, 55) = .57, p = .57), nor did the combined variables age, ADHD and ODD in block 2 (F (3, 54) = 1.5, p = .23). Age and ADHD severity were not significant individual predictors of PES in block 1 (p > .10), but in block 2 ADHD severity significantly predicted PES (p = .05) and ODD severity was a trend-level predictor (p = .08). However, since the overall model was non-significant in block 2, the predictive variables of ADHD and ODD severity are not considered further. The assumption of independent errors was met (DW = 1.7). The block 1 variables were not correlated (VIF = 1.02), nor were the block 2 variables (age VIF = 1.05; ADHD VIF = 3.40; ODD = 3.51).

Table 6-10

Summary of regression model statistics for the prediction of PES

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.04	-.03	.57				
Constant				-37.0	61.3		-.60
Age				.36	.36	.17	.99
Tics				-.41	.99	-.07	-.41
Model B							
Block 1	.02	-.02	.57				
Constant				7.4	42.6		.17
Age				.15	.22	.09	.67
ADHD				-.44	.48	-.12	-.92
Block 2	.08	.02	1.5				
Constant				10.5	41.8		.25
Age				.09	.22	.05	.40
ADHD				-1.7	.86	-.49	-2.0**
ODD				1.5	.82	.44	1.8*

* = p < .10; ** = p < .05

6.2.5.5 Nogo N2 amplitude at Fz

The regression model statistics for Nogo amplitude at Fz are presented in table 6-11. In Model A the combined variables of age and tic severity in block 1 did not predict N2 amplitude (F (2, 25) = .68, p = .52). In Model B, combined IVs in block 1 (age, ADHD severity) and block 2 (age, ADHD and ODD severity) did not significantly predict N2 amplitude in block 1 (F (2, 41) = .16, p = .85) or block 2 (F (3, 40) = 1.7, p = .18). The assumption of independent errors was met in Model A (DW = 1.5) and Model B (DW = 1.6). Tic severity and age were not correlated (VIF = 1.00), nor were the IVs in Model B (age VIF = 1.02; ADHD = 3.45; ODD VIF = 3.47).

Table 6-11

Summary of regression model statistics for the prediction of Nogo N2 amplitude at Fz

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.05	-.02	.68				
Constant				-2.6	3.6		-.70
Age				-.02	.02	-.21	-1.0
Tics				-.02	.06	-.08	-.41
Model B							
Block 1	.008	-.04	.12				
Constant				-5.6	3.8		-1.5
Age				-.01	.02	-.08	-.53
ADHD				.01	.04	.04	.27
Block 2	.12	.05	1.7				
Constant				-5.5	3.6		-1.5
Age				-.007	.02	-.06	-.37
ADHD				.14	.07	.55	2.0*
ODD				-.15	.07	-.61	-2.2**

* = p < .10; ** = p < .05; *** = p <.01; **** = p < .001

6.2.5.6 ERN amplitude at FCz

Table 6-12 presents the regression model statistics for ERN amplitude. In Model A, the combined block 1 variables (age, tic severity) significantly predicted ERN amplitude at FCz (F (2, 25) = 4.3, p = .02). Age, but not tic severity (p > .10), was a significant individual predictor (p = .007). Older age was associated with smaller ERN amplitude. This is inconsistent with the literature concerning effects of age on the ERN, which has indicated that the ERN increases with age (Hogan et al., 2005; Ladouceur et al., 2007). These findings indicate that the increased amplitude of the ERN in TS and TS+ADHD compared with ADHD was not related to current severity of tic symptoms. The assumption of independent errors was met (DW = 1.8) and the IVs age and tic severity were not correlated (VIF = 1.01).

Table 6-12

Summary of regression model statistics for the prediction of ERN amplitude at FCz

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.26	.20	4.3**				
Constant				4.8	3.2		1.5
Age				-.06	.02	-.51	-2.9***
Tics				.03	.05	.10	.56
Model B							
Block 1	.09	.04	1.9				
Constant				2.8	3.2		.89
Age				-.03	.02	-.29	-1.9*
ADHD				-.003	.03	-.01	-.08
Block 2	.11	.05	1.7				
Constant				2.9	3.2		.91
Age				-.03	.02	-.28	-1.9*
ADHD				.05	.06	.24	.86
ODD				-.06	.06	-.30	-1.1

* = p < .10; ** = p < .05; *** = p <.01; **** = p < .001

In Model B, neither block 1 variables (age, ADHD) nor block 2 variables (age, ADHD, ODD) significantly predicted ERN amplitude at FCz. Block 1: $F(2, 41) = 1.9$, $p = .16$; block 2: $F(3, 40) = 1.7$, $p = .19$. It is clear that controlling for relationships between ADHD and ODD symptomatology and the ERN suppressed the association between age and ERN amplitude. In block 1 age was only a trend-level predictor of ERN amplitude ($p = .06$), and the strength of this relationship decreased further in block 2 with the addition of ODD symptomatology ($p = .07$). As with Model A, older age was associated with smaller ERN amplitudes. The absence of a predictive association between ADHD symptomatology and magnitude of the ERN indicates that the decreased amplitude in ADHD compared with TS and TS+ADHD was not driven by current ADHD severity. The assumption of independent errors was met in Model B (DW = 1.8) and the variables age (VIF = 1.02), ADHD severity (VIF = 3.45) and ODD severity (VIF = 3.47) were not correlated.

6.2.5.7 Pe amplitude

Table 6-13 summarises the regression model statistics for Pe amplitude. In Model A, the combined variables in block 1 (age, tic severity) did not significantly predict Pe amplitude ($F(2, 25) = .50$, $p = .61$). Moreover, examination of the regression coefficients for individual IVs in Model A showed that neither age nor tic symptomatology was a significant individual predictor of Pe amplitude (all $p > .10$). Similarly, the combined variables in block 1 (age, ADHD severity, $F(2, 41) = .46$, $p = .63$) and block 2 (age, ADHD and ODD severity, $F(3, 40) = 1.5$, $p = .24$) of Model B did not predict Pe amplitude. The assumption of independent errors was met in Model A (DW = 2.1) and Model B (DW = 2.6). The IVs in Model A were not correlated (VIF = 1.01), nor were the IVs in Model B (age VIF = 1.02; ADHD VIF = 3.45; ODD = 3.47).

6.2.6 Summary of relationships between symptomatology and correlates of cognitive control

Within the TS and TS+ADHD groups, tic severity significantly predicted D-prime scores and Go RT variability, but not the other behavioural

and electrophysiological correlates of cognitive control (Nogo accuracy, PES, Nogo N2, ERN and Pe).

Table 6-13

Summary of regression model statistics in the prediction of Pe amplitude

	R^2	Adj. R^2	F	*b*	SE *b*	β	*t*
Model A							
Block 1	.04	-.04	.50				
Constant				11.4	4.4		2.6**
Age				-.01	.03	-.08	-.38
Tics				-.06	.07	-.18	-.89
Model B							
Block 1	.02	-.03	.46				
Constant				11.6	4.6		2.5**
Age				.002	.03	.01	.08
ADHD				-.05	.05	-.15	-.96
Block 2	.10	.03	1.4				
Constant				11.5	4.5		2.6**
Age				-.002	.03	-.01	-.07
ADHD				-.18	.08	-.56	-2.1**
ODD				.15	.08	.51	1.8*

* = p < .10; ** = p < .05; *** = p <.01; **** = p < .001

More severe tics were associated with lower D-prime scores and greater Go RT variability. Thus, in contrast to hypotheses, young people with less severe tics were better able to withhold inappropriate prepotent Nogo responses while producing timely and accurate Go responses than individuals with more severe tics. Young people with more severe tics produced more variable responses to Go stimuli. Scatterplots demonstrated that both TS and TS+ADHD groups exhibited these relationships between tic severity and performance. This suggests that tics influence cognitive control processes in a similar manner in young people with tics with or without ADHD.

In the whole participant sample, ADHD symptom severity was a significant predictor of Go RT variability and, when ODD symptoms were

controlled, D-prime scores. As predicted, more severe ADHD was associated with greater variability in Go responding and poorer ability to withhold inappropriate Nogo responses while responding accurately and promptly to Go stimuli. Scatterplots demonstrated that both ADHD and TS+ADHD groups exhibited these associations between ADHD symptomatology and performance. Importantly, ODD symptoms moderated the relationship between ADHD severity and D-prime scores such that these associations were suppressed if ODD associations were not controlled. ODD severity was associated with D-prime and Go RT variability, with greater ODD severity predicting better performance.

6.3 CHAPTER SUMMARY

The aim of the research presented in this chapter was to examine cognitive control in young people with TS+ADHD compared with young people with TS, ADHD and unaffected young people in order to assess how ADHD symptoms affect cognition related to tic control in TS and to investigate the basis of comorbid TS+ADHD. The approach taken was to select aspects of cognitive control that could conceivably be involved in tic control and that have been robustly associated with ADHD and examine how those processes manifested in TS+ADHD compared with the other groups. Moreover, relationships between tic and ADHD symptomatology and cognitive control processes were examined to understand how these disorder symptoms contribute to cognitive control in TS, TS+ADHD and ADHD, and how these relationships were modulated by symptoms of other commonly comorbid conditions (ODD).

Several group differences in behavioural and electrophysiological correlates of cognitive control were revealed. Additionally, severity of tics, ADHD and ODD symptoms were found to predict behavioural correlates of cognitive control that differed significantly between groups. These findings are summarised in table 6-14 and are discussed in full in chapter 7.

Table 6-14

Summary of group differences and relationships between symptomatology and cognitive control

Measure	Group differences	Predictors of cognitive control
Go accuracy	TS+ADHD < TS**/Controls** ADHD < Controls*	n/a
Nogo accuracy	ADHD < TS**/TS+ADHD**/Controls*	Age (+)**
D-prime	ADHD < TS**/Controls**/TS+ADHD* TS+ADHD < TS**	Age (+)**, tics (-)**, ADHD (- when controlling ODD)**, ODD (+)**
Go RT	n/s	n/a
Go RT variability	ADHD > TS**/Controls** TS+ADHD > TS**/Controls**	Age (-)*, tics (+)**, ADHD (+)**, ODD (-)**
Post-error slowing	TS > TS+ADHD**/ADHD*/Controls*	n/s
Go and Nogo N2	GoN2 at Pz TS < Controls**/ADHD* TS+ADHD < Controls* Nogo N2 at Pz TS < Controls** TS+ADHD < ADHD* Nogo N2 at Cz TS < Controls** TS+ADHD < Controls*	n/s
Go and Nogo P3	n/s	n/s
ERN	ERN at FCz TS > ADHD* TS+ADHD > ADHD**	Age (-)** (suppressed when controlling for ADHD and ODD)
Pe	n/s	n/s

* $p < .10$. ** $p < .05$. (+) = positive relationship between age or symptomatology and cognitive control measure. (-) = negative relationship between age or symptomatology and cognitive control measure

7. DISCUSSION

The main aims of this thesis were to explore the basis of comorbid TS+ADHD and to investigate whether comorbid ADHD symptoms have a negative impact upon aspects of cognitive function that are likely to be involved in controlling tic symptoms in young people with TS. Additionally, this thesis aimed to explore the involvement of dopamine-mediated reinforcement learning in tic formation, and the role of cognitive control in tic control. To address these aims, young people with TS, TS+ADHD, ADHD and unaffected young people performed three experimental tasks designed to assess goal-directed reinforcement learning, habit-based reinforcement learning, and cognitive control. Behavioural and electrophysiological correlates of reinforcement learning and cognitive control were compared between the groups, and the extent to which severity of tics, ADHD and ODD symptoms predicted performance and electrophysiological activity was examined. The findings from each task are summarised and discussed with reference to the main aims of this thesis in the sections below (sections 7.1-7.3). Following this, section 7.4 will discuss what can be understood about the basis of TS+ADHD and the effects of comorbid ADHD on young people with TS from the pattern of group differences and relationships with symptom severity across all three tasks. The clinical implications of these findings will also be considered. Finally, the limitations of this research will be considered in section 7.5.

7.1 GOAL-DIRECTED REINFORCEMENT LEARNING

Goal-directed reinforcement learning was examined to investigate whether additive, independent or symptomatic phenocopy models of comorbidity best apply to TS+ADHD. Young people with TS were expected to show comparable goal-directed learning as Controls. In contrast, the young people with ADHD were predicted to show impaired performance and electrophysiological correlates of goal-directed learning compared with TS and Controls. It was hypothesised that if TS+ADHD reflects additive comorbidity,

then young people with TS+ADHD should show similarly impaired performance and electrophysiological activity associated with goal-directed learning as the ADHD group. If TS+ADHD reflects a symptomatic phenocopy, young people with this comorbidity should be unimpaired and produce comparable performance and electrophysiological activity as the TS and Control groups. If TS+ADHD is an independent condition from TS and ADHD, then performance and electrophysiological activity in young people in this group should differ from those in the TS and ADHD groups. Analysis of the behavioural and electrophysiological correlates of goal-directed reinforcement learning revealed several findings that were relevant to these hypotheses. These findings are summarised in table 7-1 and discussed in the following sections. Findings in the ADHD and TS+ADHD groups will be considered first, followed by those in the TS group.

Table 7-1

Summary of findings in the goal-directed reinforcement learning task

Measure	**Group differences**	**Predictors of goal-directed learning**
Accuracy in the acquisition phase (average blocks 1-3)	ADHD < TS*/Controls** TS+ADHD < TS/Controls*	n/s
Accuracy in the reversal phase (average blocks 3-5)	ADHD < TS/Controls** TS+ADHD < TS/Controls** Block by group interaction**	n/s
Accuracy block 3	ADHD < Controls*	n/s
Accuracy block 4	ADHD < TS/Controls** TS+ADHD < TS/Controls**	n/s
Accuracy block 5	ADHD < TS/Controls**	n/s
Accuracy change (decrease) block 3 to reversal block 4	ADHD > TS/Controls** TS+ADHD > TS/Controls**	n/s
P3 amplitude increase block 1 to 2	TS > Controls**/TS+ADHD* ADHD > Controls*	n/s
FRN amplitude increase block 4 to 5	TS+ADHD > TS**/ADHD*	ADHD (-)**

* $p < .10$. ** $p < .05$. (-) = negative relationship between symptomatology and goal-directed learning measure

7.1.1 Goal-directed reinforcement learning in ADHD and TS+ADHD

Young people with ADHD were poorer than young people with TS and Controls at learning associations between stimuli and responses by positive and negative reinforcements, and in reversing and re-learning those associations following an unexpected change in reinforcement contingencies. These findings are consistent with previous research showing that children and adults with ADHD are impaired in the ability to consciously acquire and adapt new behaviours based on positive and negative reinforcements (Frank et al., 2007; Itami et al., 2002; Luman et al., 2009). As such, the current findings support the theory of dopamine-mediated impairments in reinforcement learning in ADHD (Maia & Frank, 2011; Johansen et al., 2009; Sagvolden et al., 2005).

The similarity of performance impairments in the TS+ADHD group to those in the ADHD group suggests that goal-directed reinforcement learning was also deficient in the young people with TS with comorbid ADHD symptoms. These are novel findings, since young people with ADHD and TS+ADHD have not previously been compared in this form of learning, and are important for several reasons. Firstly, the findings indicate that the comorbid ADHD symptoms in young people with TS+ADHD are genuine, rather than a mimic of ADHD as the symptomatic phenocopy model of comorbidity proposes (Banaschewski et al., 2007). Consequently, similarly impaired learning in TS+ADHD and ADHD implies that an additive model can best explain this form of comorbidity.

Secondly, these findings are informative of the neural basis of TS+ADHD. As discussed in chapter 1 (section 1.4.2), previous research examining the neuropathology of TS+ADHD is sparse. Moreover, the previous work has focused on identifying similarities and differences in the structure of grey and white matter between children with TS+ADHD and ADHD or TS (Castellanos et al., 1996; Kates et al., 2002; Fredericksen et al., 2002), which can be difficult to interpret in the absence of associations between structural changes and symptom behaviours. The impaired behavioural performance in TS+ADHD and ADHD in the current research suggests that an abnormality in goal-directed reinforcement learning pathways is present in TS+ADHD. In turn this implicates the ventral striatum, fronto-striatal CBTC circuit, and hypoactive dopamine transmission in the pathology of TS+ADHD. One point

to consider is that all young people with ADHD and TS+ADHD were off methylphenidate medication during testing. It would be interesting to examine how the impairments in goal-directed reinforcement learning in these groups would change with methylphenidate administration. In line with Frank et al.'s (2007) study showing that impairments in learning from positive reinforcements improved when adults with ADHD were on-methylphenidate medication compared with off-medication, it can be expected that accuracy performance during acquisition and reversal in young people with ADHD and TS+ADHD would improve if these individuals were on-methylphenidate. Such findings would more strongly implicate altered dopaminergic reinforcement learning mechanisms in comorbid TS+ADHD.

Finally, the current findings of impaired performance in the ADHD and TS+ADHD groups but intact performance in the TS group clearly indicate that the presence of comorbid ADHD symptoms impairs goal-directed reinforcement learning in young people with TS. This is important because the success of one of the most effective behavioural treatments for tics, habit-reversal therapy (HRT), depends on the ability to consciously prevent production of learned associations between premonitory sensory urges and motor and phonic tic responses, and implement newly-learned associations between urges and non-tic behaviours instead (Azrin & Nunn, 1973; Woods et al., 1996; Piacentini et al., 2010; see chapter 1 section 1.2 for a full discussion of habit-reversal based therapies). The finding that young people with TS+ADHD were impaired at learning the associations between stimuli and responses in the current study, and were particularly affected by the requirement to break and reverse those associations, indicates that these young people will have difficulty with HRT. This has implications for the treatment of tics in TS+ADHD and will be discussed further in section 7.4.2.

In addition to the similar deficit in performance, there were also differences in performance and neural correlates of goal-directed learning between the TS+ADHD and ADHD groups. The performance impairment during the acquisition phase was stronger in the ADHD group (significantly poorer accuracy versus Controls) than in the TS+ADHD group (trend-level poorer accuracy than Controls). Moreover, the impairment during the reversal phase of the task was restricted to the block in which the reversal of the S-R

associations took place (block 4) in the TS+ADHD group, while in the ADHD group the impairment persisted into the final task block during which the reversed associations were re-acquired. This pattern of findings indicates that the deficit was less extensive in TS+ADHD than in ADHD. This difference cannot easily be explained in terms of greater symptom severity in the ADHD than TS+ADHD group, since the groups were well matched on the CPRS-R scale scores for ADHD, and also for comorbid ODD.

The ADHD group had significantly lower IQ scores than the TS+ADHD group, which might explain the greater impairment in the ADHD group. However, the performance differences in the reversal phase remained significant when group variations in IQ were controlled in ANCOVA analyses, although this was not the case for the group effects during the acquisition phase. Nevertheless, as discussed in chapter 4 (section 4.1.5.2) covarying IQ in attempts to control confounding effects of group differences in this variable is not appropriate in the case of developmental disorders such as ADHD because lower IQs tend to be present in individuals with ADHD. Consequently, differences in performance due to IQ cannot be separated from performance differences associated with having ADHD (Dennis et al., 2009). Therefore, the possibility remains that the lower IQ of the ADHD group might have contributed to their more extensive impairment than was present in the TS+ADHD group.

Another explanation for the less extensive performance deficit in the TS+ADHD group is that these young people may have engaged in strategies to compensate for their deficit, while the ADHD group did not. This proposal is consistent with the finding that the FRN increased more in the final task block in the TS+ADHD group than in the TS and ADHD groups. This finding was unexpected because the FRN decreases as learning progresses in typically developing children and adults (Eppinger et al., 2009; Holroyd & Coles, 2002; Shephard et al., *under review* (see appendix A)). These decreases in amplitude are thought to reflect decreases in underlying dopaminergic prediction error signals because the outcome of performing the to-be-learned behaviour becomes more expected, because the behaviour is being learned (Bellebaum & Daum, 2008; Holroyd & Coles, 2002; Luque et al., 2012; Oliveira et al., 2007). Therefore, it was predicted that FRN amplitudes would decrease from the

reversal block 4, in which the newly reversed associations were first introduced and were unexpected, to the following task block 5, in which the outcome of producing the new, reversed S-R behaviours was more expected (learned). The increase in FRN amplitude in TS+ADHD was therefore unlikely to reflect dopaminergic prediction error activity. An alternative explanation of the increasing FRN in TS+ADHD is that these young people were processing the feedback information more strongly or thoroughly than the young people with TS or ADHD to compensate for their difficulty in re-acquiring the S-R associations.

This proposal has been used previously to explain smaller decreases in the FRN during reinforcement learning in typically developing children compared with adults (Eppinger et al., 2009). Hämmerer and Eppinger (2012) suggested that children's learning from reinforcements is less efficient than that of adults, and consequently children continue to rely on external feedback information to guide their performance. In contrast, adults are able to learn the new behaviour quickly and efficiently and therefore do not rely so heavily on external reinforcement of their performance (Eppinger et al., 2009; Hämmerer & Eppinger, 2012; Shephard et al., *under review* (see appendix A)).

In a similar manner, it is suggested that the TS+ADHD group was relying more heavily on feedback information to reinforce their performance to compensate for their inefficiency in learning the reversed S-R associations. This resulted in an increase in amplitude of the FRN. This increased reliance on feedback information was not present in the ADHD group, which could explain why the impairment in performance continued into the final task block in the young people with ADHD while it did not in the young people with TS+ADHD. The absent increase in the FRN in the TS and Control groups is likely to reflect the efficient learning of the reversed S-R associations in these groups, which meant that no additional processing of reinforcement feedback was necessary. The finding that greater severity of ADHD symptoms significantly predicted less increase in the FRN suggests that young people with more severe ADHD showed less compensatory enhancement in processing of the reinforcing feedback information.

If this interpretation of the FRN amplitude effects is correct, then the current findings suggest that an additive model may not be able to fully explain

TS+ADHD. Specifically, the compensatory strategy in young people with TS+ADHD suggests that factors other than ADHD influenced goal-directed learning performance and interacted with the ADHD-related impairment in reinforcement learning. Therefore, these findings indicate that the basis of TS+ADHD is complex and interactive, rather than simply involving the summed effects of TS- and ADHD- related characteristics.

7.1.2 Goal-directed learning in TS

As hypothesised, the TS group did not differ from the Control group in goal-directed reinforcement learning performance. This is consistent with the proposal that alterations in dopaminergic transmission, that is, hyperactivity of dopamine signalling, within the habit-learning system and not the goal-directed learning system are involved in the production of tics. However, analysis of the electrophysiological correlates of goal-directed learning revealed one difference between the TS and Control groups. The increase in P3 amplitude between blocks 1 and 2 was significantly greater in young people with TS compared with Controls. There were also trends for this increase to be greater in young people with TS than in young people with TS+ADHD, and in young people with ADHD than unaffected young people.

The magnitude of P3 amplitude changes during learning can be considered to index the strength of internal representations of correct S-R associations in working memory (Barceló et al., 2000; Rose et al., 2001). Therefore, increases in P3 amplitude are thought to reflect growing consolidation of the to-be-learned information (Rose et al., 2001; Shephard et al., *under review* (see appendix A)). The finding that this increase was greater in the young people with TS than unaffected young people might reflect stronger consolidation or more effective learning of the S-R associations in the TS group. However, considering the TS group was not more accurate than Controls in producing the S-R behaviours at this point in the task, this explanation is unlikely. It is certainly unlikely that this explanation of the P3 increase holds for the ADHD group, because accuracy was significantly poorer at this stage of the task in these young people compared with Controls. Another possibility is that the greater increase in P3 in TS and ADHD reflected enhanced effort in processing or attending to the stimuli. P3 amplitudes have

been shown to increase with enhanced effort in information processing or task performance (Kok, 2001). It is possible that the young people with TS and ADHD were investing more effort during the second than first task block compared with unaffected individuals, perhaps to assist with learning and to counter difficulties in acquiring the associations.

7.2 HABIT-LEARNING

The purpose of examining habit-based reinforcement learning was to further explore the basis of TS+ADHD in terms of whether additive, independent or symptomatic phenocopy models best fit this form of comorbidity. It was predicted that if TS+ADHD reflects additive comorbidity or a symptomatic phenocopy of ADHD, then young people in this group would show similar hyper-learning of the repeating sequence in the SRT task as the TS group. Conversely, if TS+ADHD reflects an independent condition, the young people in this group would show equivalent, unimpaired habit-learning as the ADHD and Control groups.

The analyses showed that, across all participant groups, RTs followed the typical decrease at the beginning of the task, increase during the disruption block when the repeating sequence was not presented, and decrease during the last task block when the repeating sequence was re-presented. These RT effects are thought to reflect the facilitation in performance by a mixture of practice and non-conscious learning of the repeating sequence at the beginning of the task, a disruption to performance due to the removal of the learned repeating sequence in block 4, and facilitation of performance when responding to the repeating sequence once more in the final block (Jackson et al., 1995; Nissen & Bullemer, 1987; Thomas & Nelson, 2001). The only group difference revealed was that the TS group produced shorter RTs, averaged across blocks 3, 4 and 5, compared with the Control and ADHD groups. Thus, the results of the analyses suggest that all groups showed the typical SRT sequence learning effects, which indicates that habit-learning was intact in all participants regardless of diagnoses.

The findings of intact habit-learning in the ADHD and TS+ADHD groups are in stark contrast to the impairment present in these young people during goal-directed reinforcement learning. These findings are consistent with previous research reporting unimpaired habit-learning in children with ADHD (Karatekin et al., 2009), and support the proposal in this thesis that reinforcement learning deficiencies are restricted to the goal-directed learning system in ADHD. This dissociation between goal-directed and habit-learning systems has implications for understanding reinforcement learning more generally.

Research in human participants and non-human subjects led to the distinction drawn between the goal-directed learning system involving the ventral striatum and prefrontal cortical regions and the habit-learning system involving the dorsal striatum and sensorimotor cortical areas (Maia, 2009; Seger & Spiering, 2011; Yin & Knowlton, 2006). This distinction was capitalised upon in the current research to formulate hypotheses concerning differential reinforcement learning deficiencies in TS and ADHD. However, it is generally agreed that in all likelihood habit and goal-directed systems interact and that both are involved, to greater or lesser degrees, in learning of any given behaviour by reinforcement (Seger & Spiering, 2011; Yin & Knowlton, 2006). The current findings indicate that it is possible for one system to be impaired, that is, the goal-directed learning system in ADHD, and the other to be unaffected, the habit-learning system in ADHD. These findings complement the vast literature reporting the reverse dissociation in adults with Parkinson's disease (PD). In these patients, dopamine is selectively depleted in lateral regions of the basal ganglia, which has been shown to result in a specific impairment in habit-learning but intact goal-directed learning (reviewed in Redgrave et al., 2010).

The absence of hyper-learning in the TS group was surprising given the strong theoretical rationale, albeit minimal evidence, for the involvement of dopamine-driven hyperactive habit-learning in tic symptoms (Leckman & Riddle, 2000; Maia & Frank, 2011) and previous findings of enhanced learning from positive reinforcements in adults with TS (Palminteri et al., 2009; Palminteri et al., 2011). Nevertheless, the current findings are consistent with Channon et al.'s (2003) study, which revealed no differences in SRT task

performance between children with TS, TS+ADHD and unaffected children. There are several possible interpretations of the discrepancy between Palminteri et al.'s (2009; 2011) findings and the current and previous (Channon et al., 2003) SRT findings in TS.

Firstly, it is possible that unlike the tasks employed by Palminteri et al. (2009; 2011) the SRT task simply does not capture alterations in reinforcement learning that are involved in the generation of tic symptoms. Reinforcements were tangible in the Palminteri tasks, consisting of monetary rewards, while in the SRT task there is no measurable reward other than the increasing ease of producing responses with sequence learning. However, the type of reward individuals with TS receive after producing a tic, that is, relief of the sensory urge, that is proposed to underlie the learning of a tic habit is more akin to the SRT task form of reinforcement than the monetary rewards used by Palminteri and colleagues. It would be useful to examine a range of habit-based reinforcement learning tasks with tangible and less-tangible rewards in young people with TS.

Another possible explanation concerns the age of participants. Palminteri et al. (2009; 2011) examined adults with TS while the current and previous SRT studies examined children and adolescents. Adults with TS are atypical of the disorder in that their tic symptoms have not remitted as they do in most individuals. On the one hand, adults with TS may have more extensive and prominent alterations in reinforcement learning, hence the persistence of tics into adulthood, which might render these atypicalities more detectable during experimental laboratory tasks. On the other hand, the altered reinforcement learning in Palminteri et al.'s adults with TS might be specific to individuals with non-remitting tics, which would indicate that such reinforcement learning atypicalities are not involved in the pathology of tics; otherwise, they would be present in all individuals with tics. A method of investigating this issue would be to compare adults with TS in whom tics have remitted with those in whom tics have persisted into adulthood. Such studies have not previously been published but would be highly informative of the basis of TS.

The absence of group differences between the TS and Control groups in RT change measures of sequence learning in the SRT task can be interpreted as

contradicting Marsh et al.'s (2004) proposed deficit in the basal ganglia concatenation mechanism in TS. This proposal was addressed specifically by carefully designing the to-be-learned sequences such that they could not be learned by forming associations between pairs of locations. Rather, the balanced nature of the sequences employed meant that learning involved the acquisition of serial location information, for example that location 1 in the sequence followed location 3 if on the previous trials location 2 followed location 4 and location 4 followed location 1 (Jackson et al., 1995). This complex structural information is acquired gradually by the habit-learning system to the point that the next location in the sequence can be predicted based on the combination of preceding locations (Rauch et al., 1998). Thus, the acquisition of sequence information in balanced sequences requires concatenating parts of the sequence into a whole chunk of behaviour, which is precisely the type of learning that Marsh et al. (2004) suggested is impaired in TS. Since the young people with TS did not differ from the unaffected young people in measures of sequence learning in the current study, it can be suggested that the concatenation function of the basal ganglia is not deficient in TS.

On the other hand, the young people with TS showed considerably less variation in RT during the sequence and non-sequence blocks than the other groups (flattened RT slope). This is indicative of (non-significantly) less learning-related change in RT in these young people. In turn, this suggests that there may have been an impairment in sequence learning in the TS group, but the low power of the study due to small sample size may have rendered this difference undetectable. Clearly, further research in children and adolescents with TS is required to elucidate the involvement, or non-involvement, of habit-based reinforcement learning in this condition.

Due to the lack of the expected hyper-learning effects in the TS group, the extent to which the current findings are informative of the basis of TS+ADHD is limited. It can be suggested that since TS+ADHD did not perform differently to the TS and ADHD groups, it is unlikely that this comorbidity is an independent condition. Moreover, the lack of impairment in SRT task performance but deficient goal-directed learning in both ADHD and TS+ADHD groups suggests that reinforcement learning was similarly affected

in these young people with ADHD regardless of the presence of tics. Consequently, an additive model of comorbidity might best explain TS+ADHD. On the other hand, if the flattened RT slope in the TS group is indicative of a subtle impairment in habit-learning, then it is clear that no such impairment is present in TS+ADHD. The RT slope in this comorbid group showed clear, typical SRT sequence learning effects.

7.3 COGNITIVE CONTROL

The aim of examining cognitive control in young people with TS, TS+ADHD, ADHD and unaffected young people was to investigate how comorbid ADHD symptoms impact upon aspects of cognition that are related to tic control in TS and to investigate the basis of comorbid TS+ADHD. Aspects of cognitive control that were predicted to be involved in tic control and/or that have been robustly associated with ADHD in previous research were examined to determine how those processes manifested in TS+ADHD. It was predicted that behavioural and electrophysiological correlates of the ability to withhold inappropriate, prepotent responses (Nogo accuracy, D-prime, Nogo N2 and P3) and the ability to monitor and adjust performance for errors (post-error slowing, ERN and Pe) would be enhanced in TS due to the likely involvement of these functions in controlling tics. In ADHD, it was predicted that behavioural and electrophysiological correlates of the ability to withhold inappropriate responses would be impaired, and that young people in this group would produce atypically high intra-individual variability (IIV), as indexed by increased Go RT variability.

In the TS+ADHD group, it was hypothesised that characteristics of both TS and ADHD would be present, resulting in impaired ability to withhold inappropriate responses and increased IIV compared with TS, but a relative enhancement in withholding inappropriate behaviours relative to ADHD due to the repeated engagement of this function in tic control. Thus, young people with TS+ADHD were expected to exhibit behavioural and electrophysiological correlates of withholding inappropriate behaviours that were intermediate to the enhancement of those correlates in TS and the impairment of those

correlates in ADHD. Finally, like the TS group, the TS+ADHD group were expected to show enhanced monitoring and adjustment for errors in performance.

The analyses of behavioural and electrophysiological correlates of cognitive control revealed several group differences that were relevant to the hypotheses of this study. Moreover, significant predictive relationships between severity of tics, ADHD and ODD symptoms were found. These findings are summarised in table 7-2 and are discussed in the following sections. Findings in TS will be considered first, followed by those in ADHD, and finally those in TS+ADHD will be discussed with reference to the main aims and hypotheses of this thesis.

7.3.1 Cognitive control in TS

The finding that young people with TS were as good as, but not better than, the unaffected young people at withholding inappropriate, prepotent responses to Nogo stimuli suggests that this ability was not enhanced in TS in contrast to hypotheses. This finding is consistent with previous reports of equivalent Nogo performance in children with TS and controls (Eichele et al., 2010; Greimel et al., 2011; Roessner et al., 2008), but contradictory to one previous study that reported enhanced Go and Nogo performance in TS (Debes et al., 2011). However, the significant prediction of D-prime scores by tic severity indicates that this ability is important in TS. Moreover, the negative direction of the relationship indicates that young people who were poorer at withholding inappropriate behaviours while maintaining on-going behaviour successfully (lower D-prime scores) had more severe tic symptoms, which might indicate that these young people had greater difficulty in controlling their tics. Therefore, although this aspect of cognitive control was not enhanced in TS at the group level, the findings indicate that it is importantly related to tic severity and, by inference, efficient control of tic symptoms.

The absence of enhanced electrophysiological correlates of withholding inappropriate behaviours (frontal N2 and P3 ERP amplitudes) in young people with TS was unexpected and contrary to previous reports of enhancement of these frontal ERPs and greater EEG coherence between frontal and central scalp sites in adults with TS during Nogo or similar task conditions (Johannes

Table 7-2

Summary of findings in the Go/Nogo cognitive control task

Measure	Group differences	Predictors of cognitive control
Go accuracy	TS+ADHD < TS**/Controls** ADHD < Controls*	n/a
Nogo accuracy	ADHD < TS**/TS+ADHD**/Controls*	Age (+)**
D-prime	ADHD < TS**/Controls**/TS+ADHD* TS+ADHD < TS**	Age (+)**, tics (-)**, ADHD (- when controlling ODD)**, ODD (+)**
Go RT	n/s	n/a
IIV (Go RT variability)	ADHD > TS**/Controls** TS+ADHD > TS**/Controls**	Age (-)*, tics (+)**, ADHD (+)**, ODD (-)**
Post-error slowing	TS > TS+ADHD**/ADHD*/Controls*	n/s
Go and Nogo N2	GoN2 at Pz TS < Controls**/ADHD* TS+ADHD < Controls* Nogo N2 at Pz TS < Controls** TS+ADHD < ADHD* Nogo N2 at Cz TS < Controls** TS+ADHD < Controls*	n/s
Go and Nogo P3	n/s	n/s
ERN	ERN at FCz TS > ADHD* TS+ADHD > ADHD**	Age (-)** (suppressed when controlling for ADHD and ODD)
Pe	n/s	n/s

* $p < .10$. ** $p < .05$. (+) = positive relationship between age or symptomatology and cognitive control measure. (-) = negative relationship between age or symptomatology and cognitive control measure

et al., 2001; Serrien et al., 2005; Thibault et al., 2009). The current findings are also inconsistent with previous reports of greater BOLD activation in prefrontal regions in children with TS than controls during cognitive control tasks (Baym et al., 2008; Jackson et al., 2011), and greater EEG coherence between prefrontal and motor scalp sites during tic suppression compared with tic expression in children with TS (Hong et al., 2013). It could be concluded based on the current N2 and P3 findings that young people with TS were not

engaging frontal cognitive control mechanisms more than unaffected young people.

Another explanation stems from the enhanced difficulty of the current Go/Nogo task compared with versions used previously. The current task used visually similar characters as Go and Nogo stimuli, which meant that participants had to attend closely to the stimuli in order to discern whether a Go response or Nogo was required on each trial. Moreover, the current task included a RT cap to limit the length of time available for participants to respond correctly to Go stimuli. These task manipulations were successful, as all participants reported that they found the task very difficult to perform. It is possible that the difficulty of the current Go/Nogo task resulted in all participants engaging frontal control regions maximally in order to successfully withhold responses to Nogo stimuli, which obliterated group differences in activity.

In support of this suggestion, accuracy in the Nogo condition was low in all groups (40.5 – 54.7%). Moreover, the typical diminishment of N2 and P3 ERPs was not found in the ADHD group compared with the Control group in this study. This ADHD effect is highly robust and has been replicated many times in previous research using the Go/Nogo and Stop-Signal tasks (Albrecht et al., 2005; Benikos & Johnstone, 2009; Fallgatter et al., 2004; Groom et al., 2008; Groom et al., 2010b; Johnstone & Clarke, 2009; Johnstone et al., 2007; Liotti et al., 2005; Wild-Wall et al., 2009). However, reduced amplitudes of these components in ADHD become more like those of controls when children are motivated to perform well (Groom et al., 2010b). In a similar manner, the difficulty of the current Go/Nogo task may have compelled the young people with ADHD to engage more fully in the task, and this resulted in typical N2 and P3 amplitudes. Therefore, it is suggested that the current findings of equivalent N2 and P3 amplitudes in the TS and Control groups reflected the difficulty in performing the task and consequent maximal engagement of frontal cognitive control regions during Nogo trials in all participants.

The other aspect of cognitive control which was predicted to be enhanced in TS was the ability to monitor and adjust performance for errors. It was suggested that this ability would be important in tic control because effective monitoring for tics (errors) and adjusting on-going behaviour

following a tic should improve the capacity to cope with tic symptoms. Consistent with this hypothesis, the TS group produced significantly greater compensatory slowing of responses following errors (post-error slowing, PES) than the TS+ADHD, ADHD and Control groups. This finding suggests that young people with TS were enhanced in the ability to exert control over and modify behaviour in light of errors in performance. Furthermore, the TS group produced greater amplitudes of the ERN, the neural correlate of error-monitoring, than the ADHD group. This finding suggests that young people with TS showed greater neural processing of errors than young people with ADHD, and provides partial support for the proposal that monitoring behaviour for errors is enhanced in TS. The findings do not fully support this proposal because the ERN was not larger in TS than Controls, although the ERN was comparable in magnitude in ADHD and Controls.

The ERN findings in the current research are consistent with one previous study that examined the ERN during a selective attention task in adults with TS (Johannes et al., 2002). On error trials, the adults with TS showed greater ERN amplitudes than unaffected adults. Johannes et al. (2002) interpreted this difference as reflecting hyperactive error signals in TS. The ERN has been linked with processing of dopaminergic negative prediction errors in regions of the prefrontal cortex, particularly the ACC, indicating that behaviour was worse than expected and should be modified (Holroyd & Coles, 2002). Therefore, larger ERN amplitudes in individuals with TS suggest that dopaminergic error signals are larger in these individuals than in unaffected controls. However, this suggestion is inconsistent with the reinforcement learning theory that hyperactivity in dopaminergic transmission results in diminished negative prediction errors and impaired learning from punishment in TS (Palminteri et al., 2009; Palminteri et al., 2011; Worbe et al., 2011). It may be however that the ERN reflects prediction error activity in a separate reinforcement learning pathway (ACC-ventral striatum) from that which is suggested to be involved in TS (sensorimotor cortex-dorsal striatum).

Another explanation is that engagement of error monitoring circuitry during tic control strengthens this circuitry sufficiently well to compensate for deficits, which leads to enhanced error processing activity in frontal cortex and behavioural indices of error processing in young people with TS. This proposal

is based on previous theories that cognitive control over motor behaviours is enhanced in TS as a result of compensatory neural changes arising from tic control (Jackson et al., 2007; Jackson et al., 2011; Marsh et al., 2007). The current proposal extends the previous compensatory hypotheses to suggest that control over non-motor functions may also become enhanced in young people with TS.

However, in the current study tic symptom severity did not significantly predict either post-error slowing or ERN amplitude, suggesting that these error processing characteristics were not associated with the severity of tic symptoms. This might indicate that error monitoring and post-error adjustment are not involved in tic control, as these abilities might be expected to vary with the severity of symptoms if this was the case. Conversely, perhaps the ability to monitor and adjust behaviour following errors is engaged and strengthened in young people with tics, regardless of how severe their tics are.

7.3.2 Cognitive control in ADHD

As predicted, young people with ADHD were significantly poorer at withholding inappropriate responses to Nogo stimuli, as indexed by lower Nogo accuracy and D-prime scores, and produced significantly greater IIV than typically developing young people or young people with TS. These findings add to the large body of previous research reporting these cognitive control impairments in ADHD (Banaschewski et al., 2003b; Benikos & Johnstone, 2009; Casey et al., 1997; Castellanos et al., 2005; de Zeeuw et al., 2008; Durston et al., 2003; Groom et al., 2008; Groom et al., 2010a; Johnstone & Clarke, 2009; Liotti et al., 2005; Oades et al., 2008; Smith et al., 2006; Tamm et al., 2004; Uebel et al., 2010; Vaidya et al., 2005; Wiersema et al., 2005). Moreover, severity of ADHD symptoms significantly predicted D-prime scores and IIV, with higher ADHD severity associated with greater impairment in these cognitive control measures. These findings indicate that these deficits are intimately linked with the pathology of ADHD, as has been proposed previously (Barkley, 1997; Castellanos & Tannock, 2002).

Symptoms of comorbid ODD, which co-occurs with ADHD in a large proportion of individuals (Yoshimasu et al., 2012), also predicted D-prime scores and IIV. Interestingly, these predictive relationships were in the opposite

direction to those of ADHD, with higher ODD severity associated with better performance (higher D-prime scores and lower IIV). Moreover, the relationship between ODD and D-prime scores moderated the relationship between ADHD and these scores such that ADHD symptoms did not significantly predict D-prime unless the extent to which ODD predicted D-prime was controlled. Banaschewski et al. (2003b) previously examined the ability to withhold inappropriate responses and RT variability in children with ADHD, ODD, and ADHD plus comorbid ODD (ADHD+ODD) and found that children with ADHD showed increased IIV compared with unaffected children while the ODD and ADHD+ODD groups were unimpaired on either cognitive control process. Based on these findings, Banaschewski et al. (2003b) suggested that ADHD+ODD is an independent condition from ADHD or ODD, rather than the additive effects of these conditions occurring within the same individuals. The current findings suggest that ODD symptoms might ameliorate cognitive control impairments in ADHD, which might explain the lack of impairments in Banaschewski et al.'s (2003b) ADHD+ODD group and indicate that this form of comorbidity is not necessarily an independent condition. However, if this suggestion is correct then the question of what causes ADHD symptoms in the absence, or amelioration, of cognitive control deficits arises. These comments are speculative only, but are worthy of investigation in future research as they may provide further insight into the basis of ADHD and comorbid ADHD+ODD.

It was surprising that the N2 and P3 electrophysiological correlates of the impaired ability to withhold inappropriate responses in ADHD were not reduced in amplitude as has been robustly reported in the literature (Albrecht et al., 2005; Benikos & Johnstone, 2009; Fallgatter et al., 2004; Groom et al., 2008; Groom et al., 2010b; Johnstone & Clarke, 2009; Johnstone et al., 2007; Liotti et al., 2005; Wild-Wall et al., 2009). However, as discussed above in section 7.3.1 it is suggested that the absence of reduced N2 and P3 amplitudes in the ADHD group reflected the high degree of effort required by these individuals in performing the task, due to the high difficulty level of the task. Regardless of the reason for equivalent N2 and P3 amplitudes in ADHD and Controls, this finding indicates that despite comparable activation of cognitive

control regions, the ADHD group was still impaired in withholding inappropriate behaviours.

Finally, the young people with ADHD performed equivalently to the Control group in post-error slowing. Furthermore, amplitude of the ERN in the ADHD group did not differ from Controls. These findings suggest that the ability to monitor performance for errors and make compensatory adjustments to response speed following error commission was unimpaired in young people with ADHD. These findings add to the mixed literature on error processing in ADHD, which has reported intact ability in some studies but impaired ability in others (Groom et al., 2010a; van Meel et al., 2007; Wiersema et al., 2005; Wild-Wall et al., 2009). However, it should be noted that Groom et al. (2010a) found comparable ERN amplitudes in children with ADHD and unaffected young people, but reduced theta-band oscillatory EEG measures associated with error processing in ADHD. These findings suggest that error processing impairments might be present in ADHD, but these are more subtle or require a different method of analysis to the traditional ERP approach to be revealed.

7.3.3 Cognitive control in TS+ADHD

To consider first the ability to withhold inappropriate responses, the TS+ADHD group, like the ADHD group, produced significantly poorer D-prime scores than the TS group, indicating an impairment in this ability compared with young people with TS without comorbid ADHD symptoms. However, like the TS group, the TS+ADHD group produced significantly higher Nogo accuracy and D-prime scores than the ADHD group, suggesting an enhancement in this ability relative to young people with ADHD without tics. Moreover, tic severity and ADHD severity significantly predicted D-prime scores, with more severe symptoms of both conditions associated with lower D-prime, that is, poorer performance. These findings have several important implications for understanding TS+ADHD.

Firstly, the similarity in impairment between TS+ADHD and ADHD groups suggests that ADHD symptoms in TS+ADHD are of the same origin as those symptoms in individuals with ADHD without comorbid tics. In both disorders, ADHD symptoms were related to deficits in the ability to withhold inappropriate, prepotent behaviours. Therefore, the current findings clearly

indicate that comorbid ADHD symptoms in young people with TS are genuine and not a symptomatic phenocopy. At the same time, the TS+ADHD group was less impaired at withholding inappropriate responses than the ADHD group. The most plausible explanation for this relative enhancement is that because young people with TS+ADHD repeatedly engage in withholding tics, this ability becomes strengthened which counteracts the deficit in this ability associated with ADHD symptoms. These findings are consistent with an additive model of comorbidity for TS+ADHD, but also highlight the likelihood that TS and ADHD symptoms are not simply summed in TS+ADHD. Rather, it seems the symptoms of each condition interact and result in subtle differences in performance and ability in young people with TS+ADHD compared with TS and ADHD.

These findings are consistent with those of Greimel et al. (2011) who reported ADHD-related impairments and TS-related enhancements in the ability to suppress interfering information, and suggested that TS-related enhancements in cognitive control might ameliorate deficits associated with ADHD in children with TS+ADHD. However, this proposal was not fully supported by Greimel et al.'s (2011) findings because the authors employed the 2 x 2 factorial approach (see chapter 2, section 2.3.3) without analysing group differences between the TS+ADHD and TS, ADHD and unaffected control groups. Therefore, there was no direct evidence that the children with TS+ADHD performed better than ADHD and worse than TS. In contrast, the current study provides clear support for the view that ADHD-related impairments are present in TS+ADHD, but that strengthening of cognitive control abilities via repeated engagement in tic control ameliorates those deficits.

As such, the current findings highlight the importance of examining group differences and relationships with symptom severity rather than, or in addition to, using the 2 x 2 factorial approach which has been used in most previous studies of TS+ADHD (Greimel et al., 2011; Roessner et al., 2007c). The current data analysed with this approach would likely have revealed a main effect of TS-present, reflecting better Nogo accuracy and D-prime scores than ADHD, and an effect of ADHD-present, reflecting poorer Nogo accuracy and D-prime scores than TS and Controls, and no interaction between these

factors. Therefore, the differences between TS+ADHD and TS and ADHD respectively would have been missed.

A final point to consider concerning the ability to withhold inappropriate behaviours in TS+ADHD is that the relative enhancement in this ability in young people with TS+ADHD compared with ADHD should not overshadow the important finding that these young people still performed more poorly than the TS group. This finding suggests that young people with TS+ADHD may find it more difficult to control tic symptoms than young people with TS without ADHD. This has implications for treatment of TS+ADHD and will be discussed in section 7.4.2.

Aside from the ability to withhold inappropriate, prepotent behaviours, the analysis of group differences in cognitive control revealed that the TS+ADHD group, like the ADHD group, produced significantly more variable RTs to Go stimuli than the TS or Control groups. This finding is consistent with previous reports of increased IIV in children with ADHD and TS+ADHD (Sukhodolsky et al., 2010). Moreover, the presence of increased IIV in TS+ADHD further supports the proposal that comorbid ADHD symptoms are genuine manifestations of the ADHD disorder, and argue against a symptomatic phenocopy explanation for TS+ADHD. Furthermore, this finding can provide insight into the neural mechanisms involved in TS+ADHD. High IIV has been associated with alterations in the norepinephrine system, cerebellar-striatal circuitry, and dopamine-mediated fronto-striatal circuitry (Castellanos & Tannock, 2002; Frank et al., 2007; MacDonald et al., 2006; Tamm et al., 2012).

The final finding from the examination of cognitive control in TS+ADHD was that this group, like the TS group, exhibited larger ERN amplitudes than the ADHD group. Thus, young people with TS+ADHD showed enhanced neural processing of errors compared with young people with ADHD without tics. This finding suggests that, as was proposed for young people with TS without ADHD, compensatory strengthening of fronto-striatal error monitoring circuitry occurs in TS+ADHD as a result of constantly engaging this circuitry in monitoring behaviour for tics. However, because post-error slowing was poorer in TS+ADHD than TS, it seems that this strengthening of error processing circuitry does not extend to improved ability

to adjust behaviour following error (tic) production. This pattern of findings further supports the view that TS+ADHD reflects additive comorbidity, and is consistent with a suggestion made by Sukhodolsky et al. (2010) that the basis of TS+ADHD is complex, with some characteristics of TS and ADHD expressed and others not expressed.

7.4 IMPLICATIONS FOR THE BASIS OF TS+ADHD AND THE IMPACT OF COMORBID ADHD SYMPTOMS ON COGNITIVE FUNCTION IN TS

7.4.1 What is the basis of TS+ADHD?

In terms of which model of comorbidity, additive, independent or symptomatic phenocopy, applies to TS+ADHD, the pattern of group differences and relationships with tic and ADHD symptom severity found across the three tasks employed in this research clearly indicates that the phenocopy model does not hold. Impairments in goal-directed reinforcement learning, the ability to withhold inappropriate prepotent behaviours, and increased IIV that have previously been associated with ADHD were present in young people with ADHD and TS+ADHD in the current research. Based on these findings, it can be concluded with some certainty that comorbid ADHD symptoms in young people with TS are genuine expressions of the ADHD disorder and are not the result of tics mimicking those symptoms.

An independent model of comorbidity was also not supported by the current research. According to this model, the pathological processes which underlie TS+ADHD differ from those that are involved in TS and ADHD. In goal-directed reinforcement learning and cognitive control, the young people with TS+ADHD exhibited similar forms of impairment as the young people with ADHD. Moreover, ADHD severity predicted cognitive control impairments in a similar manner in the TS+ADHD and ADHD groups. Specifically, greater ADHD severity predicted poorer ability to withhold inappropriate behaviours, and larger IIV. Concurrently, the young people with TS+ADHD showed similar cognitive control characteristics to the young people with TS, namely enhanced ability to withhold inappropriate behaviours

and greater amplitude of the ERN correlate of error-monitoring relative to the ADHD group. Furthermore, the same relationship between tic severity and the ability to withhold inappropriate responses was present in TS and TS+ADHD groups.

The presence of TS and ADHD characteristics in young people with TS+ADHD indicates that an additive model best explains this form of comorbidity. This is consistent with previous conclusions that TS+ADHD reflects additive comorbidity (Roessner et al., 2007c). However, several findings suggest that an additive model in which TS and ADHD characteristics are summed in TS+ADHD is too simplistic to fully encapsulate the basis of this comorbidity. These findings were the less extensive impairment in goal-directed learning performance in TS+ADHD compared with ADHD, the greater increase in the FRN correlate of goal-directed learning which was interpreted as reflecting a compensatory strategy, the absence of enhanced post-error slowing in TS+ADHD which was present in TS, and the relative enhancement and impairment in withholding inappropriate behaviours compared with ADHD and TS respectively. Consistent with Sukhodolsky et al.'s (2010) suggestion, these group differences indicate that TS+ADHD is a complex condition and that the pathological mechanisms of TS and of ADHD interact within individuals with this comorbidity. An important avenue for future research is to examine the extent to which such interactions result in between-subject variability in the expression or suppression of TS and ADHD characteristics.

Another important set of questions arise from the increasing evidence that TS+ADHD reflects the presence of the ADHD and TS disorders in the same individuals. For instance, the co-occurrence of these disorders suggests that there might be some shared genetic or neurobiological characteristics that engender vulnerability for both TS and ADHD (Angold et al., 1999; Rutter, 1997). The identification of such vulnerability markers will be important for understanding the causes of TS and ADHD, as well as TS+ADHD. The pattern of findings across the three tasks in the current research implicates a number of neurobiological abnormalities involved in TS+ADHD and ADHD. The impairment in goal-directed reinforcement learning suggests that activity within the dopaminergic pathways linking the ventral striatum with frontal

cortical regions is hypoactive in TS+ADHD and ADHD. Altered activity in fronto-striatal circuitry was also implicated by the abnormalities in withholding responses, IIV, and error monitoring. Finally, atypicalities in the noradrenaline neurotransmitter system and cerebellar circuitry can be inferred from increased IIV. The absence of impairments in the TS group in the current research limits the inference of which of these neurobiological atypicalities might be shared by all three conditions. Nevertheless, the current findings provide a useful starting point for more detailed examinations of the neurobiology of TS, TS+ADHD and ADHD; for example, neuroimaging of the structure and function of fronto-striatal and cerebellar circuits, and positron-emission studies of the densities of dopamine and noradrenaline receptors.

7.4.2 The impact of comorbid ADHD symptoms on cognitive function in TS

The findings of this research clearly demonstrate that comorbid ADHD symptoms have a negative impact on cognitive functions that are likely to be involved in controlling tics in young people with TS. In particular, the impaired ability to withhold prepotent behaviours in young people with TS+ADHD indicates that these individuals will be less able to suppress tics than young people with TS without comorbid ADHD. This indicates that the effectiveness of Exposure and Response Prevention (ER) therapy, which trains the ability to suppress tics for increasingly long periods (Hoogduin et al., 1997; see chapter 1, section 1.2), will be reduced in young people with TS+ADHD. Moreover, it has previously been shown that poorer cognitive control performance in individuals with TS is associated with poorer response to habit-reversal therapy for tics (Deckersbach et al., 2006), which suggests that this form of therapy would also be less effective in young people with TS+ADHD. The success of habit-reversal therapy, which trains the ability to extinguish and re-form learned associations between premonitory urges and tics (Azrin & Nunn, 1973; Woods et al., 1996; Piacentini et al., 2010) is also likely to be affected by the impairment in goal-directed reinforcement learning found in the young people with TS+ADHD.

In individuals with ADHD, the administration of methylphenidate medication has been shown to improve impairments in reinforcement learning

(Frank et al., 2007) and the ability to withhold responses (Groom et al., 2010b). Therefore, one method of enhancing the likelihood that behavioural therapies for tics will be effective in young people with TS+ADHD would be to treat the comorbid ADHD symptoms with methylphenidate simultaneously. This treatment approach has been suggested previously (Roessner et al., 2007c) but was based on the more general assumption that comorbid ADHD symptoms are more impairing to psychosocial and educational functioning than tic symptoms in TS+ADHD. The current study provides the first clear indication that ADHD symptoms are likely to impair the efficacy of tic therapies and that methylphenidate treatment is likely to improve not only ADHD symptomatology but also the capacity for improving tic symptoms.

In addition to these negative effects of comorbid ADHD symptoms on young people with TS, it is also important to highlight the findings that these young people, like individuals with TS without ADHD, seem to be capable of engaging in compensatory strategies to improve deficits associated with ADHD, as indicated by the FRN alterations in the goal-directed learning task, and to improve the control of tics, as reflected in the increased ERN during the cognitive control task. This capacity for compensation might be harnessed in order to improve the outcome of behavioural treatments for tics.

7.5 LIMITATIONS

7.5.1 Participant samples

One of the main limitations of this research was the restricted sample sizes of the clinical groups, particularly the ADHD group. This was due to the difficulty (low response rate, high drop-out rate) in recruiting young people with developmental disorders, particularly ADHD, to take part in the research and the limited time-scale of the project. The samples were further reduced by the exclusion of participants with atypical behavioural performance and insufficient artefact-free EEG data. These reductions were expected, especially those due to the presence of tic- and hyperactivity- related movement artefacts in the EEG data, and efforts were made to contact as many families as possible to ensure a sufficiently large sample size was obtained for the research. For

example, 77 young people with ADHD were invited to take part via their treating clinician, but this resulted in only 13 young people participating.

It is likely that the diminished sample sizes led to type II errors. An example of this is the lack of significant differences between the change measures characterising speeding and slowing of RTs between the TS and Control groups in the SRT task. These change scores were markedly smaller in the TS group (see chapter 5, figure 5-3), which may have indicated impaired habit-learning in these young people. However, these differences were non-significant in analyses. Consequently, habit-learning requires further investigation in a larger sample of young people with TS. There were also a number of trend-level effects, particularly in the analyses of ERP correlates, which might have been significant if not for the low power of this study. A power calculation was performed before beginning this study to determine the minimum number of participants required for each group in order to detect significant group effects. Based on moderate-to-large effect sizes, which have been reported previously in ERP research in these participant groups (Yordanova et al., 1997), and an alpha level of .05 and power of .90, power calculations conducted in G*Power indicated that 25 to 35 participants would be required in each group in order to detect significant main effects and interactions. Therefore, it is clear that the difficulties with recruitment led to this study being under-powered to detect effects.

Due to the low power of the study, correction for multiple comparisons was not applied to the pairwise group contrasts in this research. This may have inflated the type I error rate. In acknowledgement of this possibility, the group contrasts that would not have remained significant after correction for multiple comparisons were reported. Those findings should be interpreted with caution. It is reassuring that several of the main findings of this research, including the impairments in IIV and reversal of goal-directed reinforcement learning in TS+ADHD and ADHD groups, were highly significant and would have survived correction.

Another limitation that concerns the participant samples is the presence of selection bias. The TS, TS+ADHD and ADHD groups were recruited mainly from clinics and are therefore likely to have been influenced by referral biases, including Berkson's bias (Berkson, 1946). Berkson's bias refers to the

disproportionately high presence of comorbidity in clinical samples (compared with population or non-referred samples) due to the greater likelihood that an individual will be referred for treatment if they have two rather than one set of symptoms (Berkson, 1946; Caron & Ruttter, 1991). The presence of Berkson's bias in this study renders it possible that the findings concerning the shared impairments and compensatory characteristics of the TS+ADHD group with the TS and ADHD groups may not be fully representative of comorbid TS+ADHD, but rather only represent a proportion of individuals with TS+ADHD who are referred for treatment. Another referral bias that likely affected the current samples is the greater likelihood that an individual with more severe symptomatology will be referred for treatment compared with an individual with less severe symptoms. It is possible that the TS, TS+ADHD and ADHD samples in the current research were characterised by more severe tic, ADHD and comorbid symptomatology than individuals in the general population. The effects of referral bias should be considered when interpreting the results of this study, and the findings should be replicated in a more generalisable sample of individuals with TS, TS+ADHD and ADHD.

7.5.2 Effects of medication, behavioural therapy, and comorbid OCD symptomatology

Participants in this study varied in whether they were or had previously received medication or behavioural therapy for tics and ADHD. Dopamine-acting medications are particularly relevant to the current research due to the involvement of this neurotransmitter in reinforcement learning and cognitive control, and the evidence that administration of such medications alters these abilities. Methylphenidate medications were withdrawn from participants in this study. However, four individuals were receiving Aripiprazole which influences the dopaminergic neurotransmitter system, and other participants were receiving Clonidine, SSRIs, and Atomoxetine. It was not possible to withdraw these medications due to the possibility of adverse side-effects. Moreover, some young people in the TS group had received habit-reversal therapy for tics, which likely affected reinforcement learning and cognitive control abilities. Ideally, the effects of these treatments on performance and electrophysiological activity would have been examined by excluding

participants who were on-medication or who had received behavioural tic therapy and conducting the statistical analyses on only the participants without treatment histories. Alternatively, the type and dosage of medication and number of sessions of tic therapy could have been used as predictor variables in regression analyses. However, the small sample sizes of the clinical groups and the wide variation in type of treatment within the groups limited such an approach. It will be important in future to replicate the current findings when the potentially confounding effects of medication and tic therapy are controlled.

Similarly, it was not possible to examine relationships between OCD symptomatology and behavioural performance and electrophysiological activity. A large proportion of participants in each group did not have OCD symptoms and produced zero scores on the CY-BOCS measure of OCD; therefore, it was not possible to include these symptoms as predictors in regression analyses. Due to the small sample sizes for each group, it was not possible to exclude the participants with OCD and re-examine group effects or relationships between tic and ADHD severity and neurocognitive measures. OCD frequently co-occurs with TS (Gaze et al., 2006) and fronto-striatal CBTC circuitry has been implicated in the causes of OCD (Albin & Mink, 2006). Therefore, a main limitation of the current research was the inability to examine how OCD symptomatology affected group effects and relationships with tic and ADHD severity. This is an important issue to address in future research, perhaps by including a group of young people with comorbid TS+OCD.

7.5.3 Analysis approach

The analysis approach taken in this thesis was designed to address methodological problems with previous research in comorbid TS+ADHD, namely the use of the 2 x 2 factorial method (see chapter 2, section 2.3.3; Banaschewski et al., 2007). The current approach was to characterise the neurocognitive profile of young people with TS+ADHD compared with profiles of young people with TS, ADHD, and unaffected young people, and to examine how tic, ADHD and ODD severity predicted neurocognitive characteristics. The current method was proposed to be more informative of the

nature and impact of comorbid ADHD symptoms in young people with TS than the 2 x 2 approach. Consistent with this proposal, the findings of this research revealed a pattern of impairments and enhancements in reinforcement learning and cognitive control in young people with TS+ADHD that were similar to the ADHD and TS groups respectively.

However, the current approach is limited in that the likelihood that TS+ADHD reflects additive, independent or phenocopy comorbidity must be inferred from the pattern of similarities and differences in the TS+ADHD groups compared with the TS and ADHD groups. In other words, there is no clear 'marker' that indicates whether TS+ADHD is additive or otherwise, such as the absence of a group by group interaction in the 2 x 2 factorial approach. Nevertheless, the extent to which a lack of significant interaction truly indexes additive comorbidity is questionable (see chapter 2, 2.3.3). Moreover, the utility of such a marker is arguably secondary in importance to fully understanding the presence and nature of deficits that are introduced by comorbid symptoms, since these have implications for treatment and can be used to infer the neurobiological mechanisms involved. In turn, this information can be used to drive investigations of shared genetic abnormalities, which would most strongly indicate whether the co-occurrence of two conditions is true (additive) comorbidity.

7.5.4 Measurement of clinical symptomatology

The severity of ADHD symptoms in the current participants was measured using established rating scales which assess the type and severity of ADHD behaviours in the one week (ADHD Rating Scale IV) or six months (CPRS-R, SDQ) prior to testing. However, the young people with ADHD were tested off methylphenidate medication. This means that the level of symptom severity was rated over a period in which most young people were on medication, and therefore their symptoms would have been less severe, but the neurocognitive measures obtained on the day of testing reflected those individuals' performance and neural activity when they were off-medication and their symptoms were likely more severe. This incongruity between symptom severity ratings may have affected the regression analyses examining the extent to which ADHD severity predicted behavioural and

electrophysiological correlates of reinforcement learning and cognitive control. For instance, associations may have been weaker between ADHD symptomatology and reinforcement learning because the severity of ADHD was diminished in the scores used in the prediction. One way of avoiding this problem would have been to include only young people who were not receiving methylphenidate treatment in the research. However, given the difficulties with recruitment of young people for this group, this was not a viable option. The administration of methylphenidate to treat ADHD symptoms is common in young people in the UK, and the withdrawal of medication for 24 hours prior to testing is common practice in experimental investigations of ADHD (nearly all studies referred to in the cognitive control literature review in chapter 2 reported withdrawal of methylphenidate prior to testing). Consequently, this issue likely applies to most other research studies examining ADHD.

7.5.5 EEG processing methods

Independent Components Analysis (ICA) was used to identify and remove artefacts in the EEG data due to muscle movement, channel noise, and eye movements. This approach was necessary because the participants with TS and TS+ADHD produced tics during EEG recording, resulting in some large movement artefacts in those data. Some EEG experts argue against this approach due to the possibility that genuine brain signals will be removed along with components reflecting artefacts, and propose that ICA should only be used to remove eye movement artefacts which are clearly recognisable in the EEG and excessive channel noise that can be clearly differentiated from the on-going neural signals (Brandeis, personal communication). Therefore, the removal of movement artefacts in the present study might be considered a limitation of the research. However, to minimise the possibility that neural activity was removed alongside tic-related movement artefacts, Delorme et al.'s (2006) method for identifying artefactual components as opposed to brain activity was followed closely. Moreover, participants were excluded from analyses if it was not possible to clearly differentiate movement artefacts from neural signals.

7.6 CONCLUSIONS

The findings from the analysis of behavioural and electrophysiological correlates of goal-directed reinforcement learning and cognitive control provided important insights into the nature of TS+ADHD. Young people with TS+ADHD exhibited impairments in the ability to learn and modify goal-directed behaviours using reinforcement feedback, and in the ability to prevent the production of automated, inappropriate behaviours, and atypically high intra-individual variability. These impairments have been robustly associated with ADHD in previous research and were present in the young people with ADHD in the current research. The young people with TS+ADHD also displayed enhancements in cognitive control relative to the ADHD group, specifically in error monitoring and the ability to withhold inappropriate responses, which were also enhanced in the TS group relative to the ADHD group. There was also evidence from electrophysiological activity associated with goal-directed reinforcement learning that young people with TS+ADHD, unlike individuals with ADHD, engaged in compensatory strategies to impair their poor learning performance.

This pattern of findings indicated that characteristics of both TS and ADHD disorders were present in TS+ADHD, and that these characteristics interacted in young people with TS+ADHD to produce subtle differences in ability compared with the TS and ADHD groups. Thus, an additive of model comorbidity appears to provide the most fitting account of TS+ADHD, with the caveat that TS and ADHD are not simply summed in TS+ADHD. The current findings also implicated a number of brain regions and mechanisms that are likely to be affected in TS+ADHD, including the ventral striatum, fronto-striatal CBTC loop, dopaminergic and noradrenergic neurotransmitter systems, and cerebellar circuitry. The current findings provided evidence that comorbid ADHD symptoms create impairments in TS+ADHD that are likely to affect these young people's ability to control tics and engage effectively in behavioural tic therapies.

Finally, the current research provided support for the view that cognitive control is involved in tic control and is strengthened, or engaged

more greatly, in young people with TS, with or without comorbid ADHD symptoms. Moreover, the current results extended previous findings of enhanced cognitive control in children with TS during motor control tasks by showing that error monitoring and the modification of behaviour following errors was enhanced in the current sample of young people with TS. The results of this research concerning the involvement of habit-learning in tic production were inconclusive, although there was some indication that habit-learning might have been impaired in young people with TS. The role of reinforcement learning mechanisms in tic generation requires further investigation in future research.

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APPENDICES

APPENDIX A: A PILOT STUDY TO EVALUATE BEHAVIOURAL AND ELECTROPHYSIOLOGICAL CORRELATES OF GOAL-DIRECTED REINFORCEMENT LEARNING

The research presented in this appendix was a pilot study conducted to ensure the novel design of the goal-directed reinforcement learning task elicited reliable behavioural and electrophysiological correlates to facilitate measurement of this form of learning in the young people with TS, TS+ADHD and ADHD in the main study. This work has been produced for publication and is currently awaiting final alterations prior to approval for publication in *Developmental Cognitive Neuroscience.* The manuscript for this publication is presented below.

Learning and altering behaviours by reinforcement: Neurocognitive differences between children and adults

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Abstract

This study examined neurocognitive differences between children and adults in the ability to learn and adapt simple stimulus-response associations through feedback. Fourteen typically developing children (mean age = 10.2) and 15 healthy adults (mean age = 25.5) completed a simple task in which they learned to associate visually presented stimuli with manual responses based on performance feedback (acquisition phase), and then reversed and re-learned those associations following an unexpected change in reinforcement contingencies (reversal phase). Electrophysiological activity was recorded throughout task performance. We found no group differences in performance (reaction time, accuracy) or in the amplitude of event-related potentials (ERPs) associated with stimulus processing (P3 ERP) or feedback processing (Feedback-related negativity; FRN) during the acquisition phase. However, children's performance was significantly more disrupted by the reversal than adults and FRN amplitudes were significantly modulated by the reversal phase in children but not adults. These findings indicate that children have specific

difficulties with reinforcement learning when acquired behaviours must be altered. This may be caused by the added demands on immature executive functioning, specifically response monitoring, created by the requirement to reverse the associations, or a developmental difference in the way in which children and adults approach reinforcement learning.

Keywords: Development, reinforcement learning, P3, feedback-related negativity (FRN)

1. Introduction

1.1 Reinforcement learning in development

The ability to learn and modify behaviours based on the positive and negative outcomes of our actions is an important skill used throughout the lifespan. This skill, known as reinforcement learning (Holroyd & Coles, 2002; Thorndike, 1911), may be particularly valuable in the first two decades of life, affording the naïve developing child an effective method of identifying advantageous behaviours and discerning when and how learned actions should be adapted for changing contexts. Indeed, impaired reinforcement learning has been implicated in the pathology of several neurodevelopmental disorders, including Tourette syndrome and ADHD (Marsh et al., 2004; Sagvolden et al., 2005), although the precise deficits in these conditions are unclear. A thorough understanding of the typical development of reinforcement learning may help clarify these deficits, but few studies have examined this aspect of cognitive development.

1.2 Differences in reinforcement learning across typical development

Previous studies have consistently reported performance differences between children and adults in reinforcement learning. Younger children are less accurate when learning associations between stimuli and responses (S-R associations) by positive and negative feedback than older children and adults (Baldwin et al., 2012; Crone et al., 2004). Children learn at a slower rate than

adults (Crone et al., 2004) and show particular difficulties when reinforcements are inconsistent. Specifically, performance differences between children and adults increase when feedback is probabilistic and does not correctly reinforce performance 100% of the time (Eppinger et al., 2009; Hämmerer et al., 2010).

Neural processes underlying these developmental differences have been examined using EEG, particularly the feedback-related negativity (FRN) event-related potential (ERP). The FRN is a negative deflection in the waveform at ~250ms following feedback (Miltner et al., 1997). FRN amplitude is larger following negative than positive feedback, and in some studies positive feedback elicits a positive-going deflection in the FRN time-range, the feedback-positivity (FP) (Holroyd et al., 2008). Evidence suggests the FRN/FP is generated by prefrontal cortical regions associated with performance monitoring and reflects the processing of dopaminergic reinforcement learning signals triggered by feedback indicating behaviour was better or worse than expected (Bellebaum & Daum, 2008; Luque et al., 2012; Oliveira et al., 2007). FRN/FP amplitudes decrease during a reinforcement learning episode, likely reflecting decreased reliance on external feedback with increasing knowledge of to-be-learned behaviours (Eppinger et al., 2009; Holroyd & Coles, 2002).

Children show less enhancement of the FRN for negative compared with positive feedback, suggesting children are poorer at differentiating between types of feedback than adults (Hämmerer et al. 2010). The authors suggest this may explain why learning is more disrupted in children when feedback is probabilistic and difficult to discriminate. FP amplitude decreases less across learning in children than adults (Eppinger et al., 2009) and ERP correlates of monitoring errors in performance differentiate less between correct and error responses in children than in adults. Based on these differences between children and adults, Eppinger et al. (2009) suggested that children have weaker internal representations of whether a response is correct or erroneous (less differentiated neural responses to correct and error responses), resulting in a greater reliance on feedback processing (smaller FRN amplitude decreases) to achieve successful performance. In a recent review of this literature, Hämmerer and Eppinger (2012) proposed that increasing reinforcement learning ability reflects developing efficiency in processing feedback, using reinforcements effectively to guide goal-directed behaviour,

and building internal representations of correct behaviours, as prefrontal cortical regions mature.

However, due to the scarcity of research in this area further studies are needed (Hämmerer and Eppinger, 2012). Furthermore, previous research has not addressed an important aspect of reinforcement learning, that is, the ability to alter and re-learn behaviours following changes in reinforcements. A robust finding in the executive function literature is that children are poorer than adults in switching to new behaviours when prompted by cues (Koolschijn et al., 2011). This suggests that children will have particular difficulty with learning when reinforcement contingencies change. Furthermore, the learning tasks used previously have been complicated, with multiple feedback conditions presented for different S-R associations within task blocks, creating considerable working memory demands (Crone et al., 2004; Eppinger et al., 2009; Hämmerer et al., 2010). Crone et al. (2004) and Eppinger et al. (2009) controlled for this problem by allocating children extra response time, but nevertheless the difficulty of these tasks may have enhanced developmental differences.

1.3 Current study

The study aims were firstly to further investigate neurocognitive differences in the typical development of reinforcement learning using a simple task designed to reduce the influence of age-related performance differences on ERP correlates of learning. The intention was to ensure all participants could perform the task adequately regardless of age so that any ERP differences are more likely to reflect differences in the recruitment of neural networks underlying task performance, rather than floor or ceiling effects in one age group. Secondly, to assess developmental differences in the ability to change and re-learn acquired behaviour in response to altered reinforcement contingencies. During EEG recording typically developing children and adults performed a task in which they learned four S-R associations by positive and negative feedback and then reversed the associations after an unexpected change in reinforcement contingencies. Changes in performance and feedback processing, indexed by the FRN, related to learning and reversal were

examined across the task and between age groups. Additionally, changes in the P3 ERP, a positive deflection at ~300ms post-stimulus, were examined. P3 amplitude increases with progressing reinforcement learning in adults, which is thought to reflect increasing consolidation of to-be-learned behaviours (Rose et al., 2001). The P3 may further elucidate neurocognitive differences between children and adults, for example, children may show weaker consolidation of associations than adults reflected by smaller P3 amplitude increases with learning. We predicted children would show smaller learning-related changes in performance and ERP amplitudes during the initial acquisition of S-R mappings than adults, reflecting poorer learning ability at this age. Further, we expected children to show greater disruptions to performance and greater reliance on feedback, indexed by smaller FRN amplitude changes, when the reversal occurred.

2. Method

2.1 Participants

Fourteen 9-11 year olds (12 male, mean age: 10.2 years) and 15 adults (5 male, mean age: 25.5 years) were recruited from local primary schools and the University of Nottingham to take part in this study. Participants were typically developing with no known neurological or psychiatric problems which may have affected brain function, right-handed (determined by the dominant hand for writing) and had normal or corrected-to-normal vision. Participants were tested in accordance with procedures approved by the University of Nottingham Medical School Ethics Committee and/or the East Midlands NHS Research Ethics Committee. Monetary reimbursement (£10) was provided for taking part.

2.2 Reinforcement learning task and testing procedure

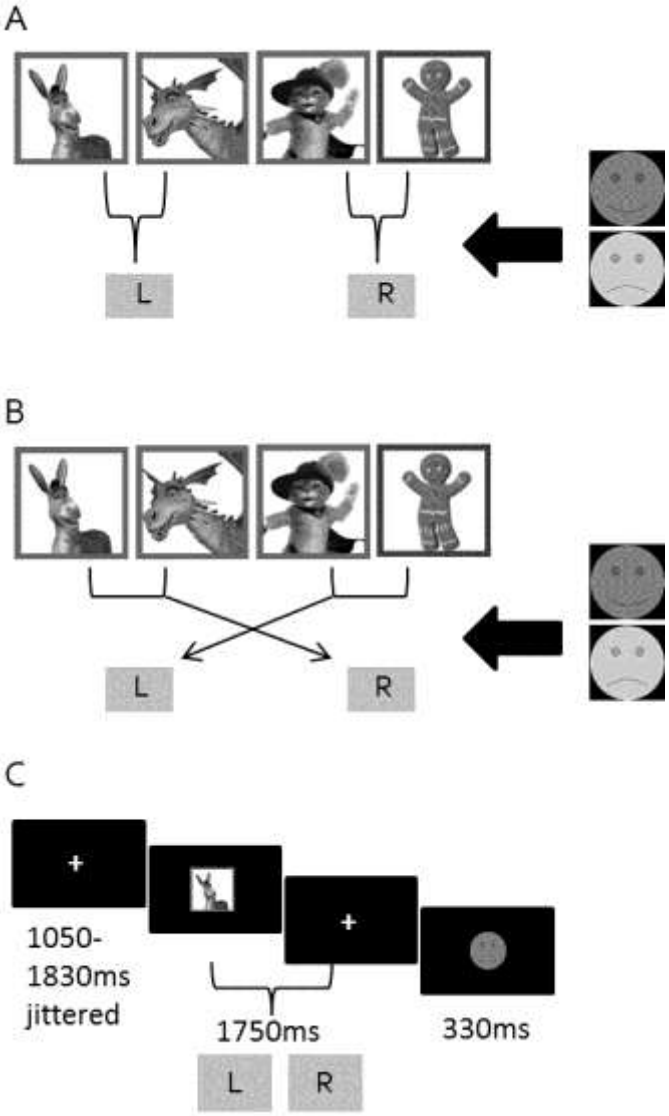
The reinforcement learning task (figure 1) required participants to learn by trial-and-error, using deterministic (always valid) performance feedback, to associate a set of two visual stimuli with a right hand button-press and another

two stimuli with a left hand button-press. Three blocks of trials were presented for participants to learn the stimulus-response (S-R) associations. The S-R mappings reversed unexpectedly in a fourth block, requiring participants to re-learn the correct response for each stimulus. In a fifth block, the mappings remained reversed. Every block contained 48 trials, with each stimulus presented 12 times in random order in each block. Particular S-R associations were counterbalanced across participants. Stimuli were four cartoon characters from a popular animated film, presented in colour and surrounded by a rectangular 3mm thick green frame. Stimuli measured 60x57mm including the frame. Circular yellow happy-face images and blue sad-face images (both 60mm in diameter) were used as positive and negative feedback. The words 'Too slow!' (10x90mm) were displayed in green for late responses.

On each trial, a white fixation cross (7x7mm) was presented for a jittered duration of 1050-1830ms followed by one of the four stimuli for a maximum duration of 1475ms. Stimulus presentation was terminated by the response and replaced by a second white fixation cross. Duration of the second fixation was dependent on the timing of the response, increasing with short latency responses and decreasing with long latency responses, resulting in a fixed time-window of 1750ms between stimulus onset and fixation offset. Participants responded using the left/right buttons on a Cedrus RB-530 response button box (Cedrus Corporation, San Pedro, California). Finally, feedback was displayed for 330ms. Correct/incorrect feedback was displayed if the participant responded before fixation offset; 'too slow' feedback was displayed otherwise to encourage prompt responses. All task objects were centrally presented on a black background on a Viglen computer (43cm monitor and 1024x768 pixels screen resolution). The task was programmed using E-Prime version 1.2 software (Psychology Software Tools Inc.).

After EEG set-up and task instructions, participants were seated in a dimly lit room at a distance of 60cm from the monitor. Four practice trials (one per stimulus) were completed followed by the five task blocks separated by self-paced rest breaks. The task was to gain as many points as possible by learning the correct button-press for each stimulus. One point was awarded per correct response and the number of points won was displayed after each block.

Figure 1 Task diagram



A. Acquisition task period (blocks 1-3). Children learned which buttons (left/right) to press for each character stimulus. Two characters required right responses; two required left responses. Children began by guessing which button to press for each character. Feedback was provided to inform whether that response was correct or incorrect for the character. Children were expected to remember (learn) which responses were correct for each character and produce those responses on all trials. Reinforcement feedback was provided throughout.
B. Reversal task period (blocks 4-5). The correct responses for each character reversed unexpectedly and children had to re-acquire the correct S-R associations using feedback. For example, the two characters previously associated with a right response were negatively reinforced when this S-R association was produced, indicating the child must change their response to a left button press.
C. Trial structure. Every trial began with a fixation screen. Next, one of the stimuli was presented followed by a second fixation screen, during which time the participant responded. Every trial ended with a feedback display.

Participants were instructed to attend closely to the feedback to ensure they were aware of the change to response mappings but were not told when this would occur.

2.3 Electrophysiological recording and data processing

EEG was recorded continuously throughout task performance using a Biosemi Active II recording system (Biosemi, Amsterdam, The Netherlands) from 128 silver/silver chloride (Ag/AgCl) scalp electrodes placed according to the 5-20 system (Oostenveld & Praamstra, 2001). The data were referenced online to the Common Mode Sense (CMS) electrode located to the left of Cz on the scalp, and sampled at a rate of 512Hz. Extra electrodes were placed on the inner orbital ridge and outer canthus of each eye and the right and left mastoids to record eye movements and non-ocular artefacts. Data were processed offline using Brain Vision Analyser 2.0 (Brain Products, Munich, Germany). Flat or noisy channels were removed prior to data processing. The data were re-referenced to the average reference and filtered with 0.5Hz high-pass, 30Hz low-pass, notch 50Hz zero-phase Butterworth 24dB slope filters. Ocular artefacts were corrected using the Gratton & Coles regression method (Gratton et al., 1983). The data were segmented into learning blocks (1-5). Within these blocks stimulus- and feedback- locked epochs were created by segmenting the data in time from -200ms to +1000ms around stimulus/feedback onset respectively. Epochs were baseline-corrected using a pre-stimulus/pre-feedback reference period of -200-0ms. Epochs were rejected if they contained amplitudes greater than ±90μv. Epochs were averaged within each block to create separate stimulus-locked and feedback-locked ERPs for blocks 1-5. Correct trials (minimum of 20 trials) only were included in the averages. No participants were excluded for failing to meet this criterion.

2.4 Analysis methods

Behavioural performance was assessed by examining changes in accuracy (% correct trials) and median RTs across the five task blocks. Electrophysiological correlates of reinforcement learning were the stimulus-

locked P3 and feedback-locked FRN ERP components. Based on parameters used in previous research and inspection of the grand and individual average waveforms, the stimulus-locked P3 was defined as the most positive peak in channel Pz in the time period 400-600ms post-stimulus and the feedback-locked FRN was defined as the most negative peak in channel FCz in the 200-350ms (adults) or 250-400ms (children) post-feedback period of the P3 and FRN were extracted for each learning block and used in analyses.

To test the hypothesis that children show poorer learning of S-R associations than adults, mixed-model ANOVAs were performed on the data from the acquisition phase, namely task blocks 1 to 3. ANOVA models consisted of within-subjects factor block (3 levels) and between-subjects factor age (2 levels) and were run separately for each dependent variable (accuracy, RT, P3 amplitude, FRN amplitude). To test the hypothesis that children will experience greater disruption than adults when the associations change, mixed-model ANOVAs with within-subjects factor block (3 levels) and between-subjects factor age (2 levels) were conducted on the accuracy, RT, P3 and FRN data from the reversal phase of the task, that is, blocks 3 to 5. Greenhouse-Geisser corrections for violations of sphericity were used where appropriate. Significant main effects of block were further investigated with paired-samples t-tests to compare dependent variables across successive learning blocks (1-2, 2-3, 3-4, 4-5). Significant interactions between block and age were further investigated by calculating difference scores to reflect the magnitude of change in a dependent variable (accuracy, RT, P3, FRN) in a given block compared with the previous block while taking into account baseline group differences in performance and amplitude. Difference scores were created for children and adults separately by subtracting dependent variable values in each block from those in the previous block, for example, RT in block 4 was subtracted from those in block 3 to characterise the extent to which RT decreased with the reversal of associations in block 4 compared with block 3. Independent-samples t-tests were used to compare difference scores across groups. Finally, to determine whether ERP amplitudes related to task performance, Pearson correlation coefficients were computed between each of the performance and electrophysiological variables across learning blocks in children and adults.

3. Results

3.1 Behavioural reinforcement learning effects

3.1.1 Acquisition phase (blocks 1-3)

3.1.1.1 Accuracy

Accuracy rates increased significantly across task blocks ($F (2, 54) = 22.84$, $p < .001$, $\eta^2 = .458$) (figure 2). Children were less accurate than adults ($F (1, 27) = 9.49$, $p = .005$, $\eta^2 = .260$). There was no interaction between task block and age. Planned paired t-tests showed that, across groups, accuracy increased significantly from block 1 to 2 ($t (28) = -4.34$, $p < .001$ (1-tailed), $d = -.76$) but not from block 2 to 3 ($p > .05$).

3.1.1.2 RT

There was no main effect of block or block*age interaction for RT, but children were significantly slower than adults overall ($F (1, 27) = 21.01$, $p < .001$, $\eta^2 = .438$) (figure 3).

3.1.2 Reversal phase (blocks 3-5)

3.1.2.1 Accuracy

Accuracy differed significantly across task blocks (accuracy: $F (2, 54) = 19.68$, $p < .001$, $\eta^2 = .422$). Children were significantly less accurate ($F (1, 27) = 12.21$, $p = .002$, $\eta^2 = .311$) than adults. Age group significantly interacted with block ($F (2, 54) = 3.23$, $p = .047$, $\eta^2 = .107$). Across groups, planned paired t-tests showed that accuracy significantly decreased from block 3 to 4 ($t (28) = 6.49$, $p < .001$ (1-tailed), $d = .98$) and increased from block 4 to 5 ($t (28) = -3.91$, $p < .001$ (1-tailed), $d = .47$). Analysis of difference scores revealed a greater decrease in accuracy ($t (27) = 2.49$, $p = .01$ (1-tailed), $d = -.89$) from blocks 3 to 4 in children than in adults (figure 4). Children and adults did not differ in the extent to which their accuracy increased across blocks 4 to 5.

Figure 2
Mean accuracy by learning block for children and adults. Error bars represent standard error.

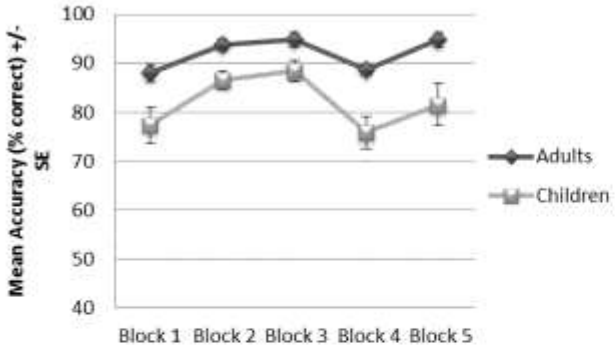


Figure 3
Mean of median RTs by learning block for children and adults. Error bars represent standard error.

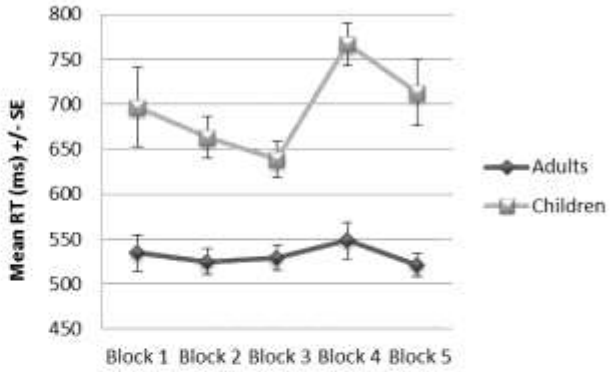


Figure 4
Mean difference scores in accuracy between blocks 3-4 and 4-5 for children and adults. Error bars represent standard error.

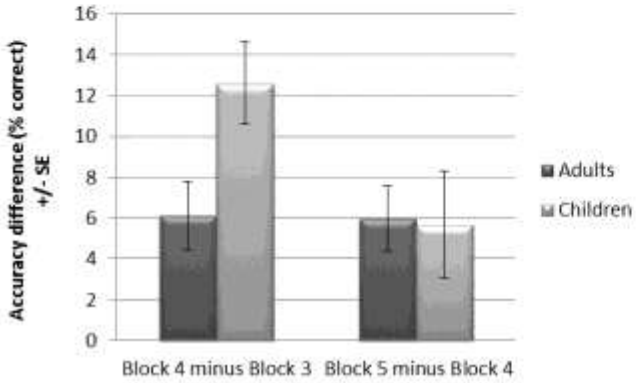
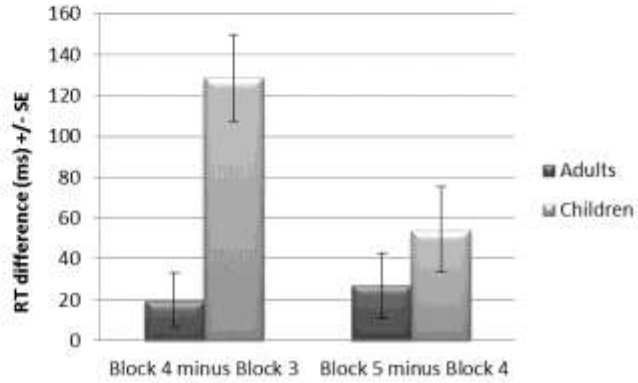


Figure 5
Mean difference scores in RT between blocks 3-4 and 4-5 for children and adults. Error bars represent standard error.



RT differed significantly across task blocks: F (2, 54) = 15.02, p < .001, η^2 = .357. Children were significantly slower than adults (F (1, 27) = 39.71, p < .001, η^2 = .595) and there was a significant block*age group interaction (F (2, 54) = 8.75, p = .001, η^2 = .245). Planned paired t-tests showed RT significantly increased from block 3 to 4 (t (28) = -4.56, p < .001 (1-tailed), *d* = -.63) and decreased from block 4 to 5 (t (28) = 3.11, p = .002 (1-tailed), *d* = -.29) across groups. Analysis of difference scores showed there was a greater increase in RT (t (27) = 4.37, p < .001 (1-tailed), *d* = -1.63) from blocks 3 to 4 in children than in adults (figure 5) but no group difference in RT decreases across blocks 4 to 5.

3.2 Electrophysiological reinforcement learning effects

3.2.1 Acquisition phase (blocks 1-3)

Amplitude of the stimulus-locked P3 differed significantly by task block (F (2, 54) = 3.51, p = .04, η^2 = .115) (figures 6, 7). Amplitudes were significantly greater in children than adults (F (1, 27) = 14.48, p = .001, η^2 = .349). There was no interaction between block and age. Across groups, P3 amplitude increased significantly from block 1 to 2 (t (28) = -2.59, p = 0.07 (1-tailed), *d* = -.21) and decreased significantly from block 2 to 3 (t (28) = 2.51, p = .009, *d* = .17).

Amplitude of the feedback-locked FRN decreased significantly across blocks (F (2, 54) = 18.63, p < .001, η^2 = .408) (figures 8, 9). Children's FRN amplitudes were significantly larger than those of adults (F (1, 27) = 6.54, p = .02, η^2 = .195). No significant block*age interaction was revealed. FRN amplitude decreased significantly from block 1 to 2 (t (28) = -4.85, p < .001 (1-tailed), *d* = -.89) but not from block 2 to 3 (p > .05) across groups.

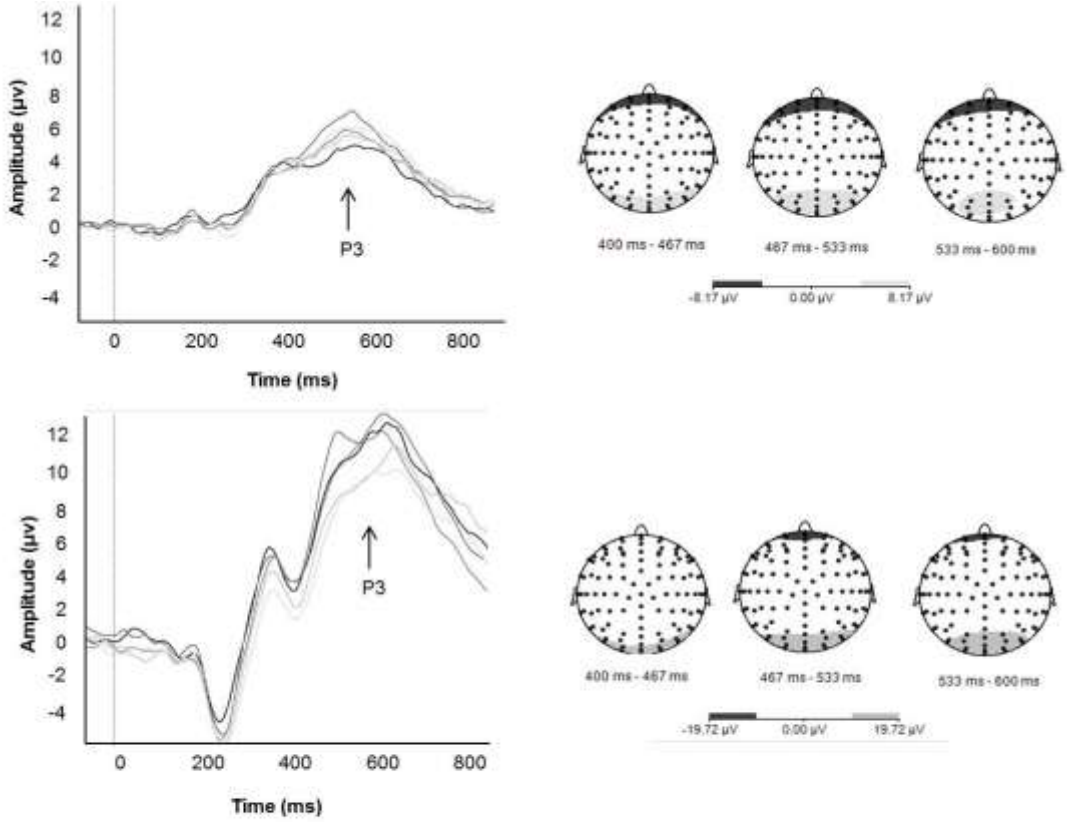
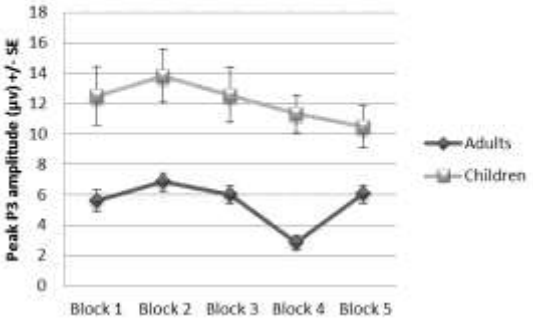


Figure 6. Stimulus-locked P3 at Pz
Left panel: Stimulus-locked grand average waveforms plotted by learning block for adults (top) and children (bottom). Black line: block 1, Dark grey line: block 2, Mid-grey line: block 3, pale grey line: block 4, lightest grey line: block 5
Right panel: scalp topography during the P3 time-range showing positivity at posterior sites for adults (top) and children (bottom)

Figure 7.
Peak P3 amplitudes plotted by learning block for adults and children



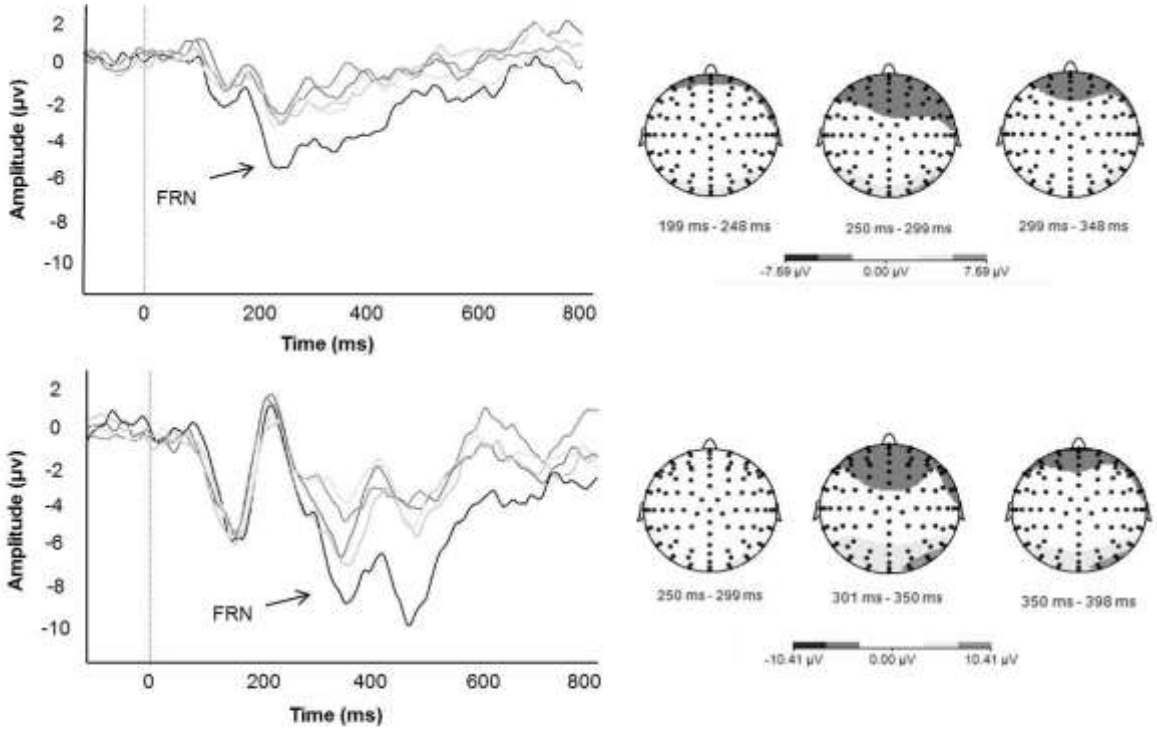
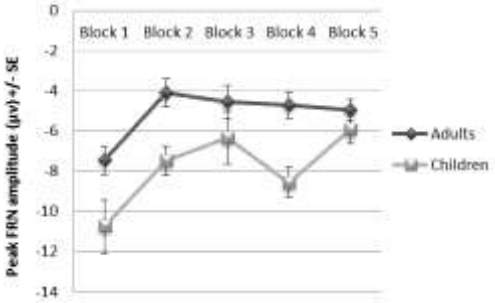


Figure 8. Feedback-locked FRN at FCz
Left panel: Feedback-locked grand average waveforms plotted by learning block for adults (top) and children (bottom). Black line: block 1, Dark grey line: block 2, Mid-grey line: block 3, pale grey line: block 4, lightest grey line: block 5
Right panel: scalp topography during the FRN time-range showing negativity at frontal sites for adults (top) and children (bottom)

Figure 9.
Peak FRN amplitudes plotted by learning block for adults and children



3.2.2 Reversal phase (blocks 3-5)

P3 amplitudes changed significantly across blocks (F (2, 54) = 8.31, p = .001, η^2 = .235) and were significantly larger in children than adults (F (1, 27) = 20.96, p < .001, η^2 = .437). There was a significant block*age interaction (F (2, 54) = 6.97, p = .002, η^2 = .205). Across groups, P3 amplitude decreased significantly from block 3 to 4 (t (28) = 3.74, p < .001 (1-tailed), *d* = .40) and increased significantly from block 4 to 5 (t (28) = -1.88, p = .04, *d* = -.25). Analysis of difference scores showed that the amplitudes of adults decreased significantly more from blocks 3 to 4 (t (27) = -3.80, p < .001 (1-tailed), *d* = .63) and increased significantly more from blocks 4 to 5 (t (27) = 2.13, p = .02, *d* = .80) than those of children.

FRN amplitudes differed at trend level between blocks (F (1.59, 43) = 3.43, p = .07, η^2 = .101) and were significantly larger in children than in adults (F (1, 27) = 5.44, p = .03, η^2 = .168). There was a significant interaction between block and age (F (1.59, 43) = 3.43, p = .05, η^2 = .113). Amplitude differences between blocks 4 and 5 were significantly larger in children than adults (t (27) = 3.44, p < .001 (1-tailed), *d* = -1.06) but did not differ between age groups for blocks 3 to 4.

3.3 Relationships between performance and electrophysiological variables

In children only, accuracy and FRN amplitude were significantly positively correlated in block 1 (*r* (14) = .631, p = .02, r^2 = .40) and block 4 (*r* (14) = .566, p = .04, r^2 = .32), reflecting more positive, i.e. reduced, FRN amplitude in participants with higher accuracy levels in the first block of the acquisition phase and on reversal of mappings in block 4. No other correlations reached significance in children or adults.

4. Discussion

This study investigated neurocognitive differences in reinforcement learning in typically developing children and adults. The aims were to extend previous research by examining developmental differences when task difficulty

was appropriate for children and when unanticipated changes in response contingencies were introduced. Analysis of performance and electrophysiological activity during a simple reinforcement learning and reversal task in children and adults revealed two important findings. First, children and adults did not differ in learning-related performance or ERP changes during the initial acquisition of S-R associations. Second, performance was significantly more disrupted in children than adults when reversal of S-R associations was required, and this was accompanied by developmental differences in neural correlates of consolidation and feedback processing, the P3 and FRN event-related potentials. These findings are discussed below.

4.1 Acquisition of simple new behaviours by reinforcement

Children and adults showed equivalent increases in accuracy and P3 amplitude and decreases in FRN amplitude as they learned the S-R associations. Therefore, in contrast to previous research (Crone et al., 2004; Eppinger et al., 2009; Hämmerer et al., 2010) children in this study acquired and consolidated new behaviours and gradually decreased their use of external feedback at the same rate as adults. Accuracy significantly correlated with FRN amplitude during the first task block in children, indicating that feedback processing was related to the correct production of S-R associations in children in this study. This extends previous research by indicating that feedback processing and guidance of goal-directed behaviour by reinforcement information is not deficient in children compared with adults, as has previously been proposed (Hämmerer & Eppinger, 2012). Our findings indicate that when reinforcement learning is straightforward, the neural mechanisms underlying this basic form of learning work as efficiently in children as in adults. Problems with acquiring new behaviours may only appear in children when reinforcement learning becomes more complicated, for instance when reinforcements are unclear, for example probabilistic, and demands on other maturing cognitive functions such as working memory or executive function are high. As such, our findings highlight the importance of ensuring task difficulty is appropriate for children in developmental investigations of reinforcement learning.

4.2 Developmental differences in altering learned behaviours by reinforcement

Performance was significantly more impaired in children than adults when reinforcements changed and the reversal of S-R associations was required in block 4 of the task. Nevertheless, following the reversal children improved their performance at the same rate as adults (task block 5). These findings suggest that children have specific performance difficulties when unexpected changes in reinforcements occur, but are eventually able to re-acquire simple behaviours in a similar manner to adults. Analysis of the P3 and FRN revealed further developmental differences in neurocognitive processes underlying performance.

The magnitude of P3 amplitude changes during learning can be considered to index the strength of internal representation of correct S-R associations in working memory (Barceló et al., 2000; Rose et al., 2001). P3 amplitude changes were significantly greater in adults than children, decreasing more during reversal of associations and increasing more with re-acquisition of reversed mappings, indicating that internal representations of the S-R associations underwent less adaptation and re-consolidation in children than adults. In contrast, FRN amplitude changes were greatest in children, decreasing more with re-learning of the associations in block 5 than in adults. Indeed, FRN amplitude showed little variation after the first task block in adults while a prominent increase with reversal and decrease with re-acquisition was observed in children, indicating that feedback processing varied more with reversal and re-learning in children than adults. Previous authors have emphasised that difficulties with feedback processing, resulting from immature performance monitoring functions of the developing prefrontal cortex, underlie children's poorer reinforcement learning performance (Hämmerer & Eppinger, 2012; Hämmerer et al., 2010). It has been suggested that children are less successful than adults in integrating feedback information with motor action plans, or that children use feedback in a less goal-directed manner than adults (Hämmerer & Eppinger, 2012; Hämmerer et al., 2010). In contrast to the latter proposal, our findings suggest that children do use feedback to drive goal-directed learning behaviour. Changes in FRN amplitude were associated with performance accuracy in children when most re-learning

was occurring (block 4). Furthermore, FRN changes were largest in children, indicating children were using feedback more than adults to guide behaviour. However, as children performed more poorly than adults, children may have had greater difficulty in integrating feedback information to consolidate S-R associations and so produce the correct behaviours.

Errors were not sufficiently numerous to allow analysis of the ERN in this study. However, the profile of P3 and FRN effects here are similar to the ERN and FP findings reported by Eppinger et al. (2009), and support the proposal put forward by those authors that children build weaker internal representations of to-be-learned behaviours and engage in greater processing of external feedback than adults when alterations in reinforcement learning are required. This may be due to interference arising from the extra cognitive processing demands of reversing the S-R associations, such as the requirement to suppress the previously correct behaviours and produce new responses that conflict with the original S-R associations. A wealth of evidence demonstrates that such executive functions are poorer in children than adults (Johnstone et al., 2005; Ladouceur et al., 2007; Rueda et al., 2004). Therefore, it may be that these additional processing requirements reduce children's cognitive capacity for learning, decreasing the efficiency of the processes of consolidating the reversed S-R associations and integrating new feedback information with behaviour plans. Children may exercise greater feedback processing to compensate for these difficulties.

Another possible explanation for our findings is that children learn in a different manner from adults. Research in adults has shown that providing information about reward likelihood enhances the reinforcement learning process. For example, Li et al. (2011) and Walsh and Anderson (2011) compared adults' performance on a probabilistic S-R learning task when no information about reinforcement probabilities was given and adults were required to learn the S-R associations solely by feedback, with a separate condition in which participants were instructed as to the probability that each S-R pair would be followed by valid feedback, for example that one S-R association would be correctly reinforced on 30% of trials. Adults' performance increased gradually in the no-instruction learning condition, but began and remained at asymptote in the instruction condition. The enhancing

effect of instruction on learning is suggested to reflect the top-down influence of rules for learning represented in prefrontal regions on striatal reinforcement learning mechanisms (Li et al., 2011).

In the current study, a rule for how the S-R associations should be re-learned would have been acquired easily after only a few trials in block 4 based on knowledge of what the original S-R mappings were and identifying that the mappings simply had to be reversed. If implemented, this rule would facilitate faster re-learning of the associations. Adults verbally reported that they realised the S-R combinations in block 4 were simply the opposite of those in blocks 1 to 3. Adults' rapid increase in consolidation of the new S-R associations, improvement in performance and minimal variation of the FRN suggests that they used this inferred rule to guide re-learning rather than relied on external feedback. Children's slower consolidation of reversed S-R associations, more disrupted performance, and greater feedback processing suggests that they were relying on external reinforcement information rather than the internally derived rule for re-learning that adults appeared to employ. Therefore, a possible explanation for the developmental difference in performance and neurocognitive processing in the reversal phase is that unlike adults, children do not infer and use rules for learning, and instead rely on slower feedback-based learning. It is unclear whether this reflects an inability of children to infer learning rules and use them to drive performance due to under-developed prefrontal regions, or a strategic preference for experience-based learning in children. Future studies comparing instruction-based and experience-based learning in children and adults would be useful in clarifying this issue.

4.3 General developmental differences in performance and ERP amplitudes

In addition to learning-related developmental differences, children showed less accurate and slower performance and larger P3 and FRN amplitudes than adults overall. This is consistent with evidence that children's accuracy rates are lower and response times are slower than adults' across a broad range of cognitive tasks, including executive function and attention (Burgund et al., 2006; Johnstone et al., 2005; Ladouceur et al., 2007). These differences are therefore more likely to be general indicators of proficiency in

performing cognitive tasks requiring coordinated manual responses and are not specific to learning. The present findings are consistent with previous reinforcement learning studies which have shown greater FRN amplitude in children than adults, possibly reflecting greater sensitivity to feedback in childhood than adulthood (Eppinger et al., 2009; Hämmerer et al. 2010). Other factors such as age differences in skull density, brain size and cortical folding cannot be ruled out (Segalowitz & Davies, 2004), although the finding reported here of greater learning effects on FRN amplitude in children than adults strengthens the hypothesis that the overall amplitude differences may reflect true differences in the electrical activity of neural networks supporting feedback processing.

5. Conclusions

The current findings revealed that children can perform as well as adults in acquiring simple new stimulus-response behaviours by reinforcement, providing the learning situation is uncomplicated with minimal demands on other cognitive abilities such as executive function and working memory. Moreover, neurocognitive processes of consolidating internal representations of correct behaviours and processing reinforcing feedback information are comparable between children and adults in simple learning situations. However, when modification of learned behaviours by reinforcement is required, children's performance is significantly more disrupted than that of adults, children show less consolidation of the new behaviours and greater reliance on feedback information than adults. These neurocognitive differences specific to altering reinforcement learning may reflect a different style of learning in children and adults, that is, internally inferred rule-based learning in adults compared with externally driven experience-based learning in children. Alternatively, children may experience a general reduction in the efficacy of reinforcement learning processes due to enhanced demands on executive function resulting from the requirement to modify behaviours.

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Conflicts of interest

The authors have no conflicts of interest.

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APPENDIX B: A PILOT STUDY TO ASSESS BEHAVIOURAL CORRELATES OF SEQUENCE LEARNING IN THE SRT PARADIGM

Introduction

This pilot study was carried out to ensure that the version of the SRT paradigm designed for the present research elicited the typical sequence learning effects associated with this task. Many previous studies using the SRT paradigm have employed unbalanced repeating sequences in sequence blocks and pseudorandom stimulus presentation in non-sequence blocks (e.g. Channon et al., 2003; Nissen & Bullemer, 1987). As discussed in chapter 5, the use of unbalanced sequences and pseudorandom non-sequence blocks is problematic when assessing possible impairments in sequence learning in TS because the structure of the blocks could potentially enable learning of pairwise associations among sequence items in sequence blocks, for example that one item in the sequence follows another most often. This associative learning might speed up RTs during sequence blocks and mask difficulties with sequence learning in TS. To address these design issues, the current SRT task used balanced sequences for the repeating sequence blocks and structurally matched, balanced non-sequence blocks. The typical SRT sequence learning effects of decreased RTs in sequence blocks versus non-sequence blocks (Jackson et al., 1995; Meulemans et al., 1998; Nissen & Bullemer, 1897) were expected to be observed in this task version.

Participants

Twelve typically developing young adults (20-35 years, mean age: 29.5 years, 3 males) were recruited from the University of Nottingham to take part in this pilot study. Participants were tested in the Division of Psychiatry, University of Nottingham and no reimbursement for participation was given. Recruitment and testing were carried out in accordance with ethical approval from the University of Nottingham Medical School Ethics Committee.

Task design and testing and analysis procedures

The SRT task was identical to that used in the main study and is described in full in chapter 5, section 5.1.1. Briefly, participants were required to press response buttons corresponding to a cartoon bomb character's location on screen. The character appeared in one of four boxes horizontally arranged along the centre of the screen on every trial and participants responded using the 1, 2, 9, 0 keys on the keyboard, corresponding to the far-left, centre-left, centre-right, far-right boxes. Five blocks of 120 trials were presented. Blocks 2, 3, and 5 were the sequence blocks in which a 12-item balanced sequence was repeated 12 times (sequence A: 019210902912 or sequence B: 120929010219 counterbalanced across participants). Blocks 1 and 4 were the non-sequence blocks in which ten different balanced 12-item location runs matched on structure to the repeating sequences were presented. Participants completed four practice trials, one for every box location the stimulus could appear in to familiarise participants with the task, and then the five experimental blocks. See section 5.1.1 for stimulus details, trial procedure and presentation equipment (laptop).

Behavioural indices of sequence learning

Behavioural indices of sequence learning were RTs in each block (median RTs per block). Sequence learning was assessed by comparing behavioural indices in sequence compared with non-sequence blocks using repeated-measures ANOVAs with block as a within-subjects factor (5 levels) and RT as the DVs. Significant effects of block were further investigated with repeated-method planned comparisons.

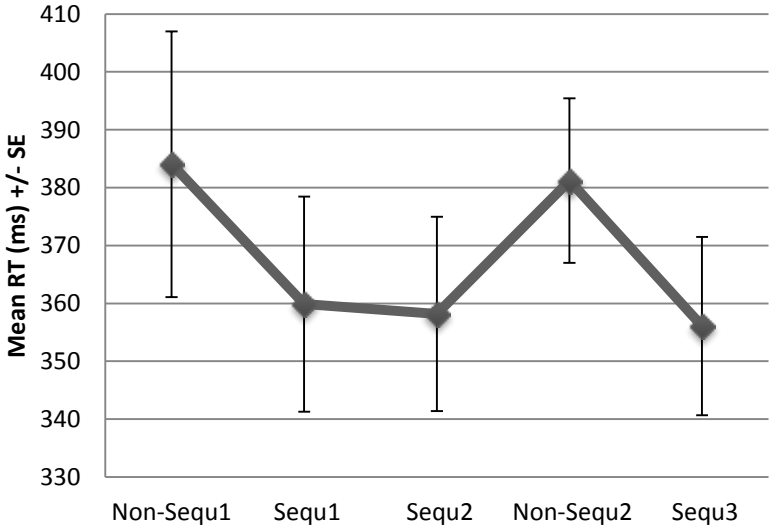
Results

Mean RTs for the sample are displayed in figure B-1. RTs showed a large decrease from the first to second task blocks (block 1: 384ms, Block 2: 359ms), likely reflecting effects of both practice and non-conscious learning of

the sequence (figure C-2). RTs decreased slightly further in the second sequence block (block 3: 358.2ms), before markedly increasing with the change to non-sequence trials in block 4 (381.2ms), and decreasing again with the return to sequence trials in block 5 (365.1ms). The effect of block on RT was significant overall ($F (4, 44) = 3.018$, $p = .028$, $\eta p^2 = .215$) and further analyses revealed RT decreases in the second and fifth sequence blocks following the previous non-sequence blocks were significant (block 2 versus block 1: $p = .044$, $\eta p^2 = .399$; block 5 versus block 4: $p = .027$, $\eta p^2 = .371$). The increase in RT in block 4 after block 3 approached significance ($p = .088$, $\eta p^2 = .242$).

Figure B-1

Mean (of median) RTs in each SRT task block. Error bars represent the standard error of the group mean.



Conclusions

As predicted, this version of the SRT paradigm produced clear and statistically significant RT effects, suggesting the task successfully engaged habit-learning processes and non-conscious learning of the repeating sequence occurred. Importantly, the effects were consistent with previous findings in

children and adults, despite the differences in structure of the task blocks across the current and previously used SRT versions. Previous work has tended to employ unbalanced sequence and non-sequence blocks (Nissen & Bullemer, 1897; Thomas et al., 2004). The present findings indicate that our structural design alterations do not weaken sequence learning in the task. Furthermore, although participants in this pilot study were adults, the sequence learning effects are consistent with those found in studies with children and adults (Meulemans et al., 1998; Thomas et al., 2004) and hence it was concluded that this version of the task would be effective with children in the main study.