Characterising the Comorbid Subtypes of Tourette Syndrome

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OVERVIEW

This study set out to examine neuropsychological function in Tourette Syndrome (TS) with particular reference to its comorbid presentation with Attention Deficit Hyperactivity Disorder (ADHD). The Literature Review outlines the clinical presentation of TS and ADHD, theories of their aetiology and the disorders that often occur comorbidly with them. This leads to an examination of the neuropsychological profile of TS and ADHD with particular emphasis on defining the concepts and tests of inhibition and attention. This review raises a number of unanswered questions in the literature. This is covered in the Empirical paper and particularly relates to the extent to which ADHD that presents comorbidly with TS is qualitatively different from ADHD that presents alone. In a novel examination of this, children with TS comorbid with ADHD were compared to individuals with TS and those with ADHD on a battery of multiple measures of motor, cognitive and trait inhibition. It was found that although the groups had a similar profile of inhibitory functioning, inhibitory deficits appeared to be most prominent in individuals with ADHD comorbid with TS. Crucially, it manifested that inhibition was not a unitary construct with motor, cognitive and trait inhibition appearing to be relatively independent processes. These findings were discussed in relation to areas of overlap between these neurodevelopmental disorders and the implications that this has on theories of their underlying aetiology and clinical management. Finally the Critical Appraisal allowed for reflection into the research process and explores experiences during interviewing and the clinical implications of this study.

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Literature Review

Characterising the Comorbid Subtypes of Tourette Syndrome

ABSTRACT

Tourette syndrome (TS) is a neurodevelopmental disability characterised by a cognitive profile of executive function deficits, particularly relating to inhibitory control. There is much evidence that TS is likely to occur comorbidly with other disorders and that this may exacerbate the presence of cognitive disruptions. Attention Deficit Hyperactivity Disorder (ADHD) is one of the neurodevelopmental disorders that TS often occurs comorbidly with. This review provides an examination of TS including its clinical presentation, aetiology, comorbidities and cognitive profiles. A similar discussion is followed for ADHD. This leads to an examination of the key processes and measures of attention and inhibition with reference to these disorders. It is hoped that by examining these shared profiles, it might lead to a greater understanding of the overlap between these two neurodevelopmental disorders.

This literature review will outline the clinical presentation of Tourette Syndrome (TS), including the aetiological theories that exist and the comorbidities that often occur. This will be followed by a similar review for Attention Deficit Hyperactivity Disorder (ADHD). This will lead to an appraisal of the neuropsychological profile of TS and ADHD with particular reference to tests of the executive function subcomponents of inhibition and attention. Whilst this review will indicate that inhibitory dysfunction is a key area to TS and ADHD research, it will aim to indicate the need for tighter methodological controls in order to elucidate the precise characteristics of similarity and difference between these two groups.

1.0 TOURETTE SYNDROME

1.1 Clinical Presentation

TS is a neurodevelopmental disorder. The diagnostic criteria specify that motor and phonic tics must be present and occur many times per day over more than one year. The criteria specify that the onset must be before age 18 years and is not due to the physiological effects of substances (American Psychiatric Association, 2000). Although TS has a life-long course, the symptoms typically wax and wane. This includes changes in variability of expression, fluctuations of severity, and exacerbations in tic severity under the influence of stress (Robertson, 2000).

Epidemiological data suggest age of onset that ranges from 6-7 years with greater occurrence in males by a factor of 3-9 times (American Psychiatric Association, 1994).

Recent prevalence estimates range from 0.8% to 1.9% in a screening of six mainstream schools (Hornsey Banerjee, Zeitlin, and Robertson, 2001); with more conservative estimates suggesting population frequencies of 0.05% or less (Apter et al., 1993) or 0.001- 0.01% (American Psychiatric Association, 1994). Robertson (2000) noted that TS is present in all cultures, countries and racial groups and is more common in males and in children with special educational needs.

Robertson (2000) has described the range of TS symptoms and notes that coprolalia (inappropriate involuntary uttering of obscenities) occurs in less than one-third of clinic TS patients, copropraxia (involuntary inappropriate obscene gestures), echolalia (imitation of sounds or words of others), echopraxia (imitation of actions of others) and palilalia (repetition of the last word, phrase or syllable of a word uttered by the patients) occur in a substantial proportion of TS clinic patients. Other behaviours that are understood to reflect disinhibition include insulting others and making socially inappropriate actions.

With regards to intellectual profile, Schuerholz et al., (1996) examined the frequency of learning disabilities and the neuropsychological profile of individuals who had TS or TS comorbid with ADHD (TS + ADHD). They found that whilst the TS only group's mean IQ exceeded that of their parents, the TS + ADHD group's mean IQ was comparable with their parents, with only 23% of their sample showing learning difficulties, all of whom had comorbid ADHD with their TS.

Clinical manifestations of TS have been investigated in a number of studies. Chang, Tu, and Wang (2004) investigated patterns of psychopathology in individuals with TS and noted that motor tics were consistently present, with those involving the head and eyes to be the first to manifest. Coprolalia occurred in 44.1% of their sample with a mean age of onset being 11.6 years. Importantly they noted that the impact of TS symptoms varied by age with older individuals reporting more emotional distress and younger individuals reporting more somatization and obsessive-compulsive symptoms. Similarly high rates of coprolalia (43%) have been reported by Eapen, Fox-Hiley, Banerjee and Robertson (2003) who raised the possibility that this higher than normal rate (typically 14%) is due to the recruitment of participants from tertiary referral clinics.

1.2 Aetiology

1.2.1 Neuroanatomy

In evaluating if there are underlying commonalities between TS and its comorbid disorders, one needs to understand the neuroanatomical regions that have been implicated in its underlying cause. Comparison of the similarities between these areas and the regions implicated in other disorders might be helpful in illuminating shared underlying mechanisms.

Limitations to the value of neuroimaging studies in TS have been thought to be because most studies are carried out on adult populations (Chowdhury, 2004). Nonetheless, Chowdhury (2000) reviewed a range of studies that suggest that the following regions and pathways of the brain are involved in TS: (i) Subcortical nuclei – including basal ganglia (caudate, putamen and globus pallidus and thalamus); (ii) Orbitofrontal

pathways; (iii) Sensorimotor pathways (iv) Temoporolimbic pathways; (vi) Cingulate cortex and (vii) Brainstem motor nuclei. Other neurological reports reiterate that the frontal–subcortical, basal ganglia–thalamocortical, and nucleus accumbens–limbic system circulatory are compromised in TS (Robertson, 2000).

There have been more systematic examinations of the basal ganglia which are thought to play a key role in TS. Schuerholz, Baumgardner, Singer, Reiss and Denckla (1996) suggest that abnormalities of the basal ganglia and its interconnecting pathways might mediate the neurocognitive characteristics of children with TS, with possible left laterlisation of basal ganglia involvement. Dale (2003) describes the basal ganglia as a collection of nuclei in the centre of the brain that contain neurones that receive and modify information from the cerebral cortex. Dysfunction to this area is proposed to result in extrapyramidal movements (chorea, hemiballismus, dystonic, tics and parkinsonism) (Dale, 2003). Furthermore, Dale (2003) noted that there is a spectrum of post-streptococcal CNS disease that induce hyperkinetic movement disorders and that tic disorders, TS and obsessive-compulsive disorder may result from immune-mediated basal ganglia processes.

In contrast to this, others have advocated that there are key areas other than the basal ganglia implicated in TS. For example, Mercadante, Rosario-Campos, Quarantini and Sato (2004) suggest that tics and TS are the result of motor circuit abnormalities that consist of projections from the motor cortex; for which individuals with TS have been reported to have abnormal volumes of the caudate nucleus, putamen and globus pallidus. Based upon this, it has been proposed that individuals with TS are incapable of

inhibiting stimuli secondary to premonitory sensory phenomena which results in the activation of the motor circuit and in the development of motor and phonic behaviours (Mercadante et al., 2004).

1.2.2 Neurophysiology

In contrast to the literature examining the neuroanatomical regions implicated in TS, there have been suggestions of abnormal cortical excitability in TS. Recent neurophysiological studies point to impaired cortical inhibition as indicative of underlying pathophysiology that leads to tics and inattentive/hyperactive behaviours (Gilbert, Bansal, Sethuraman, Sallee, Zhang, Lipps and Wasserman, 2004). Gilbert et al. (2004) assessed symptom severity in TS compared with neurophysiological measures. They found that cortical inhibition was significantly and inversely associated with greater motor tic severity in TS and more so with ADHD (particularly hyperactive/impulsive) symptom severity. These findings were seen to be consistent with the positive treatment effects of methylphenidate in ADHD (Gilbert et al., 2004).

1.2.3. Neurochemistry

1.2.3.1.Dopamine theories of TS

In contrast to the neuroanatomical and neurophysiological theories, there is much evidence that dopamine is involved in a range of clinical syndromes and plays a crucial function in TS. Once again, understanding the extent of this in TS and other disorders might help to explicate how these syndromes are linked. Supporting this notion, Sandor (1998) recognised that the evidence that dopamine receptor antagonists decrease the severity of tics suggests that TS is associated with excessive dopamine in the central

nervous system. Further, Müller-Vahl et al., (2000) noted that clinical observations support the involvement of the dopamine system in the pathophysiology of TS. For example, there is much evidence that dopamine blocking agents like haloperidol or pimozide reduce tics; whilst drugs that stimulate the domaminergic system, like amphetamine, aggravate them, thus indicating that hypersensitivity or an increased number of postsynaptic dopamine receptors characterise TS (Müller-Vahl et al., and Serra-Mestres et al., 2004).

In view of this, Müller-Vahl et al. (2000) investigated TS patients using single photon emission computed tomography (SPECT) and found evidence that the spontaneous recovery from tics that had been sometimes reported in adulthood was due to evolving decreased dopamine D2 receptor binding capacity during the course of the disease and that TS in general is associated with an increased dopamine transporter activity. Other researchers such as Serra-Mestres et al. (2004) have supported the notion that patients with TS have higher dopamine transporter binding of the basal ganglia. Whilst Sandor (1998) commented upon the changing presentation of tics in individuals with TS and noted findings that about 75% of older adolescents may experience a reduction of their symptoms as they enter their third decade.

1.2.4 Genetics

Of final importance to explorations of the aetiology of TS is that genetic factors could precede the contributors discussed. When Giles de la Tourette first described TS in 1885 he noted that the disorder was a hereditary one (Sandor, 1998). Nonetheless, there is still some uncertainty about the genetic cause of TS. There is evidence that TS runs in

families, for example Cardona, Romano, Bollea and Chiarotti (2004) found that a sample of individuals with tic disorder 56.2% had one or more family members (first and second degree relatives) who had a history of tic disorder. Early research has suggested that there is an association between TS and the X chromosome, explaining the proponderance of males with TS (Comings and Comings, 1986). Based upon the evidence in the current literature, Sandor (1998) concluded that TS is not only familial, but also likely to be inherited with an autosomal-dominant pattern, and that environmental factors may interact significantly with a genetic predisposition.

Diaz-Anzaldúa et al. (2004) noted the strong evidence supporting the involvement of genetic factors in TS, although no specific genes have been identified. Based on suggestions of chromosomal anomalies on chromosome 7q31 region they investigated the association between 7q31 markers and TS. They found significant associations between the presence of TS and two markers on the 7q31 region. Further, a study by Gadzicki et al. (2004) investigated the central cannabinoid receptor gene (*CNR1*) in view of suggestions of a therapeutic effect of *Cannabis sativa* L. They failed to find evidence that genetic variation of the *CNR1* gene explained the relationship between the cannabinoid system and TS.

In contrast to these theories, Robertson (2000) recognised that different genes may be responsible for TS in different families (genetic heterogeneity). Robertson (2000) proposed that in addition to inherited genetic vulnerability, perinatal factors reflective of a stress-diathesis model might influence the expression of TS; for example, genetic vulnerability interacting with prenatal factors or insults such as birth injuries, CNS

stimulants, stress, and infections with streptococci or viruses may affect the expression of TS.

1.3 Comorbidity

There is undoubtedly high comorbidity in TS. Highest comorbidity rates are reported between TS and Obsessive Compulsive Disorder (OCD) and/or ADHD (American Psychiatric Association, 1994). There appears to be an inextricable link between TS and other disorders. Supporting this interconnection are reports that problems with attention, hyperactivity or impulse control typically precede the onset of tics (Robertson, 2000), perhaps suggesting that these disorders are not entirely independent.

Eapen et al.'s (2003) study of psychopathology within 148 individuals with TS revealed comorbidity rates of 40-50% with ADHD; with 15.4% experiencing obsessive compulsive behaviours (OCB), 46% experiencing Obsessional thoughts and 58% experiencing compulsive rituals; Self-Injurious behaviours (SIB, for example, head banging, punching, and scratching) was present in 43%, with other symptoms such as anxiety, depression and less commonly, personality disorder, aggression, learning disabilities also present. Eapen et al. (2003) suggest that whilst obsessionality might be aetiologically related to TS, high associations between TS and anxiety and depression might have multifactorial origins. Such origins could include the severe and socially handicapping nature of TS; the effects of medications or the effects of co-morbidity and ascertainment biases within clinic populations (Eapen et al., 2003). High comorbidities (8.1%) have also been reported between TS and autism (Baron-Cohen, Mortimore, Moriaty, Izaguire, and Robertson, 1999).

Of importance to TS are the high associations between TS and OCD. OCD is a chronic disease characterised by obsessions and compulsions. It is often related to tics or TS, with epidemiological estimates suggesting that about 2-3% of adolescents are affected with 5% of OCD patients having TS and 20% having tic disorder (Mercadante, Roasario-Campos, Quarantini and Sato, 2004). A study by Müller, Putz, Kathmann, Lehle, Günther and Straube (1997) noted that between 40-90% of individuals with TS present with obsessive-compulsive symptoms. They investigated that nature of obsessive-compulsive symptoms in individuals with TS, OCD or Parkinson's disease and found that although individuals with TS and OCD reported significantly more obsessive-compulsive symptoms, there were questions raised over differentiating compulsions from tics in TS. The possibility was raised that there are qualitative differences in the nature of behaviours in TS and OCD in which symptoms of TS are erroneously classified as OCD, thus inflating the frequency of OCD (Müller et al., 1997). Perhaps adding to the notion of qualitative differences, Robertson (2000) noted that obsessive compulsive behaviour (OCB) or obsessive compulsive symptoms (OCS) are different from the OCS encountered in pure OCD, with variations reported in OCB/OCS with regard to age, duration and triggers in TS. Such evidence may lead us to consider if the OCD that presents comorbidly with TS represents the same disorder or if there are qualitative differences in presentation with similarity only linked to similar underlying neuroanatomy or neurochemistry.

TS is a condition marked by the presence of persistent tics, however it is diagnostically differentiated from tic disorder. Tic disorder is characterised by recurrent,

uncontrollable movements or by vocal outburst (i.e., sudden, rapid, recurrent, nonrhythmic, stereotyped motor movements or vocalizations), but unlike TS, not the existence of both (American Psychiatric Association, 1994). Nonetheless, it is informative to explore the comorbidities that occur in conjunction with the more subtle manifestations of TS like symptoms, particularly because often research groups may confound the two.

There is evidence that individuals with tic disorders present with higher emotional and behavioural difficulties than those seen in the general population. In view of this, Cardona Romano, Bollea and Chiarotti, (2004) investigated the psychopathological and behavioural problems in individuals affected by any tic disorder. Their patient sample of 124 children and adolescents confirmed that TS is the most common tic disorder (58.4%), and that individuals with TS suffer from a more severe tic symptomatology. Further, they reported that severe tic disorder was associated with externalising problems, whereas the duration of tic disorder was associated with internalising difficulties, (in particular depression, anxiety and attention problems). Although 31% of their patient sample presented with pathologic attention symptoms on the Child Behaviour Checklist, they noted that none of them fulfilled criteria for ADHD and postulated that most of these individuals might have been presenting with sub-threshold ADHD. Notably, they suggested that individuals with TS are likely to have a milder degree of inattention, lack of concentration and impulsivity, and that whilst this is higher than that seen in the general population, it might be lower than that seen in individuals with ADHD. Finally, they replicated findings that whilst the incidence of 35.2% of their sample did not present with any obsessive-compulsive symptoms, 45.6% presented with

either obsessions and/or compulsions that did not present as a clinically significant disorder, such that the incidence of OCD was only 19.2%. These varying rates were suggested to be because of a relationship between the amount of OC symptoms and the severity of tic disorder and that these symptoms co-vary within individuals and fluctuate across time.

In summary, one could assume that increases in TS/tic severity are correlated with the presence of a greater number of comorbid difficulties. This perhaps raises the possibility the more severe tics are indicative of greater brain pathology which in turn leads to the presence of other developmental disabilities as a consequence. Overall, the reviewed findings suggest that the quality of OCD and ADHD in TS might be different from the 'pure' conditions when they exist alone. Further, it is possible that TS represents a marker for a degree of neurological dysfunction for which the experience of tics is one side effect that inevitably coexists with the presence of other neurological disabilities, such as OCD or ADHD. Relating to this stance, Robertson (2000) has reviewed differing theories regarding the relationship between TS and ADHD including (a) that the two disorders are genetically related; (b) that there may be two types of individuals, one for whom ADHD is independent of TS and the other for whom the ADHD is secondary to TS; (c) that pure TS and pure ADHD are different phenomenologically and (d) that the nature of TS might predispose individuals to have difficulties with concentration, attention and impulse control that is at subthreshold for DSM diagnosis of ADHD.

Understanding the link between TS and its comorbid disorders will be valuable in terms of the treatment implications. For example, there are findings of an increased propensity towards deliberate, repetitive infliction of self harm in TS. Mathews et al. (2003) found that mild self injurious behaviour (e.g. i.e. behaviours that result in moderate tissue damage such as skin picking or scratching) was predicted by the presence of obsessive compulsive symptoms whilst more severe levels of self-injurious behaviour (such as those that lead to permanent potentially impairing sequelae, such as self-cutting) was associated with tic severity and lack of impulse control (Mathews et al., 2003). In view of this, it was suggested that if self-injurious behaviour in TS is compulsive, then treatments similar to those used for OCD might be of benefit, including serotonin reuptake inhibitors, perhaps in conjunction with atypical antipsychotic, and cognitive behavioural therapy (Mathews et al., 2003). A discussion of impulsivity and impulse control in TS and neurodevelopmental disabilities will follow later in this review; however, this finding is indicative of the importance of detecting the presence of any level of ADHD, particularly relating to difficulties with impulsivity, due to the other behaviours that might result from it.

Finally, recent investigations have examined the presence of social-emotional problem behaviours, adaptive outcomes and family variables that could be consequent to the experience of TS. Carter, O'Donnell, Schultz, Scahill, Leckman, and Pauls (2000) found that whilst all children with TS were at risk for difficulties in the internalising domain (anxious/depressed, somatic complaints, withdrawn); children with TS comorbid with ADHD were also at increased risk for externalising difficulties (aggressive or delinquent behaviours) and problems in social adaptation. These authors concluded that

it is important to educate parents about the greater social and emotional risks for children with both TS and ADHD compared to TS alone and to monitor family stress related to coping. Furthermore, they highlighted that early detection of attentional difficulties coupled with psychosocial and/or pharmacological interventions may enhance outcome.

It is clear from this review that multiple causes have been proposed to explain the presence of TS, some of which are related to other disabilities, such as OCD or ADHD. Nonetheless, a key feature from the literature is the overlap between TS and other psychological complaints. Questions have been raised regarding: primacy diagnosis, if the comorbid disorder really represents a comorbid manifestation of the disability that is similar to that seen in individuals who present with the difficulty alone, and finally, whether explorations of these comorbidities leads us to consider if any of these disabilities exist in isolation or if they really represent a pattern of symptoms resultant from underlying neurochemical, neurophysiological or neuroanatomical disruption that have been falsely compartmentalised as a single entity.

2.0 ADHD

2.1 Clinical Presentation

ADHD is a developmental disorder, defined by the presence of six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity (American Psychiatric Association, 2000). The diagnostic criteria specify that: (i) some hyperactive-impulsive or inattentive symptoms that cause impairment are present before age 7 years; (ii) that some impairment from the symptoms is present in two or more setting (e.g. school, work, or home); (iii) that there is clear evidence of significant impairment in social, academic or occupational functioning and (iv) that the symptoms are not accounted for by another disorder and do not occur exclusively during another disorder (American Psychiatric Association, 2000).

Robertson (2000) notes that ADHD is one of the most common psychiatric disorders affecting children and that it has an unclear aetiology. The prevalence in school children is accepted to be between 3% and 7.5% (Denckla, 2003) or less conservatively estimated to be 19.8% and 12.3% in boys and girls respectively from a sample of 612 children (Pineda, et al., 1999). Clearly there are large variations in epidemiological estimates which have been suggested to depend upon the target population being measured (e.g. Pineda et al., 1999).

Environmental factors may play a role in the presentation of ADHD and there are suggestions that the key symptoms of ADHD are affected by situational and task-related

factors (Barkley, 2002). For example, Barkley, (2002) notes that the performance of ADHD children is worse: (i) later in the day; (ii) in greater task complexity such that organisational strategies are required; (iii) when restraint is demanded; (iv) under low levels of stimulation; (v) under more variable schedules of immediate consequences in the task; (vi) under longer delay periods prior to reinforcement availability and (vii) in the absence of adult supervision during task performance.

In addition to the role that the environment may play in the presentation of symptoms, it is widely believed that there are three core clusters of poor sustained attention, impulsiveness and hyperactivity (Tannock, 1998). Tannock (1998) emphasised that symptoms of inattention are distinguished from those of impulsiveness and hyperactivity for which impulsivity and hyperactivity carry the greatest risk and are thought to be distinct in aetiology, clinical course, response to treatment and outcome than poor attention. More recently, Barkley (2002) joined the debate that has occurred in relation to ADHD subtypes, and questioned the extent to which ADHD-inattentive really represents a true subtype of ADHD or a distinct disorder, noting recent opinion that there is a subset of inattentive children with high levels of cognitive sluggishness and hypoactivity that probably represents a qualitatively different disorder of attention to that seen in ADHD.

Further weaknesses to the diagnostic criteria and presentation of ADHD have been highlighted. Barkley (2002) raised the possibility that symptom cut-off scores might need to be adjusted for sex due to males displaying more severe behaviours than females; with questions raised over the justification of the age of onset, given that

qualitative differences might not exist between late or early onset individuals; and that the duration requirement of 6 months for symptoms has been arbitrarily decided and might be too short (Barkley, 2002).

2.2 Aetiology

2.2.1 Genetics

There is much evidence for the notion that ADHD runs in families and both genetic and environmental factors have been implicated in the aetiology of ADHD. Durston (2003) has reviewed evidence suggesting that siblings of children with ADHD have a three to five fold increase in the risk of developing ADHD. Further, whilst it remains unclear which genes are responsible for ADHD, Durston (2003) notes that an abundance of research has focussed upon the dopaminergic genes. Whilst Denckla (2003) states that the genetic factors in ADHD appear to be complex, polygenetic and involving small gene effects and susceptibility genes, Tannock (1998) postulated that ADHD is a paradigm for a true biopsychosocial disorder, raising critical questions concerning the relations between genetic, biological and environmental factors.

A range of studies have investigated if there are genetic causes to ADHD. Naddler, Silbery, Rutter, Maes and Eaves (2001) conducted a multivariate genetic analysis of ADHD by examining 735 male and 819 female twin pairs using questionnaires. They found greater correlations between monozygotic than dizygotic twins confirming that ADHD has a genetic basis to it and that it is a meaningful unity that it is sufficiently separate from oppositional defiant disorder and conduct disorder.

Kuntsi and Stevenson (2001) examined the heritability of genetic mechanisms in hyperactivity of 268 twin pairs based upon behavioural genetic approaches. They found evidence of a shared common genetic factor; with heritability estimates on the Conners of 71% (parent ratings) and 57% (teacher ratings). This means that they established that a substantial proportion of the variance in hyperactivity was due to genetic effects. Following this, cognitive impairments on a range of tasks showed a less consistent shared genetic effect. For example delay aversion, a strong characteristic of hyperactivity, did not share a common genetic factor, whilst speed on the Stop task (discussed in later sections) did (Kuntsi and Stevenson, 2001).

Whilst Tannock (1998) has proposed that genes within the dopaminergic system are most implicated in the aetiology of ADHD, there are some challenges. In contrast to the notion of an inherited origin to ADHD, Durtson (2003) suggests that it is possible that there are several aetiologically distinct subtypes of ADHD with non-genetic factors, such as foetal exposure to alcohol, drugs, tobacco, perinatal complications or head trauma as possible contributors to its emergence. This highlights that identifying a genetic origin to ADHD, that might be similar to that implicated in TS, will be more complex and perhaps confounded by the effects of the environment.

2.2.2 Neuroanatomy

Dysfunction in ADHD has been proposed to be the result of either variable brain or neurotransmitter dysfunction. For example, the frontostriatal networks have been implicated (Tannock, 1998) and there is evidence of reduced cerebellar and caudate nucleus volumes in ADHD (Denckla, 2003). In a comprehensive review of

neuroimaging on ADHD, Durston (2003) concluded that there is converging evidence of the involvement of the frontostriatal circulatory in ADHD, particularly with regards to poor inhibitory control. However, she conceded that there is also evidence to suggest that other cerebral structures are involved, such as reduced volume in the retrocallosal region and the vermis of the cerebellum (Durston, 2003). Nonetheless, these frontostriatal regions have been more generally implicated in attention and arousal (Hale, Hariri and McCracken, 2000).

However, there are some contradictory findings. In another review of the literature, Denckla (2003) notes that most studies concur that there is frontal involvement in ADHD, but that the specific pattern of activation within the frontal lobes is inconsistent. Rather, Denckla (2003) focuses on the role of neurotransmitters, highlighting evidence that catecholamine deregulation is involved in the pathophysiology of ADHD, as shown by the therapeutic effects from the increase in synaptic catecholamines by stimulant drugs (e.g. methylphenidate) (Denckla, 2003).

Overall, Tannock (1998) notes that there is a mass of evidence pointing to dysfunction of the frontostriatal networks, which control attention and response organisation, and which might be genetic in origin. Further, it has been suggested that cognitive symptoms associated with ADHD may result from dysfunction to the prefrontal cortex and stimulants may act by improving prefrontal function (Durston, 2003). It is noteworthy that research groups are not explicitly clear about why this might be. Whilst one could hypothesise that specific constraints to a precise region in the prefrontal cortex leads to distinct limitations in attention; it is also possible that dysfunction (either

neuroanatomically or neurochemically) at any brain level will disrupt higher level processes in the brain leading to general deficiencies of which attention is one.

2.2.3 Neurochemistry

Psychostimulant medication such as methylphenidate is the common treatment for ADHD. Durston (2003) notes that methylphenidate works by stimulating release and inhibiting uptake of catecholamines (dopamine and noradrenaline) and thus enhances the activity of these neurotransmitter systems, reducing the symptomatology of ADHD. There are many reports of its efficacy, for example, Yang, Chung, Chen and Chen (2004) investigated the effects of methylphenidate in a group of children with ADHD and reported positive improvements in classroom and home behaviours and academic grades.

In a review of the literature, Levy and Swanson (2001) concluded that dopaminergic transmitters may be important in anterior fronto/striatal systems where a 'relative' hyperdopaminergic deficit may affect inhibition and working memory. Further, the authors also noted evidence favouring the positive effect of noradrenergic and serotonergic agents in ADHD (Levy and Swanson, 2001). These studies may draw together the aetiological literature of ADHD. Regardless of whether ADHD is genetic in origin and if these genetic vulnerabilities lead to neuroanatomical or neurochemical disruptions, it is apparent that psychostimulant medication is effective in its management of ADHD.

2.3 Comorbidity

ADHD often occurs in conjunction with tics. Significant to the current research question regarding the overlap between ADHD and TS, Spencer et al. (2001) noted that questions have been raised regarding the possibility that stimulant medication might precipitate tic disorders or worsen preexisting tics across the life cycle. In retrospectively evaluating the impact of comorbidity between ADHD and tic disorder in 312 adults with lifetime ADHD, they noted that tic disorder was overrepresented in individuals with ADHD, although, tic disorder had a mostly remitting course and did not adversely affect the course of ADHD. Most importantly they noted that although some individuals with ADHD might develop tics secondary to stimulant treatment, stimulant medication was not associated with a greater risk for tics. Thus the authors concluded that tic disorder has a remitting course in the context of ADHD and their presence has limited impact on ADHD outcome on a range of measures of functioning (Spencer et al., 2001).

There are other comorbidities in ADHD. Tannock (1998) notes that between 50-80% of children with ADHD also meet diagnostic criteria for other disorders, such as Oppositional Defiant Disorder, Conduct Disorder, internalising disorder and developmental learning difficulties. Tannock (1998) also notes that around 15-20% meet criteria for concurrent mood disorders such as anxiety. There are some reports of elevated comorbidity between ADHD and autism (Geurts, Verté Oosterlaan, Roeyers and Sergeant, 2004), mainly due to the overlap of some symptoms and the role of the frontostriatal regions in both disorders. Nonetheless, like the TS literature, these studies

are informative about the risk that the presence of one neurodevelopmental disorder has towards the occurrence of another.

3.0 MEASURING EXECUTIVE FUCNTION, INHIBITION AND ATTENTION

Simply put, "Executive function" is an umbrella term that typically is associated with frontal lobe functioning. It encompasses the processing that underlies behaviour such as planning, working memory, inhibition of prepotent responses (that is habitual or recent responses that now require suppressing) and cognitive flexibility (Hughes, Leboyer, and Bouvard, 1997). The consequences of executive dysfunction includes a marked difficulty in understanding novel, changing or ambiguous situations, whilst performance on well learned situations remains intact (Hughes et al., 1997).

Fuster (1997) claimed that there are three temporal integrative functions of the prefrontal cortex. These are (i) active short-term memory or working memory, (ii) set or motor attention, and (iii) inhibitory control. Attempts to define executive function led Roberts, Robbins and Weiskrantz (1998) to conclude that the term 'executive function' could not be a unitary construct and that there could be dissociable executive functions. Within this, Barkley (2002) noted that both attention and inhibition are multidimensional constructs. In view of this, before researching the key executive processes attention and inhibition in TS and/or ADHD, a review will be conducted in order to elucidate what these executive sub-functions are.

3.1 Attention

Attention is as a limited-capacity process that allows for preferential processing of certain imagined and sensory information to the exclusion of other available stimuli (Andrews, 2001). Andrews (2001) proposed a hierarchical system of attention in which

each attentional system is dependent upon a lower level in the hierarchy. This system includes:

(i) The Arousal System for maintaining cortical tone according to environmental demands;

(ii) The Orienting System, which is involved in detecting and orienting attention towards novel or unpredictable stimuli;

(iii) The Perceptual Attention System which is a selective attention system that allows the perception of some stimuli while ignoring others and

(iv) The Executive Attention System which is believed to control attention by inhibiting and disinhibiting, orienting responses and controlling the perceptual attention system.

In contrast to this, Stuss, Shallice, Alexander and Picton (1995) described the differentiation of an anterior attentional system centred in the frontal lobe, and a posterior attentional system centred in the parietal lobe. The posterior system appears to be responsible for the spatial allocation of attention, whereas the anterior attentional system is concerned with the executive control of attention. Stuss et al., (1995) have represented an attentional system with different sub components and distinct anatomical and physiological regions. The components of attention are listed in figure 3.1.

Figure 3.1: Attentional Tasks, Tests and Component Processes (adapted from Stuss et al., 1995)

(i)	**Sustaining** (neuropsychological tests: vigilance and numeracy); main component processes: monitoring, energising, and inhibiting; possible anatomical basis: right frontal.
(ii)	**Concentrating** (neuropsychological tests: serial choice, RT); main component processes: inhibition, energising, adjustment of contention scheduling; possible anatomical basis: cingulate.
(iii)	**Sharing** (neuropsychological tests: dual-task performance); main component processes: energising, monitoring; possible anatomical basis: cingulate, orbitofrontal.
(iv)	**Suppressing**, (neuropsychological tests: Stroop); main component processes: logic, inhibiting; possible anatomical basis: dorsolateral.
(v)	**Switching**, (neuropsychological tests: WCST); main component processes: inhibiting, energising; possible anatomical basis: dorsolateral medial frontal.
(vi)	**Preparing** (neuropsychological tests: warned RT); main component processes: energising; possible anatomical basis: dorsolateral.
(vii)	**Setting of Attention** (neuropsychological tests: redundant information RT task); main component processes: energising, monitoring, possible anatomical basis: left dorsolateral frontal.

The notion of similarly separate attentional components is also reiterated by Van Zomeren and Brouwer (1992) who included a supervisory attentional control component to their model. Nonetheless, Stuss et al.'s (1995) model of attention suggests that there is no central executive and therefore dysexecutive syndrome. They stated that the

frontal lobes (in anatomical terms) or the supervisory system (in cognitive terms) do not function (in physiological terms) as a simple inexplicable homunculus. They believe that processes such as monitoring, energising and inhibition exist at many levels of the brain because of the extensive reciprocal connections that exist between most brain regions.

Evidence perhaps supporting the separable components comes from *f*MRI studies. For example, Sylvester, Wager, Lacey, Nichols, Smith and Jonides (2003) demonstrated that there is a common cognitive mechanism involved in the allocation of attention controlled by the superior parietal cortex in counter switching and response compatibility tasks. However, there are also separable mechanisms that mediate the switching of attention and inhibition of prepotent responses, perhaps controlled by the superior parietal cortex posterior to that involved in selective attention. They concluded that rather than there being a unitary executive function, common selective attention processes are initiated and the actual manipulation of attentional information is carried out by the different neural areas that implement different cognitive functions (Sylvester et al., 2003). This notion carries much credibility and may explain why executive function encompasses so many higher order processes and that disruption at any neural level can lead to executive dysfunction in a diverse range of individuals with varied difficulties. The models (e.g. Stuss et al., 1995) specifying precise separable attentional components are perhaps most useful in predicting which measures will detect which difficulties in attention, and why one may see a dissociation in attentional skills.

Clearly attention is a broad concept including many subcomponents. This is apparent in attempts to assess attention which arguably cannot be assessed with a single test. Van Zomeren and Brouwer (1992) stated that there are methodological difficulties in attempts to study attention, simply because attention cannot be caught in a single definition nor related to a single cerebral structure. Further, whilst certain task variables such as duration and discriminability are revealing about certain aspects of attention, some processes, such as attention and memory cannot be differentiated and are occasionally mislabelled whilst other tests may tap several aspects of attention, for example divided attention and alertness (Van Zomeren and Brouwer, 1992).

There are a number of tests that have attempted to tap these specific components of attention. A review of these will follow shortly.

3.2 Inhibition

Andrews (2001) noted that cognitive flexibility reflects an individual's ability to switch from one topic to another, demanding that an individual curtails or inhibits one's behaviour spontaneously in order to commence another. Key brain regions implicated in inhibition include the right inferior prefrontal cortex (Rubria et al., 2003) and the orbitofrontal cortex (Andrews, 2001). One of the roles of the orbitofrontal cortex is to encourage new associations and to inhibit old previously learned associations (Andrews, 2001). Supporting this, lesions to medial and specific lateral regions of the orbitofrontal cortex have been shown to cause perseverative responses in rats (Chudasama et al., 2003).

Nigg (2000, 2001) has conducted a series of reviews defining inhibitory functioning with reference to developmental psychopathology. More specifically relating inhibition to developmental disorders such as ADHD, Nigg (2001) proposed a two-process conceptual framework of inhibition. This separates (i) executive inhibition, (deliberate suppression of a cognition or response to achieve a later, internally represented goal), from (ii) motivational inhibition, (draws upon Gray's notion of impeding responses or behaviour driven substantially by anxiety, uncertainty or fear).

Nigg (2000) has suggested that inhibition (executive), at the neural level of analysis, includes systems based in the orbitofrontal cortex, anterior cingulated cortex, frontal eye fields, posterior cortex, and the midbrain/superior colliculus. Importantly, he differentiated between the four different types of effortful inhibition of motor or cognitive responses (Nigg, 2000). *Behavioural inhibition* (suppressing prepotent responses and socially inappropriate responses) is described by Nigg (2000) as the automatic or intentional delay of overt motor responses and is typically assessed by tasks such as the Stop task (to be discussed). *Cognitive inhibition* (suppressing non-pertinent ideation to protect working memory/attention) requires the active suppression of mental contents in order to exclude it from working memory and includes such tasks as effortful, directed ignoring. *Interference control* (prevents interference due to resource or stimulus competition) refers to the ability to maintain response performance in the presence of competing, distracting or interfering stimuli that evoke a competing motor response, as measured by such tasks as the Stroop or flanker tasks (to be discussed). *Oculomotor inhibition* (effortful suppression of reflexive saccade) requires an individual

to resist the reflexive eye movement towards a newly appearing peripheral target and instead execute a visual saccade (eye movement) in the opposite direction.

Nigg (2000) elaborates upon these differing inhibition systems by arguing that development of these categories may not be uniform and, for example, behavioural inhibition may mature all the way up to early adulthood. Based upon this, Nigg (2000) suggested that the wide variation in the rates of development of some types of inhibition may alter with individual differences in development. This could suggest that inhibition is on a developmental continuum and that ADHD (and/or the presence of any neurodevelopmental disorder) might represent the extreme end of the continuum.

Addressing the notion that there are different facets to inhibition, Logan, Schachar and Tannock (2000) used the term 'inhibition' in a behavioural sense; depicting behaviours that are withheld or inhibited. Although they argued that response inhibition is an executive ability because the processes that underlie it operate directly on other processes, there are some opposing views to this. Kimberg and Farah (2000) argued that there is not an inhibitory module in the prefrontal cortex, and that whilst the prefrontal cortex houses certain psychological functions that are heavily taxed in tasks requiring inhibition, it does not house 'inhibition' as a fundamental psychological process. Rather, they believe that the contribution of the prefrontal cortex to the performance of tasks requiring inhibition is working memory and that the weakening of working memory (through demand) leads to disinhibited behaviour. Perhaps adding weight to this, Denckla (2003) suggested that inhibition both paves the way for and maintains the infrastructure for working memory. In contrast to this notion, are findings that children

with ADHD, who have been reported to have difficulties with inhibition, do not have impairments in verbal or spatial working memory (Karatekin, 2004).

Sergeant et al. (2003) has maintained that there is an overlap in processes subsumed under the concepts of working memory and selective attention, to which working memory may be conceived of as the selective activation of long-term memory which requires executive attention. Nonetheless, they agree that executive attention is involved in inhibitory control and monitoring, although questioned whether working memory and attention are entirely or partly independent, (Sergeant et al., 2003). In view of these findings, it is clear that tests searching for inhibitory deficits in ADHD may need to elucidate the contribution of working memory to performance.

4.0 NEUROPSYCHOLOGICAL TESTS AND CLINICAL GROUPS

4.1 Neuropsychology in TS

Current research suggests that within TS there is a different profile of neuropsychological deficits dependent upon the associated comorbid disorder. This is interesting in terms of what it might tell us about the aetiology of TS. Further description of the executive function profile in TS and its comorbid subtypes could be valuable in informing if the associated disorders have a distinct underlying pathology.

There is mounting evidence that individuals with TS are at risk of experiencing specific cognitive deficits although intellectual ability is reported to be normally distributed (Como, 2001). The cognitive features that have been identified include: visual motor integration problems, impaired fine motor skills and executive dysfunction (Como, 2001). Channon, Sinclair, Waller, Healey and Robertson (in press) examined social cognition and executive function in individuals with TS. They were assessed on a range of social measures including tests of theory of mind, story comprehension and interpersonal reactivity; in addition to non-social executive measures. These measures included tests of inhibition, rule finding/set shifting and multitasking. Channon et al. (in press) found that the TS group were significantly poorer than the control group on the inhibition test (The Hayling Test), but that uncomplicated TS was not associated with difficulties with social cognition or the other executive measures.

In contrast to this, Channon, Crawford, Vakili and Robertson (2003a) have identified poor real-life problem solving on The Predicaments naturalistic scenarios task. The TS

group generated fewer potential problem solutions, instead selecting poorer solutions to the predicaments. Further, the TS group displayed inferior performance on measures of inhibition and strategy, strategic memory deficits, poorer ratings on a questionnaire measuring dysexecutive functioning, but intact rule-finding/set shifting. The key observation of a lack of correlations between the executive and social problem solving measures led the authors to conclude that these measures might have dissociable cognitive and neural bases relating to separate frontosubcortical pathways. Critically, these findings suggest that there are intact cognitive abilities in TS but a common underlying dysfunction that leads to weaknesses in inhibition and associated functions.

Elaborating upon the notion of an underlying neuroanatomical dysfunction, LeVasseur, Flanagan, Riopelle and Munoz (2001) suggested that the underlying structures involved in TS are likely to be the basal ganglia. Using an Anti- and Pro saccade task that required the participant to look at or away from a central fixation point as it appeared or to wait for a fixation point before making an eye movement; they found that the ability to inhibit or delay a planned motor response was altered in TS. They concluded that altered cortical-basal ganglia circulatory leads to reduced cortical inhibition in TS.

In contrast to the notion of inhibitory deficits in TS, there are studies that broaden the range of difficulties that characterise TS. Johannes et al. (2001) investigated the extent to which TS is associated with an altered control of attentional processes, by recording event related brain potentials in individuals with TS whilst concurrently completing a dual (auditory and visual) target detection task. They found that whilst there were no performance differences, individuals with TS had altered electrophysiological

amplitudes to auditory targets, which was interpreted to indicate altered divided attention functioning in TS.

Furthermore, Schuerholz et al., (1996) examined the neuropsychological profile in individuals with TS +/-ADHD and found that individuals with TS only were significantly poorer on measures of letter word fluency even when full intellectual and verbal ability were controlled for. These poor findings were postulated to be related to dysfunction to frontostriatal pathways that slows mental search and linguistic productivity. This collection of findings point to a diffuse range of difficulties in TS, of which inhibition appears to be key. Nonetheless, the breadth of findings is perhaps unhelpful in clarifying understanding of the precise underlying dysfunction.

Likewise, there are some contradictory reports regarding the extent of cognitive problems in TS. For example, Ozonoff et al. (1994) demonstrated that when comparing individuals with TS to children who had autism or were normally developing, their TS group did not exhibit deficits on the Go-*No*go test of response inhibition (requires an individual to respond to frequently presented "go" targets and inhibit responses to unpredictably and infrequently "nogo" targets) or the H&S task of global-local processing. Ozonoff and Strayer (2001) found intact working memory in individuals with TS and Mahone, Koth, Cutting, Singer and Denckla (2001) reported that individuals with either TS or ADHD were both free from executive impairments on tests of verbal fluency, figural fluency, and verbal learning. Mahone et al., (2001) noted that these findings were inconclusive regarding the extent that TS, in the absence of any comorbidity, is associated with clinical impairments in response organisation.

Noting the contradictory findings regarding the neuropsychological profile in TS, Cirino, Chapieski, and Massman (2000) evaluated Wisconsin and Californian card sorting performance in individuals with TS predicting the executive dysfunction would be associated with higher levels of ADHD symptomatology. They found that TS individuals with high levels of ADHD symptomatology did not differ from those with low levels of ADHD symptomatology. They concluded that these results countered claims of executive dysfunction in ADHD (Cirino et al., 2000).

Finally, Channon (2004) has reviewed the relationship between frontal lobe dysfunction to everyday problems in relation to developmental disorders such as TS. Interestingly, she reviewed findings of inappropriate behaviour in everyday life in individuals with TS, relating to their ability to appropriately solve social problems, and perhaps related to frontal dysfunction. She concluded that there are mixed research findings in TS that tends to produce findings of either no abnormalities on executive function tests, or mild selective deficits confined to inhibitory functioning. This is helpful in drawing together the literature and explaining the pattern of inconsistencies.

4.2 Neuropsychology in TS and Comorbidity

The earlier sections of this review have indicated that TS commonly occurs in conjunction with another disorder. The importance of this is highlighted by Ozonoff et al. (1998) who suggested that neuropsychological impairments in TS appear to occur as a function of comorbidity and symptom severity. They had observed that whilst participants with TS did not differ from controls on a negative priming task of inhibitory

functioning, when the groups were separated into subgroups, individuals with TS and comorbid conditions tended to perform less well than control groups. This was most marked for individuals with more severe symptoms of TS, ADHD and OCD. These findings could be understood in terms of an additive effect of multiple types of pathology that consequently leads to greater neuropsychological dysfunction.

Further studies have begun to explore the profile of cognitive functioning in TS and how it varies according to comorbid subtype. There is much support for the associations between dysfunction of basal ganglia-thalamic frontal cortical loops in TS and OCD. This is an important question and may help us understand how the two conditions are linked. In view of this, Müller et al. (2003) hypothesised that disturbed monitoring and inhibition result from this. In order to explore this, individuals with TS comorbid with OCD were compared to individuals without any neurological difficulties on an extensive battery of tests including the Stroop, a Go-*No*go task, a test of verbal fluency and other tests of attention, planning, fluency, monitoring and response inhibition. They found that executive dysfunction manifested in individuals with comorbid OCD and TS as problems predominantly in the areas of monitoring (vigilance and alertness on the Go-*No*go) and response inhibition (the Stroop), whilst performance on tests of cognitive productivity, fluency, task management and planning were reported to be undisturbed. These findings were postulated to be the result of dysfunction in the frontal-striatal loops which Müller et al. (2003) suggested might impair error processing and self-monitoring. Such findings add weight to the notion that there are specific neurological impairments that are implicated in TS and explains not only the resultant pattern of cognitive deficits, but perhaps also the association of these deficits with other conditions.

Importantly, Channon, Pratt and Robertson (2003b) examined executive function measures of inhibition and strategy generation; multitasking; rule following and set shifting; and tests of implicit and explicit memory and learning. They found that when groups were divided according to subtypes (TS+ADHD, TS+OCD or TS alone) impairments in the TS alone group were confined to inhibitory aspects of executive functioning whilst more marked and varied executive dysfunction were present in the TS and ADHD groups.

TS comorbid with ADHD appears to be a more severe condition than ADHD or TS alone. Brand et al., (2002) investigated if individuals with TS with or without ADHD differed in cognitive functioning on the Trail Making test, The Stroop and a test of verbal fluency. These authors found that individuals with TS comorbid with ADHD performed less well than those with just TS on cognitive tasks. A key observation was that individuals with TS alone had normal Verbal and Performance IQ but that individuals with TS comorbid with ADHD tended to have lower scores. Most importantly are findings of significantly worse performance on the Verbal fluency measure by individuals with comorbid diagnoses. Whilst comorbid TS and ADHD groups also performed worse on the Stroop and the Trail making test, this failed to reach significance. This failure was suggested by Brand et al. (2002) to be due to inadequate power. These findings were taken to indicate the importance of comorbidity factors in TS. The possible role of mental flexibility as a buffer of the psychological impact of symptom severity in TS were raised as important areas for further investigation (Brand et al., 2002).

Other studies attempt to disentangle the overlap between TS and/or ADHD. Harris et al. (1995) compared children with ADHD to those with TS with or without ADHD on ten tests of executive functioning. They found that executive function impairment as measured by the Rey-Osterrieth Complex Figure test of organisation was significantly worse in individuals with TS comorbid with ADHD than those with TS after controlling for IQ. Comparability of these findings with previous studies was rendered to be weakened due to the varied medication status of their participants and the variations in the literature in how ADHD status is determined (Harris et al. 1995). Nonetheless, Harris et al. (1995) concluded that these finding indicate that children with TS have problems with output efficiency whilst the other executive function deficits might be related to the presence of comorbid conditions such as ADHD. In view of this, Harris et al. (1995) suggested that concomitant ADHD underlies the appearance of additional executive function problems in TS, which are likely to be distinct and genetically related. This study is crucially one of a few that begins to control for individual characteristics such as IQ allowing better comparison of the contribution of clinical diagnosis.

Other studies have reported that individuals with TS and ADHD exhibit lower psychosocial functioning (Spencer et al., 1998; Carter et al., 2000) and are at an increased risk for poor peer relationships (Bawden et al., 1998). For example, Spencer et al. (1998) reported high comorbidity with disruptive behaviour, mood and anxiety disorders as well as cognitive dysfunction in their study. Such findings reinforce the notion that it is the contribution of disorders comorbid with TS that give rise to findings

of varying cognitive dysfunction. It is questionable whether it is having two disorders that place one at risk for greater cognitive difficulties or whether the combined disorders result in a unique set of symptoms and cognitive difficulties.

4.3 TS Summary

In summary there is much evidence that in TS there is a pattern of neuropsychological difficulties that are exacerbated by the presence of comorbid conditions. Few publications have compared TS directly with ADHD and none known to me have examined whether ADHD that is found in TS represents the same disorder as pure ADHD. Given that children with TS comorbid with ADHD are at an increased risk for cognitive and social adaptation difficulties and externalising behavioural problems (Carter et al., 2000), understanding the precise features of the ADHD that characterise TS is of value, particularly regarding whether prime clinical attention should be placed on the diagnosis of ADHD over TS. In view of this, a discussion elucidating the extensively researched neuropsychological profile of ADHD will now follow.

4.4 Neuropsychology in ADHD

In addition to the core characteristics of hyperactivity/impulsivity and inattention, children with ADHD have been noted to have a large range of additional difficulties. Barkley (2002) records problems with (i) physical fitness, gross and fine motor coordination and motor sequencing, (ii) speed of colour naming, (iii) verbal and nonverbal working memory and mental computation (iv) planning and anticipation (v) verbal fluency and confrontation communication (vi) effort allocation (vii) developing, applying and self-monitoring organisational strategies and (viii) the internalisation of

self-directed speech (ix) adhering to restrictive instructions and (x) self-regulation of emotion. In summary of these, Barkley (2002) categorises these difficulties within the domain of executive function or meta cognition noting that this should be mediated by prefrontal lobes of the frontal cortex suggesting that executive dysfunction might be the core underlying deficit in ADHD.

In contrast to Barkley, most ADHD research has focussed on the forementioned constructs of attention and inhibition. Highlighting the challenges to the vast ADHD literature, Tannock (1998) states that there is marked overlap among measures used to assess the different construct of attention, impulsiveness, executive function and that the construct validity of the processes under investigation, or the methods used to measure the processes have been measured rigorously. In view of this, a discussion of the neuropsychological findings in ADHD will coincide with a discussion of the range of measures and what they purport to measure.

4.5 Tests of Attention with Reference to ADHD

4.5.1 The Continuous Performance Task (CPT)

The CPT is a measure that was developed to investigate the effects of monotonous viewing of radar screens during the war. Essentially this task is one of sustained attention (vigilance) that requires participants to detect and respond to infrequently presented targets from a series of distracting stimuli (Andrews, 2001). Barkley (1990) notes that there are many versions of the CPT including visual and auditory presentations.

Lin, Hsiao and Chen. (1999) demonstrated that in normally developing children, performance on the CPT improves with age, particularly during the 6-12 years age range. Further, girls perform more poorly than boys on this task (Lin et al., 1999). These developmental differences have been replicated by Jonkman, Lansbergen and Strauder (2003) who reported that children perform worse than adults on the CPT, making more omission and commission errors. Performance on the CPT has been reported in a number of studies to be significantly associated with ADHD symptomatology. Rovet and Hepworth (2001) compared children with ADHD to those with congenital hypothyroidism. Children with ADHD were shown to be more impulsive in their responding, making a greater number of commission and omission errors (Rovet and Hepworth, 2001). Epstein et al. (2003) used the Conners CPT in a large epidemiological sample and demonstrated that performance was highly related to all ADHD symptoms in children with ADHD when compared to normal controls.

An interesting conclusion drawn by Epstein et al. (2003) was that due to the high signal probability (the high rate of targets that required responding to) in the Conner's CPT, it might be a better measure of inhibition, even though it was developed as a measure of attentional vigilance. In view of this, it appears that measures of inhibition should involve inhibiting responses to infrequently presented stop stimuli, whilst attention requires the sustained initiation of responses to infrequently presented targets. There is often inadequate evaluation of the effects of subtle changes to the presentation of some tests, and one should consider the possibility that the generalisability of some studies might be weakened through subtle variations in methodology, for which tests constructs begin to overlap.

The Maudsley Attention and Response Suppression Task battery (MARS II) has developed a reward-CPT task aimed at measuring differences in responding to reward and non-reward. Rubria (2004, personal communication) reported initial findings suggesting no effects of reward on performance in children with ADHD, although they did show sustained attention deficits.

Van Zomeren and Brouwer (1992) reported that tasks such as the CPT are affected by: (i) time–on-task effects: performance changes or decrements due to practice, fatigue or boredom; (ii) lapses of attention: episodic changes in alertness resulting in decreased receptivity to stimulation manifesting in omission errors on continuous tasks and (iii) intra-individual variability which affects accuracy of responding and speed of responding. In view of this, the CPT has been criticised for the difficulty that exists in differentiating the effects of fatigue, decreasing motivation and attentional deficits (Van Zomeren and Brouwer, 1992).

4.5.2 The Test of Everyday Attention for Children (TEA-Ch)

This is a measure of attentional performance covering the attentional domains of selective attention, attentional control/switching and sustained attention. This test is based on Manly et al.'s (2001) premise that the distinct systems of attention are characterised by (a) a capacity to move attention within space (spatial attention) (b) a capacity to enhance the processing of particular target's characteristics regardless of spatial location (selective attention) and (c) a capacity to maintain a particular processing set over time (sustained attention). This test has adapted adult measures of

attention for children, whilst attempting to minimise the demands on reasoning, task comprehension, motor speed, verbal ability and perceptual acuity.

Manly et al. (2001) administered this test to 293 children aged between 6 and 16 years old. Their results illustrated that children were able to perform the tasks and that basic comprehension and perceptual demands were met whilst performance was shown to not be related to the WISC-III IQ task performance. A complementary study examining TEA-Ch performance of ADHD boys compared with the normally developing sample demonstrated that boys with ADHD exhibited significant deficits across sustained attention and attentional control subtests of the TEA-Ch (Manly et al. 2001). These differences were maintained even when groups were matched for age and performance levels on the WISC-III.

4.5.3 The Sustained Attention to Response Test (SART)

This test is a Go-*No*go paradigm (requires responding to "go" targets and inhibiting responses to "nogo" targets), developed by Manly, Robertson, Galloway and Hawkins (1999). The task presents repetitive and temporally predictable visual stimuli (digits between 1-9) to which participants are required to respond with a key press to all except digit 3. Poor performance on the SART is believed to be attributable to inefficient endogenous maintenance of attention rather than an inability to withhold a response (Manly et al., 1999). The authors postulate that this task, that requires the ability to self-sustain attention, is reliant on prefrontal lobe function, particularly that of the right hemisphere.

Manly et al. (1999) conducted a series of experiments that manipulated the SART whilst measuring errors of commission (pressing for a target) and reaction time in normal control participants. They demonstrated that attention is related to duration of time for which attention must be sustained, the rate at which targets appear and daily cognitive failures as measured by the Cognitive Failures Questionnaire. Poor performance on the SART is presumed to be due to either having an inattentive approach or to an inefficiency in applying a strategy of titrating speed of response against ones own efficacy in withholding at the appropriate moments. Shallice et al. (2002) have reported significant impairments in children with ADHD, relative to controls, on this task. The children with ADHD omission errors were reported to be five times the normal rate (Shallice et al., 2002).

4.5.4 Selective Attention

Although Brodeur and Pond (2001) reported that the variability in the methodology of studies of selective attention in ADHD has contributed to differing results, they agreed that children with ADHD appear to demonstrate selective attention deficits under some conditions but not others. Using visual and auditory flanker task, they demonstrated that children with ADHD were less efficient on the selective attention task, than those without ADHD. Both children with ADHD and younger control children were more influenced than age matched control children by visual and auditory distractors, indicative of a developmental effect. The attentional distractibility of children with ADHD was reported to be specifically improved by Methylphenidate (Brodeur and Pond, 2001).

In summary, although there are many reports of deficient selective attention in children with ADHD, there are only a limited number of studies that assess the full range of attentional subcomponents. Most research on ADHD has focussed on measures of sustained attention. This might reflect a publication bias for which only statistically significant differences between groups are reported. However, it may represent a failure of research groups to theoretically explore the full realm of attention beyond the central diagnostic areas of ADHD. The following section will review the common studies that have investigated inhibition in ADHD.

4.6 Tests of Inhibition with Reference to ADHD

4.6.1 The Wisconsin Card Sort Test (WCST)

The Wisconsin Card Sort Test requires the categorisation of visual items in accord with a temporary changing principle. Participants have to learn a rule for sorting items by a feature (e.g. colour, shape, number...), and then discard the learnt rule and identify a new one. It is not only a test of short-term memory, but also a test of the ability to withstand interference from redundant memories (Fuster, 1997). Andrews (2001) noted that perseveration occurs when a behaviour is repeated despite a history of negative feedback. Performance on this task is impaired in prefrontal syndrome resulting from dorsolateral and orbitofrontal lesions (Andrews, 2001).

The Cambridge Neuropsychological Automated Batteries (CANTAB) includes a computerised version of the Wisconsin Card Sort test, the Intradimesional/Extradimensional set shifting test (ID/ED). This test of attentional set shifting, allows for the cognitive components from the WCST to be assessed

independently in nine stages (Fray, Robins and Sahakian 1996). The CANTAB is particularly informative because performance on discrete components of the task can be observed. One problem with many studies of executive function/inhibition is that they lack appropriate control tests. The early stages of the ID/ED test, preceding the real set shift testing attentional flexibility, could control for motivation, non-specific motor skill or attention.

Kempton, Vance, Maruff, Luk, Costin, Pantelis (1999) reported specific deficits in children with ADHD on CANTAB measures of spatial short term memory (Spatial Span), spatial working memory, set shifting ability (ID/ED), planning ability (the Tower of London), spatial recognition memory and delayed matching to sample. However, children with ADHD displayed intact performance on a pattern recognition memory test. These deficits were not evident in medicated children with ADHD. It is noteworthy that children with ADHD had smaller spatial spans and performed poorly on the spatial working memory tasks. This might suggest, as discussed previously, that problems with inhibition do concur with problems with working memory or represent an overlapping construct. However, these authors suggested that these problems might reflect an inability, in children with ADHD, to develop systematic strategies to assist performance.

Other tests exploring set shifting ability in children with ADHD have reported specific deficits in children with ADHD. Cepeda, Cepeda and Kramer (2000) developed a simplified version of the WCST, the Task-Switching paradigm, in an attempt to clarify the precise effects of inhibitions, unconfounded by working memory components. This

test required individuals to make decisions about either letters or numbers (for example, if a letter is a vowel or a consonant; or a number is odd or even). Individuals with ADHD, showed large performance costs when they were required to switch between differing tasks, demonstrating difficulties with managing multiple tasks with incompatible responses. Medication was found to ameliorate these inhibition difficulties (Cepeda et al., 2000). Finally, Shallice et al. (2002) examined performance on the Brixton Spatial Rule Attainment test (a simplified version of the WCST) and reported that children with ADHD performed significantly worse than controls. Children with ADHD were said to be like frontal patients, producing an excess of 'guessing' errors and perseverative responses (Shallice et al., 2002).

4.6.2 The Six Elements Test

This task is a variant of a subtest in the Behavioural Assessment of the Dysexecutive Syndrome (BADS, Wilson et al., 1996). It is a test of planning, task scheduling and performance monitoring. Participants are required to attempt to switch between a number of tasks in a set order within a limited time frame. Clark, Prior and Kinsella (2000) reported that individuals with ADHD were significantly worse than control participants on this measure, particularly in their ability to plan, and organise information and monitor their ongoing performance.

4.6.3 The Trail-Making Test B (Reiten, 1958)

Andrews (2001) described this test purporting to measure flexibility, unconfounded by memory effects. Participants are required to join numbers and letters alternately (e.g. 1-A-2-B-3-C...) and suppress the natural tendency to join in numerical or alphabetical

order. Significantly, Van Zomeren and Brouwer (1992) noted that this test loads onto working memory through the requirement to keep in mind the alphabet and the counting. Chhabildas et al. (2001) reported deficits on this measure in individuals with the ADHD subtypes particularly those with most symptoms of inhibition.

4.6.4 The Stroop-Task (Stroop, 1935)

This task requires individuals to name a series of words that are printed in incongruent colours, requiring the inhibition of the natural inclination to read the word, rather than name the colour. Unlike previously mentioned measures of inhibition, this task does not involve the inhibition of a motor response, but requires the inhibition of a cognitive response. Vendrell Junque, Pujol, Jurad, and Grafman, (1995) claimed that the Stroop task directly assesses sustained attention and interference, sharing commonalities with the Go-*No*go task. Performance on this task is associated with heightened activation of the dorsolateral prefrontal cortex when participants are naming the colour, and activation of the anterior cingulate, perhaps in response to conflict (Andrews, 2001). Further summarising the mechanisms of inhibition in the Stroop, Nigg (2000) suggested that the Stroop effect is a marker of interference control. Drawing upon adult imaging data, Nigg (2000) noted that Stroop responding activates dorsolateral prefrontal cortex and the anterior cingulated gyrus. These regions are proposed to be associated with the deliberate control of attention and behaviour (Nigg, 2000).

In contrast to this, Vendrell et al. (1995) cited literature findings of deficits on Stroop test performance in patients with frontal dysfunction, including individuals with Parkinson's disease, Huntington's disease, OCD and schizophrenia. They used the

Stroop paradigm, in order to investigate the effects of focal prefrontal lesions on performance. When analysing six functional regions with resonance images they found that only one region in the right hemisphere, the prefrontal lateral, was consistently related to the Stroop effect. They claim that the Stroop test could not be considered globally to be a frontal lobe test because 71% of their patients with prefrontal lobe lesions performed normally, disputing the notion that the Stroop test is a test of verbal inhibition. They concluded that the right prefrontal cortex plays a role in sustained attention; although in contrast to Nigg (2000), they challenged evidence that the left prefrontal cortex is involved in the inhibition of verbal automatic responses.

Demetriou, Spanoudis, Christou and Platsidou (2001) presented a model of the Stroop phenomenon in which they argued that the Stroop effect is the result of three parameters: (i) dimension selection - decision making about which dimensions to respond to, (ii) dimension identification - encoding and identification of the relevant dimension and (iii) interference control - filtering out of interference from non-relevant dimensions. They tested this model experimentally by administering the Stroop on participants aged between 9-15 years. They found evidence supporting the existence of the three parameters that they had identified as well as their relationship to developmental level. Further, Wright, Waterman, Prescott, and Murdoch-Eaton (2003) developed a pictorial Stroop for children and demonstrated that children who performed worse on this measure tended to be those at risk for hyperactive and oppositional symptomatology.

Rucklidge and Tannock (2002) examined Stroop performance in addition to naming speed and executive deficits in groups with ADHD with and without reading disorders.

After controlling for demographic variables, children with ADHD were shown to be slower in naming colours and incongruent colour/words in addition to having slower processing speed (WISC subtests), being slower at naming objects and with inhibiting responses on the Stop signal paradigm (see below for further discussion). The authors concluded that these findings added weight to the notion that poor inhibition is a cognitive deficit specific to ADHD symptomatology (Rucklidge and Tannock, 2002). They argued that the Stroop task was a predictor of hyperactivity symptoms and a better measure of the core difficulties in ADHD than the Stop task, suggesting that it is more sensitive to the key processes of control and monitoring. Finally, Shallice et al. (2002) examined the performance of children with ADHD on a modified numerical Stroop task in which children were required to name or count numbers. Performance of children with ADHD was found to be significantly impaired relative to controls.

4.6.5 The Hayling Test

In this test, the final word of a sentence is missing, and participants are timed in their ability to complete these sentences with congruent or incongruent words. Again, this measures a very different type of inhibition, for which rather than inhibiting a motor response, the participant is required to inhibit a cognitive response. Clark et al. (2000) reported that adolescents with ADHD performed significantly worse than normal community controls on this task, requiring more additional time to produce an unrelated word and making more errors when responding, giving words that were semantically related despite instructions to the contrary. According to Burgess and Shallice (1997) a good participant will develop a strategy to help them deal with the response suppression demands of the task. Such strategies could include looking around the room in order to

find response items. Shallice et al. (2002) reported that nonmedicated children with ADHD performed significantly worse than controls on a modified child version of the Hayling sentence completion test. Interestingly, they found that whilst 18.8% of age 7-8 and 47% of age 9-12 year old control children used a strategy, only 10% of 7-8 year old and 9.5% of 9-12 year old children with ADHD reported the use of a strategy. Strategies were often concrete, such as looking around the room in order to generate a response. Whilst the authors struggled to see why the use of a strategy should circumvent problems with inhibitory control, they noted that this confirmed that a central difficulty is one of prefrontal loading (Shallice et al. 2002).

4.6.6 Go-*No*go Measures

Nigg (2000, 2001) defined the Go-*No*go task as one of intentional motor inhibition, which would be classed under the realms of executive (goal-based) inhibition. Nigg (2000) argued that a fundamental kind of inhibition is the deliberate control of a primary motor response in compliance with changing context cues, as demanded by this task that requires inhibiting a dominant of prepotent response. Crone, Jennings and van der Molen (2003) examined inhibitory function in ADHD using a Go-*No*go flanker task requiring children to respond to arrows but not diamonds. They found that children with ADHD had deficits in approach tendencies in the presence of imminent reward, rather than being unresponsive to punishment or negative feedback. They found that whilst children with ADHD were slowed when responding to flankers cueing appropriate responding, they were more slowed by flankers cuing inappropriate responses. Finally they found that children with ADHD responded less accurately under the threat of punishment relative to control children (Crone et al., 2003). Investigating the notion of

Behavioural Inhibition Systems (BIS), the authors examined skin conductance but found that cognitive and motivational inhibitions were independent arguing against a weak BIS in ADHD. Further examining Go-*No*go performance, Nyberg, Bohlin, Berlin and Janols (2002) reported that children with ADHD had significant problems with response inhibition on this measure.

Finally, in an extension to the Go-*No*go procedure, Shallice et al. (2002) examined an N-Back working memory task. Like a Go-*No*go task, this required individuals to respond after they see a specific number (0-Back condition) and not to respond when other numbers are presented. However, it also includes 1-Back and 2-Back conditions where children are required to respond if the letter on the screen is the same as that presented 1 or 2 back respectively. They found that children with ADHD performed significantly worse than control children. The authors acknowledged that this test had a working memory component to it. This is perhaps helpful in acknowledging the link between these two measures as discussed earlier.

4.6.7 The Stop Signal Paradigm

This is a task that measures 'last-minute' inhibition of an already planned motor response. Nigg (2000) describes this as an extension to the Go-*No*go task, also requiring intentional motor inhibition. Essentially, the stop signal task measures the ability to withhold a motor response that has already been triggered by a 'go' signal when a go signal is infrequently, unpredictably and quickly followed by a stop signal. Rubria et al. (2003) maintain that rather than measuring selective inhibition, which can be planned beforehand (for example, the use of careful selective attention to stimuli in the Go-*No*go

task), it measures withholding of a triggered motor response that may already be on its way to execution.

In relation to the stop signal paradigm, Logan, Schachar and Tannock (1997) developed the Race Model in which they propose that Inhibitory Control depends upon a race between the latency of the response to the go signal (go reaction time) and the latency of the response to the stop signal (stop-signal reaction time). According to the Race Model, poor inhibitory control could result from responding too quickly to the go signal or responding too slowly to the stop signal. Logan et al.'s (1997) method for estimating stop signal reaction time uses a tracking procedure in which stop-signal delay changes after every stop-signal trial, increasing by 50ms if subjects inhibit and decreasing if they respond. This tracking procedure converges on a stop-signal at which participants inhibit 50% of the time. The estimation of stop-signal reaction time is often based upon a complex calculation; however, because participants inhibit 50% of the time in Logan's approach, it is calculated by a subtraction of stop-signal delay from mean reaction time.

Rubria et al. (2003) administered an arrow variant of this task to 20 right handed males. They reported mean inhibitory control of 55% +/- 5%, with a mean reaction time to go trials of 792ms +/- 155ms and to stop failures of 880ms +/- 155ms, such that stop signal reaction time was 292ms +/- 243ms. Further, Logan et al. (1997) administered the classic stop task in which participants had to respond to the letters X or O unless a stop signal (a 1000-Hz tone) was played through the computer. They found that impulsivity as measured by Eysenck Personality Inventory schedules was related to inhibitory control – high-impulsive participants had longer stop-signal reaction times.

The MARS II contains a variant of the stop paradigm. In this stop signal task, aeroplanes pointing left or right appear and participants have to make congruent button responses. The delay between go signal and stop signal changes according to the subject's performance, so that each participant inhibits on 50% of all trials. In a study that administered subtests of the MARS battery to children with ADHD, Rubria et al. (2001) established that children with ADHD were impaired on tests of inhibition that required inhibition of a motor response (Go-*No*go, stop task and Motor tapping task) when compared to community and psychiatric control groups. Rubria et al. (2001) found that in healthy control participants, successful stopping activates inferior frontal and striatal brain regions, whereas unsuccessful stopping elicits anterior cingulate and dorsolateral prefrontal cortex activation, reflecting error detection to unsuccessful performance. In contrast to this, Rubria et al. (2001) reported evidence of reduced right prefrontal activation in children with ADHD during higher level inhibition and delay management tasks. Further studies of stop task performance in normal participants have reported superior inhibitory performance for stop signals presented in the right visual field supporting the notion that this task taps the left lateralised neural systems (Van der Schoot, Licht, Horsley & Sergeant, 2003).

Empirical research has emphasised difficulties with impulsiveness. Theories postulate that a failure to inhibit or delay a behavioural response is the central deficit in ADHD (Tannock, 1998). A catalogue of studies have emphasised specific difficulties with the demands of inhibition on stop tasks in individuals with ADHD, (Schachar Mota, Logan, Tannock and Klim, 2000, Solanto et al., 2001; and Chhabildas et al., 2001) and ADHD

specific inhibitory impairments not accounted for by age, IQ or reading ability (Nigg, 1999) nor comorbidity with a second disruptive behaviour disorder (ODD or CD) (Nigg, 1999; Solanto et al. 2001; Schachar et al., 2000). Based upon this, Schachar et al. (2000) concluded that this suggests that the presence of ADHD in comorbid conduct disorder might be more representative of a phenocopy than a variant of ADHD. Varying interpretations of findings regarding response inhibition/impulsivity suggest its cause to be either: an underlying deficit in a central act of control; a deviant cognitive style designed to reduce the subjective experience of delay; or a dysfunction in the energetical/state-regulation of motor control (Tannock, 1998).

Logan et al. (2000) demonstrated clear deficits in children with ADHD in their ability to inhibit responses in the stop signal paradigm that was not present in normally developing control children, children with learning disabilities, children with emotional disorder, and children with conduct disorder with or without ADHD. This effect is eliminated with the administration of methylphenidate, although they reported a curvilinear dose-response function. The effects of medication on response inhibition have been investigated by a number of groups. Bedard et al. (2003) replicated the consistently reported findings of inhibitory deficits on the stop signal paradigm in children with ADHD. However, this effect was examined further in the context of a randomised double blind placebo cross over trial. Bedard et al. (2003) found that this effect was attenuated with the use of methylphenidate, with children with ADHD demonstrating improved selective inhibition in addition to speed and variability of response execution. Based upon this, the authors suggested that methylphenidate might work by improving global cognitive processes such as attentional capacity and working memory that has the

knock on effect of improving inhibitory processes. In contrast to this, Van der Meere, Gunning and Stemerdink (1999) investigated the effects of methylphenidate and clonidine on individuals with ADHD as assessed on a Go-*No*go paradigm; however they failed to find a difference in responding in the treated groups.

Oosterlaan et al. (1998) conducted a meta-analysis of 456 children in 8 studies conducted between 1990 and 1997 using the stop task. They reported consistent and robust evidence for a response inhibition deficit in ADHD. This manifested as flatter inhibition functions indicative of poor response inhibition. This pattern was also present in individuals with conduct disorder. They suggested that poor response inhibition in ADHD might reflect a developmental lag, i.e. a delay in the attainment of response inhibition. In view of the weight of supportive evidence, Logan et al. (2000) contended that the stop signal paradigm is a cognitive marker for ADHD.

Nevertheless, there are some inconsistent findings. For example, Scheres et al. (2001) detected only slow and variable response execution in individuals with ADHD when measured on the Stop Signal task and failed to detect any inhibitory processing deficits. Slusarek, Velling, Bunk and Eggers (2001) considered the extent to which inhibition is a global function that influences all related processes or whether it is a differential function, dependent on specific aspects of the situation. They hypothesised that deficits in behavioural inhibition should be greatest in situations in which motivational incentives are minimal. These authors found that under conditions of low incentives, children with ADHD were less able to inhibit their reactions and had longer stop signal reaction times, but when given high incentives, children with ADHD performed the task

as well as controls. These authors emphasised the need to separate the difference between performance and ability and that children with ADHD need more external incentives in order to attain adequate motivation.

Adding to these findings, Kuntsi, Oosterlaan and Stevenson (2001) failed to find a response inhibition deficit as measured by a Stop task. They administered the Stop task, in addition to a delayed responses alternation task (computerised working memory measure) and a sentence span task. They found that children with ADHD were not less likely to trigger their inhibitory process nor was their inhibitory process more variable compared with control children. One problem may be the varying methods that have been used to measure and calculate stop signal reaction time. Standardisation of measures may help to clarify the literature.

Nigg (1999) recommends caution in interpreting the substantial support for behavioural inhibition models of ADHD, noting that the "race" model which describes the stop task is not a process model and does not specify what inhibition process is impaired or how it works. In view of this, Nigg (1999) contended that whether it is a frontal, behavioural inhibition or some other inhibition process is still unclear. Furthermore, Tannock (1998) highlights that many studies on the stop task find that children with ADHD are slower in response execution processes, raising the possibility that the performance decrement may reflect a general speed of processing deficit rather than a specific deficit in response inhibition. Also, Tannock (1998) notes that the response inhibition deficit might not be specific to ADHD and might be shared by other disruptive behavioural problems such as aggression and oppositional conduct disorder.

In an attempt to summarise the nature of inhibitory deficits in ADHD, Tannock (1999) reviewed a number of different levels of inhibitory dysfunction. This includes (i) Gray's (1982) notion that inhibitory difficulties stem from a conditioning deficit in which children with ADHD have an imbalance between control responses to signals of punishment and reward; (ii) Logan's (1994) proposal that individuals with ADHD have a deficit in the ability to inhibit prepotent courses of action, perhaps in response to an extremely fast response process or an extremely slow inhibitory process and (iii) Barkley's (1994) proposal that behavioural inhibition is the primary deficit in ADHD that leads to secondary impairments in executive function. Clearly inhibitory functioning is key to ADHD research, although there are still some outstanding questions. The use of tighter methodological controls and greater specification of the processes measured might help to clarify this.

4.7 Further Challenges and Other Executive Dysfunctions

Other groups have examined a plethora of general executive functions in ADHD. Nonetheless, there are some issues regarding the diagnostic subtypes of ADHD. Chhabildas et al. (2001) examined the neuropsychological profiles of the ADHD subtypes (hyperactive/impulsive, inattentive or combined). They found that children with ADHD-combined or ADHD-inattentive were indistinguishable, both demonstrating difficulties on measures of processing speed, vigilance and inhibition. However, individuals with ADHD-hyperactive/impulsive did not demonstrate any difficulties on the experimental tasks. They suggested that the features of ADHD may be more transient, following a developmental pathway through ADHD-hyperactive/impulsive

through to ADHD-combined through to ADHD-inattentive (Chhabildas et al., 2001).

Further exploring the specificity of the executive function Geurts et al. (2004) examined the profile of children with ADHD compared with those with high functioning autism. Whilst they found that both groups exhibited executive function deficits, they found that children with ADHD had difficulties with only two executive function areas (inhibition of prepotent responses and verbal fluency). However, these in conjunction with further difficulties were also present in individuals with high functioning autism. These findings were seen to oppose Barkley's (1997) theory that deficits in executive function are the core underlying deficit in ADHD, given that there are other groups who exhibit the same degree of executive dysfunction with a differing symptom profile and that the executive dysfunction in the ADHD was not as pervasive as might be predicted (Geurts et al., 2004).

4.7.1 Other Measures in ADHD

There is a smaller literature base that has investigated the performance of individuals with ADHD on executive functioning tests other than those directly assessing attention and inhibition. This includes findings that children with ADHD show more limited and slower learning than control children on the Paired-Associate Learning Test (PAL) that taps memory (rehearsal), organisation and elaboration (Chang et al.,1999); that they showed response perseveration as indicated by the Door-opening Task in children with conduct disorder comorbid with ADHD (Matthys, van Goozen, de Vries, Cohen-Kettenis and van Engeland, 1998) and that they demonstrate more general deficits on an extensive battery of neurocognitive tests tapping visuomotor ability, executive function

and working memory (Kalff et al., 2002). Such findings challenge the notion that there are specific deficits in inhibition and attention in ADHD, and like the pattern of difficulties that are seen in TS, could suggest a more general pattern of Neurocognitive deficits resultant from neuroanatomical disruptions.

In support of this and the breadth of difficulties reported in ADHD, Further studies have investigated the cognitive ability of individuals with ADHD. There is emerging evidence that individuals with ADHD have difficulties with self-regulation and planning/organisation or responding (Clark et al., 2000) and with brief interval time discrimination (Smith, Taylor, Warner Rogers, Newman and Rubria, 2002). In an attempt to make sense of these varying findings, there is some evidence that even when levels of ADHD and IQ are controlled for, executive function ability is influenced by levels of aggression (Séguin, Boulerice, Harden, Tremblay and Pihl, 1999). This perhaps highlights the need to strictly control for not only IQ, but extraneous variables such as traits of conduct disorder in any research. Nonetheless, it is important to note that these diverse findings may not suggest that there is a generalised pattern of cognitive deficits in ADHD given that there are findings that children with ADHD have intact visual search ability (Mason, Humphreys and Kent, 2003; Hazell et al., 1999); and verbal letter fluency (Shallice et al., 2002).

4.8 ADHD Summary

One problem with the neuropsychological literature on attention is that contradictory neuroanatomical regions are implicated to underlie certain functions. This might reflect the problems with isolating separable components during testing because attentional tasks activate multiple regions, the use of small sample sizes, or simply because early functional imaging studies were not guided by a priori hypotheses of which areas should be activated, perhaps leading to an over inclusion of the role of some regions.

There is extensive empirical research supporting executive function deficits in ADHD specifically relating to deficits with inhibition and sustained attention. Supporting this, Nigg (2001) concluded that in ADHD combined type, there is data supporting a deficit in executive motor inhibition, although raised questions over the mixed findings regarding an interference control deficit. Tannock (1998) has maintained that there is an emerging consensus that a failure to inhibit or delay a behavioural response is the central deficit in ADHD. There are varied interpretations regarding the aetiology of response inhibition or attention deficits in ADHD. Some suggest its cause to be either: an underlying deficit in a central act of control; a deviant cognitive style designed to reduce the subjective experience of delay; or a dysfunction in the energetical/state-regulation of motor control (Tannock, 1998). Although much research has been conducted into ADHD, this has been perhaps limited through its focus on the areas of sustained attention and inhibition. However, this may merely reflect the weight of the evidence maintaining that these are the central deficits that characterise the disorder.

Further relating to findings of ADHD subtypes, Oosterlaan et al. (1998) questioned the

extent to which poor response inhibition in ADHD children represents a stable deficit or a maturational lag. Kunsti, Oosterlaan and Stevenson, (2001) failed to find a response inhibition deficit as measured by a Stop task, reporting that hyperactive children were not less likely to trigger their inhibitory process nor was their inhibitory process more variable. They highlighted that even if hyperactivity was associated with a slow inhibitory process, that this does not indicate a specific response inhibition deficit but rather may indicate a slow mode of information processing. This suggests that there are varying cognitive profiles dependent upon the type of ADHD (i.e. inattentive, hyperactive/impulsive or combined type). Given that there are subtypes of ADHD, the extent to which TS comorbid with ADHD is characterised by the same features as combined ADHD is a valid area for investigation. It is noteworthy that these subtypes differ from diagnostic symptom clusters as identified by DSM-IV, and might merely indicate that within the entire group of individuals with ADHD, there may be subgroups for which diagnostic symptoms cluster together and result in a unique profile of difficulties.

4.9 General Summary and Outstanding Questions.

Clearly there are some areas of contradiction in the neuropsychological literature on ADHD and TS. Early on, Harris (1995) noted suggestions (e.g. Como, 1993) that ADHD might have a different aetiology and neuropsychological manifestation than ADHD in people with TS, suggesting that impaired attentional ability is greatest in individuals with 'pure' ADHD than comorbid TS/ADHD and hence factors other than attention may be more important in ADHD among people with TS (Harris, 1995). Adding to the notion of qualitative differences in TS, Harris (1995) notes that others

such as Pauls et al. (1993) have suggested that ADHD may be linked to TS in some people and independent of TS in others, with the association between the two defined by the timing of ADHD and TS onset.

In a review of the literature, Durston (2003) concluded that the evidence from neuropsychological studies support the notion that poor inhibitory control is central to ADHD. In view of this, it appears that any research investigating the core deficits in groups with ADHD symptomatology should investigate inhibitory function. Although inhibitory dysfunction has been repeatedly demonstrated in studies of ADHD and TS, clarifying the precise level of inhibitory deficits with stricter methodological controls is an area of importance.

The extent to which ADHD comorbid with TS shares the same cognitive features as pure ADHD is unknown despite the overlap in the frontal brain regions implicated. This suggests that the aetiology of TS may also be causal to the development of ADHD at a greater frequency than would be expected by normal population frequencies. However, this could establish that disruption to neural circuitry at any level in the developing brain places a child at risk for cognitive difficulties, reflecting the existence of two distinct disorders with only shared similarities through limited (although not identical) means of cognitive expression. Exploring these questions with reference to inhibitory function is a key area for further research.

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Empirical Paper

Characterising the Comorbid Subtypes of Tourette Syndrome

ABSTRACT

Tourette syndrome (TS) is a neurodevelopmental disorder that often occurs in conjunction with Attention Deficit Hyperactivity Disorder (ADHD). There is emerging evidence that individuals with TS comorbid with ADHD exhibit executive dysfunction that is particularly evident on tests of inhibition. However, it is still uncertain whether ADHD comorbid with TS is similar to ADHD that presents alone in terms of its cognitive profile. This study set out to examine the extent to which ADHD that occurs comorbidly with TS represents the same disorder as ADHD that occurs alone. Individuals with TS comorbid with ADHD were compared to groups who had ADHD alone or TS alone on a battery of multiple levels of inhibition. Whilst there was not a uniform profile of disinhibition, individuals with ADHD (with or without TS) exhibited the most inhibitory deficits, particularly during verbal and design fluency tasks. These findings suggest that neurological disorders have a high degree of overlap for which they share a continuum of difficulties that could result from a common underlying neuroanatomical pathology.

1.0 INTRODUCTION

1.1 Tourette Syndrome

Tourette Syndrome (TS) is a neurodevelopmental disorder. The diagnostic criteria specify motor and phonic tics that occur many times per day and are not due to the physiological effects of substances (American Psychiatric Association, 2000). Epidemiological data suggest an age of onset that ranges from 6-7 years with a greater occurrence in males by a factor of 3-9 times (American Psychiatric Association, 1994). Recent prevalence estimates range from 0.8% to 1.9% (Hornsey, Banerjee, Zeitlin, and Robertson, 2001), with more conservative estimates suggesting population frequencies of 0.05% or less (Apter et al., 1993) or 0.001- 0.01% (American Psychiatric Association, 1994).

High comorbidity rates are reported between TS and Obsessive Compulsive Behaviours (OCB) and Attention Deficit Hyperactivity Disorder (ADHD) (American Psychiatric Association, 1994). Neurological reports suggest that abnormalities in the basal ganglia and its interconnecting pathways (Schuerholz, Baumgardner, Singer, Reiss and Denckla, 1996) or more generally in the frontal-subcortical, basal ganglia-thalamocortical, and nucleus accumbens-limbic system circulatory (Robertson, 2000) are compromised in TS. However, there is also extensive evidence that TS is associated with increased dopamine sensitivity or receptor activity (Müller-Vahl et al., 2000; Sandor, 1998; Serra-Mestres et al., 2004).

1.2 Cognitive Function in TS

Individuals with TS are at risk of experiencing cognitive deficits, although intellectual ability is reported to be normally distributed (Como, 2001). The cognitive features that have been identified include: visual motor integration problems, impaired fine motor skills and executive dysfunction (Como, 2001). More specifically, research has identified poor real-life problem solving, inferior performance on measures of inhibition and strategy, strategic memory deficits, poorer ratings on a questionnaire measuring dysexecutive functioning (Channon, Pratt and Robertson, 2003) and poor letter word fluency (Schuerholz et al., 1996).

There are some contradictory reports regarding the extent of these cognitive problems. For example, Ozonoff, Strayer, McMahon and Filloux. (1994) demonstrated that when comparing individuals with TS to children who had autism or were typically developing, the TS group did not exhibit inhibition deficits and Ozonoff and Strayer (2001) found intact working memory in individuals with TS. However, whilst Schuerholz et al. (1996) reported that groups with TS were significantly poorer on measures of letter word fluency, Mahone, Koth, Cutting, Singer and Denckla (2001) reported that individuals with either TS or ADHD were both free from executive impairments on tests of verbal fluency, figural fluency, and verbal learning.

Ozonoff et al. (1998) suggested that neuropsychological impairments in TS appear to occur as a function of comorbidity and symptom severity. They had observed that on a negative priming task of inhibitory functioning, individuals with TS and comorbid conditions tended to perform less well than control groups. This was most marked

for individuals with more severe symptoms of TS, ADHD and Obsessive Compulsive Disorder (OCD). Nonetheless, it is unclear from this study which comorbid condition was most significant or if their findings represent an additive effect of multiple types of pathology that consequently lead to greater neuropsychological dysfunction.

Further studies have begun to explore the profile of cognitive functioning in TS and how it varies according to comorbid subtype. It has been found that whilst individuals with comorbid OCD and TS manifested with problems predominantly in the areas of competence for self monitoring, error detection and response inhibition (Müller et al., 2003) impairments in a TS alone group were confined to inhibitory aspects of executive functioning whilst more marked and varied executive dysfunction were present in groups with TS+ADHD (Channon et al., 2003).

TS comorbid with ADHD appears to be a more severe condition than ADHD or TS alone. Additional disruptions are reported in individuals with TS comorbid with ADHD when compared to those with pure TS on measures of psychosocial functioning, verbal and performance intelligence and word fluency but not on measures of cognitive flexibility (Brand et al., 2002). Other studies that have attempted to disentangle the overlap between TS and/or ADHD have found that individuals with ADHD comorbid with TS had worse performance on the Rey-Osterrieth Complex Figure test of organisation (Harris et al., 1995) and exhibit lower psychosocial functioning (Spencer et al., 1998; Carter et al., 2000). Such findings reinforce the notion that it is the contribution of disorders comorbid with TS that give rise to findings of varying cognitive dysfunction. However, no studies to date have

explored this explicitly and it is questionable whether it is having two disorders that place one at risk for greater cognitive difficulties or whether the combined disorders result in a unique set of symptoms and cognitive difficulties.

In summary current research suggests that within TS there is a profile of neuropsychological deficits dependent upon the associated comorbid disorder. This is interesting in terms of what it might tell us about the aetiology of TS. Further description of the executive function profile of TS and its comorbid subtypes could be valuable in informing if the associated disorders have a distinct underlying pathology. Few publications have compared TS directly with ADHD; particularly with reference to whether ADHD that is found in TS represents the same disorder as pure ADHD. Given that children with TS comorbid with ADHD are at an increased risk for cognitive and social adaptation difficulties and externalising behavioural problems (Carter et al., 2000), understanding the precise features of the ADHD that characterise TS is of value, particularly regarding whether prime clinical attention should be placed on the diagnosis of ADHD over TS.

1.3 ADHD

ADHD is a developmental disorder, defined by the presence of six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity that present before age 7 and are not accounted for by another disorder (American Psychiatric Association, 2000). The prevalence in school children is accepted to be between 3% and 7.5% (Denckla, 2003) or less conservatively 19.8% and 12.3% in boys and girls respectively (Pineda, 1999). Both genetic and environmental factors are implicated in the aetiology (Denckla, 2003).

1.4 Cognitive Function in ADHD

There has been an abundance of empirical research conducted on ADHD that has emphasised the presence of specific difficulties with attention and inhibition. Following from theories advocating that attentional impairments are a core feature in ADHD (e.g. Manley et al., 2001; Rovet and Hepworth, 2001; Epstein et al., 2003), there are theories that postulate that a failure to inhibit or delay a behavioural response is the central deficit in ADHD (Tannock, 1998). Much research has demonstrated specific deficits in inhibitory functioning in individuals with ADHD on a variety of tests. This includes: the Hayling Sentence Completion task (Shallice, 2002); the Trail Making test, (Chhabildas, Pennington and Willcutt, 2001), the Stroop task (Wright, Waterman, Prescott and Murdoch-Eaton, 2003, Rucklidge and Tannock, 2002 and Shallice, 2002), the Go-*No*go task (Nyberg, Bohlin, Berlin, and Janols, 2003; Crone, 2003) and the Stop task (Oosterlaan, Logan and Sergeant, 1998, Nigg, 1999; Schachar, Mota, Logan, Tannock and Klim 2000; Logan, Schachar and Tannock, 2000; Solanto et al., 2001).

Such a diversity of inhibitory deficits reiterates the notion that inhibitory functioning is also a key deficit in ADHD. Varying interpretations of findings regarding response inhibition/impulsivity suggest its cause to be either: an underlying deficit in a central act of control, a deviant cognitive style designed to reduce the subjective experience of delay, or a dysfunction in the energetical/state-regulation of motor control (Tannock, 1998).

There are some issues regarding the diagnostic subtypes of ADHD. Chhabildas et al.

(2001) examined the neuropsychological profiles of the ADHD subtypes (hyperactive/impulsive, inattentive or combined). They found that children with ADHD-combined or ADHD-inattentive were indistinguishable, both demonstrating difficulties on measures of processing speed, vigilance and inhibition. However, individuals with ADHD-hyperactive/impulsive did not demonstrate any difficulties on the experimental tasks. They suggested that the features of ADHD may be more transient, following a developmental pathway through ADHD-hyperactive/impulsive through to ADHD-combined through to ADHD-inattentive (Chhabildas et al., 2001).

Further relating to this finding, Oosterlaan et al. (1998) questioned the extent to which poor response inhibition in ADHD children represents a stable deficit or a maturational lag. Some studies have failed to find a response inhibition deficit as measured by a Stop task (Kuntsi, Oosterlaan and Stevenson, 2001; Scheres, 2001) and there is evidence that inhibitory function is on a continuum and that there are varying cognitive profiles dependent upon the type of ADHD (i.e. inattentive, hyperactive/impulsive or combined type, e.g. Chhabildas et al., 2001). Given that there are subtypes of ADHD, the extent to which TS comorbid with ADHD is characterised by the same features as ADHD alone is a valid area for investigation. Examination of this area might reveal that it merely represents the presence of difficulties associated with a milder subtype.

1.5 Research Aims

This study will be exploratory in nature and will aim to investigate the extent to which ADHD comorbid with TS shares the same cognitive features as pure ADHD. It will also examine the extent to which these two groups differ from individuals with

TS alone, who are not expected to share the same degree of inhibitory deficits. This could clarify if the aetiology of TS is causal in the development of true ADHD at levels greater than would be expected by normal population frequencies, or if ADHD comorbid with TS is a milder variant of ADHD that occurs alone. However, the findings could establish that the presence of any neurodevelopmental disorder places a child at risk for cognitive difficulties, reflecting the existence of two distinct disorders with only shared similarities through limited (although not identical) means of higher level cognitive expression (i.e. disinhibition). The crucial implications for this research are that if ADHD that is comorbid with TS has different qualitative features than ADHD that occurs alone, then these two conditions would warrant different clinical treatment.

Given that there is much research advocating aberrations of inhibitory processes in these two groups, this study will focus upon a detailed examination of the similarities and differences between different types of inhibitory function. This focus is necessary in order to guarantee that a thorough hypothesis driven examination of inhibition is conducted. This might help to reduce the ambiguities in the literature. It is possible that discrepant findings might be the consequence of varying methodologies or the evaluation of poorly defined constructs.

As discussed in the literature review, there are a range of measures that purport to directly assess behavioural, cognitive and trait inhibitory functioning. A classic test of cognitive inhibition is the Stroop (Stroop, 1935). This is associated with right prefrontal lobe function (Vendrell, Junqué, Pujol, Jurad and Grafman, 1995) and specifically heightened activation of the anterior cingulate, (Andrews, 2001). Other

well known tasks include The Go-*No*go test of intentional motor inhibition, also associated with right prefrontal activation (Rubria et al., 2001; Jonkman, Lansbergen and Stauder, 2003) and the Hayling Sentence Completion cognitive inhibition test (Burgess and Shallice, 1997) for which inhibition (response suppression) is associated with activation of the left frontal operculum, inferior frontal gyrus and right anterior cingulate gyrus activation whilst response initiation (generation) is associated with left-sided activation of the frontal operculum, inferior frontal gyrus, middle temporal gyrus and right anterior cingulate gyrus activation (Nathaniel-James et al., 1997).

Some of the tasks reported in the inhibition literature examine generation as well as inhibition (e.g. Hayling Sentence Completion test initiation, Verbal Fluency test, Design fluency tests). Like tests of inhibition, both verbal and design fluency tests are associated with left frontal activation (Elfgren and Risberg, 1998) which has been reported to be disrupted in individuals with TS (e.g. Brand et al., 2002) and discriminates individuals with TS from those with ADHD (Harris et al., 1995). In view of this, all of these tasks are valuable in measuring response inhibition in TS +/- ADHD. Finally, tasks such as the Trail Making test measure flexibility (Andrews, 2001), which overlaps with cognitive inhibitory processes. Nathaniel-James et al. (1997) have raised the possibility that initiation (generation) and suppression (inhibition) are related skills, subserved by similar but overlapping subsystems and functional regions.

This study will focus on groups with TS, TS+ADHD and ADHD. There is much evidence that these groups differ from typically developing groups; however such

comparisons fail to disentangle the overlap between these groups and explicitly address what is the contribution of TS or ADHD to the cognitive profile. The proposed research questions are:

1. Does TS + ADHD produce inhibitory deficits that are similar or differing in nature to that in pure ADHD or TS alone?
2. By addressing question 1, it is hoped that this study will be able to answer whether ADHD that often presents comorbidly with TS may be of the same severity in inhibitory terms as pure ADHD or if it represents a more transient form of ADHD with a cognitive profile that is closer to that of TS alone.

2.0 METHOD

2.1 Participants

TS group

Children with TS with no comorbid disorders, aged eighteen years or younger were recruited from the tertiary TS clinic patient population at Great Ormond Street Hospital. They were diagnosed by either a Consultant Psychiatrist, Neurologist or Clinical Psychologist according to DSM-IV-TR criteria. Exclusion criteria were:

- TS comorbid with any disorder that meets DSM-IV-TR criteria
- English not the first language
- IQ less than 70

TS comorbid with ADHD group (TS+ADHD)

Children with TS comorbid with ADHD aged eighteen years or younger were recruited from the same clinic. They were diagnosed as before. Exclusion criteria were:

- TS comorbid with any disorder that meets DSM-IV-TR criteria other than combined ADHD
- English not the first language
- IQ less than 70

ADHD group

Children aged eighteen years or younger who met DSM-IV-TR criteria for ADHD combined type (hyperactive/impulsive and inattentive) were included in the study. They were diagnosed by the Child Psychiatrist, Clinical Psychologist or Paediatrician at their local clinic. Exclusion criteria were:

- Any other comorbid disorder that meets DSM-IV-TR criteria is present
- English not the first language
- IQ less than 70

In order to guarantee that this group was not comprised of the comorbid cases that are often seen at Great Ormond Street Hospital, the target population was approached through four local Child and Family Community Mental Health Services. They were matched to the TS and the TS+ADHD group by age, sex and ability level.

For the recruitment of the TS groups 100 recruitment letters were mailed out over four large mailings and in response to an initially slow and limited response rate. From those invited, 39 cases replied. One case was subsequently excluded due to comorbid OCD whilst another was excluded because they were too young. For the recruitment of participants with ADHD, approximately 60 recruitment packs were passed onto child psychiatrists or paediatricians. However only thirteen cases returned completed information packs, one of whom subsequently dropped out before the study began due to 'research fatigue'. Two individuals did make telephone contact in order to request that they could participate in the study; however, they failed to send the consent information that would have identified themselves to me.

Ethical approval was attained from Barnet, Enfield and Haringey Local Research Ethics Committee (LREC), Camden and Islington LREC and Cambridgeshire and Peterborough LREC. An extension to an existing ethical application was granted from Great Ormond Street Hospital LREC. (See Appendix for copies of approval).

2.2 Materials and Procedure

General Ability

1. ***The Wechsler Abbreviated Scale of Intelligence*** (WASI, Wechsler, 1999). In order to match for IQ, each participant was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI), which has good psychometric properties. There were no significant differences between the TS, TS+ADHD and ADHD groups for Full Scale IQ (FSIQ) ($F(2, 48) = 1.08$, $p=0.350$) or age ($F(2, 48) = 0.44$, $p=0.645$) (see table 2.11).

Table 2.11: Mean (Standard Deviation (SD)) Demographic and Diagnostic Information for Each Group With Significance Values

	TS	TS+ADHD	ADHD
Number	17	20	12
Age	13.06 (2.40)	12.60 (2.81)	12.16 (2.37)
Sex (M:F)	17:0	19:1	12:0
Full Scale IQ	100.18 (20.57)	93.05 (10.87)	98.58 (13.35)
Vocabulary Scaled Score	52.24 (14.24)	43.85 (10.73)	49.33 (11.20)
Matrix Reasoning Scaled Score	46.18 (12.71)	47.25 (7.00)	47.58 (9.05)

(* = $p<0.05$, ** = $p<0.0005$)

Trait Disinhibition and Diagnostic Screens:

1. ***Conners Parent Rating Scale-Short:*** (Conners, 1996). The Conners' Rating Scales Revised were used to provide a measure of trait inhibition and the other features associated with ADHD. It is a questionnaire set of standardised measures for assessing ADHD in children and adolescents that correspond with symptoms

used in the DSM-IV as criteria for ADHD. This version included 27 items measuring four scales.

(i) *Oppositional*: Individuals scoring high on this scale are likely to break rules, and are easily annoyed and angered.

(ii) *Cognitive Problems/Inattention:* Identifies inattentive individuals who may have trouble concentrating on tasks that require sustained mental effort.

(iii) *Hyperactive Impulsive*: Identifies individuals who are restless and impulsive and have the need to always be on the go.

(iv) *Conner's ADHD Index:* Identifies individuals "at risk" for ADHD.

Parents completed this questionnaire, for which they were required to rate the presence of each item in their child's behaviour over the preceding month. Each item was then scored by the experimenter and scores were translated into t-scores which produced the profile for each participant according to their age and sex.

2 *DSM-IV Screen interview*:

Participants were screened for the presence of a psychiatric disorder/symptomatology including ADHD, OCD, depression, anxiety disorders and psychosis using the Structured Clinical Interview for DSM (SCID-CV) (First, Spitzer, Gibbon, & Williams, 1996). This also provided another measure of trait inhibition/impulsivity (see table 2.11, 3.1, further results are in Appendix 1).

This interview was administered by the examiner to both the child and the primary caregiver(s). Responses were written down verbatim and later scored according to

whether or not an individual reached criteria for a clinical disorder and for the degree to which they exhibited symptoms of a clinical disorder. Participants who reached criteria for a clinical disorder other than that laid out in the inclusion criteria were excluded. Scores from the ADHD inhibition/impulsivity interview section were used as another measure of trait inhibition.

EXPERIMENTAL MEASURES[1]:

Cognitive Disinhibition: visual (pictures/words/numbers)

1. The Stroop (Colour Word Interference Test).[2]

The D-Kefs Colour-Word Interference Test, (Delis-Kaplan Executive Function System (D-KEFS) Delis, Kaplan and Kramer, 2001) based on the Stroop (1935) was used. *Condition 1: Colour Naming (low level inhibition).* Participants were required to name patches of colour as quickly as possible without making any mistakes. *Condition 2: Word Reading (low level inhibition).* Participants were presented the rows of words printed in black ink and told to read the words aloud as quickly as possible without skipping any or making any mistakes. *Condition 3: Inhibition (high level inhibition):* Participants were presented with rows of words printed in dissonant ink colours. They were required to name the colour of ink that the words were printed in and not read the words. *Condition 4: Inhibition/Switching (high level inhibition).* Participants were presented with the stimuli showing the words printed in dissonant ink colours, half of which were contained in a box. They were instructed to name the colour of the ink and not to read the words. If a word was inside a little box, they were required to read the word and not name the colour.

For each condition, participants were given two practice lines. The participant's completion time was noted with incorrect responses or nonsense words recorded verbatim as were self-corrections.

1. The Trail Making Test (D-KEFS).

The D-Kefs Trail Making Test: consists of a visual cancellation test and a series of

[1] Further descriptions of all of the experimental measures are provided in Appendix 2
[2] Directions used were replicated from the Delis-Kaplan Executive Function System (D-KEFS) Dean C Delis, Edith Kaplan and Joel H Kramer, 2001 manual.

connect-the-circle tasks. *Condition 1: Visual Scanning (low level inhibition).* Participants were instructed to put a mark each time they saw a number three on the page without missing any. *Condition 2: Number Sequencing (medium level inhibition).* The participant was required to connect just the numbers (and not the letters) in numerical order. *Condition 3: Letter Sequencing (medium inhibition).* The participant was required to connect just the letters (and not the numbers) in alphabetical order. *Condition 4: Number-Letter Switching (high level inhibition).* The participant was instructed to switch between connecting the numbers and letters in order (e.g. draw a line from A to 2, 2 to B, B to 3 and so on) without making mistakes. *Condition 5: Motor Speed (low inhibition).* The participant was required to draw a line over the dotted line.

For each condition participants were instructed to respond as quickly as they could. They were given a series of practice items and their test completion time was recorded. Responses were rated according to set loss errors (the examinee connected a line to a series that belongs in the wrong set of symbols) and sequencing errors (the examinee connected the items in the wrong order).

2. The Design Fluency Test (D-KEFS)

Condition 1: Filled Dots (low level inhibition). The participant was instructed to make as many different designs in each square by connecting dots using only straight lines. They were required to make their designs with four straight lines with each line drawn starting from a dot. *Condition 2: Empty Dots only (medium level inhibition).* This time the participant was required to make designs as before but only connecting the empty dots (and so ignoring the filled dots). *Condition 3:*

Switching (high level inhibition). Like before, participants were instructed to make a different design in each square but this time they needed to switch from an empty dot to a filled dot.

Again for each condition they were given practice items. Each condition was terminated after 60 seconds. Responses were scored according to the presence of set loss designs (where they failed to follow the rules, for example drew designs with an incorrect number of lines) and repeated designs (when the same design was drawn two or more times within a condition).

3. The Verbal Fluency Test (D-KEFS)

The D-Kefs Verbal Fluency Test comprises three testing conditions: Letter Fluency, Category Fluency and Category Switching. *Condition 1: Letter Fluency (low level inhibition).* The participant was given a letter of the alphabet and required to say as many words as they could that began with that letter within 60 seconds. None of the words could be names of people or places or numbers. The letters F, then A, then S were presented to the participant in three trials. *Condition 2: Category Fluency (low level inhibition).* The participant was required to name as many animals as they could within 60 seconds. For trial 2, the participant was required to tell the examiner as many boys' names as they could. *Condition 3: Category Switching (high level inhibition).* The participant was required to switch back and forth between saying as many fruits and as many pieces of furniture as they could in 60 seconds.

Responses were rated for set loss errors (rule violations, e.g. failure to start with the target letter) and repetition errors (repeated responses within a trial).

4. ***The Hayling Sentence Completion test*** (Burgess and Shallice, 1997). In section 1 (*low level inhibition*), participants were read a series of sentences, each of which had the last word missing from it. They were required to give a word which completed the sentence (e.g. The crime rate has gone up this:...*year*). In section 2 (*high level inhibition*) participants were required to give a word that was completely unconnected to the sentence in every way (e.g. Her new shoes were the wrong:....*computer*). For section 2 there were two types of errors, errors that were connected to the sentence (e.g. *size*) or errors that were somewhat connected (e.g. *feet*).

They were given two practice items before the start of each trial. The stopwatch was started as soon as the examiner stopped speaking, and stopped as the subject started their reply. Responses and response latencies were recorded.

Behavioural (Motor) Inhibition and Working Memory

1. ***The Go-Nogo test*** and ***The 2-Back Test*** (computerised self-programmed test of working memory/inhibition). This task required the participant to press the left mouse button as quickly as they could in order to indicate 'yes' to the presence of a specific letter presented individually on the computer screen (Go trials, *low level inhibition);* but to not press when the target was absent (Nogo trials, *high level inhibition*). Measures included response time to go targets, and correct scores to go and nogo targets.

For the ***Go-Nogo/0-Back*** condition (involving attentional inhibition, but no working memory load). Each participant was presented with three conditions of the test. The slow condition had an inter-trial interval (ITI) of 2 seconds and the participant had to respond as quickly as possible when the letter B was presented, the medium condition had an ITI of 1.5 seconds and the participant had to respond as quickly as possible when the letter P was presented on the screen, and the fast condition had an ITI of 1 second and the participant had to respond as quickly as possible when the letter A was presented on the screen. Participants were given a script to read which included the directions and a series of practice items and examples (See appendix 3 and 4). At the end of each block, the participants received a set of continuation directions on the screen, and the test could be paused if they needed a break.

Each condition was divided into four blocks. Each block consisted of 40 trials. In the analysis, block 1 was considered as a practice block and responses of blocks 2-4 were used in order to calculate the number of correct responses and median reaction times to targets and all trials. The tasks were matched such that 25% of the letters within each block were targets and 75% were distractors. The participant was required to inhibit the urge to respond to distractors.

For the ***2-Back test***, there was only one condition of this test. The ITI was 2 seconds, and each participant was presented with four blocks of 42 trials. Again, the analysis was based on block 1 being a practice trial and blocks 2-4 used in order to calculate the number of correct responses and median reaction times to targets and all trials. The participant had to press the left mouse button as quickly as possible whenever the letter on the screen was the same as the letter presented two trials previously.

Participants were given a script of directions to read (see appendix 5 and 6) including a series of practice items and examples. At the end of each block, the participants received a set of continuation directions on the screen, and the test could be paused if they needed a break.

Participants were tested in a quiet room in their home. Each session lasted about three hours. Presentation order was randomly allocated using a counterbalancing grid. Cases were matched between groups in order to guarantee that each participant in the other group received the same random presentation order of the tests.

2.3 Power Analysis

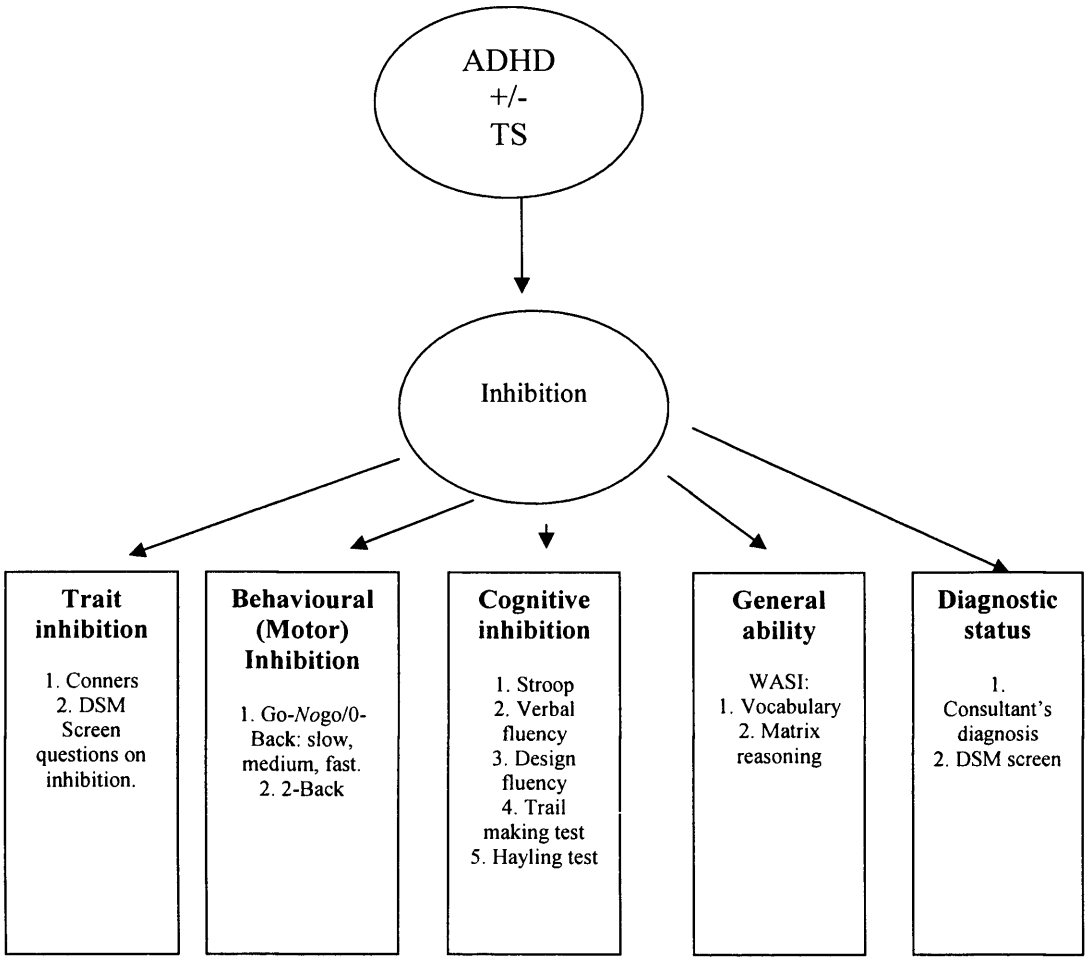
Given that these measures are quite robust, according to Cohen's (1992) conventions the number of participants needed when using an Analysis of Variance with three groups for a large effect size is approximately 20 ($p=0.05$).

2.4 Data Analysis

Where the data were normally distributed, parametric analyses of variance were used in order to examine between group differences with maximum power. Bonferonni statistical adjustments were made to control for multiple testing. The data were initially checked for the extent to which they deviated from the normal distribution. There was no marked skew or kurtosis, so transformation of the data were not conducted. Error analyses were not calculated for the D-Kefs measures where errors were extremely rare and distributions thus skewed. This also helped to reduce the heightened type I error rate that might have emerged through multiple comparisons.

2.5 Diagram of Protocol

Figure 2.51: Model Specification: Schematic Diagram of the Constructs Measured in this Study



3.0 RESULTS

Trait Disinhibition and Diagnostic Status:

Conners Parent Rating Scale and SCID-CV DSM-IV Screen interview:

The results of the Conners Parent Rating Scale and the SCID-CV DSM-IV interview are presented in table 3.1. The means suggest that, as expected, the groups displaying the most marked symptoms of ADHD were the TS+ADHD group and the ADHD group. Interestingly there were relatively high rates of cognitive problems/inattention and possibly sub-threshold symptoms of ADHD displayed by the TS group. On most of the Conners measures the TS group were scoring well above the normative mean t-score of 50 which would place them in the "borderline range"; however, both ADHD groups were scoring above 70 which is in the "significant problem range" demonstrating "markedly atypical symptoms" (Conners 1996).

Table 3.1: Mean (SD) Diagnostic Information for Each Group With Significance Values

	TS	TS+ADHD	ADHD
Conners: Oppositional	60.40 (13.84)*	74.60 (10.36)*	73.00 (11.17)*
Conners: Cognitive Problems/Inattention	58.47 (13.96)*	71.30 (16.72)*	68.18 (4.31)*
Conners: Hyperactivity/Impulsivity	58.20 (18.44)**	83.20 (8.38)**	73.82 (15.33)**
Conners: ADHD Index	59.60 (12.70)**	76.95 (6.48)**	71.27 (6.40)**
DSM: Inattention	4.18 (1.74)**	6.95 (2.21)**	6.92 (2.35)**
DSM: Hyperactivity	2.47 (1.55)**	4.60 (1.60)**	5.17 (1.95)**
DSM: Impulsivity	0.94 (1.03)*	2.30 (0.86)*	2.25 (1.76)*

(* = $p<0.05$, ** = $p<0.0005$)

A repeated measures Analysis of Variance (ANOVA) was conducted in order to examine group differences for each level of the Conners scale (Oppositional, Cognitive problems/inattentive, Hyperactivity/Impulsivity, and ADHD Index). There was a significant main effect of group: ($F(2, 45) = 6.83$, $p=0.003$). Post-hoc Bonferonni adjusted pairwise comparisons indicated that there were significant differences between groups on a subset of these measures. For Conners Oppositional, The TS+ADHD group ($p=0.003$) and the ADHD group ($p=0.030$) showed significantly greater symptomatology than the TS group, but this was not so for comparisons between the TS+ADHD and ADHD group ($p=1.00$). For Conners Cognitive Problems/Inattention the TS+ADHD group showed significantly greater symptomatology than the TS group ($p=0.028$), although this was not so for the TS versus ADHD groups ($p=0.252$) or the TS+ADHD versus ADHD groups ($p=1.00$). For Conners Hyperactivity/Impulsivity the TS+ADHD group attained significantly greater symptomatology than the TS group ($p<0.0005$), as did the ADHD group ($p=0.022$), but there were no significant symptomatology differences between the TS+ADHD and ADHD groups ($p=0.245$). Finally, for Conners ADHD Index score, the TS+ADHD group scored significantly higher than the TS group ($p<0.0005$), as did the ADHD group ($p=0.006$), although there were no significant differences in symptoms between the TS+ADHD and ADHD ($p=0.298$) groups.

A repeated measures ANOVA was conducted in order to examine group differences for each level of the ADHD-related DSM domains (Inattention, Hyperactivity, Impulsivity). Again, the main effect of group was significant: ($F(2, 48) = 9.62$, $p<0.0005$). Post-hoc Bonferonni comparisons showed that for Inattention, the TS+ADHD group scored significantly higher than the TS group ($p=0.001$), as did the

ADHD group (p=0.003). However, there were no significant differences in symptoms between the TS+ADHD and ADHD groups (p=1.00). For Hyperactivity, the TS + ADHD group scored significantly higher than the TS group (p=0.001), as did the ADHD group (p<0.0005), but there were no significant differences between the TS+ADHD and ADHD groups (p=1.00). Finally, for Impulsivity, the TS+ADHD group attained significantly higher scores than the TS group (p=0.004), as did the ADHD group (p=0.017); but there were no symptom differences between the TS+ADHD and ADHD groups (p=1.00).

Cognitive Disinhibition: visual (pictures/words/numbers)

The Stroop (Colour Word Interference Test).

Table 3.2: Mean (SD) Scaled Score Completion time for Stroop Test Measures

Test	TS	TS+ADHD	ADHD
LI Colour naming	10.00 (2.57)	9.15 (2.89)	9.75 (3.39)
LI Word reading	10.00 (3.86)	9.80 (3.17)	10.25 (3.36)
HI Inhibition	10.71 (3.02)	8.10 (3.39)#	9.92 (2.84)
HI Inhibition switching	9.88 (2.62)	8.65 (3.71)	8.67 (3.80)

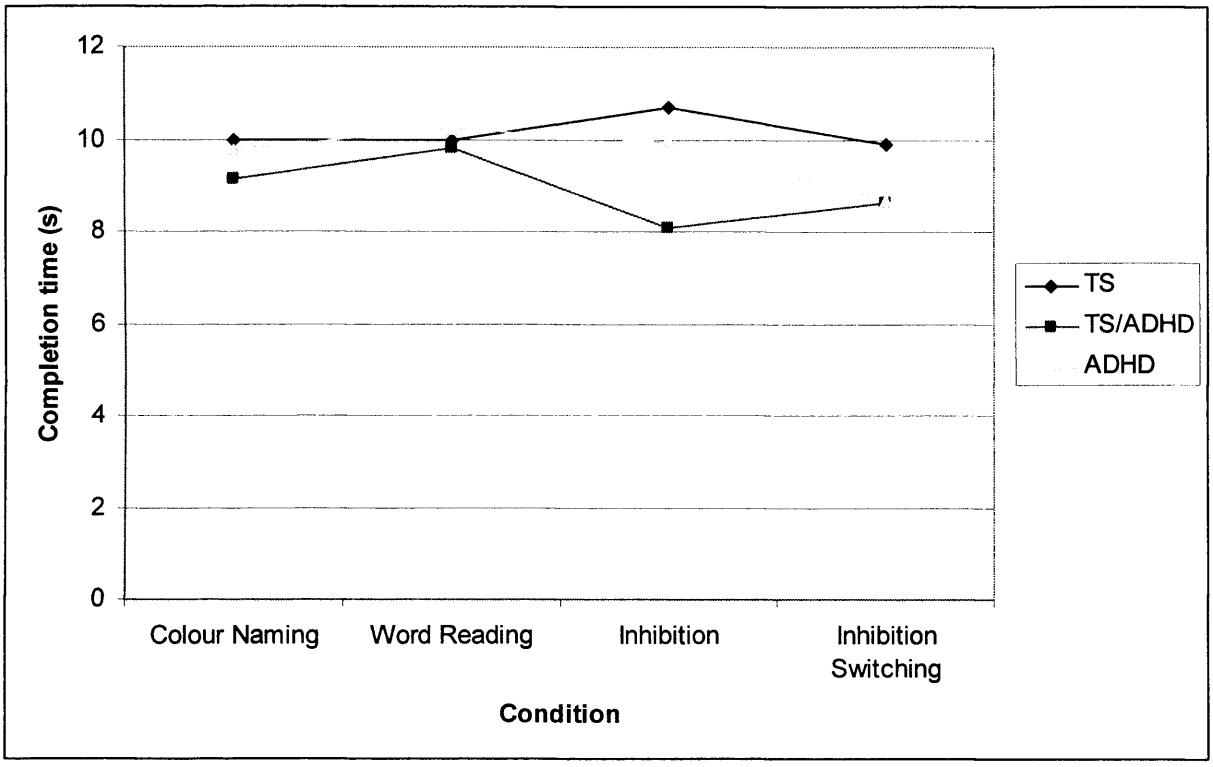
(# = Significantly Different from Test Normative Sample p<0.05)

Response time: A repeated measures ANOVA was conducted in order to examine differences in scaled score completion time for the Stroop under the differing inhibitory conditions. There were three levels of the between participants' factor of group (TS, TS+ADHD, ADHD) and four levels of the within participants' factor of condition (low inhibition (LI) colour naming, LI word reading, high inhibition (HI) inhibition and HI inhibition/switching). The group by condition interaction was not significant: (F (6, 138) = 1.43, p=0.209); nor was the main effect for group: (F (2,

46) = 0.95, p=0.396), or condition: (F (3, 138) = 1.73, p=0.164).

Each of these conditions represented scaled scores with a mean of 10 and a standard deviation of 3 (Delis et al., 2001) for the normal healthy sample for the test. For completion time on the high inhibitory measures (Stroop inhibition and Stroop inhibition switching), a series of one sample t-tests showed only the TS+ADHD group to score significantly below the test norm[3] mean score for Stroop Inhibition Completion time (See appendix 7 for further details). None of the groups differed significantly from the test norm means on the low inhibitory colour naming or word reading measures.

Figure 3.1 Scaled Score Completion Time by Group for the Stroop



[3] All norms used for the D-Kefs were individually age matched

The Trail Making Test

Response time: A repeated measures ANOVA was conducted involving group (TS, TS+ADHD, ADHD) and condition (LI visual scanning condition, medium inhibition (MI) number sequencing condition, MI letter sequencing condition, HI number-letter switching condition and LI motor speed condition). The group by condition interaction was not significant: ($F(8, 184) = 1.24$, $p=0.279$); nor was the main effect for group: ($F(2, 46) = 1.12$, $p=0.336$) or condition: ($F(4, 184) = 1.37$, $p=0.246$).

One sample t-tests indicated that only the TS+ADHD group attained scores that were significantly lower than the test norms for the high inhibition number-letter switching completion time, and medium inhibition number sequencing and letter sequencing conditions (see appendix 7). Neither the TS nor the ADHD groups differed significantly from these norms on the low inhibition measures of visual scanning or motor speed, or on the medium inhibition number sequencing or letter sequencing conditions.

Figure 3.2: Scaled Score Completion Time by Group for the Trail Making Test

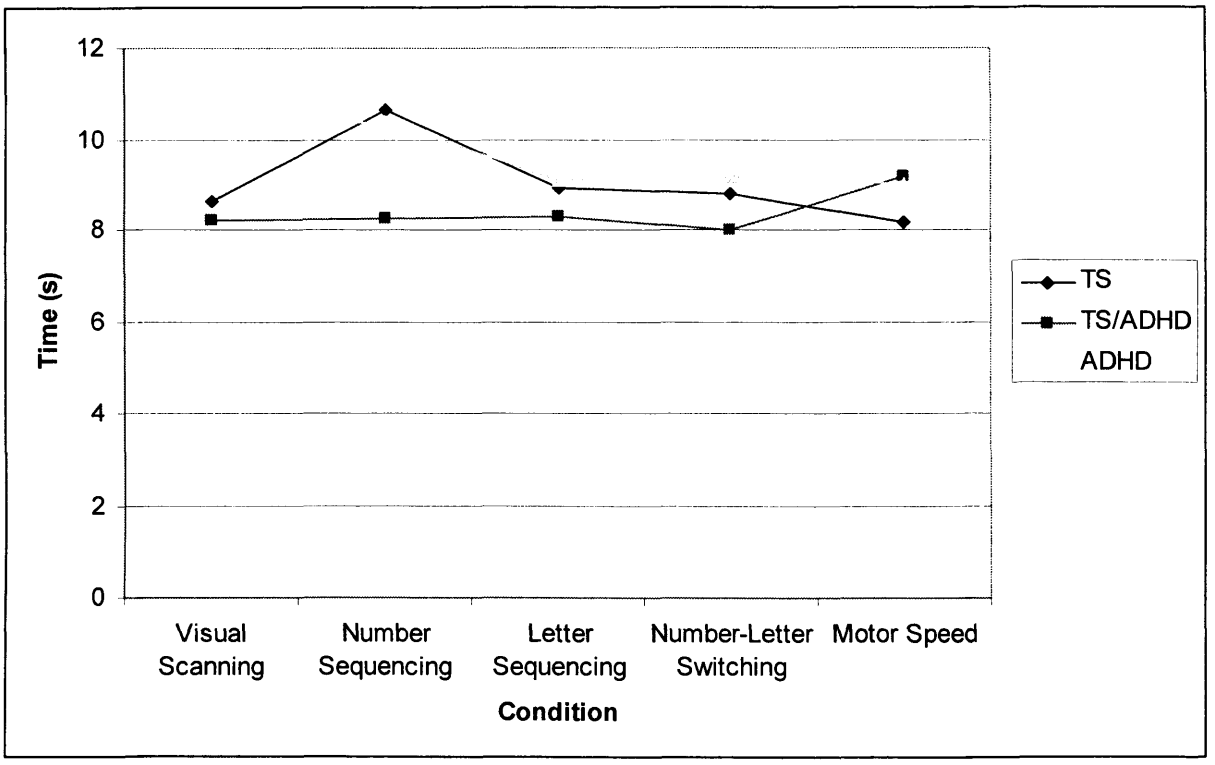


Table 3.3: Mean (SD) Scaled Score Completion Time for The Trail Making test measures

Test	TS	TS+ADHD	ADHD
LI Visual scanning	8.65 (3.41)	8.20 (3.98)	10.25 (2.53)
MI Number sequencing	10.65 (1.96)	8.25 (3.00)#	10.42 (1.31)
MI Letter sequencing	8.94 (3.19)	8.30 (3.42)#	9.08 (3.26)
HI Number-letter switching	8.82 (3.03)	8.00 (3.68)#	9.17 (3.01)
LI Motor speed	8.18 (4.08)	9.20 (3.07)	9.00 (3.72)

(# = Significantly Different from Test Normative Sample $p<0.05$)

The Design Fluency Test

Correct scores: In order to examine the scaled score for the number of correct designs, a repeated measures ANOVA was conducted involving group (TS, TS+ADHD, ADHD) and condition (LI filled dots condition, medium inhibition (MI) empty dots condition and HI switching condition). The group by condition interaction was not significant: ($F(4, 92) = 2.26$, $p=0.069$); nor was there a significant main effect for group: ($F(2, 46) = 0.28$, $p=0.757$) or condition: ($F(2, 92) = 0.85$, $p=0.429$).

One sample t-tests indicated that the TS group scored significantly differently from test norms, scoring above the norm for the high inhibition measure (Design fluency switching total correct scaled score) whilst the ADHD group scored above the norm for the low inhibition measure (Design fluency filled dots correct scaled score) (see appendix 7).

Figure 3.3 Scaled Score Correct Score by Group for the Design Fluency Test

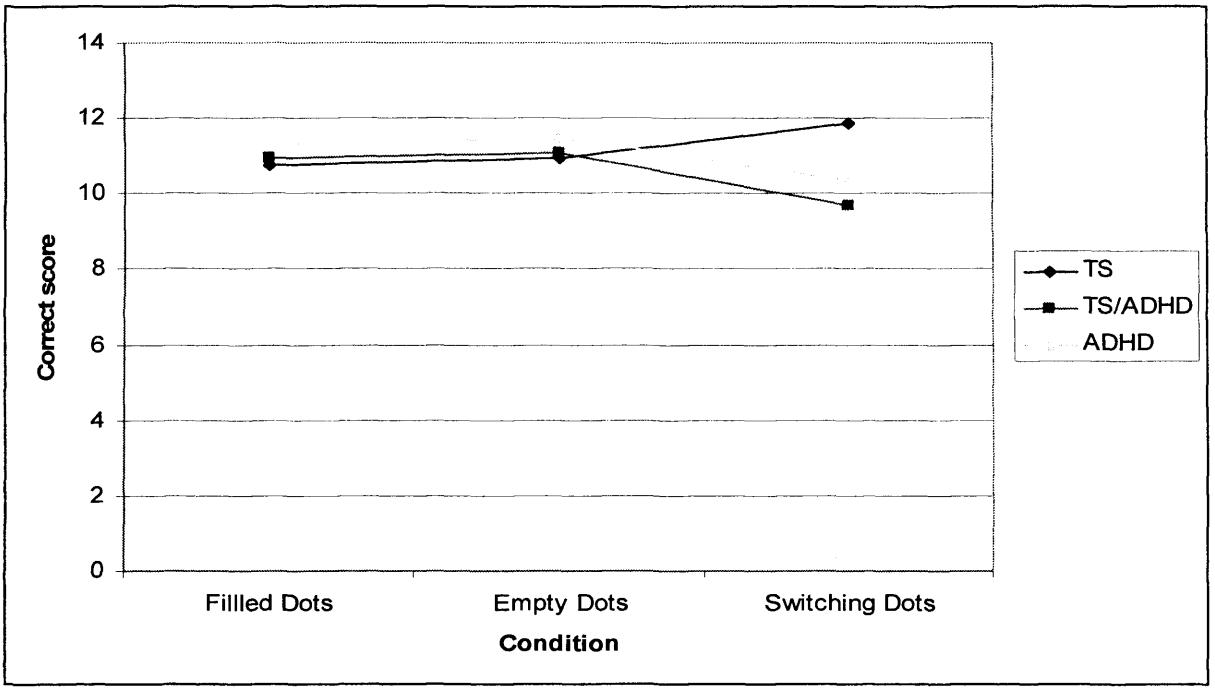


Table 3.4: Mean (SD) Scaled Score Correct Scores and Error Rate Raw Scores for The Design Fluency Test

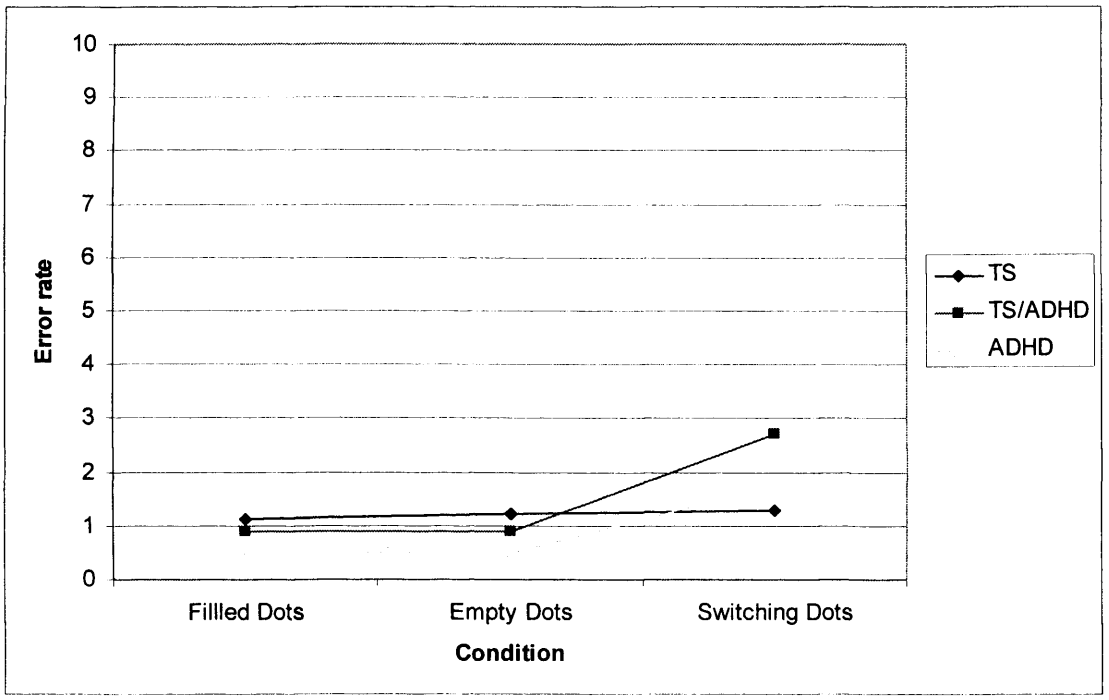
Test	TS	TS+ADHD	ADHD
LI Filled dots: correct	10.76 (2.73)	10.95 (2.95)	11.33 (2.02) #
MI Empty dots: correct	10.94 (3.40)	11.10 (3.06)	11.50 (3.61)
HI Switching dots: correct	11.88 (3.31)#	9.70 (3.23)	10.33 (3.20)
LI Filled dots: set loss errors	1.12 (2.71)	0.90 (2.10)	0.50 (0.80)
MI Empty dots: set loss errors	1.24 (2.39)	0.90 (1.65)	0.50 (0.67)
HI Switching dots: set loss errors	1.29 (1.72)	2.70 (2.74)	1.75 (1.48)
LI Filled dots: repeated design errors	1.00 (2.22)	1.25 (1.68)	1.42 (1.93)
MI Empty dots: repeated design errors	1.31 (1.40)	3.00 (3.42)	1.67 (1.61)
HI Switching dots: repeated design errors	0.38 (0.50)	0.25 (0.44)	1.67 (2.74)

(# = Significantly Different from Test Normative Sample $p<0.05$)

Error rates: Two ANOVAs were conducted in order to examine the rates of the different types of errors: set loss design errors and repeated design errors. For set loss errors, a repeated measures ANOVA was conducted involving group (TS, TS+ADHD, ADHD) and condition (LI filled dots condition, MI empty dots

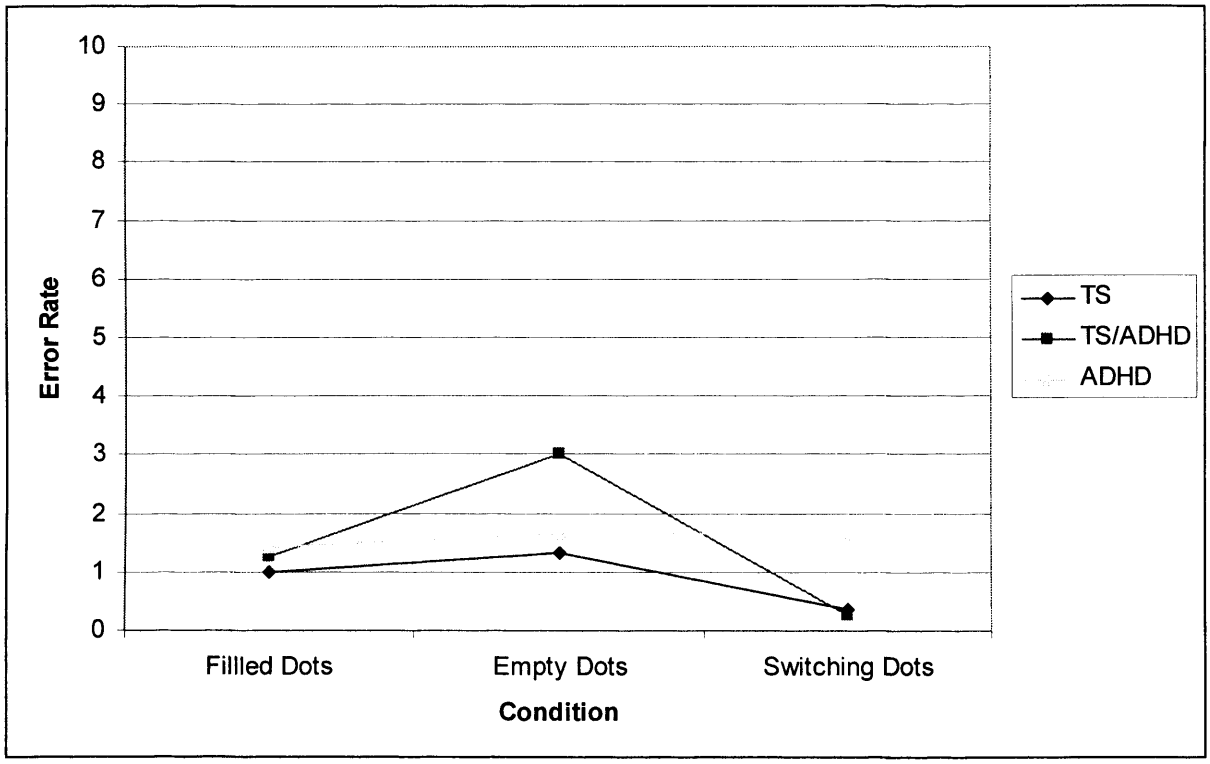
condition and HI switching dots condition). The group by condition interaction effect was not significant: (F (4, 92) = 1.66, p=0.167); nor was there a significant main effect for group: (F (2, 46) = 0.55, p=0.579). There was a significant main effect for condition: (F (2, 92) = 6.52, p=0.002), indicating that as the inhibitory level increased, individuals across groups made a greater number of set loss errors (table 3.4, figure 3.4).

Figure 3.4 Set Loss Error Rate by Group for the Design Fluency Test



For raw score repeated designs errors, a repeated measures ANOVA was conducted involving group (TS, TS+ADHD, ADHD) and condition (LI filled dots condition, MI empty dots condition and HI switching dots condition). The group by condition interaction effect was significant: (F (4, 90) = 3.08, p=0.02). Post-hoc Bonferonni comparisons revealed that the ADHD group made significantly more errors than the TS+ADHD group on the HI: switching dots condition (p=0.026). There were no other significant differences between the groups (p<0.05).

Figure 3.5 Repeated Designs Error Rate by Group for Each Condition of the Design Fluency Test



The Verbal Fluency Test.

Correct scores: For the scaled scores for the number of correct responses for each condition, a repeated measures ANOVA was conducted involving group (TS, TS+ADHD, ADHD) and condition (LI letter fluency condition, LI category fluency condition, HI category switching condition). The group by condition interaction effect was not significant: ($F(4, 92) = 0.10$, $p=0.983$); nor was there a significant main effect for group: ($F(2, 46) = 1.79$, $p=0.179$). However, the main effect for condition was significant: ($F(2, 92) = 6.48$, $p=0.002$). Mean scores (table 3.5, figure 3.6) indicated that low inhibition letter fluency scores were lower than low inhibition category fluency and high inhibition category switching scores.

Figure 3.6: Correct Scaled Score by Group for the Verbal Fluency Test

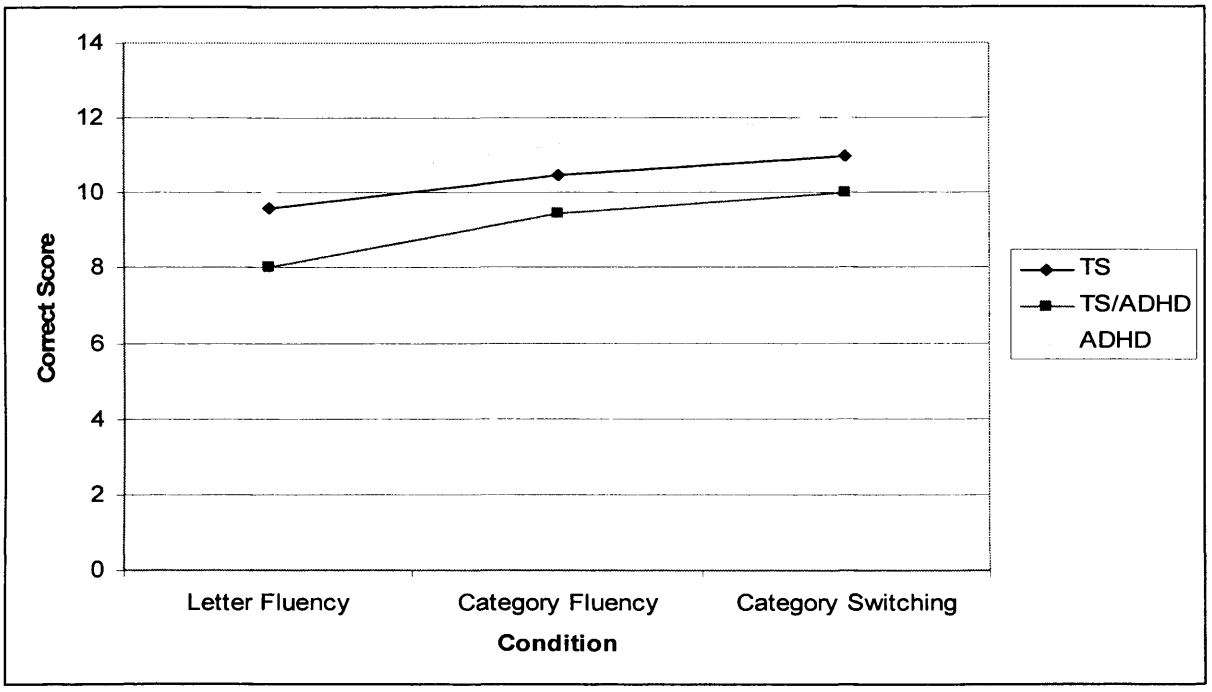


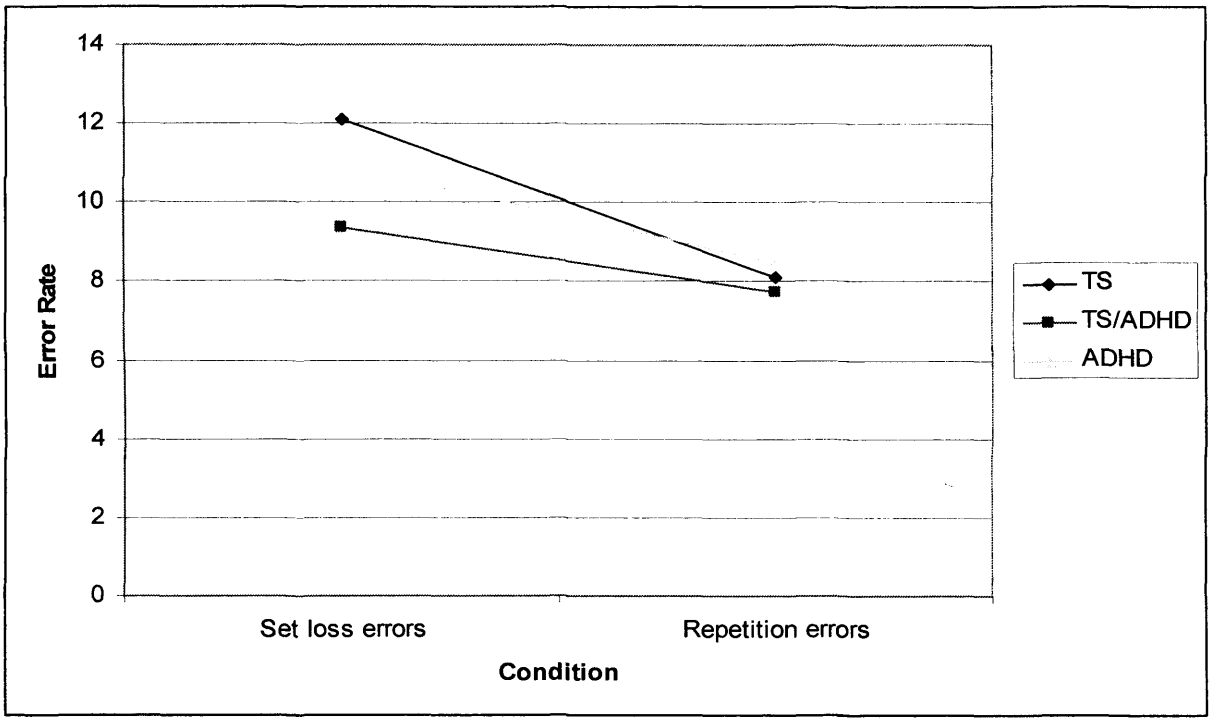
Table 3.5: Mean (SD) Scaled Score Correct and Error Rates for The Verbal Fluency Test

Test	TS	TS+ADHD	ADHD
LI Letter fluency: correct	9.59 (4.84)	8.00 (2.36)#	10.17 (3.49)
LI Category fluency: correct	10.47 (3.43)	9.45 (4.06)	11.33 (2.67)
HI Category switching: correct	11.00 (4.14)	10.00 (3.71)	12.08 (3.09)#
Verbal set loss errors	12.12 (1.27)#	9.35 (3.45)	10.92 (1.44)#
Verbal repetition errors	8.12 (2.39)#	7.75 (2.47)#	8.50 (1.24)#

(# = Significantly Different from Test Normative Sample $p<0.05$)

Error rates: A repeated measures ANOVA was conducted in order to examine scaled score error rates for both set loss errors and repetition errors across all of the tasks combined. The ANOVA involved group (TS, TS+ADHD, ADHD) and condition (total set loss errors scaled score and total repetition errors scaled score). The main effect by condition interaction was significant: ($F(2, 46) = 3.86$, $p=0.028$). Post-hoc Bonferonni comparisons revealed that TS+ADHD group made significantly more errors than the TS group for set loss errors only ($p=0.004$). There were no other significant differences between the groups ($p<0.05$).

Figure 3.7: Scaled Score Error Rate[4] by Group for Each Condition of the Verbal Fluency Test



One sample t-tests for the high inhibition measures comparing performance against the test norms indicated that for scaled score category switching correct, only the

[4] Please note that scaled (standard) scores were used in reporting error rate. These scores have a mean of 10 and a high score indicates a lower rate of errors.

ADHD group differed significantly from these, scoring significantly better than the test norm mean. For Verbal set loss errors, the TS group and the ADHD group both scored significantly better than the test norm, whilst for Verbal repetition errors, all three groups were scoring significantly below the test norm (see appendix 7). For the low inhibition conditions of letter fluency and category fluency, there were no differences from test norms for the TS or the ADHD groups, although the TS+ADHD group performed significantly worse than the test norm for letter fluency.

The Hayling Sentence Completion test.

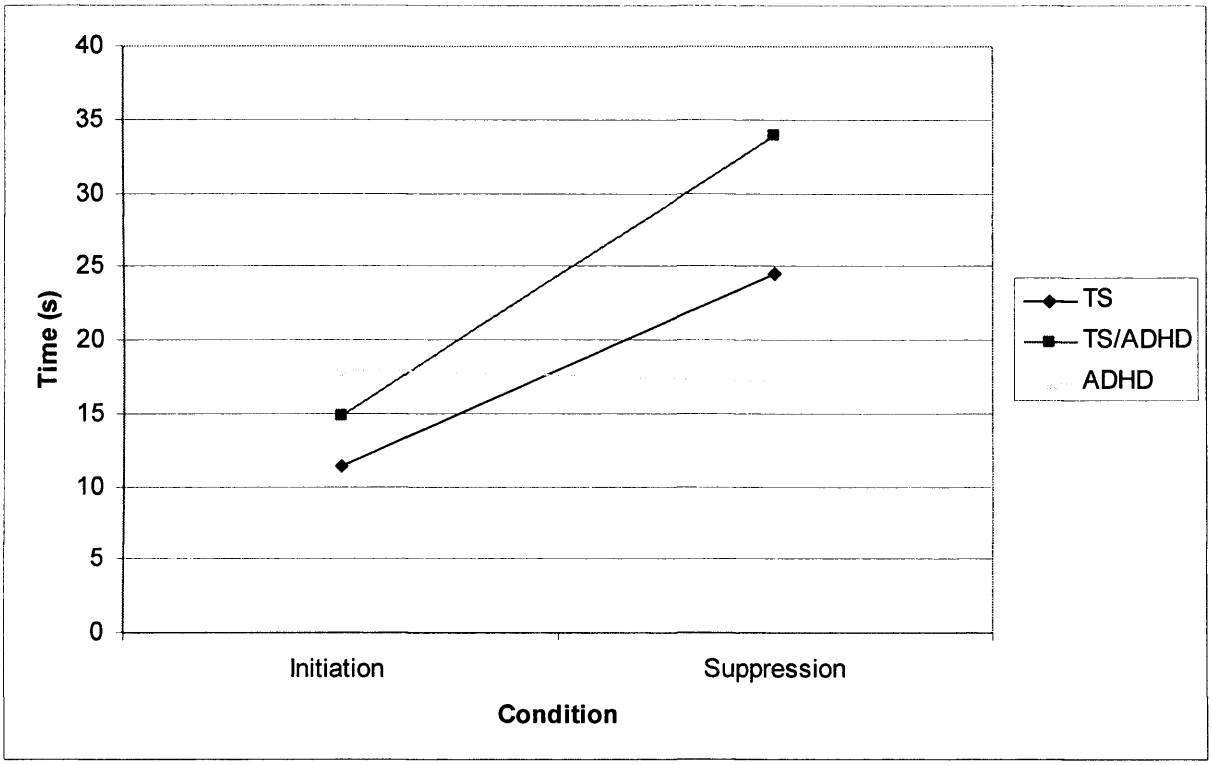
Initiation time and suppression time: A repeated measures ANOVA was conducted in order to examine differences in time for sentence completion for the two conditions. This involved group (TS, TS+ADHD, ADHD) and condition (low inhibition: initiation and high inhibition: suppression conditions). There was a statistically significant group by condition interaction: ($F(2.46) = 3.63$, $p=0.034$) (table 3.6, figure 3.8). Post-hoc Bonferonni comparisons were conducted. No differences were found for either initiation time or suppression time for all groups ($p<0.05$). However, mean analysis indicated that the differences were approaching significance, particularly with the TS+ADHD group requiring longer to respond during suppression conditions, whilst the ADHD group showing no changes in impulsive responding.

Table 3.6: Means (SD) for The Hayling Sentence Completion Test

Test	TS	TS+ADHD	ADHD
Initiation completion time (s)	11.41 (10.32)	14.85 (12.25)	18.00 (16.80)
Suppression completion time (s)	24.47 (18.91)	33.95 (32.70)	17.17 (12.42)
Suppression errors scaled score	4.94 (2.49)	4.90 (2.71)	5.08 (2.47)
Overall efficiency scaled score	4.82 (1.67)#	4.90 (1.68)#	4.92 (1.68)#

(# = Significantly Different from Test Normative Sample $p<0.05$)

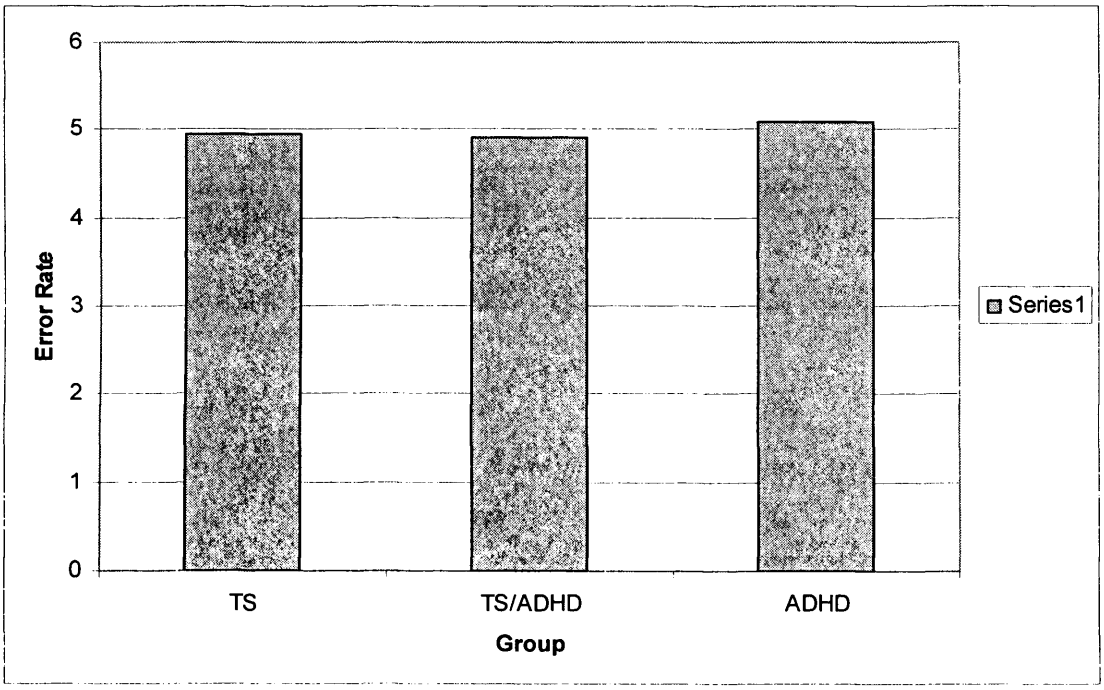
Figure 3.8: Response Time By Group for Each Condition of the Hayling Sentence Completion Test



Errors during the suppression condition: An evaluation of errors made during the suppression condition (see table 3.6, figure 3.9) was conducted using a one-way

ANOVA comparing the groups (TS, TS+ADHD, ADHD) on scaled score for errors. The main effect for group was not significant: (F (2, 48) = 0.02, p=0.981).

Figure 3.9: Error Rate By Group for Each Condition of the Hayling Sentence Completion Test



Overall efficiency score: Finally a one way ANOVA was conducted comparing the groups (TS, TS+ADHD, ADHD) on overall efficiency scaled score. Again, the main effect for group was not significant: (F (2, 48) = 0.01, p=0.986) (table 3.6).

One sample t-tests were carried out in order to test how the groups's scaled scores were differing from the test norm[5] mean of 6 (Burgess and Shallice, 1997). This showed that whilst none of the groups differed from the test norm mean for suppression errors, the TS, TS+ADHD and the ADHD groups were all performing significantly worse than test norms for overall efficiency score.

[5] Test norms were not age matched

Behavioural (Motor) Inhibition

The Go-NoGo/0-Back test

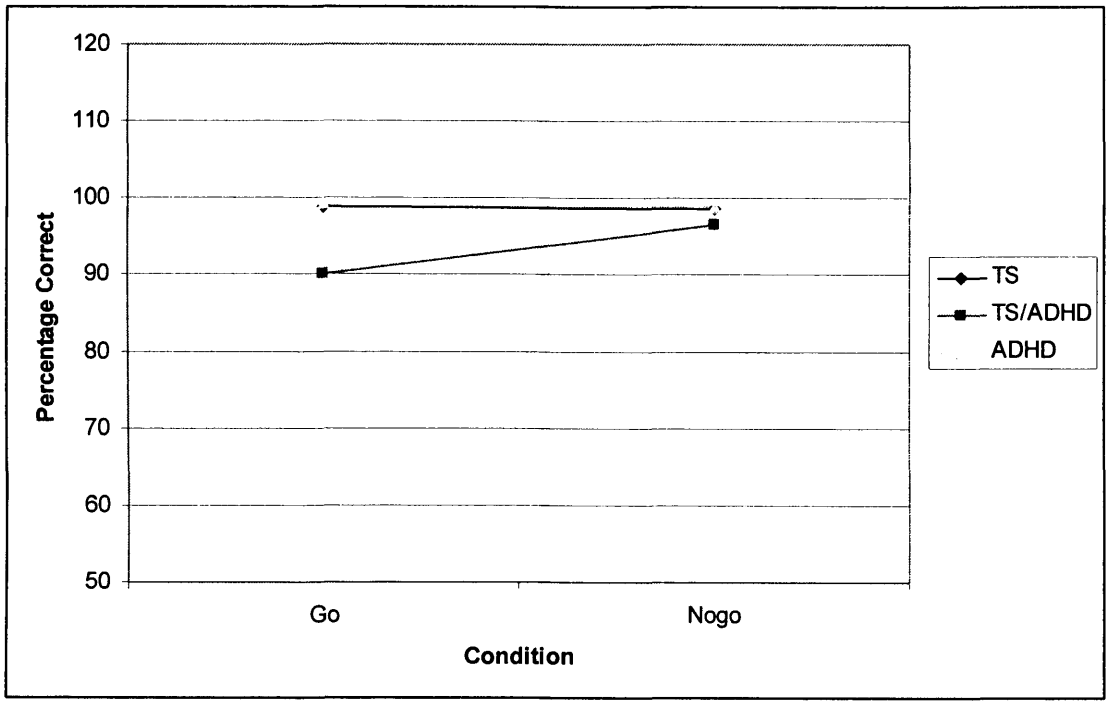
A series of repeated measures ANOVAs were conducted in order to compare go and no go responses for the differing conditions.

Table 3.7: Percentage Correct and Median Reaction Time (RT) Means (SD) for the N-back Tests

Test	TS	TS+ADHD	ADHD
Slow correct Go trials	98.82 (2.62)	90.17 (16.98)	99.44 (1.30)
Slow correct Nogo trials	98.56 (1.95)	96.50 (5.31)	98.98 (1.80)
Medium correct Go trials	95.29 (8.00)	93.67 (14.59)	97.78 (6.72)
Medium correct Nogo trials	97.84 (2.62)	95.44 (8.58)	96.94 (5.67)
Fast correct Go trials	96.86 (7.31)	90.33 (18.95)	98.61 (4.37)
Fast correct Nogo trials	98.89 (1.30)	97.39 (5.63)	96.85 (5.84)
2-Back correct Go trials	96.86 (7.31)	90.53 (19.44)	98.61 (4.37)
2-Back correct Nogo trials	81.99 (11.42)	82.57 (10.23)	80.38 (15.66)
Slow Go RT (ms)	515721.21 (125362.16)	549146.58 (103223.89)	489889.13 (90024.24)
Medium Go RT (ms)	483943.09 (106845.21)	567197.13 (136793.93)	497860.25 (87337.25)
Fast Go RT (ms)	467947.94 (87960.99)	491661.00 (75986.58)	453626.21 (121772.93)
2-Back Go RT (ms)	506879.50 (74071.00)	651213.87 (169951.26)	677053.50 (291082.94)

Slow Go v Nogo percentage correct: For percentage correct in the slow condition, the ANOVA involved group (TS, TS+ADHD, ADHD) and condition (Go: low inhibition and Nogo: high inhibition responses). The group by condition interaction effect was not statistically significant: ($F(2, 46) = 2.04$, $p=0.142$), nor was the main effect for condition: ($F(1, 46) = 1.26$, $p=0.267$). However, the main effect for group was significant ($F(2, 46) = 5.23$, $p=0.009$). Evaluation of the means indicated that the TS+ADHD group attained the fewest correct responses across the task.

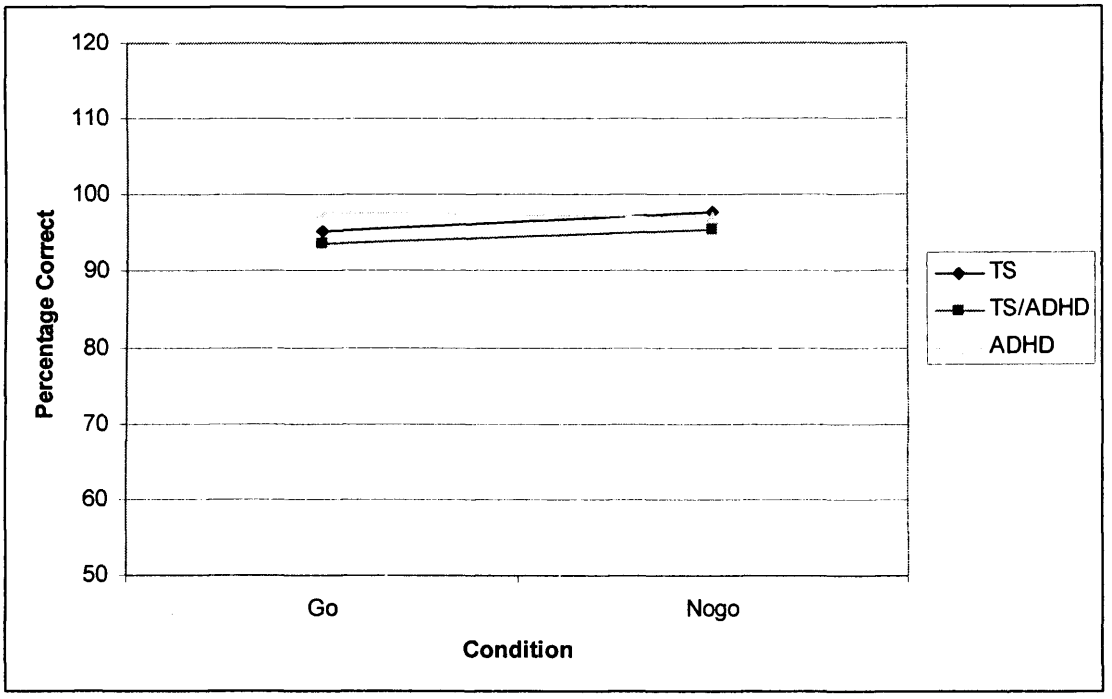
Figure 3.10: Percentage Correct Reponses for Go and Nogo Responses on the Slow Go-Nogo Task



Medium Go v Nogo percentage correct. A repeated measures ANOVA was conducted in order to compare go and nogo responses for the medium speed Go-*No*go task conditions. For percentage correct in the slow condition, this involved group (TS, TS+ADHD, ADHD) and condition (Go: low inhibition and Nogo: high inhibition responses). The group by condition interaction was not statistically

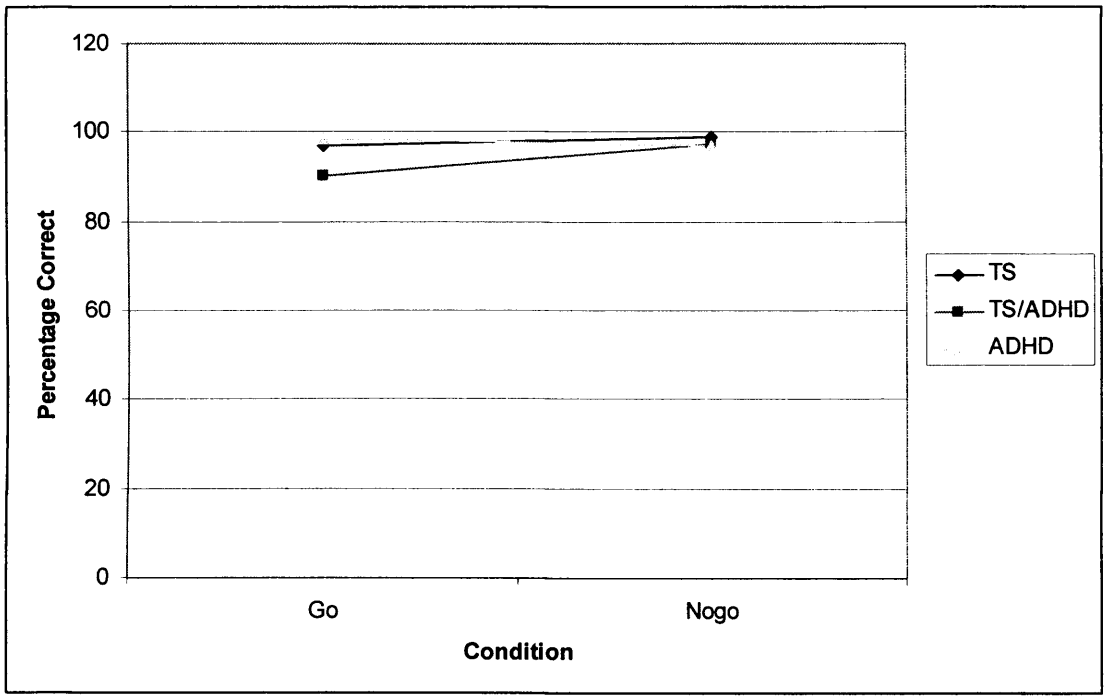
significant: (F (2, 46) = 0.61, p=0.549), nor was the main effect for group: (F (2, 46) = 0.55, p=0.582) or condition: (F (1, 46) = 0.91, p=0.346).

Figure 3.11: Percentage Correct Reponses for Go and Nogo Responses on the Medium Go-Nogo Task



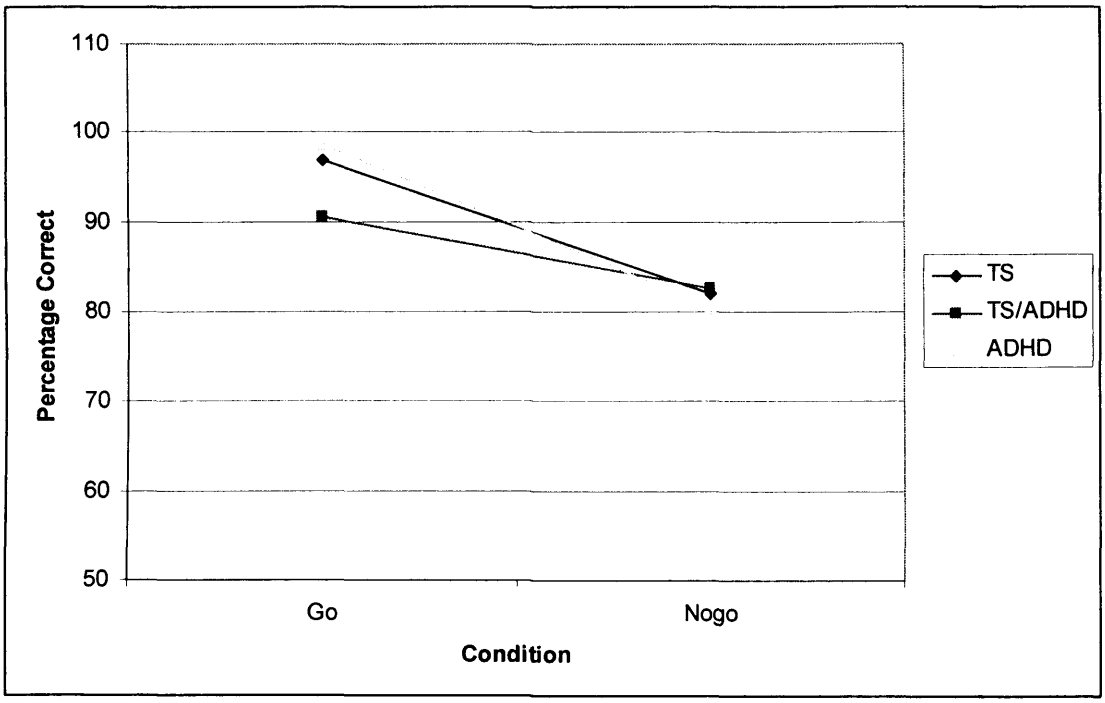
Fast Go v Nogo percentage correct: A repeated measures ANOVA was conducted in order to compare go and nogo responses for the fast Go-*No*go task. This involved group (TS, TS+ADHD, ADHD) and condition (Go: low inhibition and Nogo: high inhibition responses). The group by condition interaction was not statistically significant: (F (2, 46) = 1.46, p=0.242); nor was the main effect for group: (F (2, 46) = 2.10, p=0.134) or condition: (F (1, 46) = 1.33, p=0.255).

Figure 3.12: Percentage Correct Reponses for Go and Nogo Responses on the Fast Go-Nogo Task



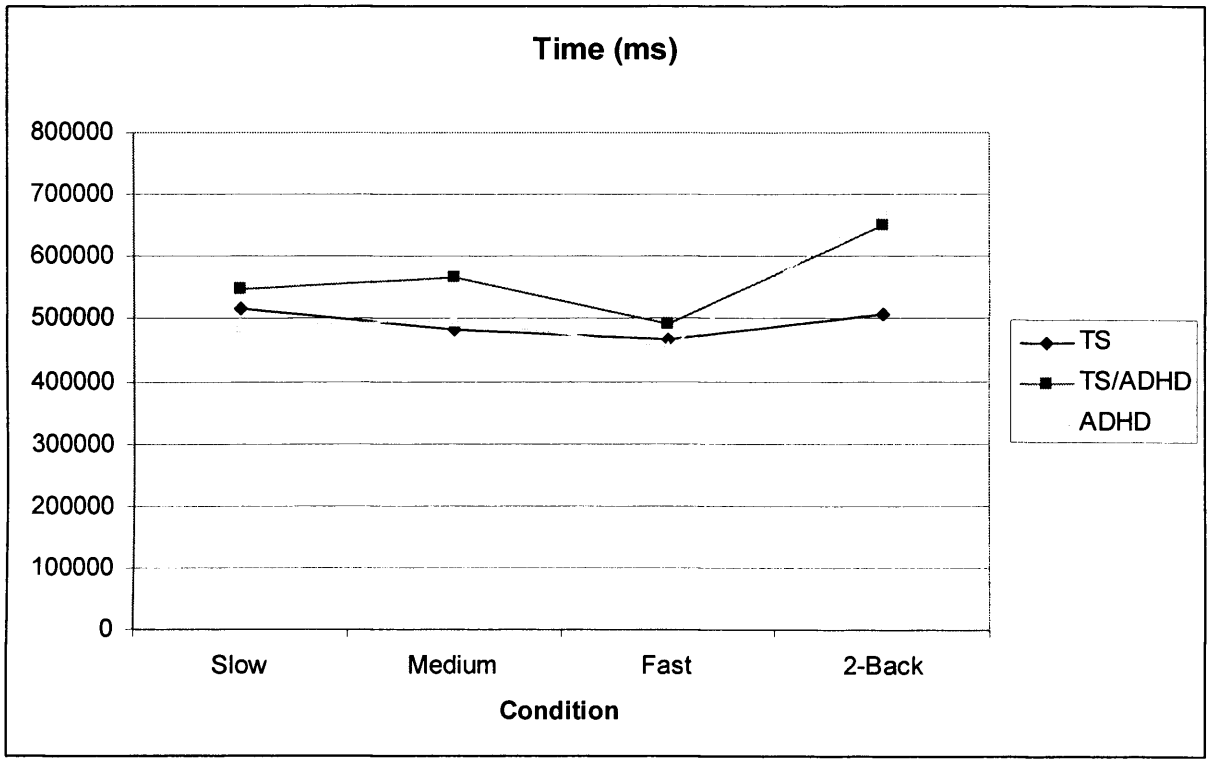
2-Back Go v Nogo percentage correct: A repeated measures ANOVA was conducted in order to compare percentage correct go and no go responses in the 2-Back condition. This involved group (TS, TS+ADHD, ADHD) and condition (Go: low inhibition and Nogo: high inhibition responses). The group by condition interaction effect was not statistically significant: ($F(2, 45) = 1.21$, $p=0.308$); nor was the main effect for group: ($F(2, 45) = 0.68$, $p=0.512$). However, the main effect for condition was significant: ($F(1, 45) = 24.03$, $p<0.0005$). Evaluation of the means indicated that a greater percentage of correct responses were attained across groups in response to the low inhibition Go target condition.

Figure 3.13: Percentage Correct Reponses for Go and Nogo Responses on the 2-Back Task



Median reaction time to correct Go trials: A repeated measures ANOVA was conducted in order to examine median reaction time for correct Go trials. This involved group (TS, TS+ADHD, ADHD) and condition (slow 0-back, medium 0-back, fast 0-back and 2-back). The group by condition interaction was significant: ($F(6, 135) = 3.64$, $p=0.002$). Post-hoc Bonferonni comparisons revealed that differences between pairs of groups did not reach significance ($p<0.05$). Mean results (table 3.7, figure 3.14) indicated that whilst the TS group maintained an even speed of responding across the different condition, the TS+ADHD and the ADHD groups tended to slow up as task complexity increased on the 2-Back task.

Figure 3.14: Mean Median Reaction Time for Correct Go Reponses on the N-Back



Tests of Association

A series of carefully selected Pearson's correlations was conducted in order to examine patterns of associations between the tests with the greatest inhibitory requirements. This included the score from each of the cognitive measures which were compared against the measures of trait inhibition (DSM impulsivity score[6]), and the subtest that loaded most on motor inhibition.

When correlations between trait (DSM impulsivity score) and the cognitive (Trail number letter switching completion time, Verbal fluency category switching, Verbal fluency set loss errors and Verbal fluency repetition errors, Design fluency switching

[6] DSM Impulsivity score was used in preference to Conners Hyperactivity/Impulsivity in order to have a purer measure

total correct, Stroop inhibition completion time and Stroop inhibition switching completion time) and motor inhibition (0-back fast nogo responses) measures were examined, there were no statistically significant associations between the measures aside for the TS+ADHD group on Stroop inhibition switching and the ADHD group on Verbal fluency category switching (table 3.8).

Table 3.8: Pearson's Correlations for Trait Impulsivity (DSM impulsivity) and Inhibitory Measures

Test	TS	TS+ADHD	ADHD
Hayling response suppression errors	(r=-0.47, p=0.060)	(r=-0.08, p=0.749)	(r=-0.38, p=0.221)
HI Trail number-letter switching completion time	(r=0.18, p=0.496)	(r=0.13, p=0.579)	(r=0.49, p=0.108)
HI Verbal fluency category switching correct	(r= -0.06, p=0.823)	(r=0.00, p=1.00)	(r=0.71, p=0.009)*
HI Design fluency switching correct	(r= -0.08, p=0.773)	(r=0.41, p=0.072)	(r=0.11, p=0.727)
HI Stroop Inhibition switching time	(r= 0.23, p=0.376)	(r=0.49, p=0.027)*	(r=0.33, p=0.302)
HI fast 0-Back nogo responses:	(r=-0.21, p=0.425)	(r=-0.31, p=0.182)	(r=0.29, p=0.362)

(* = $p<0.05$, ** = $p<0.0005$)

Table 3.9: Pearson's Correlations for Motor Impulsivity (Fast 0-Back Nogo responses) and Inhibitory Measures

Test	TS	TS+ADHD	ADHD
DSM impulsivity score	(r=-0.21, p=0.425)	(r=-0.31, p=0.182)	(r=0.29, p=0.362)
HI Hayling response suppression errors:	(r=0.58, p=0.015)*	(r=0.10, p=0.661)	(r=0.50, p=0.100)
HI Trail number-letter switching completion time	(r=-0.02, p=0.946)	(r=0.05, p=0.841)	(r=0.50, p=0.095)
HI Verbal fluency category switching correct	(r=0.08, p=0.768)	(r=0.15, p=0.533)	(r=0.11, p=0.744)
HI Design fluency switching correct	(r=-0.03, p=0.902)	(r=0.20, p=0.393)	(r=0.40, p=0.237)
HI Stroop Inhibition switching time	(r= 0.29, p=0.305)	(r=-0.31, p=0.186)	(r=0.08, p=0.815)

(* = $p<0.05$, ** = $p<0.0005$)

When correlations between the motor inhibition measures (Fast 0-Back nogo responses) and the cognitive (Trail number letter switching completion time, Verbal fluency category switching, Verbal fluency set loss errors and Verbal fluency repetition errors, Design fluency switching total correct, Stroop inhibition completion time and Stroop inhibition switching completion time) and trait inhibitory (DSM Impulsivity) measures were examined, there was only a significant association for the TS group for Hayling response suppression errors. There were no significant

associations between Fast 0-Back nogo responses and the other cognitive and trait inhibitory measures.

3.1 Summary of Results

Table 3.10: Summary of Results

Test	Summary of Findings
Trait inhibition	• All groups exhibited levels of trait disinhibition.
Stroop	• No differences between groups. • TS+ADHD group were significantly worse than test norm for HI inhibition completion time.
Trail making test	• No between group differences for completion time. • TS+ADHD group significantly worse than test norm on HI number letter switching completion time, MI number sequencing and MI letter sequencing completion times.
Design fluency test	• No between group differences for correct score. • Repeated design and set loss error rate increased for all groups as task complexity increased (significantly most marked for ADHD group in high inhibition switching dots condition for repeated design errors). • TS only group were significantly better than test norm for design fluency switching correct score.
Verbal fluency test	• No differences between groups for correct score. • All groups attained significantly fewer correct responses as inhibition level increased. • TS+ADHD group made significantly more errors than TS group across all inhibitory conditions for set loss errors. • TS group significantly better than test norm for set loss errors but were significantly poorer for repetition errors.

	• ADHD group significantly poorer than test norms for category switching correct scaled score, repetition errors scaled score, but above test norm for set loss errors scaled score. • TS+ADHD group significantly poorer than test norms for repetition errors scaled score and verbal letter fluency.
Hayling Sentence Completion	• Although non significant, TS and TS+ADHD groups slowed in their completion time for high versus low inhibition conditions, whilst ADHD group did not alter speed of responding as inhibitory requirements increased. • No differences in error rates or overall inhibitory performance. • For overall test efficiency, all groups were significantly worse than test norms.
Go-Nogo test	• Slow Go-*No*go: TS+ADHD group attained fewest correct Go and Nogo responses. • No group differences for Go or Nogo accuracy for medium or fast presentation. • 2-back condition, significantly greater percentage of correct responses attained on low inhibition (Go) trials than high inhibition (Nogo) trials for all groups. • Go response time: significant interaction, post-hoc non-significant although means indicate TS group maintained even response speed, TS+ADHD and ADHD groups slowed up as task complexity increased.
Correlations	• Motor, Trait and Cognitive inhibition are relatively independent.

4.0 DISCUSSION

This study has attempted to clarify the inhibitory profile of individuals with ADHD, TS +ADHD and TS. The strongest finding that emerges is that individuals with TS, TS+ADHD or ADHD are not markedly different from one another in terms of their motor, trait and cognitive inhibitory functioning. Test analyses and matched normative comparisons indicated that across the three groups, performance worsened specifically during the higher level cognitive inhibition tasks. Further, this appeared to be most marked for the TS+ADHD group followed by the ADHD group. Finally, not only did the tests tap inhibitory deficits, but many of the measures assessed fluency. There was evidence to suggest that although these processes may overlap, fluency was also an area of difficulty. These results are extremely valuable in aiding understanding of the cognitive inhibitory difficulties that these individuals face, the shared degree of overlap between these conditions and most importantly the contribution of ADHD in exacerbating these difficulties.

Finally, a series of correlations were conducted in order to examine the associations between the motor, trait and cognitive inhibition for each of the clinical groups. There was not a strong pattern of association between these measures suggesting that there may be different underlying foundations to the various inhibitory processes. This could suggest that there is an independent locus of origin to cognitive and motor disinhibition in individuals with TS, TS+ADHD and ADHD and that this is a separate and additional disability to clinical/diagnostic symptomatology of trait impulsivity.

4.1 Current and Previous Findings

The current pattern of results helps to clarify past empirical findings. There is much evidence that individuals with TS demonstrate frontal lobe dysfunction that manifests on tests of inhibitory functioning, although it is still questionable whether this is the result of frontal deficits or disruptions to basal ganglia pathways. Discrepant findings are believed to be due to the contribution of comorbid disorders in exacerbating inhibitory deficits.

4.11: The Stroop

When one systematically examines the results, the Stroop task failed to discriminate the groups in terms of their inhibitory functioning. Individuals with TS comorbid with OCD (Müller et al. 2003), TS comorbid with ADHD (Brand et al., 2003) or just ADHD (Rucklidge and Tannock, 2002; Shallice et al., 2002) have been found to display problems on the Stroop cognitive inhibition task. Although the present study demonstrated that on the Stroop, the TS+ADHD group performed worse than population norms, there did not appear to be a discriminating effect of TS or ADHD, but perhaps more of an additive effect of combined diagnosis.

Vendrell et al. (1995) reviewed past studies showing that abnormality on Stroop test performance indicates frontal dysfunction; however, they found that patients with prefrontal lobe lesions performed normally on this measure. This led them to conclude that the Stroop is not just a test of verbal inhibition of the prefrontal cortex, but that the right lateral prefrontal cortex might be involved in the attentional component of the task, which allows the task to be performed correctly over a period of time. This suggests a more complex contribution of neurological dysfunction to

Stroop task impairment, perhaps either frontally or through the interconnecting pathways and thus may indicate that one could pass or fail this test for several reasons.

4.12: The Hayling

There is much evidence that individuals with ADHD (e.g. Clark et al., 2000, Shallice, 2002) and TS (Channon et al. in press) have specific deficits on the Hayling test. The present results are less clear. Although the groups did not differ from one another, their scaled scores were indicative of overall disrupted inhibitory skills and that the comorbid TS+ADHD group struggled most with responding quickly when the inhibitory requirements of the task increased.

Nathaniel-James et al. (1997) examined the functional anatomy of verbal initiation and suppression using the Hayling Test. They noted that verbal initiation and suppression are cognitive skills believed to be subserved by the frontal lobes. However, the number of regions activated in their position emission tomography (PET) study led them to conclude that verbal inhibition deficits are the consequence of a complex pattern of neural function that could be disrupted at different levels. In the present study, the Hayling test might not have discriminated the groups in terms of errors made or overall efficiency perhaps because different groups could fail this task due to disparate disruption to any of the implicated regions. In view of this, individuals could present with the behavioural characteristics of disinhibition or impaired initiation that still stem from a different neural locus of origin.

4.13: The Trail Making Test

There have been fewer studies on the Trail making test. Groups with ADHD have been found to show deficits on this measure (Chhabildas et al., 2001) whilst there is evidence that individuals with TS+ADHD perform less well than those with just TS (Brand et al., 2002). This was not found in the current study, although there was evidence to suggest that the TS+ADHD group were performing worse on the high and medium level inhibition conditions than test normative samples. Brand et al. (2002) reported weaker, although non-significant differences on the Trail making test in TS+ADHD compared with TS. This helps to contextualise the current set of findings and suggests, that whilst individuals with TS, TS+ADHD or ADHD did not display a markedly different inhibitory profile, the extent of their inhibitory deficits are quite subtle and manifest most clearly in the TS+ADHD combined group.

4.14: Verbal and Design fluency

On a measure of letter word fluency, individuals with TS have been found to be significantly poorer than those with ADHD (Schuerholz et al. 1996). Likewise, individuals with TS comorbid with ADHD have been found to perform significantly worse than participants with TS (Brand et al., 2002; Harris et al., 1995). This was replicated in part in the current study. On the verbal fluency test, all groups struggled as the inhibitory level increased and when scores attained by normative samples were compared with the present results, all groups attained greater repetition errors and the TS+ADHD group had a poorer letter fluency score. A similar pattern of performance decrements associated with an increase in test inhibitory requirements was also found on the design fluency test. In contrast to this, groups with TS, ADHD (Mahone et al., 2001) and TS comorbid with ADHD (Müller et al.,

2003) have been found to be free from executive impairments on tests of verbal and figural fluency. Juxtaposed with the present findings, it appears that findings of fluency deficits are inconsistent, perhaps because they are relatively mild. Our discrepant findings could be explained because whilst the clinical groups did not differ from one another, they were subtly performing worse than normative samples as indicated by test population norms.

Brand et al. (2002) suggested that mental flexibility may play a role as a buffer for psychological impact of symptom severity and suggested that their results were relevant clinically in that for patients who are low on cognitive flexibility, treatment of symptoms (through the training of cognitive flexibility) could be the preferred way to psychosocial well-being. The present results could have similar implications and in line with the experimental questions, the more severe cognitive inflexibility that appeared in the TS+ADHD group over the ADHD or the TS groups may suggest that cognitive inflexibility should be a focus for clinical intervention.

Elfgren and Risberg (1998) examined participants' responses used to obtain information about their cognitive strategy while solving verbal and design fluency tasks. This led to the finding that the use of different strategies was reflected in different patterns of brain activation. Unfortunately strategy was not overtly recorded in the present study. However, the increase in set loss errors made by all groups during high inhibition tasks of the design fluency test and the below average scaled score for verbal fluency repetition errors might indicate that participants did not utilise a strategy.

4.15: The Go-*No*go test

Although there are consistent findings of inhibitory deficits in Nogo responding on the Go-*No*go task in individuals with ADHD (e.g. Shallice et al., 2002; Nyberg et al., 2003; Crone et al., 2003) the findings in the TS literature are much more incongruent. Ozonoff et al. (1994) found that their TS group did not exhibit deficits on the Go-*No*go task when compared with typically developing and children with autism, whilst Müller et al. (2003) reported that individuals with TS comorbid with OCD displayed problems on the Go-*No*go task. A curious pattern emerged in the present study. The groups did not struggle with inhibiting Nogo responding. They responded as accurately in response to Go and Nogo targets until the more complex 2-Back task was introduced where there was a significant effect of the high inhibition correct score across all groups. Furthermore the TS+ADHD and the ADHD group demonstrated significantly longer response times for the 2-Back task. It is possible that in the presence of average intellectual functioning, the groups were able to compensate for motor inhibitory deficits until task demand was increased through the added working memory component. In line with Kimberg and Farah's (2000) postulations this may lead to disinhibited behaviour. This might support the contribution of working memory deficits to disinhibition, which could be the focal deficit in these groups.

It is interesting that participants did not show a performance deficit on the Go-*No*go measure as presentation speed increased. Why the TS+ADHD group struggled with the slow Go-*No*go task is hard to explain and could be due to distracted attention during this relatively easy and slow paced condition. Observation of the administration of this task suggests that individuals might have struggled with

boredom during the slow speed presentation conditions. Borger and van der Meere (2000) examined visual behaviour, particularly looking away during a CPT. They speculated that visual behaviour of ADHD interferes with reaction time performance. They found that ADHD children looked away more frequently and for longer durations than their peer controls. Looking away behaviour was not measured in this study, although there were indications that individuals looked away and tried to engage the examiner in conversation during the slow presentation speeds of this task. It is possible that the Go-*No*go task used in the current study was also one of sustained attention in addition to inhibition. All individuals struggled with maintaining an attentional set on this task, and perhaps looking away behaviour resulted in a failure of this measure to really tap inhibitory behaviour, due to lack of initial attentional engagement.

4.2 Cognitive, Motor Inhibition and Relationship Between TS and ADHD

Given that one of the key features of TS are the motor tics that are difficult to inhibit, the literature and present findings do not appear to support the notion that individuals with TS are universally impaired on measures of motor inhibition. This is unexpected, particularly when it has been suggested by Ozonoff et al., (1998) that the construct of motor inhibition may be closer to the phenomenology of TS (i.e. inhibition of tics) than that of cognitive inhibition. Exploring this further, Serrien et al. (2005) recorded EEGs in patients with TS on the Go-*No*go task of motor inhibition and during a self control task of tic suppression. They found that the same frontomesial network was overactive in TS patients compared with healthy participants even when suppression of voluntary movement rather than tics was required during a Go-*No*go task. Importantly they found that task related coherence

in the connections between sensorimotor cortex and prefrontal and midline areas was increased during the Go and *No*go trials. This indicates that tic and motor inhibition may be controlled by similar brain regions. The correlations that were carried out between the different types of inhibitory tests suggest that cognitive and motor inhibition may be distinct processes, rather than one being a precursor to the other. One explanation for the failure to detect TS specific motor inhibitory deficits in this study could be because these deficits were present in the ADHD group, reflecting similar disrupted prefrontal processes. It is then unsurprising that tic disorder often occurs in ADHD (e.g. Spencer, et al., 2001), thus explaining why all of the groups performed similarly on the motor inhibition measures.

As discussed in the literature review chapter, Robertson (2000) has reviewed differing theories regarding the relationship between TS and ADHD including (a) that the two disorders are genetically related; (b) that there may be two types of individuals, one for whom ADHD is independent of TS and the other for whom the ADHD is secondary to TS; (c) that pure TS and pure ADHD are different phenomenologically and (d) that the nature of TS might predispose individuals to have difficulties with concentration, attention and impulse control that is at subthreshold for DSM diagnosis of ADHD. The present pattern of results could be seen to support all of these relationships, although greatest support might be given towards the notion that TS predisposes individuals towards symptoms of ADHD, although for some subgroups this is as severe as that seen in 'pure' ADHD.

An alternative notion is that the present findings, particularly for the 2-back measure, suggest that for all groups, inhibitory deficits manifest as inhibition and/or working

memory requirements increase. This fits with Kimberg and Farah's (2000), notion that there is not an inhibitory module of the prefrontal cortex but that the prefrontal cortex houses psychological functions that are heavily taxed in tasks requiring inhibition that weaken working memory. This notion allows for groups with distinct conditions to perform similarly, but still present with separate underlying pathologies. In view of this, it is still unclear what causes disinhibition, but it appears that groups with compromised prefrontal function are likely to be impaired on these measures. This could reflect similar or distinct underlying pathologies.

4.3 Sample Size

A drawback to the current study is the size of the ADHD group. Over sixty individuals were invited to participate in this group, however, a high number of individuals did not respond, were not identifiable for follow up through strict ethical guidelines or declined through experiencing too many life stresses or struggling with diagnosis related behaviour problems. This could suggest that in studies examining ADHD there is a recruitment bias in which individuals selected are those experiencing fewer problems resulting from their diagnosis. Furthermore, pure ADHD is a relatively rare group. One clinician contacted could only think of about six individuals on their books who met the requirement for no comorbidity. However, it is imperative that research groups are strict about exclusion criteria given that there is some evidence to suggest that comorbidity could result in a different pattern of cognitive findings. For example, Tannock (1998) noted that response inhibition deficits might not be specific to ADHD but present in other disruptive behavioural problems such as aggression and oppositional conduct disorder whilst Nigg (2001) noted that unsocialised conduct disorder may introduce

its own inhibitory confounds. There were relatively high rates of oppositional behaviour reported by the parents of all groups, although this often tends to be typical in parental report measures due to their perceptions of their child's behaviour in the unstructured home environment. This supports the recruitment endeavour to not compromise on exclusion criteria of individuals with ADHD with comorbid disruptive behaviour, thus helping to reduce the inevitable impact of oppositional and conduct disorder on the findings.

In view of this it was preferable to have a small but select group of individuals who met this strict diagnostic requirement. This will affect statistical power and it is possible that a difference in performance between groups might have been masked because of the low sample size. However, the possibility that such a Type 2 error occurred is unlikely given that observations of participants' performance suggested that there was limited variability between groups. Thus, although the small sample size might reduce power and increase the likelihood of a Type 2 error, it is preferable to have a pure sample which increases the generalisability of findings to specific groups with pure ADHD.

4.4 Intelligence Ability

When one considers the current pattern of results with that reported in the literature, there are a few inconsistencies. In this study, although we had intended to match for intellectual ability, there were no Full Scale IQ differences between groups and matching was not needed. Schuerholz et al. (1996) reported that their TS only participants had significantly higher Full Scale IQ than children with TS+ADHD, noting that other studies had also reported similar findings. They concluded that the

absence of a learning disability in their TS group reveals the important contribution of ADHD to the academic profile of children with TS. The groups in the current study all presented with a mean IQ in the normal clinical range; although there was a non-significant pattern in which the TS only group appeared to be slightly superior to both ADHD groups, in line with what has been reported in the literature. Nonetheless, it is possible that the higher ability level in the current TS+ADHD and the ADHD group from those in other studies might have masked the degree of inhibitory deficits.

Further supporting this, Nigg (2001) noted that if lowered IQ is a developmental consequence of ADHD, then covarying for IQ would amount to unwisely covarying a portion of the ADHD syndrome. Ozonoff et al. (1998) found in their study of TS and comorbid conditions that the cognitive dysfunction extended beyond the domain of executive processes as their subgroup with comorbidity exhibited significantly lower IQ scores than both the typically developing controls and individuals mildly affected with TS without comorbidity. This study did not find a significantly lowered IQ in the ADHD groups and this might explain the comparatively mild profile of inhibitory deficits that were detected.

4.5 Role of Gender

The generalisability of this study might be weakened through its focus on males. However, this reflects population frequencies of both TS and ADHD to an extent. There was one female included in the study. Her inclusion was justified because reanalysis of the data without her scores did not change any of the results. Further, there are no gender effects described in the inhibition literature. For example,

Rucklidge and Tannock (2002) found no gender differences on executive measures in their ADHD groups. They concluded that females were as impaired as males on their level of inhibition, response execution and naming speed. However, Nigg (2001) noted that it is not clear if ADHD in boys and girls is driven by the same psychological dysfunction, noting that ADHD is more common in boys in clinic and population samples. He noted that few studies had compared sex effects and that research evidence is clearer for boys than for girls because of this sampling tendency. Further research examining sex differences in groups with TS and/or ADHD will be of value in clarifying this.

4.6 ADHD Subtypes

This study followed recent DSM-IV guidelines and did not differentiate ADHD groups by subtype. However, Nigg (2001) noted that for ADHD "combined subtype" data support a deficit in executive motor inhibition, but less so for interference control or cognitive inhibition. A range of diagnostic questions may be raised by the current study. For example, the ADHD free TS group did display some symptoms that one would expect in ADHD groups (e.g. Conners cognitive problems/inattention). This might support the presence of an inattentive ADHD subtype in all individuals with TS. As noted earlier, Ozonoff et al. (1998) found that when their sample was subdivided into more and less severe subgroups, those with more symptoms of TS, ADHD, OCD performed significantly less well on inhibitory variables than both controls and individuals with fewer symptoms of TS. Further, Comings et al. (1999) noted the strength of examining a quantitative trait variable such as the ADHD score, rather than a dichotomous variable (presence or absence of ADHD) is that the quantitative variable utilises the entire range of the phenotype

rather than some arbitrary cut off. This supports the notion that it is better to construe ADHD as a continuum of symptoms rather than a discrete entity. This study used diagnostic cut-offs in order to separate cases into groups. However, further studies that use large TS populations could separate them according to degree of comorbid symptoms which might shed light on the contribution of the presence of milder, subclincial symptoms to the inhibitory profile. This could have significant clinical implications, such as whether clinicians should shift from treating only the presence of ADHD in TS groups to focusing on ameliorating individual symptoms of ADHD in all TS groups.

4.7 Role of Medication

It was hoped that most individuals recruited into this study would have recently received a diagnosis and hence be medication naïve. However, this was not attainable in all cases. Some research that has recruited individuals on medication has included a wash out period of medication abstinence in order to eliminate effects on the tasks. This could be deemed to be unethical, particularly when one considers the unpleasant side effects of medication withdrawal, and so was not considered in this study. Reassuringly, Ozonoff et al. (1998) reported that their study did not find any evidence that the medications typically used to control the symptoms of TS had any effect on cognitive processing. Nonetheless, medication used to manage ADHD symptoms may impact upon the cognitive measures used in this study. It had been hoped that the use of a case controlled design in this study could ensure that participants who were on medication were matched between groups by medication type, however, the nature of using different diagnostic groups meant that this was not possible. Appendix 8 lists medication by group. This indicates that between 10-49%

of the participants were unmedicated. However, this varied by group. It is possible that the use of medication attenuated some of the inhibitory deficits in the groups. This is supported by reports in the DSM interview where participants and carers felt that behaviour typically reflecting ADHD was lessened when the individual was on medication.

Bedard et al. (2003) found that inhibitory deficits as detected in Stop task paradigms is attenuated with the use of methylphenidate, with children with ADHD demonstrating improved selective inhibition in addition to speed and variability of response execution. Based upon this, the authors suggested that methylphenidate might work by improving global cognitive processes such as attentional capacity and working memory that has the knock on effect of improving inhibitory processes. In contrast to this, Van der Meere et al. (1999) investigated the effects of methylphenidate and clonidine on individuals with ADHD as assessed on a Go-*No*go paradigm; however, they failed to find a difference in responding in the treated groups. Further, Yang et al. (2004) reported a rapid improvement in academic grades following methylphenidate treatment, but found that only one item of WCST: perseverative responses, was improved by methylphenidate treatment. They felt that children showed more behavioural than cognitive improvement and that methylphenidate helps approximately 68-78% of ADHD children to improve behaviours in the classroom and at home. This supports the separation between behavioural and cognitive inhibition found in this study. In summary, it is not clear whether one would expect medication to affect the current results. This in conjunction with anecdotal reports might suggest that medication is more ameliorative than curative and one would anticipate that the typical pattern of

inhibitory and attentional difficulties are still present in the context of medication use.

4.8 Strengths

A major strength of this study was its investigation of multiple types of inhibitory function. It considered that inhibitory functioning is not a unitary construct by examining a range of different levels of inhibition in order to explore similarities and differences in groups who have been reported to experience these difficulties. The results from the present study indicated that different levels of inhibition are not as linked with one another as might be anticipated. Further examination of different types of inhibitory function, particularly conducting an exhaustive examination of many measures of motor inhibition may prove to be a fruitful avenue for future research.

Further, this study did not follow the trend in the ADHD literature to examine motor inhibition using the Stop task. This was mainly due to weaknesses we perceived, through its inability to allow for manipulations to task complexity. Our decision to use the Go-*No*go and 2-Back measure is supported by Nigg (2000) who noted that one problem with the Stop task is that it pits a visual-motor go task against an auditory motor stop signal and that for some children with ADHD, this could introduce a confound, for instance children with ADHD may have a particular difficulty processing information in the auditory modality. The present computerised test used one visual medium only, but allowed for manipulations to stimulus presentation speed. Likewise, all of the experimental measures examined gradations in inhibitory levels. This allows for extrapolation of extraneous variables (e.g.

reading speed, response speed) from inhibitory functioning and helped with the finding that rather than inhibition being a discrete impairment, performance appears to worsen as inhibitory requirements increase.

4.9 Limitations and Future Directions

This study asked whether inhibitory deficits were similar in nature in groups with TS + ADHD as those with ADHD and questioned the extent to which the presentation of ADHD in these disorders is equivalent. It found that individuals with TS, TS+ADHD and ADHD share a similar profile of varied disinhibition as measured by tests of trait and cognitive inhibition. Findings of motor inhibition were less clear, although all groups struggled as inhibitory requirements increased. The most marked finding is that individuals with TS+ADHD are at greatest risk for disinhibition followed by those with ADHD and those with TS, although group differences are very subtle. This is a key finding and highlights how individuals with a comorbid diagnosis experience ADHD that is as severe as those with a unitary ADHD diagnosis, and that the contribution of two diagnoses might increase cognitive disturbances.

These findings open up areas for further research. It appears that individuals with TS share some subthreshold trait features of ADHD. Evaluation of if this is universal in all groups with TS, or if it varies by symptom severity will have implications for medical treatment. Clearly greater emphasis needs to be made of ADHD in TS clinics, and it is still unclear whether these two conditions are genetically and neurologically linked, which warrants further investigation. Furthermore, the purpose of this study was to investigate how these three clinical groups differed in

their inhibitory profiles. This study highlighted the extent of group similarities. In view of this specific focus, a typically developing control group was not used and it is acknowledged that the use of test normative sample means is not equivalent to this. However, future research could expand upon the current findings by evaluating the present pattern of results in comparison with a matched typically developing control group or other neurodevelopmental groups such as autism. This may clarify if all neurodevelopmental groups display test deficits that are a product of any developmental brain pathology weakening prefrontal function or if these inhibitory deficits are linked to an underlying neurological disruption that is specific to TS and ADHD. This would be especially relevant for the tests where the normative data were not specifically matched for age (the Hayling test), or available (the Go-*No*go tests).

Furthermore, Ozonoff et al. (1998) noted that not only did neuropsychological impairments in TS occur as a function of comorbidity, but that symptom severity played a role. An extension to this study would be to examine inhibitory profile according to tic severity. Likewise, further examination of strategy and techniques used during these tests may discriminate these groups, as might an exploration of differences in inhibitory presentation according to gender and the contribution of working memory impairments to inhibition.

Finally, the age of the participants was relevant. This study examined inhibitory functioning in children. It is anticipated that this is the period of greatest risk for such difficulties. However, it is possible that these groups were presenting with either a stable deficit or a developmental lag (e.g. Nigg, 1999) that could improve as

they get older. Following up on the inhibitory profile of these groups across the lifespan would be helpful in clarifying this, and might indicate further areas in which the groups diverge in their developmental inhibitory profile.

It is apparent from these results that rather than seeing comorbid diagnostic status (i.e. ADHD) as a discrete category, it might be on a continuum for individuals with TS. Therefore the TS+ADHD group may represent a set of individuals who are above cut-off, but by no means indicates that those in the TS only group do not display a lesser degree of similar symptoms. In line with this, these findings suggest that there are not pervasive differences between groups with TS, TS+ADHD or ADHD in terms of their cognitive profile, although there are indications that individuals with ADHD with or without TS might be at a greater risk for cognitive impairments, particularly for inhibition during verbal and design fluency tasks, than individuals with TS alone. This study raises the possibility that all of these groups have cognitive, trait and motor inhibitory impairments but that these impairments are independent of each other. This is highly important and has not been addressed previously. It is possible that this reflects similarly disrupted brain processes. An alternative is that the similar levels of performance come from different neural disruptions, test strategies or error types which appear the same as test scores. A further discussion of this will follow in the critical appraisal chapter.

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Critical Appraisal

Characterising the Comorbid Subtypes of Tourette Syndrome

This appraisal will aim to critically review this research project. This will begin with a review and discussion of the findings of the research. This will include an evaluation into the wider implications of the research, particularly what these findings reveal about inhibition, the overlap between different clinical groups, and the impact of the research interviews. This will finally lead to a discussion of my experiences whilst conducting the study and of the different clinical implications.

1.0 Background to the Research

My interest in researching Tourette syndrome stemmed from my fascination with neurodevelopmental disorders. Key to this was the notion that individuals presenting with one developmental complaint were often clear that this existed in the presence of another. Whilst there is much research on high comorbidity rates between neuropsychological disabilities (e.g. TS and autism; Baron-Cohen et al., 1999), there are also popular misconceptions that this is due to families over reporting the presence of symptoms, perhaps in an attempt to find an alternative diagnosis, or to explain their unique experiences of stresses and strains.

High comorbididty rates between ADHD and other neurodevelopmental disorders support the biological origins of ADHD (e.g. Tannock, 1998; Eapen et al. 2003; Spencer et al. 2001). I was profoundly astonished to meet individuals who were experiencing severe and quite debilitating motor and vocal tics who reported that they had no difficulties coping with the TS but that it was the ADHD that caused most disruption to themselves and family life. This supported my endeavour to examine the quality of ADHD comorbid with TS and explore if this ADHD really

presents as the same pattern of difficulties as pure ADHD. Whilst my initial hypotheses were guided by the possibility that it might be a milder form of ADHD, like the Obsessional phenomenon that is often reported comorbid with TS (e.g. Müller et al., 1997), it did not occur to me until I began my interviews that the ADHD symptoms might be perceived to be more severe. Nonetheless, for me these questions and concerns validated the clinical importance of conducting my research on this area. When this is put into the context of the current findings, it appears that symptoms of ADHD are extremely pervasive in clinical groups where it is not the primary diagnosis.

2.0 Summary of Findings

This study examined inhibitory processes in individuals with TS with and without ADHD. It found that groups with ADHD with or without TS were more likely to exhibit inhibitory deficits, but this was not universal to all types of inhibitory measures. Trait and cognitive inhibitory deficits were more likely to emerge than motor inhibitory deficits. In view of this, it appears that ADHD is more associated with difficulties with inhibitory functioning than TS. It is possible that subthreshold ADHD in groups who present with a diagnosis of TS in the absence of any comorbidity might explain the emergence of cognitive difficulties in this group.

One of the main strengths of this study was its simultaneous examination of a number of different types of inhibitory functioning. The dissection of different inhibitory skills aids the understanding of what the nature of inhibition is, particularly which processes are connected or independent. Further, it enables a greater specification of the disrupted processes in TS and/or ADHD allowing for

enhanced understanding of the overlap between these two disorders. Rather than seeing inhibition as a unitary concept, there is sufficient evidence to suggest that this exists on a range of different levels that is subsumed by different brain regions and thus could be disrupted in different individuals to different extents (e.g. Nigg, 2000, 2001). Nonetheless, future studies could extend this area of research by examining the qualitative nature of these differences. For example, further probing of the strategies that participants use when completing these tasks, including if they demonstrate insight into their poor performance, could add a descriptive element to the understanding of their inhibitory problems.

3.0 Insight into inhibitory Processing

Mahone et al. (2001) noted that a potential drawback among existing clinical measures of executive function, particularly those involving organised search and efficient production of responses (e.g. fluency, recall and learning measures) is the interpretation of the total outcome score, without directly assessing the response organisation strategies (i.e. "how") used to arrive at a score or the interfering behaviours ("when") which may impede output. They argued that carefully observing these process variables is particularly salient in TS and ADHD and inefficient use of strategies and disinhibition could be considered markers for executive dysfunction in a wide range of neurodevelopmental disorders.

Mahone et al. (2001) hypothesised that children with TS would show deficits, relative to controls, on measures of response preparation ("how") due to slowing in organised search and retrieval, while children with ADHD would show deficits relative to controls in both response preparation ("how") and disinhibition ("when")

measures. In attempt to examine this in greater detail, they administered measures of fluency (verbal, design and figural) to individuals with TS, ADHD and controls. They only found significant group differences on intrusions during the Californian Verbal Learning Test, with the TS group having more intrusions than controls. They felt that this did not support the prediction that children with ADHD would show more impairment on executive function measures than the TS only group. They concluded that the present findings provided limited support for the notion that TS, in the absence of other comorbid conditions, is associated with clinical impairments in response organisation/clustering aspects of executive function as measured by slowing on verbal memory search or inefficient organisation on recall and fluency.

Interestingly, in Mahone et al's (2001) participant demographic section, although their ADHD group had a significantly higher Attention Problems score on the Child Behaviour Checklist than the TS or control group, the TS group's scores were significantly higher than those found in the controls, although Mahone et al. (2001) reported that their mean score was within the average range. Once again this might highlight the subtle and potentially complex, but pervasive effect of comorbidities as discussed in the Empirical paper of this thesis. It also highlights that it is not unusual to find that groups with TS and/or ADHD perform quite similarly when they are compared with each other on a battery of executive function tests or that they often present with overlapping symptoms.

4.0 The Overlap Between Neurological Conditions

The main conclusion that was drawn from the Empirical paper was that neurodevelopmental groups with TS and/or ADHD share similar profiles in

inhibitory/cognitive and behavioural terms. An example of this is that the presence of tic disorder has been recorded in individuals with ADHD. For example, Spencer et al. (2001) examined tic disorder in ADHD groups and found that tic symptoms included frequent multiple, jerky repetitive nonrhythmic motor movements, with and without abnormal vocalisations, which varied in location and that OCD was specifically associated with tic disorder in their study group. This is similar, but perhaps milder to the pattern seen in TS. Spencer et al. (1998) reported that whilst they found high rates of OCD and ADHD in their sample of TS, other comorbidities with disruptive behaviour mood and anxiety disorders were indistinguishable in comparison between children with TS and ADHD and children with ADHD alone. This suggests there is much overlap between these two groups.

In view of this, one needs to consider the extent to which ADHD and TS are really separable conditions. There could be two extreme views on this. On one hand, one might postulate that both TS and ADHD represent the same spectrum of neurodevelopmental disorders of behavioural control; whilst at the other extreme one might propose that they are entirely distinct disorders, but that disruption to any level of brain function leads to a shared pattern of symptomatology. Spencer et al. (1998) noted that although most individuals in their TS subgroup did not meet full criteria for ADHD, most had some symptoms of ADHD. Further, in their sample, children without full ADHD displayed relatively high rates of OCD, anxiety disorder and lower rates of mood, disruptive, elimination and language disorders as well as school, cognitive and psychosocial dysfunction. In view of this, it appears that when an individual has difficulties with one area of brain functioning, there is a high risk that this will overlap or exist in conjunction with other disabilities. Why this is so

remains unclear, although clinical treatment implications are that clinicians should assess for the full range of neurodevelopmental disabilities and not be distracted by the primary diagnosis.

5.0 Recruitment

I owe much gratitude to the Great Ormond Street TS clinic for their support of my research recruitment. In order to aid this process I attended the TS monthly specialist TS clinic for about 20 months whilst conducting this research project. However, it was the endless support and encouragement of the lead consultant psychiatrist that facilitated the ascertainment of individuals from this rare group. Key to my involvement in this research was feeling a part of the TS clinic team. As cases were reviewed at the end of the clinic, I was privileged to share in the unique experiences and struggles of each individual family, and the difficult questions that the multidisciplinary team of clinicians encountered in the clinical management of a complex pattern of symptoms.

Nonetheless, recruitment of the TS group (with and without ADHD) was a huge venture. Past clinical letters were reviewed in an attempt to check for diagnoses. 100 recruitment letters were mailed out to TS families, which reflected the painstaking slow response rate to attempts to recruit the target number of 40 (20 TS, 20 TS + ADHD). These participants were recruited over four large mailings and in response to an initially slow and limited response rate. Most families were keen to take part in the research, but their hectic lives often made if difficult for them to respond promptly and might be a further indication of the stresses and strains that some of them were experiencing.

From those invited, 39 cases replied. Although an early review of case letters and clinic review comments had attempted to screen cases that did not fulfil the inclusion criteria, one case was subsequently excluded due to comorbid OCD whilst another was too young.

Surprisingly, greater difficulties were encountered with the recruitment of participants with ADHD. Five local child and family consultation clinics participated. One later dropped out due to restructuring and personnel difficulties. From these clinics approximately 60 recruitment packs were passed onto child psychiatrists or paediatricians. Again, more packs were sent out in response to the low recruitment rate. However only thirteen cases returned completed information packs, one of whom subsequently dropped out before the study began due to 'research fatigue'. Two individuals did make telephone contact in order to request that they could participate in the study; however, they failed to send the consent information that would have identified themselves to me.

Strict ethical guidelines meant that identifying information about ADHD participants who had been invited into the study was not released to me until the participant made themselves known by returning the recruitment pack including a slip with their name and contact details. This would inevitably mean that for both groups, there would have been families interested in participating but excluded from the study due to their failure to be proactive and return the consent details to me. It also may lead to an ascertainment bias in which the individuals who participated in the project were made up from the more organised and assertive families. This might explain the

especially low response rate from families with a child with ADHD. Relating to this, there could have been familial genetic components that affected response rates. The genetic nature of TS and ADHD is such that family members are likely to experience similar symptoms. Whilst extenuating difficulties and ethical restrictions could have affected recruitment, another influence could have been limitations to focus or organisational strategies that would be needed to promptly return their details to me. This in itself is an interesting notion and further highlights the difficulties that these families might have to deal with.

Finally, there is evidence that individuals with ADHD are an extremely well- (or over-) researched group. Families are often coping well with medication treatment and not looking for answers to questions that might motivate them to participate in a research study.

There could have been opportunities to recruit individuals with ADHD by less stringent criteria, e.g. going through schools, sending out individuals to a greater number of clinic cases by including those with comorbid oppositional defiant disorder. However, as discussed in the Empirical paper, it was necessary to the research question to keep this as a select group of individuals with "pure" ADHD (i.e. no comorbidities).

6.0 Experience of Interviewing

Spencer et al. (1998) noted that irrespective of the uncertain etiological association between ADHD and TS, little doubt remains that ADHD is highly prevalent in patients with TS and often represents the main clinical concern and the principal

source of dysfunction and disability. This was observed in families with TS + ADHD. As I visited families, they were keen to voluntarily share with me their difficult experiences with their child's diagnosis. I was surprised to discover that even in the presence of the most severe complex vocal and motor tics, individuals expressed that the TS was manageable. They felt that the inattentive and hyperactive behaviours of ADHD were those that caused greatest disruption to the individual in terms of social, family and academic functioning. This was apparent during the administration of the Structured Clinical Interview for DSM (SCID-CV). This gave families the opportunity to share with me their experiences of TS and/or ADHD. There were a few occasions where participants struggled to hear their parents reporting their difficulties and became upset. However, I mostly found that participants and parents enjoyed engaging in the joint venture of describing their difficulties. It was positive to see how many parents allowed their child to take the lead in describing their difficulties, and then collaboratively discussed areas of disagreement.

7.0 Effects of One-to-One Attention and Possible Further Clinical Interventions

The test battery lasted approximately three hours. It had been planned to intersperse the testing with frequent breaks. I had anticipated that I would revisit families on more than one occasion to allow the child to cope with the effects of boredom or attentional fatigue, but none of the families needed to be revisited. This is significant when considered alongside the observation that most of the participants were able to complete the test in one session, with only a few requiring brief refreshment breaks. Parents were very surprised by this, noting that it had been the first occasion that

they had seen their child being attentive and focussed for so long. Clearly, there was an effect of having a novel interviewer in the home; however, one might anticipate that this novelty would wear off after three hours. My sense was that the one-to-one attentional focus and encouragement from an adult had a very powerful effect on maintaining attention on the task at hand. Further, other clinicians in the team were surprised that testing was completed in one session, highlighting the importance of using clinical psychology skills in order to keep an individual engaged throughout the session. This is an example of how clinical training is a great asset to the research endeavour.

Barkley (2003) noted that environmental factors play a role in the presentation of ADHD and that the key symptoms of ADHD are affected by situational and task-related factors. For example, Barkley, (2003) notes that the performance of ADHD children is worse: (i) later in the day; (ii) in greater task complexity such that organisational strategies are required; (iii) when restraint is demanded; (iv) under low levels of stimulation; (v) under more variable schedules of immediate consequences in the task; (vi) under longer delay periods prior to reinforcement availability and (vii) in the absence of adult supervision during task performance. Although most of the children were interviewed over the weekend, some of the children in the study were assessed after school. However, this time of day did not appear to affect performance. Key to motivation appeared to be the immediate reinforcement of having the examiner present, offering constant encouragement and attention and maintaining a rapid pace of test administration by the swift transition from one task to another.

In view of this, there appears to be a powerful effect of the immediate reinforcement of adult attention in enhancing distractible attention and hyperactivity. This was reinforced by the change in behaviour when the Structured Clinical Interview for DSM (SCID-CV) (First et al., 1996) was administered to the participant together with the main carer(s) which often resulted in a more active and disruptive pattern of behaviour. This might have been because this interview was administered towards the end of the assessment when the participant was tired; however, participant behaviour, which included jumping about or trying to direct the interviewer, suggested some attempt to regain my attention. In view of this, one must not underestimate the power of attentional reinforcement as a therapeutic modulator of behaviours typically seen in ADHD.

8.0 Effects of Computer Medium on Inattentive Children

In addition to the role of one-to-one attention, the tests used in the study were relatively fun. The participants appeared to enjoy the competitive challenge, particularly of performing under timed conditions! Although participants were initially excited by the opportunity to participate in the N-Back computerised tests, towards the end of the set of tests, some of their enthusiasm had waned. Nonetheless, I often found it hard to leave the participant's home without them attempting to download computer games or pieces of school work onto my computer, in their attempt to show me how much they enjoy and are motivated by computer work.

Luciana et al. (2003) evaluated computerised assessment of neuropsychological function in children. She noted that advantages of computerised tests were through the highly standardised administration and automated response recording that would

be difficult to accomplish by hand. However, crucial to the current assessment administration were her findings that in general, children found the computerised testing format of tests to be interesting and motivating. Further, she noted that computerised test administration can result in relative purity of the test because it is not confounded by social influences and is free of many sources of extraneous variables. Therefore it is possible that computerised assessment might mask deficits that would otherwise be apparent in some populations. It is likely that if the N-Back test had been attempted by hand, the presentation of 808 trials under four conditions (slow, medium, fast and 2-Back) might have resulted in little completion compliance. Nonetheless, all children appeared to enjoy the computer administration, and the use of this in academic settings might facilitate learning and motivation.

9.0 Clinical Implications and Interventions:

As discussed earlier, I felt that participants, some of whom had been discharged from the tertiary service, found that the administration of the DSM/SCID-CV interview was facilitative and therapeutic, giving individuals an opportunity to review and process their experiences. Nonetheless, I felt that it was not all positive, and there were instances, where I felt families were struggling with the clinical management of their symptoms and the discussion of their current difficulties helped them to consider seeking further local help or requesting another referral to the TS clinic. Revisiting TS cases who had been discharged from the clinic alerted me to some unmet need. This is inevitable when following up cases from a tertiary clinic where geographical restrictions means that treatment mainly consists of advice and consultation to families and local services. Local services are often intimidated by TS, but once you understand the pattern of symptoms, and improve knowledge by

research, the profile of TS is similar to that typically seen in local services (e.g. behavioural disinhibition, distractible attention...).

The typical course of TS means that individuals may oscillate between periods of improvement or exacerbation in symptoms (Robertson, 2000). The TS Clinic at Great Ormond Street Hospital was influenced by an emphasis on the medical medication management of TS. This is likely to be due to the high efficacy of such treatments. Robertson (2000) has reviewed the pharmacological treatments that are typically used for TS. These include the use of dopamine-modulating drugs (typical neuroleptics/dopamine antagonists) such as Haloperidol or Sulpride; atypical neuroleptics such as Risperidone, Clozapine, Olanzapine; Dopamine agonists; Noradrenergic-modulating drugs (such as Clonidine) and stimulants such as Methylphenidate, Dexamphetamine (mainly to improve concentration and hyperactivity). It is noteworthy that many of these treatments do not have a specific neurological effect, but perhaps mirroring the disorders they treat, affect a range of behaviours.

There is much research that has explored other treatments used in groups with TS. Eapen et al. (2003) noted from their study of a TS cohort of 148 individuals, that tic symptomatology was improved by relaxation in 52.7%, concentration in 23.1% and sport in 8.8%. In contrast to this, it was noted that tic symptomatology was aggravated by stress in 83.5%, tiredness in 7.7%, and boredom in 3.3% of their sample. Elaborating upon this, Chowdhury (2004) reviewed a series of beneficial interventions. These include reassurance and psychoeducation, stress reduction, relaxation, exercise, guided imagery, massed practice (practicing tics before going

into specific environments) and habit reversal (selection of an alternative, incompatible response). There are treatments that focus on the comorbidities, for example, treatments that include cognitive behavioural therapy or relaxation therapy, and these are said to be more effective in alleviating associated conditions (e.g. OCB) rather than tics (Robertson, 2000).

In addition to the medical focus of the clinic, the lead consultant psychiatrist was keen to recommend and implement psychotherapeutic treatments as an adjunct to medication management. This was lead by the clinic psychologist and I was invited to co-facilitate the group. This group ran during the evening once per month for six months. The implications from the current study might be that TS treatment need not focus solely on TS but also needs to consider the impact of the comorbidities. When we considered individuals that might be invited to the TS group, myself and the clinical psychologist reviewed the families that had attended the clinic, most of whom I had recently visited. Central to our discussions was the notion that it was not the individuals with the greatest or most severe symptomatology that were struggling or in need of additional help. Fundamental to coping appeared to be the individual's own perception and management of their symptoms and possibly the meaning and narratives that they attached to this. In view of this, the group was comprised of a range of individuals, including those who had good management of symptoms, those with severe symptoms, those with additional psychological or adjustment difficulties, or those who might have one specific difficulty, often linked to the presence of a comorbid disorder (e.g. ADHD, OCB).

Although a larger number of individuals were invited, only six children and adolescents attended the group due to time or travel constraints. Sessions covered coping with Tourette syndrome and tics, Self-Esteem, School and Bullying, Anger Management and OCD. If this group could have been planned with the results of the present study, the inclusion of a module addressing coping with symptoms of ADHD would have been key. This illustrates how easily symptoms of ADHD can be erroneously overlooked in psychological interventions that address the management of TS. Nonetheless, the group was extremely positively received.

10.0 Future Directions

As discussed, further research should examine in greater detail the qualitative differences in how individuals with TS differ from those in ADHD in solving tasks that involve inhibition. Particular emphasis of strategies used and how these differ will need to be made. Finally, the conclusions drawn from the present study suggest that the clinical management of TS will be inadequate without any consideration or emphasis of coping with comorbid ADHD symptoms. In view of this, treatment programmes will need to focus on comorbid disorders such as ADHD as much as they do on TS.

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Appendix 1

	TS	TS + ADHD	ADHD
OCD Obsessions	1.47 (1.62)	1.40 (2.06)	1.33 (2.15)
OCD Compulsions	1.47 (1.91)	0.90 (1.16)	0.42 (0.79)
Major Depressive Episode	2.53 (2.94)	1.60 (2.87)	0.92 (1.88)
Manic Episode	0.00 (0.00)	0.20 (0.89)	0.00 (0.00)
Anxiety - Panic	0.12 (0.49)	0.00 (0.49)	0.00 (0.00)
Anxiety – GAD/Agoraphobia/Social Phobia	1.0 (1.22)	1.25 (1.33)	1.17 (1.47)

Mean (Standard Deviation) Demographic and DSM Diagnostic Information for Each Group With Significance Values [* = $p<0.05$, ** = $p<0.0005$]

Appendix 2

Further Description of Experimental Measures

1. ***The Stroop (Colour Word Interference Test).***[1]

(Delis-Kaplan Executive Function System (D-KEFS) Delis, Kaplan and Kramer, 2001). The D-Kefs Colour-Word Interference Test, based on the Stroop (1935) was used. According to Delis et al., (2001):

"The primary executive function measured with this test is the examinee's ability to inhibit an overlearned verbal response (i.e. reading the printed words) in order to generate a conflicting response of naming the dissonant ink colours in which the words are printed. The D-Kefs has two baseline conditions that measure key component skills of the higher level tasks: basic naming of the colour patches (condition 1) and basic reading of colour-words printed in black ink (condition 2). Condition 3: Inhibition is the traditional Stroop task for which the examinee must inhibit reading the words in order to name the dissonant ink colours in which those words are printed. The D-Kefs included a new executive-function task, condition 4: Inhibition/Switching. For this condition, the examinee is asked to switch back and forth between naming the dissonant ink colours and reading the words. This condition is thus a means of calculating both inhibition and cognitive flexibility."

1. ***The Trail Making Test (D-KEFS).***

D-Kefs Trail Making Test: consists of a visual cancellation test and a series of connect-the-circle tasks. According to Delis et al., (2001):

"The primary executive-function task is condition 4: Number-Letter Switching, which is a means of assessing flexibility of thinking on a visual-motor sequencing task. The other four conditions of this test allow the examiner to quantify and derive normative data for several key component processes necessary for performing the switching task. These include visual

[1] Directions used were replicated from the Delis-Kaplan Executive Function System (D-KEFS) Dean C Delis, Edith Kaplan and Joel H Kramer, 2001 manual.

scanning, number sequencing, letter sequencing and motor speed. With these measures, the examiner can determine whether a deficient score on the switching condition is related to a deficit in cognitive flexibility and/or to an impairment in one or more underlying component skills."

2. ***The Design Fluency Test (D-KEFS)***

According to Delis et al., (2001), the D-Kefs Design Fluency Test:

"measures an examinee's ability to draw as many different designs as possible in 60 seconds. In condition 1: Filled Dots, the response boxes contain only filled dots and the examinee is asked to draw the designs connecting those dots. In condition 2: Empty Dots Only, the response boxes contain both filled and unfilled (empty) dots; the examinee is required to connect only the unfilled (empty) dots and to inhibit the previous response of connecting the filled dots. In condition 3 (Switching), the boxes contain both filled and unfilled dots; the examinee is asked to draw the designs, by alternately connecting filled and empty dots. Thus, condition 1 provides a basic test of design fluency, condition 2 measures both design fluency and response inhibition and condition 3 measures both design fluency and cognitive flexibility."

3. ***The Verbal Fluency Test (D-KEFS)***

D-Kefs Verbal Fluency Test comprises three testing conditions: Letter Fluency, Category Fluency and Category Switching. According to Delis et al., (2001):

"For the Letter fluency condition, the examinee is asked to generate words that begin with a particular letter as quickly as possible. For the Category Fluency condition, the examinee is asked to generate words that belong to a designated semantic category as quickly as possible. For the Category Switching condition, the examinee is required to generate words, alternating between two different semantic categories as quickly as possible. This test measures the examinee's ability to generate words fluently in an effortful, phonemic format (Letter Fluency), from overlearned concepts (Category Fluency) and while simultaneously shifting between overlearned concepts (Category Fluency)."

4. ***The Hayling Sentence Completion test*** (Burgess and Shallice, 1997). The Hayling test is divided into two sections. Section 1 consists of 15 sentences missing the last word. The participant is required to verbally complete the sentence as quickly as possible. Section 2 consists of 15 sentences, again missing the last word. Participants are required to verbally complete the sentence with a word that is unconnected to the sentence in every way. This provides three measures of executive function (1) response initiation which is the sum of response latencies in section 1; (2) Response suppression in section 2 (i) error score (connected or somewhat connected errors) and (ii) time taken to respond. These three scores can be combined into one overall efficiency score.

Appendix 3

[An example of directions used for the Go-Nogo/Back fast condition]

In this task you are going to see a series of different letters on the screen, one at a time.

Press the YES button on the LEFT when the letter is A
DO NOT PRESS A BUTTON for any other letter

For example:

J	No
A	Yes
A	Yes
S	No
W	No
W	No
A	Yes
J	No
A	Yes
S	No

Now you try some:

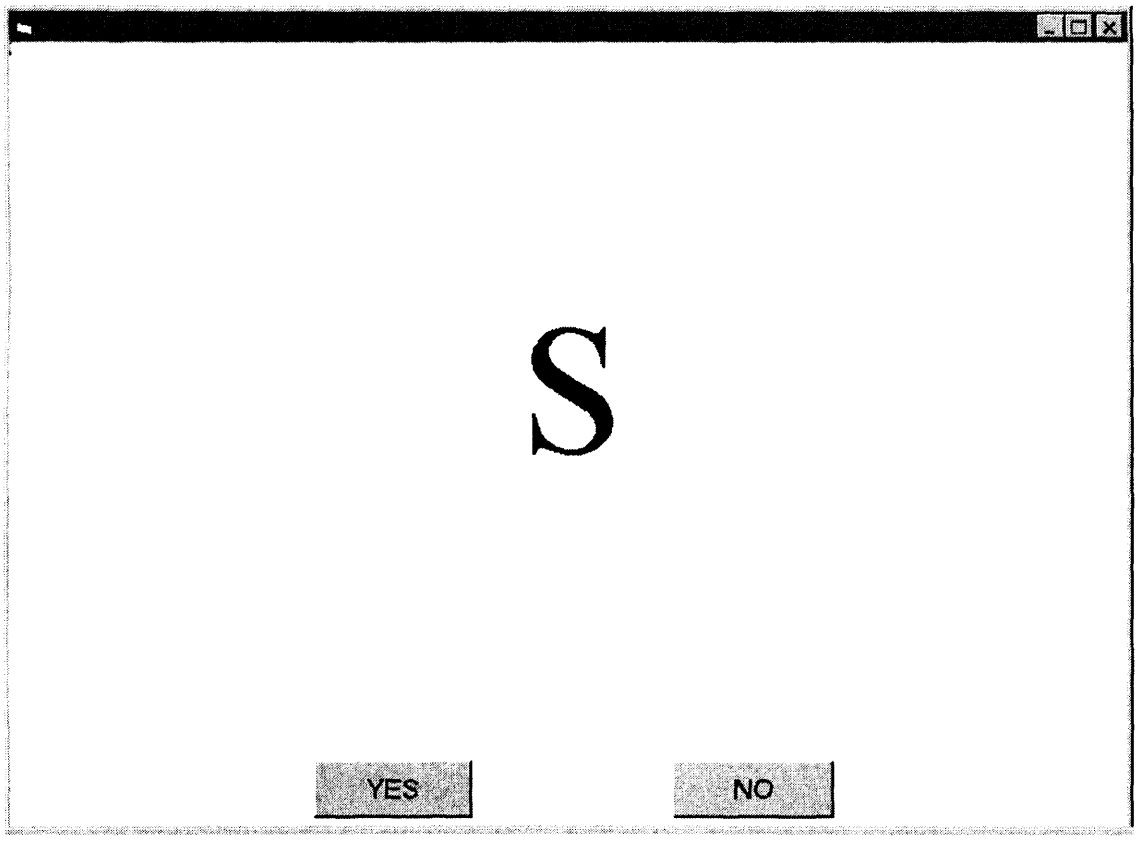
W
A
S
A
J
J
A
A
A
S

The correct answers are:

W	No
A	Yes
S	No
A	Yes

J No
J No
A Yes
A Yes
A Yes
S No

Here's an example of how it will look.



Remember, press YES for an A, and DO NOT PRESS for any other letter.

Work as **quickly** and **accurately** as you can.

Are you ready?

Appendix 4

[An example of continuation directions used for the Go-Nogo/Back fast condition]

Now we're carrying on again.

Remember, press YES for A only.

Work as **quickly** and **accurately** as you can.

Are you ready?

Appendix 5

[An example of directions used for the 2 Back test]

In this task you are going to see a series of different letters on the screen, one at a time.

You are looking out for any repeating letters with one letter in between.

For example, if the letter on the screen is T, you are looking for whether the next letter but one is also T. The letter in between may be the same or different. For instance, you might see T then C then T, or you might see T then T then T.

In either case, press the YES button when you see a letter the SAME as the one before last. It doesn't matter which letter it is, so long as the two letters are the same.

If the letter is different from the one before last, DO NOT PRESS A BUTTON

.

For instance:

T	No
C	No
T	Yes
T	No
T	Yes
T	Yes
H	No
R	No
H	Yes
H	No

Now you try some:

C
R
C
C
T

H
T
H
H
R

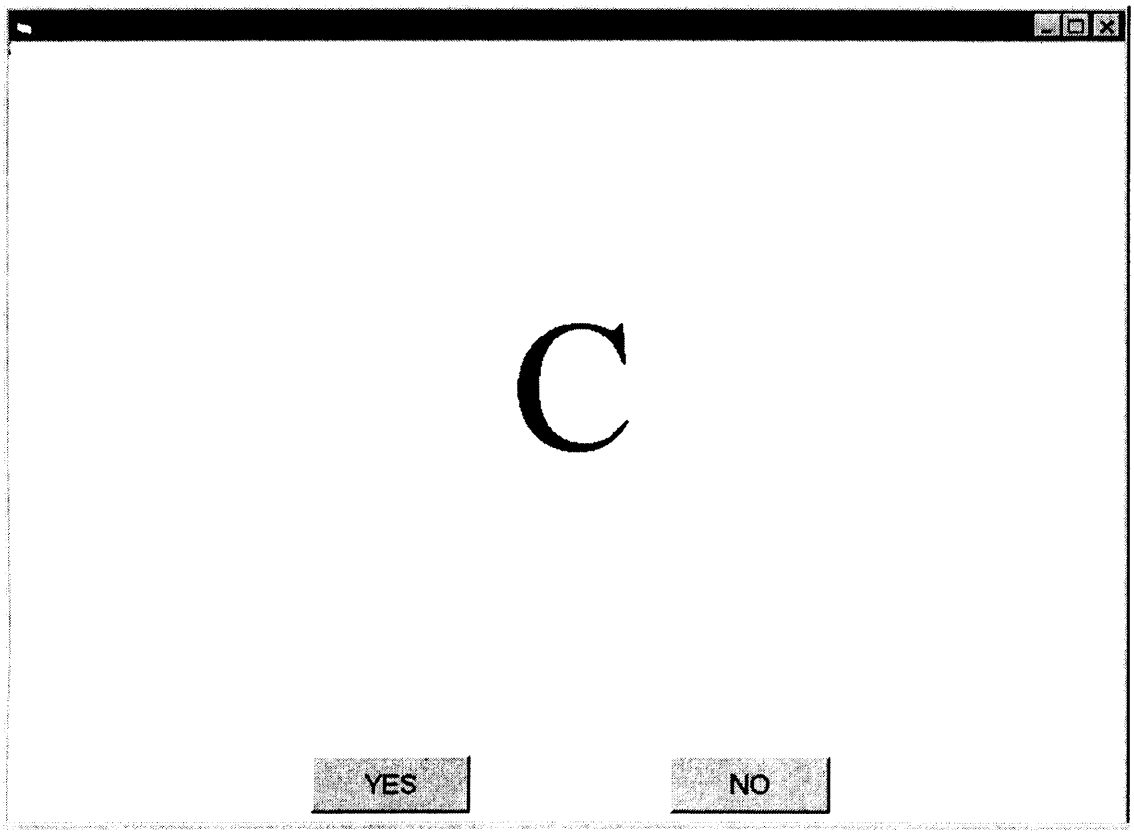
The correct answers are:

C	No
R	No
C	Yes
C	No
T	No
H	No
T	Yes
H	Yes
H	No
R	No

So:

Press the YES button on the left if the letter is the SAME as the one before last
DO NOT PRESS A BUTTON t if the letter is DIFFERENT from the one before last

Here's an example of how it will look.



Remember, press YES if the letter is the SAME as the one before last, and DO NOT PRESS A BUTTON if it is DIFFERENT from the one before last.
If you get behind, just pick up from where you are as quickly as you can.

Of course, the first two answers will always be No.

Work as **quickly** and **accurately** as you can.

Are you ready?

Appendix 6

[An example of continuation directions used for the 2 Back test]
Now we're carrying on again. If you get behind, just pick up from where you are as quickly as you can.

Remember, press YES if the letter is the SAME as the one before last, and DO NOT PRESS A BUTTON if it is DIFFERENT from the one before last.

Again, the first two answers will always be No.

Work as **quickly** and **accurately** as you can.

Are you ready?

Appendix 7

Comparison of scaled score test performance with test normative sample

Test	TS	TS + ADHD	ADHD
Stroop colour naming time	(t (16) 0.0, p=1.0)	(t (19) –1.32, p=0.204)	(t (11) –0.26, p=0.803)
Stroop word reading completion time	(t (16) 0.0, p=1.0)	(t (19) –0.282, p=0.781)	(t (11) 0.258, p=0.801)
Stroop inhibition completion time	(t (16) 0.97, p=0.349)	(t (19) -2.51, p=0.021)	(t (11) -0.10, p=0.921)
Stroop inhibition/switching completion time	(t (16) -0.19, p=0.855)	(t (19) -1.62, p=0.121)	(t (11) -1.22, p=0.249).
Trail visual scanning completion time	(t (16) –1.64, p=0.121)	(t (19) –2.02, p=0.058)	(t (11) 0.35, p=0.74)
Trail number sequencing completion time	(t (16) –1.36, p=0.194)	(t (19) –2.60, p=0.017)	(t (11) 1.10, p=0.295)
Trail letter sequencing completion time	(t (16) –1.37, p=0.190)	(t (19) –2.22., p=0.039)	(t (11) –0.97, p=0.351)
Trail number-letter switching completion time	(t (16) -1.60, p=0.128)	(t (19) -2.43, p=0.025)	(t (11) -0.96, p=0.358)
Trail motor speed completion time	(t (16) –1.84, p=0.084)	(t (19) –1.17, p=0.258)	(t (11) -0.93, p=0.371)
Design fluency filled dots total correct	(t (16) 1.16, p=0.265)	(t (19) 1.44, p=0.166)	(t (11) 2.29, p=0.043)
Design fluency empty dots total correct	(t (16) 1.14, p=0.270)	(t (19) 1.61, p=0.124)	(t (11) 1.44, p=0.177)
Design fluency switching total correct scaled	(t (16) 2.34, p=0.032)	(t (19) -0.42, p=0.683)	(t (11) 0.36, p=0.725)
Verbal fluency repetition errors	(t (16) -3.24, p=0.005)	(t (19) -4.08, p=0.001);	(t (11) -4.18, p=0.002
Verbal fluency set loss errors	(t (16) 6.88, p<0.0005)	(t (19) -0.84, p=0.410)	(t (11) 2.20, p=0.050)
Verbal fluency letter fluency correct	(t (16) –0.35, p=0.730)	(t (19) –3.79, p=0.001)	(t (11) 0.17, p=0.871)
Verbal fluency category fluency	(t (16) 0.57, p=0.579)	(t (19) –0.61, p=0.552)	(t (11) 1.73, p=0.112)
Verbal fluency category switching correct scaled score	(t (16) 0.99, p=0.334)	(t (19) 0.00, p=1.00)	(t (11) 2.34, p=0.039)
Hayling suppression errors	(t (16) –1.76, p=0.098)	(t (19) –1.81, p=0.086)	(t (11) –1.29, p=0.224)
Hayling overall efficiency score	(t (16) –2.91, p=0.010)	(t (19) –1.81, p=0.009)	(t (11) –2.24., p=0.047)

Appendix 8

Summary of Medication by Group

1. TS GROUP

	Frequency	Percent
Haleperidol	1	5.9
Clonidine	4	23.5
None	5	29.4
Not known	4	23.5
Cetriline and Clonidine	1	5.9
Sulpride	2	11.8
Total	17	100.0

2. TS/ADHD GROUP

	Frequency	Percent
Haleperidol	2	10.0
Hydrochloroquine (for TS and ADHD)	1	5.0
Concerta	3	15.0
Clonidine	4	20.0
Ritalin	1	5.0
Concerta and Risperidone	1	5.0
Ritalin and Clonidine	2	10.0
None	2	10.0
Not known	4	20.0
Total	20	100.0

3. ADHD Group

	Frequency	Percent
Concerta	3	25.0
Ritalin	5	41.7
None	1	8.3
Not known	1	8.3
Strattera	2	16.7
Total	12	100.0

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE
LONDON

Great Ormond Street Hospital NHS
for Children NHS Trust

Great Ormond Street Hospital NHS
for Children NHS Trust

Dear Participant,

Thank you for expressing an initial interest in this study. Please find enclosed an information sheet containing some details about the research project and a consent form for participation in the project.

If it would be helpful to you, I would be very happy to go through the information sheet and consent form with you and answer any further questions that you may have. Please feel free either to telephone or to write to me at the contact details above. This will not commit you to participation in the research project. Your decision whether or not to take part in this study will not affect your present or future medical care in any way.

Many thanks for considering this study.

Yours sincerely

Dr Catherine Harter
Research and Trainee Clinical Psychologist

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE
LONDON
GOWER STREET LONDON WC1E 6BT

Great Ormond Street Hospital for Children NHS Trust

Dr Catherine Harter
Trainee Clinical Psychologist

Child Sheet: Multiple Measures of Disinhibition in Tourette's syndrome II

Aim

This study is about Tourette's syndrome. As you know, people who have Tourette's syndrome make movements and noises that they cannot help. These are called tics. We know that some people find it difficult to think before they do or say something. In other words, they can be a bit hasty. We want to do this study because we think that having tics might have something to do with being a bit hasty. We don't know if everyone with Tourette's syndrome tends to be hasty - that is what we want to find out.

Why is the study being done?

Being a bit hasty covers lots of different things. We need to look at all the different things at the same time to figure out if being hasty has anything to do with having tics.

We want to find ways of bossing back the tics. Medicine can help, but some people can learn to manage their tics themselves. If we can sort out what tics and being a bit hasty have got to do with each other, we might be able to figure out some better ways to boss the tics back.

What will happen?

If you take part, you will be invited to come and see us for a few hours.

You will be asked to do lots of different games and puzzles. Children usually enjoy doing them. For example, in one game, you will be asked to press a button every time you see a letter flash up on a computer screen.

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE
LONDON
GOWER STREET LONDON WC1E 6BT

Great Ormond Street Hospital for Children NHS Trust

Dr Catherine Harter
Trainee Clinical Psychologist

Parent Information Sheet: Multiple Measures of Disinhibition in Tourette's syndrome II: A follow Up Study

Aim

As you know, your child has Tourette's syndrome, and has tics. We think that tics are related to difficulties suppressing responses – known as disinhibition. We want to know more about the relationship between disinhibition and tics.

Why is the study being done?

We do not know exactly how tics are related to disinhibition. There are lots of different types of disinhibition and lots of different ways to measure it. We need to look at all these different aspects of disinhibition in one study to figure out how they relate to tics. Some types of disinhibition may be more closely related to tics than another. By understanding the relationship between disinhibition and tics, we may be able to develop better self-management strategies to manage the tics.

How is the study to be done?

If you decide to take part, you and your child will be invited to the hospital for an appointment at a time that suits you. Only one visit will be necessary. You and your child's travel expenses will be paid, if you are making a special journey to the hospital to take part. If it is more convenient for you, we will be happy to visit you at your home.

At this appointment, your child will be asked to do lots of different games and puzzles. For example some tests require your child to press a button on a computer screen every time he or she sees a letter. Other tests mean that your child has to do something, rather than say it. For example, he or she might be asked to join some dots, that alternate between numbers and letters in their respective order. Children usually enjoy doing them.

While your child is doing the games and puzzles, we will ask you to complete some brief questionnaires about your child's behaviour.

What are the risks and discomforts?

There are no risks or discomforts associated with the games and puzzles we are doing. Children usually enjoy doing them.

Who will have access to the case/research records?

Only the researchers and the clinical team at Great Ormond Street Hospital will have access to the data collected during the study.

The use of some types of personal information is safeguarded by the Data Protection Act, 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to

people about whom information is held. If you have any questions about data protection, contact the Data Protection officer via the switchboard on extension .

What are the arrangements for compensation?
This research has been approved by an independent Research Ethics Committee, who believe that it is of minimal risk to your child. However, research can carry unforeseen risks, and we want you to be informed of your rights in the unlikely event that any harm should occur as a result of taking part in this study.

No special compensation arrangements have been made for this project but you have the right to claim damages in a court of law. This will require you to prove a fault on the part of the Hospital and/or any manufacturer involved.

What are the potential benefits of this study?
If we can learn more about which aspects of disinhibition are related to tics, it may help us develop self management techniques.

Do I have to take part in this study?
If you decide, now or at a later stage, that you do not wish to participate in this research project, that is entirely your right and it will not in any way prejudice any present or future treatment.

Who do I speak to if problems arise?
If you have any complaints about the way in which this project has been or is being conducted, in the first instance, discuss them with Dr Catherine Harter or Dr Jane Gilmour. If the problems are not resolved, or you wish to comment in any way, please contact the Chairman of the Research Ethics Committee, by post, via the Research and Development Office, Institute of Child Health, , or if urgent, by telephone on and the Committee administrator will put you in contact with him.

Details of how to contact the researcher.
Dr Catherine Harter can be contacted by telephone on or by post at The Sub-Department of Clinical Health Psychology, University College London, .*

* You may notice that the return/contact address is different from previous studies in which you might have partaken. This change is to enable a prompt response from the research team.

CONSENT FORM

Title of Project: Multiple Measures of Disinhibition in Tourette's syndrome II: Follow up Study

Name of Lead Investigators: Dr Catherine Harter and Dr Jane Gilmour

Please initial box

1. I confirm that I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I am interested in finding out more about this study. ☐

4. I agree to take part in the above study. ☐

Name of Research Subject *(Please print)*	Date	Signature
Name of Parent or Guardian *(Please print)*	Date	Signature
Name of Witness to Signature (Must **not** be member of research team) *(Please print)*	Date	Signature
Name of Research Team member *(Please print)*	Date	Signature

3 copies required: top copy for researcher; one copy for patient; one copy to be kept with research subject's notes.

Participant details

Please return this section to us in the prepaid envelope provided.

Name.....

Date of
Birth.....

Address.....

.....

.....

Telephone
number.....

E-mail
address.....

Sub-Department of Clinical Health Psychology
UNIVERSITY COLLEGE
Sub-Department of Clinical Health Psychology
LONDON UNIVERSITY COLLEGE
GOWER STREET LONDON WC1E 6BT

Great Ormond Street Hospital for Children NHS Trust

Dr Catherine Harter
Trainee Clinical Psychologist

Dear Participant,

Thank you for expressing an initial interest in this study. Please find enclosed an information sheet containing some details about the research project and a consent form for participation in the project.

If it would be helpful to you, I would be very happy to go through the information sheet and consent form with you and answer any further questions that you may have. Please feel free to either telephone or write to me at the contact details above. This will not commit you to participation in the research project. Your decision whether or not to take part in this study will not affect your present or future medical care in any way.

Many thanks for considering this study.

Yours sincerely

Dr Catherine Harter
Research Psychologist and Trainee Clinical Psychologist

Attention and Task Switching in Children

1. **What is the purpose of this study?** Sometimes it is hard to switch from one subject to another. We are interested in looking at how easy children who have ADHD find changing topic or being quick on some puzzles and games.

2. **Why have I been chosen?** You have been chosen because you have been treated in the local services for ADHD. This means that sometimes you may find it difficult to sit still or keep your attention on one thing for a long time.

3. **What do I have to do?** When we meet you, at an appointment time that suits you, you will take part in a series of puzzles and games. For example, you may be asked to join some dots that alternate between numbers and letters in that respective order, or to follow patterns on a computer. People often find this to be fun.

4. **Do I have to take part in this study?** No you do not, and you are allowed to withdrawal at any time from this project without stating why and this will not affect your current or further treatment in any way.

Thank you very much for considering taking part in this study

Participant details

Please return this section to us in the prepaid envelope provided.

Attention and Task Switching

Name.....

Date of Birth.....

Address.....

.....

.....

Telephone number.....

E-mail address.....

Attention and Task Switching in Children

1. **What is the purpose of this study?** Sometimes it is hard to switch from one topic to another. We are interested in looking at how children who have ADHD perform on a series of puzzles and games that measure this. This will allow us to know which strengths and weaknesses you have.

2. **Why have I been chosen?** You have been chosen because you have been treated in the local services for ADHD. This means that sometimes you may find it difficult to sit still or keep your attention on one thing for a long time.

3. **Who is organising this study?** This study is being organised by a group of clinical psychologists who are based at Douglas House, the Child and Family service in Cambridge and University College London.

4. **What do I have to do?** When we meet you, at an appointment time that suits you, you will take part in a series of puzzles and games. For example, you may be asked to join some dots that alternate between numbers and letters in that respective order, or to follow patterns on a computer. People usually enjoy doing this. While you are doing the games and puzzles, I will ask your carer to complete some brief questionnaires about your behavior. You will only need to be seen once; however, if you prefer, we can meet over two short sessions.

5. **What are the possible benefits of taking part?** Your taking part will help us to understand ADHD more, in particular the things that someone with ADHD might be particularly good at, and the things that someone with ADHD might find difficult.

6. **Will my GP be informed?** We will not be telling GPs that you will be taking part in this study, although we will be happy to inform them if you would like us to.

7. **Do I have to take part in this study?** If you decide now or at a later stage that you do not wish to participate in this research project, this is entirely your right. You are allowed to withdrawal at any time from this project without stating why and this will not affect your current or further treatment in any way.

Thank you very much for considering taking part in this study

Participant details

Please return this section to us in the prepaid envelope provided.

Attention and Task Switching

Name.....

Date of Birth.....

Address.....

.....

.....

Telephone number.....

E-mail address.....

CONSENT FORM

LREC Reference Number: 04/Q0108/57

Title of Project: Attention and Inhibition in ADHD

Name of Lead Investigator: Dr Catherine Harter

Please initial box

1. I confirm that I have read and understand the information sheet dated ... (version ...) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I am willing that my general practitioner is notified of my participation in this research. ☐

4. I am interested in finding out more about this study. ☐

5. I agree to take part in the above study. ☐

Name of Research Subject *(Please print)*	Date	Signature
Name of Parent or Guardian *(Please print)*	Date	Signature
Name of Witness to Signature (Must **not** be member of research team) *(Please print)*	Date	Signature
Name of Research Team member *(Please print)*	Date	Signature

3 copies required: top copy for researcher; one copy for patient; one copy to be kept with research subject's notes.

Attention and Task Switching in Children

1. **What is the purpose of this study?** Sometimes it is hard to switch from one topic to another. We are interested in looking at how children who have ADHD perform on a series of puzzles and games that measure this. This will allow us to know which strengths and weaknesses they have on measures of task switching and holding back a response.

2. **Why have I been chosen?** Your child has been chosen because they have been treated in the local services for ADHD. This means that sometimes they may find it difficult to sit still or keep their attention on one thing for a long time.

3. **Who is organising this study?** This study is being organised by a group of clinical psychologists who are based at Douglas House, the Child and Family service in Cambridge and University College London.

4. **What do I have to do?** If you are interested in finding out more, then please return the attached contact slip to me. I will contact you to discuss the project and if you want to take part. I will then organise a time that I could visit you at your home or at our clinic if you would prefer. Your travel expenses will be repaid. When we meet you, at an appointment time that suits you, your child will take part in a series of puzzles and games. For example, your child may be asked to join some dots that alternate between numbers and letters in that respective order, or to follow patterns on a computer. Children usually enjoy doing this. While your child is doing the games and puzzles, I will ask you to complete some brief questionnaires about your child's behavior. You will only need to be seen once; however, if you prefer, we can meet over two short sessions. You will receive a £5 gift voucher as a thank you for your time.

5. **What are the possible risks/side effects of taking part?** There are no risks or discomforts associated with the puzzles or games that we are doing. Children usually enjoy them.

6. **What are the possible benefits of taking part?** Your taking part will help us to understand ADHD more, in particular the things that someone with ADHD might be particularly good at, and the things that someone with ADHD might find difficult.

7. **Confidentiality - who will have access to the data?** Your data will only be accessed only by individuals in the research team and your health clinic. The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use your personal information, but also gives rights to people about whom information is held. This project is covered by UCL Data Protection Registration, Reference No.Z6364106, Section 19, Medical Research. If you have any questions you can contact the Data Protection officer on Tel: Ext.

8. **What will happen to the study results?** If you would be interested in finding out how your child performed, then we will be happy to send you a letter informing you how they got along.

9. **Will my GP be informed?** We will not be telling GPs that you will be taking part in this study, although we will be happy to inform them if you would like us to.

10. **Do I have to take part in this study?** If you decide now or at a later stage that you do not wish to participate in this research project, this is entirely your right. You are allowed to withdrawal at any time from this project without stating why and this will not affect your current or further treatment in any way.

11. **What are the arrangements for compensation?** This research has been approved by an Independent Research Ethics Committee who believe that it is of minimal risk to your child. However, research can carry unforeseen risks and we want you to be informed of your rights in the unlikely even that any harm should occur as a result of taking part in this study.

    No special compensation arrangements have been made for this project, but you have the right to claim damages in a court of law. This will require you to prove a fault on the part of the Hospital and/or any manufacturer involved.

12. **Details of how to contact the researcher.** You may contact the team by telephoning Dr Catherine Harter on or writing to the Sub-Department of Clinical Health Psychology, University College London,
    or at

Thank you very much for considering taking part in this study

Participant details

Please return this section to us in the prepaid envelope provided.

Attention and Task Switching

Name.....

Date of Birth.....

Address.....

.....

.....

Telephone number.....

E-mail address.....

Child age12-16 years

CONSENT FORM

Attention and Task Switching in Children

LREC Reference Number: 04/Q0108/57
Title of Project: Attention and Inhibition in ADHD
Name of Lead Investigator: Dr Catherine Harter

Please initial box

1. I have read and understand the information sheet dated 7th July (version 1.) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is my choice and I can change my mind or not take part whenever I want to and without giving a reason. This will not affect my medical care. ☐
3. I am willing that my general practitioner is notified of my participation in this research. ☐
4. I am interested in finding out more about this study. ☐
5. I agree to take part in the above study. ☐

Name of Research Subject *(Please print)*	Date	Signature
Name of Parent or Guardian *(Please print)*	Date	Signature
Name of Witness to Signature (Must **not** be member of research team) *(Please print)*	Date	Signature
Name of Research Team member *(Please print)*	Date	Signature

3 copies required: top copy for researcher; one copy for patient; one copy to be kept with research subject's notes.

Child age 7-12 years

CONSENT FORM

Attention and Task Switching in Children

LREC Reference Number: 04/Q0108/57
Title of Project: Attention and Inhibition in ADHD
Name of Lead Investigator: Dr Catherine Harter

Please initial box

1. I have read and understand the information sheet for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is my choice and I can change my mind or not take part whenever I want to and without giving a reason. This will not affect my medical care. ☐
3. I am willing that my general practitioner is notified of my participation in this research. ☐
4. I am interested in finding out more about this study. ☐
5. I agree to take part in the above study. ☐

Name of Research Subject *(Please print)*	Date	Signature
Name of Parent or Guardian *(Please print)*	Date	Signature
Name of Witness to Signature (Must **not** be member of research team) *(Please print)*	Date	Signature
Name of Research Team member *(Please print)*	Date	Signature

3 copies required: top copy for researcher; one copy for patient; one copy to be kept with research subject's notes.

Version No: ...1 / *Dated:* ...7th July 2004

FILE COPY

Great Ormond Street Hospital for Children NHS Trust / The Institute of Child Health
Local Research Ethics Committee
Institute of Child Health

19th February 2004

Dr J Gilmour
BBSU
ICH

Dear Dr Gilmour,

Title: **Multiple measurements of Disinhibition in Tourette's syndrome**
R&D registration number: **01BS08**
Protocol number/version: **N/A**

Thank you for your letter dated 16th February 2004. The Chairman of the Research Ethics Committee, Dr , has on behalf of the Committee, approved the amendment to the above study such that data collection will be carried out by Catherine Harter.

The decision will be ratified at the full Committee meeting that will take place on Wednesday 7th April 2004 (Please note that you will not receive a letter confirming the above ratification).

Yours sincerely

Research Ethics Coordinator

cc. Catherine Harter, GOSH
Isobel Heyman, GOSH
, ICH

NHS

Barnet, Enfield & Haringey Local Research Ethics Committee

13 July 2004

Dr. Catherine Harter
Trainee Clinical Psychologist
Sub Department of Clinical Health
Psychology
University College London,

Dear Dr. Harter,

Full title of study: Multiple Measures of Disinhibition In Tourette Syndrome and ADHD: Characterising the Comorbid Subtypes of Tourette Syndrome through an Examination of the Extent to which ADHD that Presents Comorbidly with Tourette Syndrome is Commensurate with Pure ADHD
REC reference number: 04/Q0509/27
Protocol number: 1

Thank you for your letter of 9th July, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Chairman.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type: Application
Version:
Dated: 10/06/2004
Date Received: 10/06/2004

Document Type: Investigator CV
Version: 1
Dated: 10/06/2004
Date Received: 10/06/2004

Document Type: Protocol
Version: 1
Dated: 10/06/2004
Date Received: 10/06/2004

Document Type: Covering Letter
Version:
Dated: 07/06/2004
Date Received: 10/06/2004

Document Type: Summary/Synopsis
Version: 1
Dated: 10/06/2004
Date Received: 10/06/2004

Document Type: Details of DMC
Version:
Dated: 10/06/2004
Date Received: 10/06/2004

Document Type: Letters of Invitation to Participants
Version: 1
Dated: 10/06/2004
Date Received: 10/06/2004

Document Type: Participant Information Sheet
Version: 2
Dated: 02/07/2004
Date Received: 12/07/2004

Document Type: Participant Information Sheet
Version 1 Age 12-16 yrs
Dated 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Information Sheet
Version 1 Age 7-12 yrs
Dated 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version: 1
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version 1 Child age 7-12 years
Dated: 07/07/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version 1 Child age 12-16 years
Dated: 07/07/2004
Date Received: 12/07/2004

Management approval

You should arrange for all relevant host organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Statement of compliance *(from 1 May 2004)*

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: 04/Q0509/27 **Please quote this number on all correspondence**

Yours sincerely,

Administrator

Encs: Standard approval conditions

Cambridge Local Research Ethics Committee

13 July 2004

Dr. Catherine Harter
Sub Department of Clinical Health Psychology
University College London,

Dear Dr. Harter,

Full title of study: Multiple Measures of Disinhibition In Tourette Syndrome and ADHD: Characterising the Comorbid Subtypes of Tourette Syndrome through an Examination of the Extent to which ADHD that Presents Comorbidly with Tourette Syndrome is Commensurate with Pure ADHD
REC reference number: 04/Q0108/57
Protocol number: No version

Thank you for your letter of 28 June 2004, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Chairman, Dr

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

The favourable opinion applies to the following research site:

Site: Cambridge & Peterborough Mental Health Partnership
Principal Investigator: Dr. Catherine Harter

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type: Application
Dated: 06/06/2004
Date Received: 07/06/2004

Document Type: Investigator CV
Dated: 07/06/2004
Date Received: 07/06/2004

Document Type: Protocol
Version: No version
Dated: 06/06/2004
Date Received: 07/06/2004

Document Type: Letters of Invitation to Participants
Version: No version
Dated: 06/06/2004
Date Received: 07/06/2004

Document Type: Participant Information Sheet
Version: 1
Dated: 07/06/2004
Date Received: 07/06/2004

Document Type: Participant Information Sheet
Version: V2 7.6.04
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Information Sheet
Version: V1 age 7-12 yrs
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Information Sheet
Version: V1 Age 12-16yrs
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version: V2 7/6/04
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version: V1 Age 7-12yrs
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version: V1 Age 12-16yrs
Dated: 07/06/2004
Date Received: 12/07/2004

Document Type: Participant Consent Form
Version: 1
Dated: 07/06/2004
Date Received: 07/06/2004

Document Type: Response to Request for Further Information
Dated: 28/06/2004
Date Received: 12/07/2004

Management approval

The study may not commence until final management approval has been confirmed by the organisation hosting the research.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: 04/Q0108/57 **Please quote this number on all correspondence**

Yours sincerely

Chairman

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

Enclosure 1

List of Names and Professions of Members who were Present at the Meeting or who Submitted Written Comments

Dr
NeuroPsychiatrist

Dr
Paediatrician

Dr
Consultant Anaesthetist

Revd. Dr
Chaplain

Dr
Gastroenterologist

Dr
Consultant Psychiatrist

Dr
Statistician

Mrs

Dr
Paediatrician

Mr
Head of Tissue bank

Mr
Pharmacist

Mrs
Administrator

Mrs
Assistant Administrator