UNIVERSITY OF SOUTHAMPTON

DISSECTING THE NEUROPSYCHOLOGICAL STRUCTURE OF ADHD: INHIBITORY CONTROL AND DELAY AVERSION

by

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To my parents Niko and Lenia
who supported me in every possible way
and they helped me to make my dream come true.
You will always hold the hand of my heart...

Στους γονείς μου Νίκο και Λένια
που με στηρίξανε με τον κάθε δυνατό τρόπο
και με βοηθήσανε να κάνω το όνειρό μου πραγματικότητα.
Θα κρατάτε για πάντα το χέρι της καρδιάς μου...

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ABSTRACT

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES

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Attention-deficit/hyperactivity disorder (ADHD) has been characterised as a clinically and genetically heterogeneous disorder. Over the past decades, researchers have studied the neuropsychological causal factors associated with this heterogeneity. Neuropsychological deficits such as inhibitory control (Barkley, 1997) and delay aversion (Sonuga-Barke et al., 1992) have been associated with ADHD. However, none of these unitary causal models can fully explain the aetiology of the disorder. In fact, there is a theoretical and empirical focus on identifying multiple causal pathways (Sonuga-Barke, 2002). To date, very few studies have been conducted to distinguish these different causal pathways to ADHD by using multiple indicators of these neuropsychological domains. In the present thesis 71 pairs of children with ADHD and their unaffected siblings and 50 control children were examined on inhibitory control and delay aversion tasks as part of the Southampton site of the International Multicenter ADHD Genetics study (IMAGE project). First, these two neuropsychological deficit domains were found to be two separate latent constructs. Second, these latent factors of inhibitory control and delay aversion deficits were found to be associated with ADHD. Third, a comparison of probands and their siblings found little evidence of familial effects on either construct. Confounding effects such as age, gender, non-executive processes, IQ, and comorbid ODD were also investigated in a secondary analysis. The current thesis provides strong support for the dual pathway model of ADHD – but leaves open the question of whether these effects are familial or genetic in nature. Based on the present results, clinical and research implications on using neuropsychological subtypes, as part of the clinical diagnosis, are discussed.

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CHAPTER ONE: Introduction to Attention Deficit Hyperactivity Disorder (ADHD): Clinical Characteristics

1.1. Introduction

Attention Deficit/Hyperactivity Disorder (ADHD) is a common disorder of impulse, attention and activity (Taylor & Sonuga-Barke, 2007). It affects individuals across the life span from pre-school, through childhood, adolescence and adult life. Individuals with ADHD have difficulties in sustaining their attention and concentrating for long periods of time. Moreover, they tend to be overactive and sometimes they may act or speak without thinking as a result of their impulsivity. Inattention, overactivity and impulsivity symptoms are often associated with impairment for the individual with ADHD, and are disruptive and demanding for the people surrounding them. At school, for instance, children with ADHD might stand up or speak during the lesson, which can be frustrating for a teacher and the other students. Inattentive symptoms (e.g. do not seem to listen, lose things, forgetful etc.) can also have an effect on the academic performance and employment prospects of individuals with ADHD. Families of individuals with ADHD are concerned by the hyperactive and impulsive symptoms of their relatives, as they can be dysfunctional in social environments (e.g. the child runs around or interrupts conversations), and they can also increase the risk for accidents. Symptoms of ADHD and specifically inattention are also problematic for adults, since they find it very difficult to focus on their work. Moreover, their difficulty to organise and finish tasks can make them less productive at work and less efficient compared to their co-workers. Impulsive symptoms may cause problems in social communication and relationships.

In chapter one the current and alternative systems of clinical diagnosis of ADHD will be briefly discussed, and the epidemiology and prevalence of the disorder will be described in brief. The impact of age, gender and comorbidity will also be highlighted and how these factors can contribute to symptomatic expression of the disorder by different types of individuals.

1.2. Taxonomic issues in relation to disorders of impulse, attention and activity

Whether ADHD is best understood as a discrete condition or as an extreme variant on a behavioural continuum is one of many controversies that surround the disorder. Traditionally, disorders of inattention, overactivity and impulsiveness have been

represented in categorical terms – as qualitatively distinct from normality rather than being at the end of a continuum of normal variation. Categorisation of disorders, embodied in diagnostic systems such as the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM-IV-TR; APA, 2000), has been seen as a practical necessity in clinical and research practices. Both clinician and researcher need to be able to identify those who are mentally disordered and those who are not, in order to be able to apply adequate treatment and to interpret research findings respectively (Sonuga-Barke, 1998). According to categorical models of classification the normal differs from the pathological by kind rather than by degree (Wilson, 1993) and that distinctions can be drawn between qualitatively different types of disorder (Kendall, 1991). In fact, extensive data challenge the idea that psychopathological variation is best conceptualised in terms of hundreds of distinct categories, such as those in DSM-IV.

Clark, Watson, and Reynolds (1995) have argued that the categorical approach has two main shortcomings: high levels of comorbidity between and heterogeneity within disorders undermines the practicability of the categorical approach and therefore its clinical and research utility. Various pathophysiological disorders, such as Conduct Disorder (CD) or Oppositional Defiant Disorder (ODD), exhibit symptoms of inattention, hyperactivity and impulsivity that lead to the question whether these symptoms could be unique to ADHD. Sondeijker and colleagues (2005) have recently suggested that the often used taxonomy of three distinct disorders, ADHD, ODD, and CD is not the most useful approach to find homogeneous groups in a general population sample of adolescents. The authors have identified two subtypes of disruptive behavior disorders. The first subtype contained symptoms of ADHD, ODD, and CD (subtype 1; also found by Banaschewski et al., 2003), whereas the second subtype contained symptoms of ADHD and ODD only (subtype 2). This indicates that the distinction between moderate (subtype 2) versus severe (subtype 1) behavior disorders is related with the presence or absence of CD symptoms. However, these results may be reflective of problematic and not well defined diagnostic criteria that are based on categorical diagnosis.

Although clinicians are based on normed diagnostic classifications (i.e. DSM and International Classification of Disease of the World Health Organisation (ICD-10; WHO, 1992)), the clinical validity of the disorder might not be sufficient, and ADHD's clinical heterogeneity may be due to taxonomic issues. The problem with heterogeneity is less researched but its impact is no less significant for clinical and

research utility. There are two types of heterogeneity of significance. First, there is within-category heterogeneity of defining features (Faraone et al., 1995), where there is a great diversity of individuals within each category. Second, there are mixed symptom patterns that fall between categories (Sonuga-Barke, 1998). Krueger, Watson, and Barlow (2005) argued that the heterogeneity problem can be handled by isolating correlates of specific dimensions in models that control for the influence of other psychopathological dimensions. Moreover, data can be used to shape and refine these dimensions so as to maximise their homogeneity and minimise their co-occurrence. The diagnostic criteria provided by the DSM-IV are only based on behavioural aspects of the disorder and do ignore differences between developmental stages and between males and females (discussion follows). Moreover, the comorbid effect leads us to the question of whether the disorders are appropriately classified or whether there is a need for a different classification system.

An alternative approach to describe and study psychopathology is the dimensional approach that has some apparent advantages. For example, Krueger et al. (2005) have argued that one can describe psychopathological variation in terms of multiple dimensions of disordered thought, affect and behaviour. In this way, a disorder will fall at the end of a seamless trait distribution, differing from normality only by degree and it should therefore be explained with reference to normal behavioural variation (Haslam et al., 2006). Empirical research provides some evidence that ADHD could be a continuous disorder. Levy, Hay, McStephen, Wood, and Waldman (1997) obtained heritability estimates that did not differ whether ADHD was assessed as a categorical diagnosis or as a quantitative trait, suggesting that the disorder has no specific genetic contribution beyond the heritable component of the trait. In addition, strong associations between ADHD and dimensions of normal personality imply that the disorder is continuous with normality (Nigg et al., 2002). Only one study, using appropriate statistical techniques to directly address the question of whether ADHD is best understood as a categorical or dimensional disorder, exists on a large population sample of children and adolescents (Haslam et al., 2006). In this study, several taxometric analyses of the latent structure of ADHD were used (Meehl & Yonce, 1994; Ruscio, 2004). The findings of this study favoured the continuum view of ADHD in childhood and, somewhat less strongly, in adolescence, which implies that many causal factors could be combined to determine each person's position in terms of underlying risk for the disorder and the subsequent severity of the symptoms.

Although there is some evidence to support the idea that no clear and 'objective' diagnostic boundary exists for ADHD, this does not mean that categorical diagnosis is inappropriate or that a threshold can only be set arbitrarily. Categorical diagnostic decisions are pragmatically necessary in many clinical contexts. Impairment may tend to become clinically meaningful at a certain level of severity, at which a categorical diagnosis might reasonably be made. Taxons help the clinician to identify the severe cases that require adequate treatment, and facilitates researchers in justifiably interpreting research findings. Indeed, because categorical studies with clinical groups seem most applicable to clinical problems, those types of studies remain the norm. In summary, dimensional systems may reflect the underlying structure of the disorder but they may be difficult to implement in a way that maintains the practical benefits of the current system.

1.3. Current diagnostic criteria

The diagnosis of ADHD is based on the DSM-IV-TR (APA, 2000). However, some European countries use the alternative World Health Organisation diagnosis of hyperkinetic disorder (HKD), as defined by the ICD-10 (WHO, 1992). Both diagnoses identify children displaying developmentally inappropriate levels of inattention, hyperactivity and impulsivity that begin in childhood and cause impairment to school performance, intellectual functioning, social skills and occupational functioning (Biederman, 2005). The differences between the two diagnostic classifications come in the ways that the symptoms are weighted and combined into categories. Both require a degree of pervasiveness but that requirement is stronger in ICD-10. The key differences between the two systems relate to the issues of (i) comorbidity and (ii) the specification of subtypes.

Table 1.1 displays the diagnostic criteria for ADHD and HKD based on the DSM-IV and ICD-10 respectively. In terms of subtypes DSM-IV allows for three diagnostic subtypes of ADHD based on two symptom dimensions, namely inattention and hyperactivity/impulsivity. The first subtype is the Predominantly Inattention subtype (ADHD-IA), in which children have six or more inattentive symptoms but fewer than six hyperactive/impulsive symptoms. The second is Predominantly Hyperactive/Impulsive subtype (ADHD-HI), in which children have six or more hyperactive/impulsive symptoms but fewer than six inattentive symptoms. Finally, the third is the Combined subtype (ADHD-C), in which children show six or more

symptoms on both dimensions. In contrast, in the ICD-10 there are no subtypes and some symptoms from all three domains of attention, hyperactivity and impulsivity should be present. ADHD-IA is somewhat more common in girls and more often associated with internalizing disorders (Nigg, 2006). ADHD-HI is relatively uncommon in clinical samples after preschool, and appears to have aetiological determinants distinct from those of ADHD-C in childhood (Willcutt, Pennington, & DeFries, 2000). When identified in preschool, it is often, but not always, a precursor to the later ADHD-C (Lahey, Pelham, Loney, Lee, & Willcutt, 2005). There has also been substantial debate as to whether ADHD-IA is a completely distinct disorder from ADHD-C (Lahey, 2001; Milich, Balentine, & Lynam, 2001). Although these two subtypes have distinct external correlates, one subtype can develop into the other over time (Lahey et al., 2005). Some children diagnosed with ADHD-IA might have some milder version of ADHD-C, and some others might be characterised by symptoms of underactivity rather than overactivity (Carlson & Mann, 2002). The individual differences on subtype division may rely on the questionable validity and clinical utility of this categorical approach to classification of ADHD. Recent research has proposed that these three subtypes differ on factors such as age of onset, gender (Lahey et al., 1994) and comorbidity with other childhood disorders (Willcutt, Pennington, Chhabildas, Friedman, & Alexander, 1999). Moreover, research findings indicate that the three subtypes of ADHD also differ in terms of their underlying pathophysiology, with symptoms of inattention rather than symptoms of hyperactivity/impulsivity being associated with neuropsychological impairment (Chhabildas, Pennington, & Willcutt, 2001).

In terms of comorbidity, HKD combined with conduct disorder form a different diagnostic category in ICD-10, whereas in DSM-IV does not make any special provision for conduct disorder as a comorbid condition. Other comorbid conditions such as anxiety and mood disorders are exclusion criteria for the diagnosis of HKD, whereas DSM-IV allows the diagnosis of ADHD with comorbid anxiety and mood disorders. These broader comorbid inclusion criteria in DSM-IV could explain why DSM-IV has higher rates of diagnosis than the ICD-10 criteria for HKD (Hill & Taylor, 2001).

Table 1.1: Symptom domains for ADHD/HKD in DSM-IV and ICD-10 (cited by Swanson et al., 1998b)

Inattention	Hyperactivity	Impulsivity
Fails to attend to details	Fidgets with hands or feet	
Difficulty sustaining attention	Leaves seat in classroom	
Does not seem to listen	Runs about or climbs	
Fails to finish tasks	Difficulty playing quietly	
Difficulty organising tasks	Motor excess ("on the go" in DSM-IV)	
Avoids sustained effort	Talks excessively (DSM-IV)	Talks excessively (ICD-10)
Loses things		Blurts out answers to questions
Distracted by extraneous stimuli		Difficulty waiting turn
Forgetful		Interrupts or intrudes on others

Both diagnostic systems, although well-established, do not have developmentally sensitive definitions to help clinicians and researchers differentiate ADHD symptoms from developmentally appropriate levels of inattention, hyperactivity, and impulsivity. In addition, clinicians often receive diagnostic data from multiple informants (e.g. parents and teachers), but DSM-IV and ICD-10 provide no guidelines to integrate this information (Biederman & Faraone, 2005). Likewise, the diagnostic manuals do not incorporate the significant effect of gender differences in the expression of ADHD symptomatology. Despite these limitations, the current diagnostic systems facilitate clinicians and researchers to identify the severity and subtypes of ADHD. Development and revision of the DSM and ICD manuals is currently ongoing and a refined set of diagnostic criteria are expected to be published after systematic research of key issues in 2011.

1.4. Comorbidity

ADHD often co-occurs with other pathophysiological disorders, such as CD, ODD, emotional disorder, pervasive developmental disorder, reading disorder (RD) and Tourette's syndrome (Angold, Costello, & Erkanli, 1999; Pennington & Ozonoff, 1996; Taylor, 1998). ODD and CD are present in approximately 40-70% of children with ADHD (Faraone & Biederman, 1994) and 25-75% of adolescents with ADHD (Barkley, 1998). In a sample of 9- to 16-year-old children with ADD with or without hyperactivity, 48% had comorbid depression/dysthymic disorder, 36% had comorbid ODD/CD and 36% had comorbid anxiety disorder (Bird, Gould, & Staghezza, 1993). Furthermore, children with ADHD are at increased risk for developing substance abuse as they grow older (Schubiner, Tzelepis, & Milberger, 2000).

However, none of these comorbid disorders share a set of causal pathways with ADHD (Taylor, 1998). For instance, according to Nigg (2003) ADHD is predominantly

associated with dysfunctional executive inhibition (i.e. suppression of an immediate motor response), whereas conduct disorder is predominantly associated with dysfunction in the motivational inhibition process (i.e. interruption of behaviour in the context of unexpected or punishment-cue indicators), with secondary effects in executive control. Furthermore, previous research has suggested that some neuropsychological functions of ADHD, like executive functioning, are not unique to the disorder (Oosterlaan, Logan, & Sergeant, 1998), and that deficits in executive functioning have been identified in other comorbid disorders, such as ODD and CD. However, recent research (Oosterlaan, Scheres, & Sergeant, 2005) suggest that executive functioning deficits are associated only with ADHD and that the presence of comorbid ADHD accounts for the executive functioning deficits in children with ADHD+CD or ODD. In summary, ADHD and other mental disorders are distinct to some extent but often overlap with each other.

1.5. Epidemiology and prevalence of childhood ADHD

ADHD is a prevalent disorder, estimated to affect 3-7% of children (APA, 2000). Epidemiological studies have suggested higher prevalence rates of 8-12% (Faraone, Sergeant, Gillberg, & Biederman, 2003). According to Taylor (1994) DSM-IV defined ADHD was reported as more prevalent than ICD HKD, since the latter classification is more restrictive (see above). A recent review of 50 epidemiological studies reported the prevalence of DSM-defined ADHD to be similar across different countries worldwide (i.e. 6-12%; Doyle, 2004).

The administrative prevalence – the rate at which the disorders are in practice recognised – often differs from the epidemiological prevalence (Taylor et al., 2004). Administrative prevalence depends on factors that affect referral and access to service and cultural factors that influence symptom tolerance by adults (Swanson et al., 1998b). In 1989, the administrative prevalence was found to underestimate the epidemiological prevalence of HKD in the UK by 0.05% and of ADHD in the USA by 1.5% (Taylor, Sandberg, Thorley, & Giles, 1991).

According to Nigg (2006), studies that rely only on rating scale scores from a single informant cannot be considered estimates of the prevalence of ADHD as a defined DSM-IV. In fact, prevalence estimates are much lower when more rigorous methods are used such as structured interviews or multiple informants, together with the DSM-IV criteria. Specifically, these prevalence rates are estimated at around 2.9% for

ADHD-C, 3.2% for ADHD-IA, and only 0.6% for ADHD-HI, with a total of 6.8% (Nigg, 2006). In summary, ADHD is a prevalent disorder, but prevalence rates vary due to different sources of information.

1.6. Developmental trajectory of ADHD

Symptoms of ADHD typically manifest early in life, prior to the age of 7 years (APA, 2000). The peak age of onset of ADHD is between 3 and 4 years of age (Taylor et al., 1998). Follow-up studies have found that 5-60% of children with ADHD persist with this disorder in adulthood (Biederman et al., 1993; Mannuzza, Klein, Bessler, Malloy, & LaPadula, 1998). The large range of estimated persistence exists because of the criteria used to select the original sample, the edition of DSM used to make diagnoses of adult cases, and whether adult symptom assessment was based on self-reports or informant-reports (Biederman, 2005). Moreover, DSM-IV criteria for ADHD were developed with children in mind and offer only limited guidance regarding adult ADHD, which might lead to under-diagnosis of the disorder in adults.

1.6.1. Preschool

Preschool hyperactivity shares many of the characteristics with school-age ADHD symptoms and by the age of 4 years a diagnosis of ADHD is likely to persist into school age (Lahey et al., 2004). Preschool children with ADHD are more likely to experience motor coordination problems and have accidents than control children (Lahey, Pelham, & Stein, 1998). They are more non-compliant towards their parents and conversely parents are more likely to display negative behaviour towards their children with ADHD (DuPaul, McGoey, Eckert, & VanBrakle, 2001). In addition, they are less socially skilled than control children on behaviour rating skills (DuPaul et al., 2001), engage in more sensori-motor play and less social interaction in group situations (Alessandri, 1992) and may be aggressive towards their peers (Barkley et al., 2000). Symptoms of preschool inattentiveness, impulsivity and overactivity have been found to cluster together (Sonuga-Barke, Thompson, Stevenson & Viney, 1997). Moreover, 4 year old children exhibit reliable and valid scores on attention tasks (e.g. Berger, Jones, Rothbart & Posner, 2000) but not on inhibitory and working memory tasks (e.g. Kalff et al., 2002). Interestingly, Hanisch, Konrad, Günther, and Herpertz-Dahlmann (2004) found that neuropsychologically (but rating scale based) preschoolers do have attentional problems that are comparable to those found with school-age children with ADHD.

Although preschool ADHD classification would be clinically and scientifically useful (Sonuga-Barke, Auerbach, Campbell, Daley, & Thompson, 2005), case identification remains problematic, due to lack of age-appropriate diagnostic items, definitions and thresholds (Taylor et al., 2004). Specifically, preschool ADHD classification would need a differentiation of normative, age-related behaviour that is frustrating to adults, from actual symptoms of preschool ADHD (Sonuga-Barke et al., 2005). Although Campbell (2002) has suggested that a syndromatic definition of preschool hyperactive behaviour might be possible on the basis of the frequency, severity and duration of the behaviour compared to the typical behaviour for the child's age, caution is required in order to avoid pathologizing normal behaviour in young children.

1.6.2. Childhood and Adolescence

From preschool to childhood and adolescence the core behaviours tend to continue but in a different form, as the child enter the school and has different environmental input. For instance, they continue to be overactive and impulsive, as they have difficulties taking turns, or remaining seated, but symptoms of inattention are more apparent, as they have difficulties sustaining their attention during the lesson, or they are forgetful and disorganized. As children get into adulthood, overactive symptoms take the form of fidgeting and they are more prone in risk-taking, whereas the inattentive symptoms remain. About half of previously diagnosed cases will still meet diagnostic criteria from childhood into adolescence (Klein & Mannuzza, 1991).

Biederman and colleagues have worked extensively on the persistence of ADHD from childhood into adolescence and they have found some contradictory results. In a longitudinal study, Biederman and colleagues (1998) reported that children and adolescents diagnosed with ADHD did not differ from each other in terms of the mean number of ADHD symptoms that they exhibited at either baseline or follow-up after four years, indicating that the phenotypic expression of ADHD remains the same from childhood into adolescence. This replicated previous results of 85% persistence rate in ADHD (Biederman et al., 1996). However, further analysis of the same sample differentiated hyperactive, impulsive and inattentive symptom domains and considered the developmental course of these symptoms as a function of age rather than a pure distinction between childhood and adolescence. Specifically, hyperactivity, impulsivity and inattention were reported to significantly diminish with increasing age (Biederman, Mick, & Faraone, 2000).

1.6.3. Adulthood

If childhood ADHD persists into adulthood, adults with ADHD should exhibit similar correlates as children with ADHD (Willoughby, 2003). However, results from studies with children and adults with ADHD suggest that the expression of ADHD symptomatology is different for adults. Evidence shows that during adolescence and adulthood, ADHD hyperactivity often declines while attention deficits, disorganisation, and impulsivity persist in older ADHD patients (Biederman et al., 2000; Hart, Lahey, Loeber, Appelgate, & Frick, 1995; Kessler et al., 2005; Kooij et al., 2005). It is not known yet whether the reduced hyperactivity is transformed into an inner restlessness and fidgetiness, which could still be impairing for the individual, or whether this is a shift towards normality (Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005).

It is noteworthy that adult ADHD may be under-diagnosed, since adults may exhibit less symptoms of ADHD compared to children. Although there is evidence for ADHD-IA and ADHD-H/I subtypes, Kooij and colleagues (2005) argued that adults have on average less symptoms of ADHD than children and adolescents. In fact, Kooij and colleagues (2005) suggested a cut-off of four symptoms per subtype rather than six for diagnosing ADHD in adults to avoid possible under-diagnosis. Unfortunately, DSM-IV has not yet been adapted for adult ADHD diagnosis, and diagnostic items such as 'runs around or climbs' or 'difficulty playing quietly' are inappropriate for adults. Thus, the number of symptoms should be reconsidered for valid diagnosis in adulthood and a more realistic criteria should be developed that would be relevant to an adult life. Finally, since high prevalence rates of adult ADHD may also rely on the high degree of comorbidity (Kessler et al., 2006), clinicians should be cautious on whether ADHD criteria are met because of the presence of another adult disorder or whether ADHD is causing other mental disorders (Taylor and Sonuga-Barke, 2007). In summary, ADHD is an early developmental disorder that can persist into adulthood, although the expression of ADHD symptomatology might change through life.

1.7. Gender differences

A striking feature of ADHD is its differential incidence in males and females. The vast majority of the studies that have been conducted to examine gender difference on ADHD have been with clinical samples (Biederman et al., 2002b; Rucklidge & Tannock, 2001). Thus, prevalence rates vary, with male to female ratios in clinic-

referred samples ranging 9:1 to 6:1 (Biederman et al., 2002; Lahey et al., 1994; Sandberg, 1996), while ratios from population-based studies are approximately 3:1 (for review see Jud & Faraone, 2006). Thus, the male to female ratio for the disorder is greater in clinical studies than in community studies, which suggest that female individuals with the disorder are less likely to be referred for services than male individuals. This difference in referral rates by sex is possibly because of ADHD being less disruptive in women than in men (Biederman & Faraone, 2004), and the raised population prevalence in male individuals could be due to their increased exposure to environmental risk factors, such as head injury (Faraone et al., 2000).

More interesting though is the possible difference on the expression of ADHD symptomatology between boys and girls. Preliminary studies suggest that girls with ADHD may be less vulnerable to the executive deficits displayed by boys, as girls with ADHD and control girls exhibited similar performance on tests of executive functioning (Seidman et al., 1997). Other researchers have suggested that girls with ADHD have similar executive functioning compared with boys with ADHD (Houghton et al., 1999; Rucklidge and Tannock, 2002; Seidman et al., 2005a). On the other hand, findings from a meta-analysis of 17 studies on ADHD gender differences (Gaub & Carlson, 1997) indicated no differences between boys and girls with ADHD on impulsiveness, global academic performance, and social/peer functioning. However, girls rated lower on hyperactivity and externalizing behaviours. In summary, gender differences are apparent in ADHD, although further research is required to identify the possible reasons that cause this differentiation.

1.8. Issues in assessment

Clinical diagnosis is typically based upon reports from multiple sources and self-reports, and the clinician, through the interview process with the parents (or guardians), needs to judge whether the level of the behaviour reported by the informants is appropriate for the child's developmental stage and intellectual level.

Clinicians elicit the history of specific symptoms from those who know the child best – usually the parents/guardians and teachers. Rating scales (e.g. Conner's rating scales) have been developed and are useful as a supplement to the clinical interview, but not a replacement. These reports, especially from the parents, may overestimate the child's behavioural symptoms, and clinicians should be cautious in wrongly identifying a non-hyperactive child as ADHD on the basis of these

instruments (Swanson et al., 1998b). Teacher reports of hyperactive and inattentive symptoms can provide further information about children's behaviour, especially in a setting outside home. Teacher reports are seen as especially important in establishing pervasiveness. Parents and teachers of children with ADHD, especially pre-schoolers, might overestimate behavioural problems because they may lack knowledge of the developmental norms for that age, or because they contrast the child's behaviour with that of other members of the family or school setting (Taylor & Sonuga-Barke, 2007). Self-reports have also been developed for children, adolescents and adults (e.g. Strengths and Difficulties questionnaire), although they have been found to have more value for detecting emotional problems than for detecting the presence or absence of diagnostic symptoms (Taylor et al., 2004).

Observational approaches, especially valuable for preschoolers, may increase the validity of the diagnosis. The child is first observed in the clinical setting, although the symptoms may not be present in a novel and arousing setting (Taylor et al., 2004). If the clinician has doubts about the information received from parents or teachers, then observations in the natural setting of the home or school might be needed. Diagnosis requires that there should be clear evidence of clinically significant functional impairment in the major life domains of the child (e.g. at home and at school) alongside high severity or frequency of the symptoms (Taylor et al., 2004).

Although neuropsychological and biological tests are not recommended for routine clinical use (APA, 2000), both might be used by researchers to investigate links between symptoms and underlying neuropsychological processes and brain function (Swanson et al., 1998b). Tests of attention, impulsivity and brain function are still research tools, and have not been standardised for individual diagnosis, but they can give clues to the nature of the problem in an individual case (Taylor et al., 2004). Although no specific psychological tests exist for diagnosing ADHD, clinicians find it useful to assess the IQ of the child in order to determine academic performance versus academic potential. Height, weight, and head circumference is recorded as an indication of normal development. When there is suspicion of neurodevelopmental immaturity, a more thorough physical examination is required to investigate for genetic disorders that may cause hyperactive symptoms (e.g. Fragile X and Williams syndrome). In summary, during assessment clinicians should take into consideration possible biased parental reports and the age-appropriateness of the child's behaviour. Moreover, observational and neuropsychological approaches could help in reducing misdiagnosis of ADHD.

1.9. Summary

ADHD is a highly prevalent condition with serious consequences for children, their families and society more widely. In this chapter, the taxonomic status of ADHD, its diagnostic criteria, prevalence, assessment methods and the impact of age, gender, and comorbidity have been reviewed. It is apparent that ADHD is a clinically complex disorder, as children within the same diagnostic category my have a different expression of the disorder. Advances in diagnostic criteria have helped clinicians and researchers to understand the basic pathophysiology of ADHD. In the next chapter the familial aetiological factors (i.e. genetic and environmental) that lead to the clinically heterogeneous image of the disorder will be reviewed.

CHAPTER TWO: Aetiology of ADHD – Genes and Environments and their interplay in a complex clinical phenotype

2.1. Introduction

As made clear in Chapter 1, ADHD has a complex clinical phenotype. Over the past decades, researchers have studied the aetiological factors associated with this phenotype. Research has focused on genetic and environmental factors, and more recently on the role of gene-environment interplay. Molecular genetic studies demonstrate how individual variation in liability to ADHD is associated with specific genetic markers. In addition to these studies, behavioural genetic studies (i.e. twin and adoption studies) provide information on the heritability and familiality of the disorder, by estimating the similarity found between family members that can be attributed to genetic rather than shared or non-shared environmental effects. Prenatal, perinatal and postnatal environmental factors have also been found to have an effect on ADHD outcome. Finally, genetic and environmental factors associated with ADHD can either interact or correlate with each other (Nigg, 2006). In the first case, genotypic expression is moderated by environmental factors. In the later case, the genotypic risk is correlated with environmental risk making it difficult to identify their relative contribution (see below for a discussion). It is now clear that identifying risk factors associated with ADHD is not a straight forward task, since there are multiple genetic and environmental factors each of small effect that can also interplay with each other. Most importantly, not all children with ADHD are affected by all risk factors associated with the disorder: ADHD is aetiologically heterogeneous, as well as clinically heterogeneous disorder (see chapter 1). In this chapter the aetiological complexity of ADHD, at a genetic and environmental level will be reviewed. Different strategies have been developed to partition this causal heterogeneity and these will be highlighted.

2.2. Genetics of ADHD

Genetic studies of ADHD provide evidence for the complexity of the disorder at a genetic level (for reviews see Faraone et al., 2005 and Waldman & Gizer, 2006). Behavioural genetic studies (i.e. family, adoption, and twin studies) investigate how much of the individual variation in liability to ADHD is shared between individuals with ADHD and their family members who share a known proportion of their genes (i.e., adopted parent and child 0 percent, biological parent and child 50 percent; dizygotic

twins 50 percent; monozygotic twins 100 percent). Molecular genetic studies (i.e. linkage and association studies) investigate possible chromosomal regions and genes that might make individuals susceptible to ADHD.

2.2.1. Behavioural genetics

Several studies have reported an elevated prevalence of ADHD among family members of individuals with ADHD. Family studies have confirmed the familiality of ADHD, after controlling for factors such as gender, socioeconomic status, and intactness of family (Biederman et al. 1992; Faraone et al., 2000). Moreover, adoption studies have found rates of ADHD to be greater among biological relatives of non-adopted children with ADHD than adoptive relatives of adopted children with ADHD and that adoptive relatives had a risk for ADHD similar to the risk in relatives of control children (Sprich, Biederman, Crawford, Mundy, & Faraone, 2000). A more direct method of examining the heritability of ADHD is to study twins. The concordance of genetically based disorders should be higher in monozygotic (MZ) twins (who have 100% of their genes in common) than in dizygotic (DZ) twins (who share only 50% of their genes). Faraone and his colleagues (2005) have reported that the mean heritability estimate from 20 twin studies is 76%, indicating that ADHD is among the most heritable of psychiatric disorders.

Several factors though could influence the increased heritability estimate of ADHD. First, heritability estimates for ADHD is higher according to parent ratings of ADHD, (ranging from 60 to 90%; e.g. Faraone et al., 2000; Thapar, Harrington, Ross, & McGuffin, 2000) compared to teacher ratings (ranging from 60 to 70%; e.g. Thapar et al., 2000). Second, heritability estimates vary according to the ADHD scale that has been used. A review of studies using DSM-IV criteria for ADHD gave evidence that between 60% and 94% of the influence on ADHD is due to genetic factors (Faraone & Doyle, 2001). By using a more empirically derived instrument, such as the Child Behavior Checklist (CBCL), in a twin study (Rietveld, Hudziak, Bartels, van Beijsterveldt, & Boomsma, 2003), the heritability estimate drops to moderate levels, 60-70%. Finally, when the Conners' rating scale is used in twin studies, heritability estimates become even lower at 48% (Hudziak, Derks, Althoff, Rettew, & Boomsma, 2005).

In sum, although the heritability estimates tend to change due to rater or measurement bias, behavioural genetic studies provide evidence that ADHD is a

heritable disorder. Increased heritability estimates have lead researchers to search for genetic markers associated with the disorder.

2.2.2. Molecular genetics

Research on the molecular genetics of ADHD has been focused on two approaches: whole-genome scans and candidate gene association studies.

2.2.2.1. Genome wide scans

The six genome-wide scans (i.e. investigation of shared chromosomal regions among ADHD-affected family members) conducted so far are inconclusive. Chromosomal regions such as 5p12, 10q26, 12q23, 16p13 (Fisher et al., 2002; Smalley et al., 2002) 5p13, 6q12 (Ogdie et al., 2004) 15q15, 7p13, 9q33, 13q33 (Bakker et al., 2003) 8q12, 11q23, 4q13, 17p11, 12q23 and 8p23 (Arcos-Burgos et al., 2004) have been identified. Some of these chromosomal regions have also been identified in autism, indicating that they are not unique to ADHD. There is some limited overlap of genomic regions implicated by these studies. However, the power of these studies individually is probably too low to detect linkage to genes of small effect (Faraone et al., 2005). A pooled analysis of the data from Ogdie et al. (2004) and Bakker et al. (2003) showed a significant effect at the 5p13 locus that had emerged in each sample separately (Ogdie et al., 2006). On the other hand, Hebebrand and colleagues (2006) found a stronger effect at the 5p17 locus. This provides the basis for replication and fine mapping of candidate regions.

2.2.2.2. Candidate gene studies

Case-control and family-based studies have used the association method to identify candidate genes influencing the susceptibility of ADHD. Candidate gene studies typically focus on specific genetic polymorphisms of theoretical interest (Nigg, 2006). Several candidate genes have been investigated for their association to ADHD but only a few of them have provided significant results. The two most widely studied ones are the dopamine D4 receptor (DRD4) and dopamine transporter gene (DAT1).

DRD4: The DRD4 and specifically the 7-repeat allele has been found to be associated with ADHD (Brookes et al., 2006; Faraone et al., 2001; Grady et al., 2003; Holmes et al., 2002b; Roman et al., 2002). However, these results were not replicated by others (e.g. Kustanovich et al., 2003; Mill et al., 2001). Moreover, other researchers have found an excess of short alleles (i.e. 2-5 repeats) in ADHD participants (Manor et al., 2002; Smith et al., 2003). Results of these latter two

studies raise the possibility of allelic heterogeneity in DRD4. Despite the divergent findings, Faraone and his colleagues (2005) argued that by pooling these studies together the association between DRD4 and ADHD remains statistically significant. The DRD4 7-repeat allele has been found to be associated with impaired neuropsychological performance in children with ADHD (Langley et al., 2004) although in a more recent study, no significant behavioural differences were found to be associated with DRD4 (Barkley, Smith, Fischer, & Navia, 2006).

DAT1: The most recent gene association study, with a large sample of 776 ADHD-C children, has indicated that DAT1 is associated with ADHD, with an odds ratio (OR) of 1.26 (an OR higher than 1.00 indicates that the allele increases risk for ADHD; Brookes et al., 2006). DAT1 is on chromosome 5, with a polymorphism 5p15.3 (Barr et al., 2001). In contrast some studies have failed to find an association between DAT1 10-repeat allele and ADHD (Curran et al., 2001; Maher, Marazita, Ferrell, & Vanyokov, 2002; Purper-Ouakil et al., 2005; Todd et al., 2001). When Faraone and his colleagues (2005) pooled family studies together, they found an overall small but significant association between DAT 10-repeat allele and ADHD.

Other genes of interest: A number of other catecholamine-related genes have been examined in fewer studies, with particular interest on dopamine D5 receptor (DRD5) and dopamine beta-hydroxylase (DBH). A meta-analysis of family based studies found a significant association with DRD5 in ADHD (Maher et al., 2002). More recently, other family based studies have identified a significant association of the 148-bp allele with ADHD (Lowe et al., 2004; Manor et al., 2004). The DBH is the primary enzyme responsible for conversion of dopamine to norepinephrine. Several studies have found an association between DBH Taq1 polymorphism and ADHD (Cubells et al., 1998; Daly, Hawi, Fitzgerald, & Gill 1999; Roman et al., 2002; Smith et al., 2003) and some others have not (Payton et al., 2001; Wigg et al., 2002). Despite these inconsistent results, when family based studies were pooled, they suggested a significant association between ADHD and the DBH Taq1 polymorphism (Faraone et al., 2005).

The hunt for ADHD genes has not only been restricted to the dopaminergic system, but has been extended to the serotonergic system as well. Preliminary findings suggest an association between the serotonin receptor HTR1B gene and ADHD (Hawi et al., 2002; Quist et al., 2003). The results for the long allele of the serotonin transporter gene (5-HTTLPR) are also controversial. However, when the 5-HTTLPR

studies were combined together, the association between the long allele of the 5-HTTLPR gene and ADHD was found to be significant (Faraone et al., 2005). Finally, the synaptosomal-associated protein 25 (SNAP-25) has also been found to be associated with ADHD (Brophy, Hawi, Kirley, Fitzgerald, & Gill, 2002; Mill et al., 2004).

The biggest gene association study so far (Brookes et al., 2006) indicate that alongside DRD4, DAT1, and SNAP-25, 15 more genes are nominally associated with ADHD (TPH2, ARRB2, PNMT, SLC9A9, NET, ADRB2, HES1, ADRA1A, PER2, MAOA, DDC, FADS2, SYP, CHRNA4, and HTR1E). Meanwhile, a number of other genes have been examined in fewer studies, such as DRD1, DRD2, DRD3, COMT, TH, LPHN3, KCNJ6, adrenergic receptor genes (e.g. ADRA1C, ADRA2C, and ADRA2A) and MAOB, and nicotine acetylcholine receptor genes (CHRNA4 and CHRNA7), but these effects are still emerging and further research is required before drawing any conclusions about their association with ADHD.

In summary, meta-analytic studies (e.g. Faraone et al., 2005) have identified seven candidate genes that may influence the susceptibility of ADHD: DRD4, DRD5, DAT, DBH, 5-HTT, HTR1B, and SNAP-25. According to Faraone and his colleagues (2005) the OR for these associations range from 1.18 to 1.46. The small OR indicates that the genetic vulnerability to ADHD is mediated by many genes of small effect, meaning that the genetic architecture of ADHD is complex. Further research is required to identify whether different genes are associated with different subtypes, and whether gene-gene interactions explain more variance in ADHD symptoms. Although ADHD is a genetically heterogeneous disorder, the heritability estimates reported by behaviour genetic studies do not fully explain the variability of the disorder. Consequently, other factors, such as shared and non-shared environmental factors may interact with the candidate genetic markers. Therefore, the gene-environment interplay could be subsumed to the heritability estimate of ADHD to explain the remaining unexplained variance. In the following sections, the environmental effects on the disorder will be discussed, as well as the importance of gene-environment interplay.

2.3. Environmental factors

2.3.1. Prenatal and perinatal risk factors

Several authors have suggested that nicotine may damage brain functioning at critical times during the development of the foetus (e.g. Milberger, Biederman, Faraone, Chen, & Jones, 1996). Specifically, nicotine has been found to cause dysfunction of the dopaminergic system, which is also dysfunctional in children with ADHD (Ernst et al., 1999). One of the consequences of maternal smoking during pregnancy is ADHD (see for review Linnet et al., 2003). The OR for developing ADHD due to prenatal smoking ranges from 0.44 to 4.4 in different studies. It has been suggested that this large range of risk might be due to dichotomized assessment of smoking as well as lack of investigation on gender and ADHD subtype effects (Rodrigues & Bohlin, 2005). Recently, Nigg (2006) estimated that 7% of the variance of ADHD is attributable to maternal smoking during pregnancy if we assume straightforward main effect. Moreover, he argued that this estimated prevalence is independent of maternal ADHD and CD. One important bias related to the maternal-pregnancy smoking effect on ADHD is that most of the studies rely on retrospective reports of the mothers on their smoking habits during pregnancy. When this confound was eliminated by using prospective information about maternal smoking habits during pregnancy, it was found that mothers who smoked during pregnancy had a 3-fold increased risk for having a child with hyperkinetic disorder compared to non-smokers (Linnet et al., 2006). This relative risk did not change after controlling for socio-economic status, history of mental disorder in the parents or siblings, parental age, low birth weight, premature birth, and children's comorbidity (including CD). Not only is prenatal smoking is associated with ADHD phenotype, but it has also been reported in a longitudinal population-based study on hyperactive symptoms as a significant risk factor for persistent high-level hyperactive symptoms in children at age 7 (Romano, Tremblay, Farhat, & Côté, 2006). Moreover, recent results indicate that children of mothers who smoked during pregnancy exhibited problems in regulating motivation (using the DeFT task – Bitsakou et al., 2006) and also had more conduct and hyperactivity-inattention problems than non-exposed children (Huijbregts, Warren, de Sonneville, & Swaab-Barneveld, in press). Finally, Thapar et al. (2003) reported that in a twin sample, smoking accounted for about 1% of the variance in ADHD symptoms, independently of genetic and other effects. Therefore, although maternal prenatal smoking exerts a small effect on development of ADHD, it is still a risk factor that can be prevented by more consistently informing mothers of the negative effects of prenatal smoking.

Prenatal alcohol exposure has also been related to impulsivity, hyperactivity or inattention, independently of maternal ADHD, smoking during pregnancy, and parental antisocial behaviour (Mick, Biederman, Faraone, Sayer, & Kleinman, 2002a). Moreover, children who were prenataly exposed to alcohol have been found to have cognitive and attentional deficits that are also found in children with ADHD (Streissguth et al., 1994). However, there is a question of whether low levels of alcohol use during pregnancy can contribute to ADHD, as five out of nine studies on prenatal alcohol drinking failed to find an association (for review, see Linnet et al., 2003). In an attempt to answer this question, Knopik and colleagues (2006) found that 7% of ADHD cases were affected by low levels of alcohol use (i.e. < 11 days; never heavily) and 10.5% were affected by high levels of alcohol use during pregnancy (i.e. <11days of heavy drinking). Finally, mothers who had an alcohol use disorder (AUD) or who were unaffected but had a MZ co-twin with AUD, had a 2.5-fold increased risk of having a child with ADHD, compared to unaffected mothers who had or did not have an affected DZ co-twin (Knopik et al., 2006). The authors concluded that either there are some genetic markers that influence the vulnerability to both maternal AUD and childhood ADHD (i.e. pleiotropic genetic effects), or that ADHD is a direct risk-factor for AUD. As with prenatal smoking, although the effect is small and cannot fully explain ADHD, it is important and could be preventable.

Low birth weight (LBW) has been suggested as another environmental risk factor for ADHD. Specifically, LBW has been found to contribute independently to ADHD even after controlling for prenatal smoking and alcohol use, parental ADHD, child conduct problems, parent antisocial behaviour and child IQ (Mick, Biederman, Prince, Fisher, & Faraone, 2002b). Mick and colleagues (2002b) have estimated that LBW could be a direct contributory factor in about 14% of ADHD cases. This estimation is similar to the 12.8% estimation that was reported by Hoyert, Mathews, Menacker, Strobino, and Guyer (2006). Although LBW can be caused by premature birth (Nigg, 2006), there are children who were born at term and still had LBW. In a recent study, these children have been found to have a 90% increased risk of hyperkinetic disorder compared with children born at term and normal birth weight (Linnet et al., 2006). Gestational age has also an impact on the development of ADHD symptoms. Children born preterm and also close to term (i.e. before 34 weeks and 34-36 weeks respectively) have an increased risk of clinically verified hyperkinetic disorder compared to children born at term (rate ration 2.7 and 1.7 respectively; Linnet et al., 2006). Finally, prospective population-based studies have shown that maternal

anxiety in late pregnancy predicted hyperactivity and inattention symptoms in 4-year old boys and at follow-up in 8-year-old boys and girls (O'Connor et al., 2003) and that maternal stress during the first half of the pregnancy predicted ADHD symptoms in 7-years old boys, independent of prenatal smoking (Rodriguez & Bohlin, 2005). Therefore, there is some evidence that maternal anxiety during pregnancy might be a significant risk factor of ADHD.

2.3.2. Family and other psychosocial risk factors

The family is an important aspect of a child's environment that has been linked to variability in comorbidity, academic performance, and social difficulties for children with ADHD (Johnston & Mash, 2001). Rutter, Cox, Tupling, Berger, and Yule (1975) revealed six risk factors within the family environment that correlated significantly with childhood mental disturbances: 1) severe marital discord, 2) low social class, 3) large family size, 4) paternal criminality, 5) maternal mental disorder, and 6) foster placement. Using Rutter's indicators of adversity, Biederman and colleagues (1995) found that the odds of having ADHD were 7.4 times greater in children having one indicator compared with children having none of Rutter's indicators. The odds were greater, if the child was exposed to more family risk factors (9.5, 34.6, and 41.7 with 2, 3, and 4 indicators, respectively).

Family adversity and parental psychopathology can be associated and have a causal effect on childhood ADHD. Parental ADHD has been found to increase family conflict and decrease family cohesion (Biederman, Faraone, & Monuteaux, 2002a). In a recent study, in which the birth order of affected siblings was taken into account, it was found that maternal ADHD was associated with family disorganization, which in turn predicted ADHD in the younger sibling (9 years old) of the family (Pressman et al., 2006). The authors argued that this effect could be explained by the fact that the effects of mother-child interaction is stronger for younger siblings of the family, as the mother plays an important role in structuring and supervising school tasks and peer and community experiences compared to the father (Pressman et al., 2006).

Many studies have shown that maternal depression is a risk factor for childhood ADHD (e.g. Pressman et al., 2006; Ramchandani et al., 2005; Romano et al., 2006). In a longitudinal study on risk factors and persistence of hyperactive symptoms from 2 to 7 years, children with a depressed mother were 2 times more likely to have high and persistent levels of hyperactive symptoms than children with a non-depressed mother (Romano et al., 2006). However, maternal depression might not be directly

associated with children's ADHD psychopathology, as there is evidence that maternal depression (similarly to parental ADHD; Biederman et al., 2002a) predicts increase family conflict and decreased family cohesion, which in turn predicts childhood ADHD (Pressman et al., 2006).The effect of postnatal paternal depression has also been found to have a significant association with hyperactive outcomes in children aged 3.5 years (especially in their sons). This effect persisted after controlling for later paternal depression, suggesting that depression of fathers in early months of a child's life might have a persisting detrimental effect on their children's hyperactive outcomes (Ramchandani et al., 2005). Finally, paternal mood disorder (as well as paternal substance abuse) has shown to have a direct effect on the child's ADHD impairment during its early adolescence (Pressman et al., 2006).

Negative parenting practices, as a possible result of parental psychopathology, could also be perceived as placing the child at risk for ADHD. Family intervention studies have demonstrated improvements in ADHD symptoms, when parents have been taught alternative parenting skills (Sonuga-Barke, Daley, Thompson, Weeks, & Laver-Bradbury, 2001). Although there is a study showing that hostile parenting increases children's risk for hyperactivity (Romano et al., 2006), parenting and childhood ADHD is a two-way relationship interaction, between the parent (most studied are mothers) and the child. This makes it difficult to disentangle the direction of causal effects. Therefore, the relationship between childhood ADHD and parenting may result from both negative aspects of the child influencing the parent's behaviour, and negative aspects of the parent influencing the child's behaviour (Daley, 2006). Studies investigating mother-child interaction have found that children with ADHD are less compliant and responsive to their parents compared to controls (Befera & Barkley, 1985). On the other hand, parents of children with ADHD are more negative, controlling, intrusive, disapproving, demanding, and power assertive (Buhrmester, Whalen, Henker, MacDonald, & Hinshaw, 1992; Gardner, 1994). Finally, parenting practices might be influenced by the parent-child interaction, but they could also be a result of parental psychopathology. For instance, a number of studies have shown that negative parenting practices might mediate the impact of maternal depression on childhood ADHD (e.g. Lesesne, Visser, & White, 2003), although a recent study has shown that maternal ADHD is associated with positive parenting on ADHD (Psychogiou, Daley, Thompson, & Sonuga-Barke, in press).

2.4. Gene-Environment interplay

Until the last decade, researchers on ADHD had explored genetic and environmental main effects independently. There had been an assumption of a linear relation between a gene or an environmental factor and the psychiatric behaviour. Based on this approach, researchers had tried to correlate ADHD with individual differences in DNA sequence or environmental influences. This approach though is now perceived as inappropriate, first because multiple genetic and environmental factors are found to be associated with the disorder (as reviewed in previous sections of this chapter), and second because there are four reasons to lead us to the conclusion that gene-environment interplay is important for the development of psychiatric disorders, including ADHD (Rutter, Moffitt, & Caspi, 2006).

First, from an evolutionary standpoint, genes are involved in the adaptation of organisms to their environment; organisms in a species will not respond to environmental conditions in the same way, and this within-species variation in response involves individual differences in genetic endowment. Second, human development is an environment-dependent process, and it is implausible that genetic factors do not play a role in moderating that process (Johnston & Edwards, 2002). Third, genes influence the biological and psychological function of humans, and it would be doubtful if the variability of individual's behavioural responses to environmental risks is outside the sphere of genetic influence (Rutter et al., 2006). Finally, there is growing evidence in mental disorders research, and specifically in ADHD research, that genes and environment can interact or correlate with each other (e.g. Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005b; Larsson, Larsson, & Lichtenstein, 2004).

Two general gene-environment interplay approaches have been introduced in the research of mental disorders, and these approaches have also started being adapted in ADHD research. According to the *gene-environment interaction* approach (G x E), there is no expectation of a direct gene-to-behaviour association in the absence of an environmental pathogen (Caspi & Moffitt, 2006). In fact, gene-environment interaction approach assumes that environmental factors cause disorder, and that genes influence susceptibility to these factors. For instance, according to this approach, two different children will respond to the same environment in different ways, because they have different temperamental predisposition that are rooted in different genotypes (Nigg, 2006).

The *gene-environment correlation* approach (rGE), on the other hand, assumes that parents pass on both gene and environment to their children and it is more difficult to separate these two effects as the correlations are not all passive. In fact, Plomin, DeFries, and Loehlin (1977) differentiated among 'passive', 'active', and 'evocative' rGE. The term 'passive' rGE refers to the fact that the genetic influences on individual differences in environmental risk exposure are independent of actions of the individual child. 'Active' and 'evocative' rGE are different in that they concern the child's genes. An 'active' rGE occurs when genetic effects influence the selection or shape of non-shared environmental experiences (e.g. a child with ADHD might be drawn to risk-taking peers, whose influence then leads to further risk-taking or impulsive behaviours). Finally, an 'evocative' rGE occurs when a child evokes a particular response from the shared-environment. For instance, evocative rGE approach might explain why there is more negative parenting towards the child with ADHD (Gardner, 1994). If children with ADHD are less compliant and responsive to their parents compared to controls, then that could elicit more negative responses from caregivers. Interestingly, when children with ADHD are on medication, parents show more positive parenting as they provide more praise, more warmth, and less hostility and criticism (Danforth, Barkley, & Stokes, 1991).

Recent research on ADHD has been focused on the investigation of gene-environment interplay, and how this can influence the heritability estimates. As mentioned previously in this chapter, heritability *main* effects have been suggested to account for 76% of the variance of the disorder (Faraone et al., 2005), although this can be influenced by rater bias and measurement tools. Moreover, Nigg (2006) reported that shared environmental *main* effects for ADHD are small and non-shared environmental *main* effects account for approximately 20% of variance in ADHD symptoms. Longitudinal twin studies not only can disentangle the genetic, shared and non-shared environmental effects on the liability in ADHD, but they can also shed some light on whether these effects change as individuals move from childhood to adolescence.

Three big longitudinal twin studies that explored the genetic, shared and non-shared environmental effects, have reported that ADHD symptoms show moderately stability across development, which was mainly due to shared genetic effects that accounted for 70-90% of the variance (Kuntsi et al., 2005b; Larsson et al., 2004; Rietveld et al., 2003). Rietveld and colleagues (2003) argued that some of the genes operating at

one age of development do so at a later age, but that the gene overlap was not complete, indicating that some genes might have an effect at later life, whereas they were 'inactive' during childhood. Therefore, the question is why do some genes get 'activated' at specific periods of development. The answer could come from the gene-environment interplay studies. Taking into consideration that the individual genotype is relatively stable across life span (with some genes been activated and some others not), and environmental inputs change during development, this could suggest that new genetic effects are getting 'activated' later on in life due to the environmental effects. Larsson and colleagues (2004) found a decline in shared environmental effects and an increase of non-shared environmental effects from childhood to early adolescence, which reflects a true developmental change in the behaviour, perhaps because of less influence from parenting (also reported by Kuntsi et al., 2005). Moreover, they found that genetic effects also increase from childhood to adolescence in boys with ADHD. Therefore, these environmental changes could be the reason why new genetic effects are triggered.

To date there have been few published studies examining G x E in ADHD using molecular genetics. For instance, a recent study found that association between a DAT1 halpotype and ADHD was stronger when the mother had drunk alcohol during pregnancy (Brookes et al., 2006). Another research group suggested that the DAT1 risk allele previously found to be associated with ADHD was associated with hyperactive-impulsive symptoms only in those who had been exposed to maternal smoking during pregnancy (Kahn, Khoury, Nichols, & Lanphear, 2003). Neuman and colleagues (2007) argued that prenatal exposure to smoking was associated with DAT1 440 allele (OR = 2.9) and DRD4 7-repeat allele (OR = 2.8) in children with ADHD combined type. While these studies focused on single environmental risks, in a recent study (Laucht et al., 2007) a composite measure of family adversity was used as a potential moderator of genetic risk. Laucht and colleagues (2007) found that family adversity moderate the impact of the DAT1 gene on the development of ADHD symptoms, as only individuals exposed to psychosocial adversity had a DAT1 effect. Finally, children with ADHD and CD who carried the COMT gene risk variant appeared to be more susceptible to the adverse effects of LBW (Thapar et al., 2005). Although these findings require replication, the evidence so far suggests that some genes may influence the origins and developmental course of ADHD by affecting individual sensitivity to environmental adversity.

2.5. Strategies for partitioning causal heterogeneity of ADHD

As reviewed in previous sections of this chapter, there is evidence that different mixes of the multiple genetic and environmental factors (i.e. different genes and environmental risks) can cause ADHD in different individuals, which in turn would cause different profiles at the clinical phenotypic level (as reviewed in Chapter 1). For instance, specific genes might be more susceptible to specific environmental risks, which would form a specific pathway leading to ADHD. Since there are multiple genetic and environmental factors, there is a possibility that there might be several combinations that would create different pathways to ADHD phenotype and these would be operative in different individuals (i.e. heterogeneity). This heterogeneity represents a significant barrier to the study of aetiology in ADHD. Progress in this area will depend of the successful development of strategies for partitioning this variance.

If we are to successfully identify causal factors it therefore becomes important to attempt to isolate more aetiologically homogeneous ADHD entities or subtypes. One way to partition this causal heterogeneity would be to isolate clinical subtypes based on symptom structure, comorbidity and developmental course of the disorder and see if subgroups based on these characteristics were associated with a specific GxE interaction. For instance, Neuman et al. (2007) argued that smoking during pregnancy is associated with specific subtypes of ADHD in genetically susceptible children. Specifically, they found that the odds of a diagnosis of DSM-IV combined subtype was 2.9 times greater in twins who had inherited the DAT1 440 allele and who were exposed to prenatal smoking, than in unexposed twins without the risk allele. The OR was 2.6 in the population-defined subtype. In addition, odds ratios for the DRD4 seven-repeat allele were 3.0 (2.8) in the population-defined (DSM-IV) combined ADHD subtypes. In another study, Seeger, Schloss, Schmidt, Ruter-Jungfleisch, and Henn (2004) investigated a possible relationship between the DRD4 7R allele and HKD and CD in association with the season of birth. They found an interaction between the seasons of birth and the expression of the DRD4 candidate gene in children with HKD and CD as well as in controls, which differ significantly from each other. Depending on the season of birth, children carrying the DRD4 7R allele showed different relative risks for developing HKD and CD. Finally, children with ADHD and CD who carried the COMT gene risk variant appeared to be more susceptible to the adverse effects of LBW (Thapar et al., 2005).

An alternative and increasingly popular approach to address the challenge of isolating more aetiologically homogeneous ADHD entities is to identify endophenotypes; a process or structure that plays a causal role in mediating the path between the genotype and the phenotype of a disorder (e.g. Alsamy and Blangero, 2001; Gottesman and Gould, 2003).

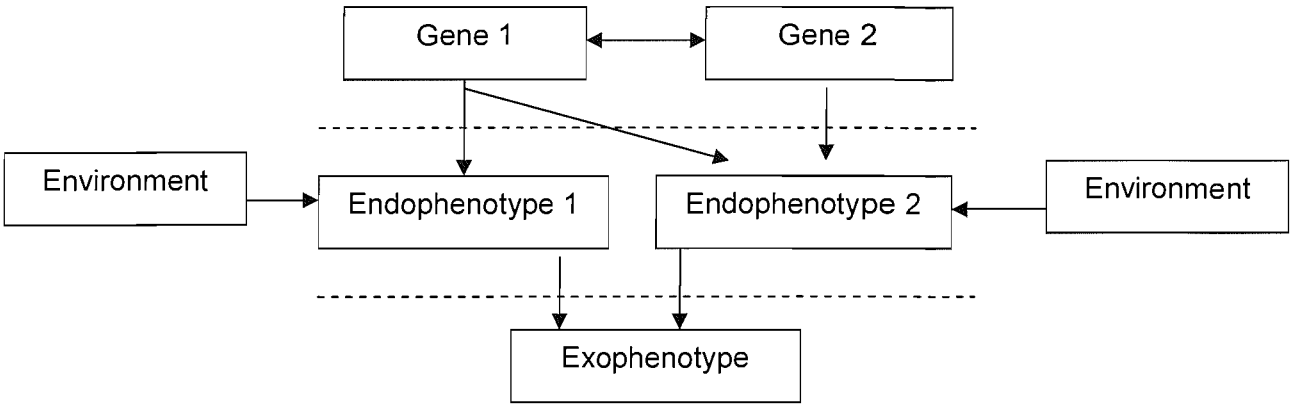


Figure 2.1: Schematic representation of the role of endophenotypes on a complex psychiatric disorder (adapted from Morton & Frith, 1995).

Figure 2.1 gives a schematic representation of the role of endophenotypes as a mediating path between the genetic aetiology of a complex disorder and its clinical exophenotype. One or more genes, which are associated with the disorder, influence the internal mechanisms (i.e. endophenotypes) associated with the disorder. These internal mechanisms can be biochemical, endocrinological, neuroanatomical, neurophysiological, or neuropsychological in nature (Leboyer et al., 1998). Endophenotypes are assumed to have simpler genetic underpinnings than disorder themselves, and therefore, it should be easier to identify genes associated with endophenotypes than genes associated with their correlated disorders (e.g. Alsamy & Blangero, 2001; Gottesman & Gould, 2003). The endophenotype, in turn, influences the expression of the outcome of the disorder, hence its clinical phenotype. Moreover, environmental factors, such as school and family, can affect the expression of endophenotypes.

Various criteria have been proposed for useful endophenotypes in psychiatry (e.g. Almasy & Blangero, 2001; Bearden & Freimer, 2006; Coghill, Nigg, Rothenberger, Sonuga-Barke, & Tannock, 2005; Gottesman & Gould, 2003) but most of them share

several key elements. Specifically, Doyle and her colleagues (2005c) have summarized these criteria into the following:

1. Endophenotypes should be associated with the disorder. They are not necessary to be universal as the underlying disorder might be heterogeneous.
2. Endophenotypic measures should have good psychometric properties.
3. The endophenotype should show evidence of heritability.
4. It should also show familial-genetic overlap (i.e. familial co-segregation) with the disorder. More specifically, the endophenotype should appear in individuals who carry genes for a condition but do not express the disorder itself, that is, the unaffected relatives of diagnosed individuals.

The concept of an endophenotype has been widely used the last few years in order to explain the causal interaction of genotype and phenotype in several complex neuropsychiatric disorders. In schizophrenia, for instance, the search for candidate endophenotypes has been very productive. Neuropsychological findings suggest that schizophrenic patients have deficits in sensory motor gating, that is to filter information from multiple sources (Braff, Geyer, & Swerdlow, 2001), and in eye tracking (Calkins & Iacono, 2000). One of the strongest endophenotypes of schizophrenia is working memory. Gasperoni and colleagues (2003) have found that poor visual working memory performance was highly significantly linked with to chromosomal region 1q21, a region previously suggested to be associated with schizophrenia (e.g. Millar et al., 2000). The fact that previous linkage studies have identified an association between schizophrenia and 1q41 and that poor working memory performance of patients with schizophrenia is also linked to this region, strengthens the claim that this endophenotype may be relevant to the pathophysiology of schizophrenia.

Interest in the role of endophenotypes has recently grown in ADHD as researchers have realised the implications of causal heterogeneity for 'gene-hunting' in relation to ADHD (Castellanos & Tannock, 2002; Coghill et al., 2005; Nigg, Blaskey, Stawicki, & Sachek, 2004a; Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005). However, current findings do not as yet allow one to identify endophenotypes that meet all the criteria listed above. In large part this has to do with the fact that there has been little study of the familiality and heritability of potential endophenotypic characteristics. However, the search for endophenotypes is being pursued by many groups because of the possible advantage they give in the search for genes for complex and multiple

determined conditions. Endophenotypes are less genetically complex than the disorder it underlies because they are more proximal to the disorder's biological aetiology (i.e. genes) and because they have the potential to target one of likely several pathophysiological deficits that could lead to the disorder (Doyle et al., 2005c).

2.6. Summary

Molecular genetic studies have identified several candidate genes independently associated with ADHD. However, all these genes seem to have a small OR, which suggests that there are several aetiological pathways that might lead to ADHD. Moreover, environmental effects also contribute to the disorder. These environmental risks can be found either during the prenatal and perinatal period, or during childhood and adolescence. As with the genetic effects, environmental risk factors seem to have small effect in accounting for ADHD expression. Recent evidence indicates that genetic and environmental factors can interact to increase the risk of the expression of ADHD symptomatology. ADHD is clearly a complex and causally heterogeneous disorder. The search of candidate endophenotypes could enable us to partition causal heterogeneity, and identify more homogeneous pathways leading to ADHD. In the following chapter the importance of the search for endophenotypes at the neuropsychological level in identifying more homogeneous pathways to ADHD will be discussed, and candidate neuropsychological causal models will be introduced.

CHAPTER THREE: Neuropsychological models of ADHD: Focusing on the role of Executive Dysfunction and Delay-Related Motivational processes

3.1. Introduction

ADHD has been characterised as a clinically and genetically heterogeneous disorder. One way of partitioning the causal complexity of psychiatric disorders is using endophenotypes (see Chapter 2 for more details). Endophenotypes are influenced by fewer genetic and environmental risk factors than the disorder as a whole, and their use would result, theoretically, in greater statistical power to detect the effects of the individual genes (Doyle et al., 2005c). Endophenotypes can be neuroanatomical, neurochemical, neurophysiological or neuropsychological in nature (Leboyer et al., 1998).

In the current thesis we will investigate the neuropsychological function of ADHD as there are practical benefits to operating at this level. Neuropsychological tests are cheap, easy to implement, highly transportable from lab to lab and easy to analyse compared with tests of more basic biological processes and/or brain structure and function. However, as it will be reviewed, ADHD is characterized by neuropsychological heterogeneity. Several neuropsychological models have been proposed for ADHD. However, none of these causal models can fully explain the aetiology of the disorder. In fact, there is a theoretical and empirical shift away from searching for a core neuropsychological deficit of ADHD, and a focus on identifying multiple causal pathways, as these are more likely to provide a more unitary aetiology of the disorder (Sonuga-Barke, Sergeant, Nigg, & Willcutt, 2007).

In this chapter we compare a number of different neuropsychological models, and specifically Executive Function (EF) and Delay Aversion (DAV). Our initial selection of neuropsychological markers to review is driven by currently available causal models of ADHD – giving them theoretical plausibility.

3.2. Causal models of ADHD

While the majority of ADHD studies have been correlational, researchers have often inferred cause. This assumption has recently been explicated in attempts to develop and test causal models of ADHD (Coghill et al., 2005; Sonuga-Barke, 2005). A complete causal model for ADHD will require integration of genetic, neural, cognitive

and behavioural mechanisms to describe complete causal chains occurring in development (Morton & Frith, 1995). For instance, several genes have been associated with the overall ADHD diagnosis, although a smaller number of genes have been associated with ADHD-related neuropsychological dysfunction (Doyle et al., 2005b). This is because the neuropsychological dysfunctions of ADHD (and of any other psychiatric disorders) are mediators of the complex genotype-phenotype pathway of the disorder. Therefore, the use of neuropsychological markers, as mediating factors in the causal chain leading to the disorder, would result in greater statistical power to detect the effects of individual genes (Doyle et al., 2005b).

Given the wide range of possible causal models, which could be reviewed, our treatment is necessarily selective. We acknowledge but do not have space to review models such as reward sensitivity (Tripp & Alsop, 1999; 2001), working memory deficit (Pennington & Ozonoff, 1996), attention deficit (Posner & Peterson, 1990), optimal stimulation (Zelazo, Muller, Frye, & Marcovitch, 2003) and default mode interference (Sonuga-Barke & Castellanos, 2007). However, state regulation (Sergeant, 2005) and temporal processing (Castellanos & Tannock, 2002) causal models have attracted increased attention as potential neuropsychological markers of ADHD and they will be briefly reviewed. Finally, as is the focus of the current thesis, we will present an extensive review of perhaps the two most studied neuropsychological markers of ADHD: Executive Function (EF) and delay-related motivational processing.

3.2.1. State regulation

According to the state regulation deficit model of ADHD, which was first proposed by Douglas and Parry (1983) and developed by Sergeant (2000) and van der Meer (1996), the ability to regulate activation-state, to maintain effort and remain aroused/alerted over time is particularly likely to be impaired in ADHD. Sergeant (2005) suggested that an underlying neural substrate for state regulation involves the basal ganglia, particularly the corpus striatum, hippocampus, amygdala, and dysfunction of the noradrenergic system.

Directly investigating the energetic state is quite complicated and difficult to disentangle from other neuropsychological processes. Most empirical evidence on state regulation derives from reaction performance tasks. Children with ADHD generally perform more poorly in tasks involving very slow or very fast event rates

(Sonuga-Barke, 2002b), which the state regulation theory would predict as the children become under-aroused and over-aroused respectively. Physiological studies also suggest that the heart rate of children with ADHD before the onset of stimuli (an index of motor preparation) is less pronounced compared to controls, indicating less effort in engaging to the task (Börger & van der Meere, 2000).

The finding of response variability in ADHD could also be perceived as additional support to the state regulation deficit model. If children with ADHD experience low levels of arousal and effort, then they would be less willing to engage to a task, especially if the task is cognitively demanding or non-stimulating. Hyperactive individuals have been reported to be more variable than control participants in their speed and be generally slow and inaccurate in responding (Klein, Wendling, Huettner, Ruder, & Peper, 2006; Kuntsi, Oosterlaan, & Stevenson, 2001a; Oosterlaan et al., 1998), especially under slow conditions (Andreou et al., 2007). However, there are other studies where no such differences were reported (e.g. Saldana & Neuringer, 1998), or where children with ADHD show a continued variable response irrespective of slow or fast conditions (Raymeakers, Antrop, van der Meer, Wiersema, & Roeyers, 2007).

The study of the heritability, genetic liability, and familiality of this model is still in its infancy. One study has provided evidence of moderate heritability estimates (68%) of reaction time performance (Swan & Cannelli, 2002). Moreover, a genetic study has shown that DRD4 is associated with slow and variable responses in individuals with ADHD without the 7-repeat allele (Swanson et al., 2000). Finally, two family studies (Nigg et al.,. 2004; Waldman et al., 2006) and one twin study (Kuntsi & Stevenson, 2001) have shown that state regulation can be co-segregated within families. Nigg and colleagues (2004) assessed the variability of reaction time (RT) on EF measures and they found that mothers of children with ADHD were impaired on RT variability. In addition, unaffected siblings of ADHD probands have been found to be intermediate between the ADHD probands and control children on their RT variability at the Stop Signal task (Waldman et al., 2006). Finally, Kuntsi and Stevenson (2001) found a statistically significant genetic overlap between extreme hyperactivity and RT variability ($h^2_g = .64$).

3.2.2. Temporal processing

Two mechanisms are involved in human temporal information processing: a sensory

mechanism for processing durations in the range of milliseconds and a cognitively controlled mechanism for processing durations in the range of seconds (Rammsayer & Ulrich, 2005). Ivry (1996) has suggested that processing short intervals (milliseconds) may be more related to an internal timing mechanism or cerebellar processes, while longer intervals (seconds) may be more related to working memory processes and prefrontal cortex.

Temporal processing skills can be divided into two categories: a) time perception; an ability to estimate, anticipate and reproduce time and b) motor timing; an ability to synchronize motor response to visual or auditory stimulation. Evidence suggests that children with ADHD have difficulties in co-ordinating their motor response (Ben-Pazi, Gross-Tsur, Bergman, & Shaley, 2003; Pitcher, Piek, & Barratt, 2002; Rubia, Taylor, Taylor, & Sergeant, 1999b; Rubia et al., 2001; Rubia, Noorloos, Smith, Gunning, & Sergerant, 2003; Slaats-Willemse, de Sonneville, Swaab-Barneveld, & Buitelaar, 2005) and in processing and estimating time (Barkley, Koplowitz, Anderson, & McMurray, 1997; Barkley, Murphy, & Bush, 2001b; Rommelse, Oosterlaan, Buitelaar, Faraone, & Sergeant, 2007; Rubia et al., 2003; Smith, Taylor, Rogers, Newman, & Rubia, 2002; Toplak, Rucklidge, Hetherington, John, & Tannock, 2003). These deficits have been found in the range of both seconds and milliseconds. Moreover, intra-individual variability in temporal processing has been found to be increased in children with ADHD compared to control children (Mullins, Bellgrove, Gill, & Robertson, 2005; Rubia et al., 1999b, 2003; Toplak et al., 2003).

No evidence so far exists for the heritability and genetic liability of temporal processing in ADHD. On the other hand, only two family studies have examined whether time perception and motor timing are co-segregated within ADHD families. In the first, children with ADHD and their unaffected siblings were less precise than controls on time perception tasks (Rommelse et al., 2007). In the second study, Slaats-Willemse and colleagues (2005) investigated the familiality of motor timing and specifically motor fluency and flexibility. Results showed that unaffected siblings of ADHD probands had problems with motor movements that required higher-order cognitive processing (i.e. motor flexibility) and the authors argued that only motor flexibility (and not motor fluency) could be familial.

3.3. ADHD as an executive dysfunction disorder

3.3.1. The model

Executive Function (EF) has been perceived as the most dominant model of ADHD (e.g. Pennington & Ozonoff, 1996), and a great amount of research has been focused on this neuropsychological function. EF has been perceived as a system that is involved in the deliberate or goal-oriented control of behaviour (Nigg, 2006).

Several theories of EF exist. Norman and Shallice (1986) posit a supervisory attention system that presumably incorporates multiple operations. Pennington (1997) provide a heuristic framework that includes working memory, inference control, set shifting, response inhibition, and planning. Zelazo and colleagues (2003) emphasize a problem-solving model in which the key operations are problem representation followed by execution and evaluation. Fuster (1997) has argued that the hallmark of EF is the temporal organization of complex behaviour, emphasizing working memory, set shifting and inhibitory control components. Sonuga-Barke (2005) has also highlighted the environmental factors in the development of EF deficits, such as negative feedback from adults and limited exposure to executive related tasks.

EF is implicated in many disorders and children with ADHD have been found to be impaired in several EF domains, such as working memory, planning and set-shifting (Pennington & Ozonoff, 1996). However, it has been suggested that the primary deficit of ADHD is inhibitory control (IC; Barkley, 1997; Quay, 1997; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Children with ADHD have been found to have an inability to inhibit ongoing, inappropriate responses. Specifically, in his influential theory of ADHD, Barkley (1997) suggested that behavioural inhibition (i.e. inhibitory control) is related to three processes: inhibition of prepotent response, inhibition of an ongoing response, and interference control (Figure 3.1). Behavioural inhibition can directly influence the motor system. According to Barkley (1997) behavioural inhibition deficit creates disturbances in four neuropsychological functions: working memory, self-regulation of affect/motivation/arousal, internalization of speech, and reconstitution. Importantly, Barkley (1997) has argued that response inhibition deficits are unique to ADHD, a suggestion that was contradicted by Oosterlaan and his colleagues (1998), who they found that both children with ADHD and CD showed flatter inhibition functions. Moreover, children with HKD with comorbid conduct

problems differed most from typical children on event-related potentials (ERP) measures of response inhibition than children with only HKD (Banaschewski et al., 2004).

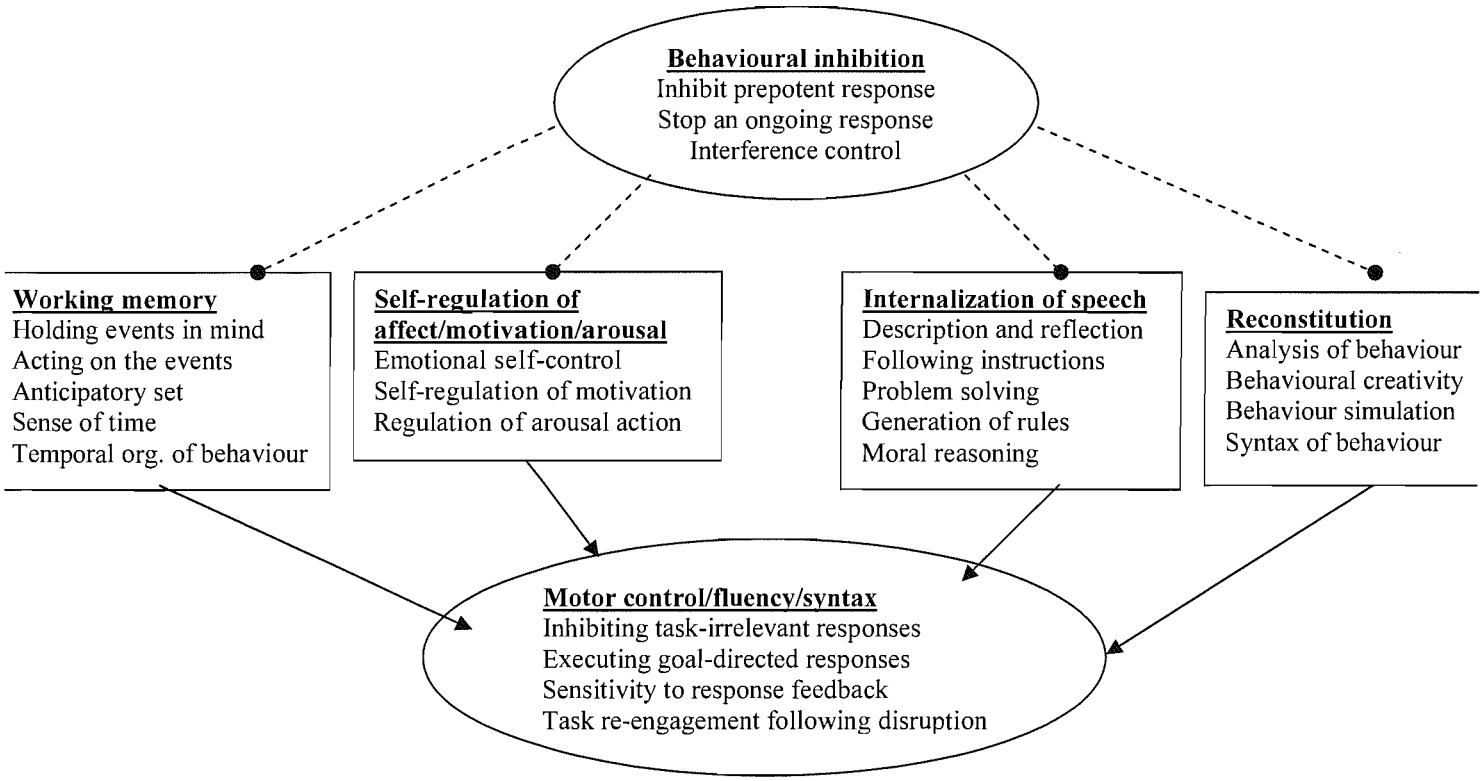


Figure 3.1.: Schematic representation of a conceptual model of behavioural inhibition (cited by Barkley, 1997).

3.3.2. The evidence: Is ADHD an EF disorder?

Although several EF domains are impaired in children with ADHD, such as "set-shifting, set maintenance, interference control, inhibition, integration across space and time, planning and working memory" (Pennington & Ozonoff, 1996; pp. 55), Barkley's (1997) EF model makes strong claims about the role of inhibitory control as a pathophysiological core of ADHD. We will address this by examining data at four levels; neuropsychological, neuro-anatomical including structural neuroanatomy, neuro-chemical and genetic.

3.3.2.1. Neuropsychology

Although inhibitory control is not unique to ADHD (Banaschewski et al., 2004; Oosterlaan et al., 1998; Sergeant et al., 2002), several studies have reported the

significant role of inhibitory control in ADHD. These studies have been subject to systematic review (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). 83 studies that administered response inhibition, working memory, planning, vigilance and set shifting/task switching measures (all of them being constructs of EF; 13 tasks in total) to groups with ADHD and without ADHD have been included in the most recent meta-analytic review (Willcutt et al., 2005). Significant differences were found between groups with and without ADHD on all 13 EF tasks. However, the most consistent results of this meta-analysis were obtained for inhibitory control (IC) and spatial working memory tasks (see Table 3.1). Moreover, the weighted mean effect size across all comparisons was .54 and IC measures had moderate weighted mean effect size (Table 3.1). Other meta-analytic studies have also supported significant differences between children with ADHD and controls on IC measures (Lijffijt, Kenemans, Verbaten, & van Engeland, 2005; Oosterlaan et al., 1998; Sergeant et al., 2002). However, inhibitory deficit has also been found in other clinical groups such as ODD and CD (Oosterlaan et al., 1998; Sergeant, Geurts, & Oosterlaan, 2002), indicating that response inhibition is not specific to ADHD.

Although fewer studies have examined the relationship between ADHD and working memory (WM), initial results are promising. According to Willcutt et al.'s (2005) meta-analysis (see Table 3.1), significant group differences were reported by 55% of the 11 studies that included one of the verbal working memory tasks (d = .55), and 75% of the 8 studies that included one of the spatial working memory tasks (d = .63). In a more detailed working memory meta-analysis, Martinussen, Hayden, Hogg-Johnson, and Tannock (2005) found that children with ADHD exhibited deficits in multiple components of WM that were independent of learning difficulties and IQ. Moreover, they found greater effect sizes for spatial working memory (spatial storage, d = .85; spatial central executive WM, d = 1.06) than for verbal working memory (verbal storage, d = .47; verbal central executive WM, d = .43).

Table 3.1.: Weighted mean effect sizes of EF measures (cited by Willcutt et al., 2005)

Task Name	*EF construct*	*Effect size (d)*	*% of studies that found sign. group differences*
SSRT	Response Inhibition	.61	82
CPT commission errors	Response Inhibition	.51	61
CPT omission errors	Vigilance	.64	77
WCST perseverative errors	Set-shifting	.46	46
Trailmaking Test Part B	Set-shifting	.55	57
Tower of Hanoi	Planning	.69	57
Tower of London	Planning	.51	50
Porteus Mazes	Planning	.58	80
ROCFT	Planning	.43	56
WM Sentence Span & DB	Verbal working memory	.55	55
Self-ordered pointing & CANTAB SWM	Spatial working memory	.63	75

Note: CPT = Continuous Performance Test; DB = Digit Backward; ROCFT = Rey-Osterreith Complex Figure Test; SSRT = Stop Signal Reaction Time; SWM = Spatial Working Memory; WCST = Wisconsin Card Sorting Test; WM = Working Memory

Finally, in Willcutt et al. (2005) meta-analysis, Wisconsin Card Sorting Test (WCST) perseverative errors were more weakly related to ADHD than many of the other EF tasks and the mean effect size was among the lowest of all the tasks (d = .46). This pattern of results is similar to the findings of recent meta-analyses of interference control – an IC domain (mean d =.35; van Mourik, Oosterlaan, & Sergeant, 2005) and covert visuospatial attention (Huang-Pollock & Nigg, 2003). These small effects and inconsistent results suggest that weaknesses in set-shifting, Stroop interference control, and visuospatial orienting of attention are poor candidates for a primary neuropsychological deficit in ADHD. Moreover, Sergeant and his colleagues (2002) found that interference control is significantly deficient in children with ADHD, but also in other clinical groups such as ODD and CD.

EF deficits have been evident across the age range (for reviews see Faraone et al., 2001; Woods, Lovejoy, & Ball, 2002). Most of the cognitive deficits that appear in childhood have also been described in adults with ADHD, indicating that these deficits persist until adulthood. However, some deficits might be more pronounced before adolescence, such as response disinhibition and spatial working memory deficit (Drechsler, Brandeis, Földényi, Imhof, & Steinhausen, 2005; Martinussen et al., 2005; Nichelli, Scala, Vago, Riva, & Bulgheroni, 2005). On the other hand, a meta-analysis study of neuropsychological performance in adult ADHD (Schoechlin & Engel, 2005) indicated that only complex attention variables and verbal working memory discriminated best between adult ADHD patients and controls. In summary, this indicates that ADHD might change form of expression into adulthood.

3.3.2.2. Brain structure and function

At a neurobiological level, EF is underpinned by higher order executive control circuits of the brain (fronto-dorsal-striatal brain circuit connecting pre-frontal striatal and thalamic regions). As shown in Figure 3.2, this executive circuit involves glutamatergic excitatory pathways from the prefrontal cortex (Aron, Robbins, & Poldrack, 2004) to the dorsal portion of the neostriatum and specifically the caudate nucleus (Eagle & Robbins, 2003). Reciprocal pathways pass via inhibitory connections through the basal ganglia to the dorsomedial thalamus with excitatory glutaminergic cells connecting back to the prefrontal cortex (Heyder, Suchan, & Daum, 2004). Dopamine and norepinephrine that are implicated in ADHD on the basis of pharmacologic and genetic studies (Levy & Swanson, 2001) are key neuromodulators of this circuit (Nieoullon & Coquerel, 2003).

Middleton and Strick (2001) have demonstrated cerebellar-cortical-basal ganglia connections that provide an anatomical substrate for a cerebellar-prefrontal circuit in the pathophysiology of ADHD, which detects disparities between expected and observed outcomes (Nigg, 2006). Working memory functions have also been found to be associated with the cerebellum (Gottwald, Mihajlovic, Wilde, & Mehdorn, 2003; Lalonde & Strazielle, 2003). However, further research is required to identify the role of cerebellar-prefrontal circuit on EF deficits.

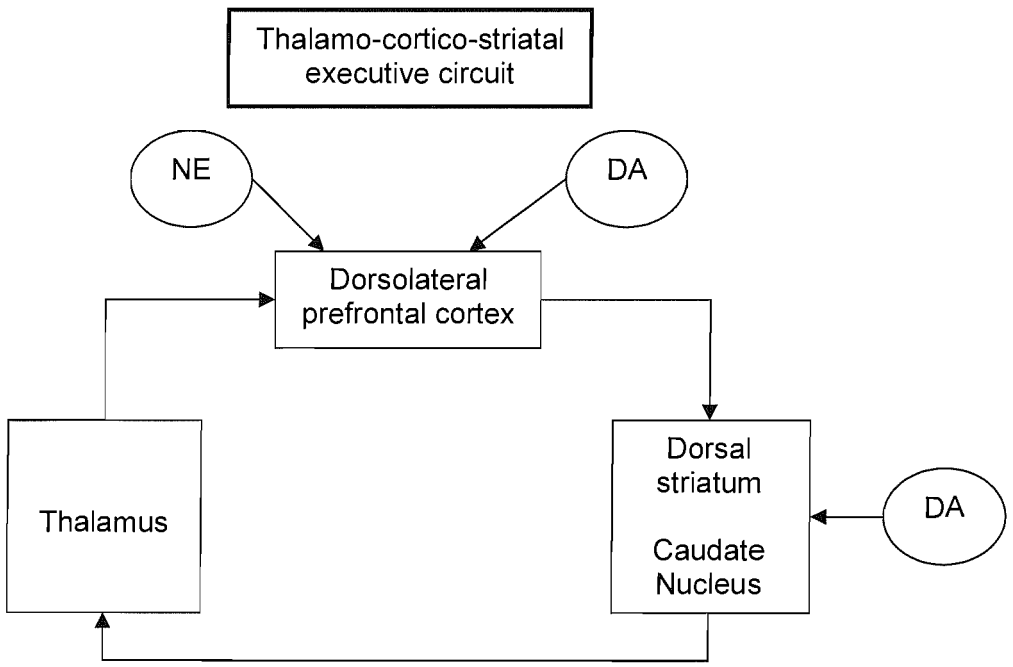


Figure 3.2.: Schematic representation of a simplified account of the neurobiological function of the EF model (Sonuga-Barke, 2005). DA = dopamine; NE = norepinephrine.

Structural and functional Magnetic Resonance Imaging (MRI) studies have shown an association of dorsolateral prefrontal cortex (DLPFC) and caudate nucleus and IC in ADHD (e.g. Casey, Thomas, Davidson, Kunz, & Franzen, 2002; Castellanos et al., 2002; Rubia et al., 1999a; Seidman, Valera, & Makris, 2005a). Several studies of children with ADHD have identified smaller prefrontal volumes in areas corresponding to the DLPFC (Castellanos et al., 1996; 2001; 2002; Durston et al., 2004; Filipek et al., 1997; Hill et al., 2003; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopoulos, 1990; Kates et al., 2002; Mostofsky, Cooper, Kates, Denckla, & Kaufmann, 2002). Recently in an fMRI study, Rubia and her colleagues (1999a) found that adolescents with ADHD showed smaller responses in the right inferior prefrontal cortex and left caudate during a response inhibition task. Furthermore, it has been suggested that interference control tasks activate the anterior cingulate cortex (Cabeza & Nyberg, 1997), and response inhibition tasks activate the inferior regions of DLPFC (Baddeley & Hitch, 1994; Konishi et al., 1999; Vaidya et al., 1998). In addition, findings of Vaidya et al (1998), Rubia et al (1999a), and Casey et al., (1997) suggested that striatal abnormalities and specifically lower left caudate activity might play a role in ADHD and response inhibition. While most of the structural MRI studies to date have reported decreased caudate volumes and reversed asymmetry in comparison to controls, the laterality of these differences and direction of asymmetry have been inconsistent across studies. Castellanos and colleagues (1996) and Casey and colleagues (1997) found a smaller caudate nucleus on the right side. The laterality of caudate nucleus abnormality has also been found on the left side of the brain in other studies (Castellanos et al., 2001; Filipek et al, 1997). Finally, a structural MRI study with neuropsychological measurements also indicated that children with ADHD, who performed worse on EF, also had smaller right sided basal ganglia (Casey et al., 1997).

Another body of literature has documented an association between ADHD and electrophysiological measures (i.e. event-related potentials - ERPs and electroencephalographic measures - EEG). EEG measures, which assess the wavelike background electrical activity in the brain, suggest that ADHD subjects exhibit greater slow-wave (delta and theta) activity as well as reduced alpha and beta waves, compared to control subjects (e.g. Clarke et al., 2007; Hobbs, Clarke, Barry, McCarthy, & Selikowitz, 2007). These results suggest hypoarousal in areas including frontal regions, which are associated with IC. Moreover, ERP research has been focused on the negative 200 (N2) and the positive 300 (P3) components to

investigate IC deficits in ADHD. IC deficits, as reflected by reduced No-go P3, are found in children with ADHD (Brandeis, van Leeuwen, Steger, Imhof, & Steinhausen, 2002; Fallgatter et al., 2004; Rubia, Oosterlaan, Sergeant, Brandeis, & van Leeuwen, 1998). Most ERP studies have found that children with ADHD have an enlarged N2 component in No-go compared to Go trials during Go-No-Go tasks (Banaschewski et al., 2004; Fallgatter et al., 2004; Overtoom et al., 1998, 2002; Wiersema et al., 2006). Interestingly, this enlargement has specifically been associated with inhibition (Falkenstein, Hoormann, & Hohnsbein, 1999; Jodo & Kayama, 1992; Sasaki et al., 1996; Schroger, 1993). Similarly, inhibitory deficits are seen in children with ADHD during the Stop task, as their reduced activity to Go-signals precedes an attenuated right frontal N2-activity to Stop-signals (Albrecht, Banaschewski, Brandeu, Heinrich, & Rothenberger, 2005; Brandeis et al., 1998; Pliszka, Liotti, & Woldorff, 2000).

In summary, data from structural and functional neuroimaging studies as well as EEG and ERP studies support the hypothesis that deficits in inhibitory based executive functions in ADHD are associated with disturbances in this circuit (Aman, Roberts, & Pennington, 1998; Booth et al., 2003; Brandeis et al., 1998; Durston et al., 2003; Fallgatter et al., 2004; Kondo, Morishita, Osaka, & Osaka, 2004; Konishi et al., 1999; Markela-Lerenc, Kaiser, Fiedler, Mundt, & Weisbrod, 2004; Pliszka et al., 2000; Rubia et al., 1999a; Schulz et al., 2004; Sullivan & Brake, 2003; Zang et al., 2005).

3.3.2.3. Neurochemistry

Pharmacological studies provide evidence for the neurotransmitter systems involved in EF and specifically IC deficit. As already mentioned, IC deficit is associated with dysfunction in the prefrontal cortex. This cortical area is very sensitive to levels of catecholamines (Figure 3.2), involving the dopamine (DA) and norepinephrine (NE) neurotransmitter systems (Pliszka, 2005; Pliszka, McCracken, and Maas, 1996). Berridge et al. (2006) have now shown that low doses of stimulant medication methylphenidate, produce marked increases in norepinephrine and dopamine release in the prefrontal cortex (PFC), whereas having only subtle effects on subcortical catecholamine release. This has been also supported by Arnsten and Dudley (2005), who found that moderate levels of stimulant drugs engage postsynaptic alpha2A-adrenoceptors and D1 receptors and improve prefrontal regulation of behavior and attention, while high levels impair prefrontal function via alpha1-adrenoceptors and excessive D1 receptor stimulation.

In animal studies, low doses of DA agonists have been found to improve working memory and attention regulation (Cai & Arnsten, 1997; Granon et al., 2000), while high levels of DA release (e.g. during stress exposure) impair PFC function (Murphy, Arnsten, Goldman-Rakic, & Roth, 1996). In humans, it is now known that low doses of stimulants focus attention and improve EF in ADHD subjects (Langleben et al., 2006), irrespective of subtype (O'Driscoll et al., 2005). Therefore, there is evidence that the catecholamine system is associated with EF. However, although all EF domains (e.g. working memory, inhibition, planning, and set shifting) are improving with stimulant medication, only inhibition is not reaching 'normal' levels of functioning (Shuai, Yang, Cao, & Wang, 2007; Qian, Cao, & Wang, 2007). In summary, both dopaminergic and noradrenergic systems have been associated with EF deficits in ADHD. Although limited research suggests that the serotonergic system is not associated with response disinhibition (Chamberlain et al., 2006), further investigation is required in identifying the role of alternative neurotransmitter systems on ADHD-related IC deficit.

3.3.2.4. Is EF deficit in ADHD heritable, genetic, and familial?

Given the high heritability of ADHD and the growing evidence for the specific links to particular genes and their interaction with the environment, an important criterion for the validity of any causal model of ADHD is whether it shows familiality, heritability and links to specific genes (Doyle et al., 2005c). If EF deficit is marked by specific genes and is inherited through generations, then EF could be part of the causal model chain. Moreover, unaffected relatives (i.e. siblings or parents of ADHD probands) share between 25-50% of their genes with ADHD probands. If the neuropsychological deficits of the disorder have specific genetic markers, then unaffected relatives will possibly carry genes associated with the condition, although they would carry fewer genes than individuals with the full disorder. Therefore, one would expect that unaffected relatives will also show neuropsychological deficits but to a lesser degree than that of ADHD probands.

Heritability: Very few twin studies exist so far that have examined the heritability of EF deficit in ADHD. According to these studies the intraclass correlation between MZ twins is higher than for DZ twins for most measures (for review see Doyle et al., 2005b). Heritabilities range from zero to 88% for EF measures, with the majority of studies showing at least some genetic influence (Doyle et al., .2005c). Specifically, only one study has provided heritability data on response inhibition ($h^2 = .88$), set shifting heritability ranged from 0 to .56, working memory heritability ranged from .32

to .49, and only one study measured interference control heritability (h^2 = .50). However, most of these studies had a small sample size and limited number of measures was used, therefore the reported heritabilities should be interpreted with caution. A recent longitudinal twin study on EF has shown that for EF measures the heritability estimate accounted for around 50% of the variance at both age 5 and age 12 (Polderman et al., 2006). Finally, EF measures have lower heritability than ADHD, which may reflect methodological issues such as error variance, low reliability and violating assumptions of a normal distribution. However, EF measures may still be more useful for finding genes than the disorder itself. For example, if a smaller number of genes contribute to EF heritability of .5, then that would be more powerful than a bigger number of genes contributing to the overall ADHD diagnosis (Doyle et al., 2005b).

Heritability estimates have also been found for brain regions associated with EF deficits in ADHD. Two twin studies reported heritability of .5 - .9 for frontal regions (Carmelli, Swan, DeCarli, & Reed, 2002; Thompson, et al., 2001) and one twin study reported heritability estimates of .56 - .97 for subcortical and cortical volumes. Finally, a meta-analytic review of twin studies of electrophysiological measures indicated that genetic factors contribute significantly to both ERP and EEG measures (van Beijsterveldt & van Baal, 2002), with heritability of EEG alpha power and alpha peak frequency estimated to be .8 and ERP P3 amplitude and latency .6 and .5 respectively. These heritability estimates have also been replicated in a family study (Chorlian et al., 2007).

Genes: The small number of molecular genetic studies on ADHD and EF measures are generally inconclusive. Three studies (Langley et al., 2004; Manor et al., 2002; Swanson et al., 2000) suggest that the short alleles of DRD4 were associated with slow, variable, and impulsive response on response inhibition tasks, raising the possibility that both high and low levels of synaptic dopamine could be associated with neuropsychological deficits (Doyle et al., 2005c), although in a more recent study, no significant behavioural differences were found to be associated with DRD4 (Barkley et al., 2006). Moreover, Auerbach, Benjamin, Faroy, Geller, and Ebstein (2001) examined the relation between DRD4 and cognitive functions relevant to ADHD in healthy one-year-old infants. Those infants who had the DRD4-7 allele and were homozygous for the short allele of the serotonin transporter gene promoter (5-HTTLPR) showed lower sustained attention. Finally, a significant independent association has been found between the DAT1 10/10-repeat genotype and measures

of selective attention and response inhibition in a community sample of boys with high- and low-ADHD symptoms, after adjusting for age, IQ, and ADHD symptoms (Cornish et al., 2005). However, in the same study no association was found between DAT1 and any working memory components.

Several studies (e.g. Egan et al., 2001; Malhotra et al., 2002) have demonstrated an association between the COMT Val allele and increased perseverative errors on the WCST (a set-shifting construct of EF) in schizophrenic patients, with this genotype explaining 4.1% of the variance in this measure. Since several of the EF deficits found in schizophrenic patients are also apparent in children with ADHD, Taerk and colleagues (2004) investigated the relationship between a Val108/158 Met polymorphism of the COMT gene and EF performance (set-shifting, planning and spatial working memory) in these children. Results indicated that this polymorphism does not appear to modulate any of the three constructs of EFs in children with ADHD. Finally, measures of planning, set-shifting, response inhibition and interference control have shown association with ADRA2A, as well as moderation of its association with ADHD (Waldman et al., 2006).

Familiality: Whether EF deficits co-segregate within families can be investigated with twin, adoption and family studies. Two twin studies (Chhabildas, Willcutt, & Pennington, unpublished data, cited by Doyle et al., 2005b; Kuntsi and Stevenson, 2001) examined the bivariate heritability of hyperactivity and measures of EF. Kuntsi and Stevenson (2001) found that bivariate heritability estimates were relatively high for a measure of IC (i.e. commission errors; $h^2_g = .60$). However, these were not statistically significant due to high standard errors and the small sample size. In a twin study with a larger sample Chhabildas and colleagues (unpublished data; cited by Doyle et al., 2005b) found that bivariate heritability estimates of EF measures (i.e. response inhibition, working memory, vigilance, set-shifting, and processing speed) were somewhat lower than those obtained by Kuntsi and Stevenson (2001; $h^2_g = .20$-.38), but were significant for all neuropsychological measures with the exception of set-shifting measure. Although more twin studies are needed to investigate the bivariate heritability of EF deficit, evidence so far indicated that IC might co-segregate within families.

In family studies, EF deficits are expected to appear in unaffected relatives of ADHD probands, but to a lesser extent than in relatives affected with the disorder. So far, eight family studies have explored familial co-segregation of EF. Two of them have

failed to find neuropsychological deficits in parents of ADHD probands on measures of EF (Asarnow et al., 2002; Murphy & Barkley, 1996). However, these two studies did not distinguish between parents with or without the disorder. In the remaining six studies (Bidwell, Willcutt, DeFries, & Pennington, 2007; Doyle, Biederman, Seidman, Reske-Nielsen, & Faraone, 2005a; Nigg et al., 2004a; Schachar et al., 2005; Slaats-Willemse, Swaab-Barneveld, de Sonneville, van der Meulen, & Buitelaar, 2003; Waldman et al., 2006), where relatives were distinguished as affected or unaffected, unaffected relatives of ADHD probands showed subtle deficits in response inhibition and interference control measures compared to control children. However, in one study (Nigg et al., 2004a) these results were complicated by the fact that response inhibition deficits were only found in relatives of girls with ADHD, and response variability deficits were found in only mothers of probands with ADHD. Finally, in one study interference control was not found to distinguish unaffected siblings from their ADHD probands and control children (Waldman et al., 2006), although that was not supported in Doyle's et al. (2005a) study. In sum, family studies suggest that unaffected relatives have intermediate EF ability between ADHD probands and control groups. No adoption studies exist so far that directly examine EF deficit in biological and adopted relatives of ADHD probands (but see Alberts-Corush, Firestone, & Goodman, 1986; Nigg, Swanson, & Hinshaw, 1997 on familiality of attention and reaction time measures).

3.4. ADHD and delay-related motivational processes

3.4.1. The model

Another candidate causal model of ADHD is motivational dysfunction. Motivational processes that are delay-related, such as delay of gratification, delay aversion, and delay-related frustration, have been found to be impaired in children with ADHD (e.g. Douglas & Parry, 1994; Sagvolden, Aase, Zeiner, & Berger, 1998; Sonuga-Barke, Taylor, Sembi, & Smith, 1992; van der Meere, 1996).

Douglas and Parry (1983; 1994) first proposed that children with ADHD have an unusually strong need to seek immediate reward. This hypothesis was supported by studies where children with ADHD consistently chose small immediate rewards over larger delayed rewards (e.g. Rapport, Tucker, DuPaul, Merlo, & Stoner, 1986; Sonuga-Barke, Taylor, Sembi, & Smith, 1992). In fact, Douglas and Parry (1994) found that children with ADHD have such an unusually strong need for immediate

reward that they become abnormally frustrated when expected rewards fail to appear (e.g. they pull a lever with significantly more force, especially when reward delivery fails progressively). These results were not replicated in a study with adults with ADHD (Lee & Zentall, 2006).

Sagvolden and his colleagues (1998) took this theory further and suggested that children with ADHD are abnormally sensitive to variations in temporal features of attentional tasks and reinforcement schedules. The reinforcing effect is largest, when the reinforcer is delivered immediately after the occurrence of the response, and declines as a function of the delayed delivery of the reinforcer. This relation between the effect of the reinforcer and the time interval between response and reinforcer is commonly known as the delay-of-reinforcement gradient or delay gradient. The altered-reinforcement hypothesis predicts that the delay of reinforcement gradient is steeper and shorter for children with ADHD than for typical children (Sagvolden et al., 1998). Consequently, a reinforcer in close proximity to a response should be relatively more effective in individuals with ADHD and therefore produce faster/impulsive responses. This account is supported by the consistent finding that children with ADHD often display a hypersensitivity to delay and have difficulties in waiting for motivationally salient outcomes, as well as in working effectively over extended periods of time (Kuntsi, Oosterlaan, & Stevenson, 2001; Neef, Bicard, & Endo, 2001; Schweitzer & Sulzer-Azaroff, 1995; Sonuga-Barke, Williams, Hall, & Saxton, 1996; Tripp & Alsop, 2001).

Based on these findings, Sonuga-Barke (2005; 2003; 2002a) has extended his previous findings on the effect of delay on choice in children with ADHD (Sonuga-Barke et al., 1992) into the Delay Aversion hypothesis (DAV; Figure 3.3 for schematic representation). According to this later hypothetical motivational model, alternations in the neuropsychological reward circuits impair the signalling of delayed rewards, which leads to impulsiveness. Impulsivity leads to failures to effectively engage with, and operate in, delay environments. This failure to engage has the potential to elicit a negative response from a parent or other adult (e.g. teacher), which over time leads to delay aversion. Moreover, the failure to engage also constrains the experience of managing delay-demanding activities and so reduces the opportunities to develop the organizational skills and strategies required to do this. As a result, in a delay-rich environment children will engage in delay-related inattention and hyperactivity in order to keep themselves occupied. This is in line with the optimal stimulation theory (Zentall & Zentall, 1983). According to this theory the activity of children with ADHD

increases when they are confronted with a stimulus-poor environment due to the need to meet their high stimulation threshold. Consequently, children with ADHD appear to produce more activity than control children when confronted with low levels of stimulation (Antrop, Roeyers, van Oost, & Buysse, 2000; van der Meer, 1996). Interestingly, when children with ADHD are provided with a stimulation condition during delay, their performance 'normalizes' in that they are as likely to choose large delayed rewards as control children (Antrop et al., 2006).

Some researchers (Castellanos & Tannock, 2002; Nigg, 2006; Sonuga-Barke, 2002a) have argued that the inability to tolerate waiting periods, may rely on difficulties with time processing. The 'internal clock' of individuals with ADHD might be faster that typical individuals, and as result, children with ADHD might perceive time passing more slowly, which could increase intolerance of delayed periods.

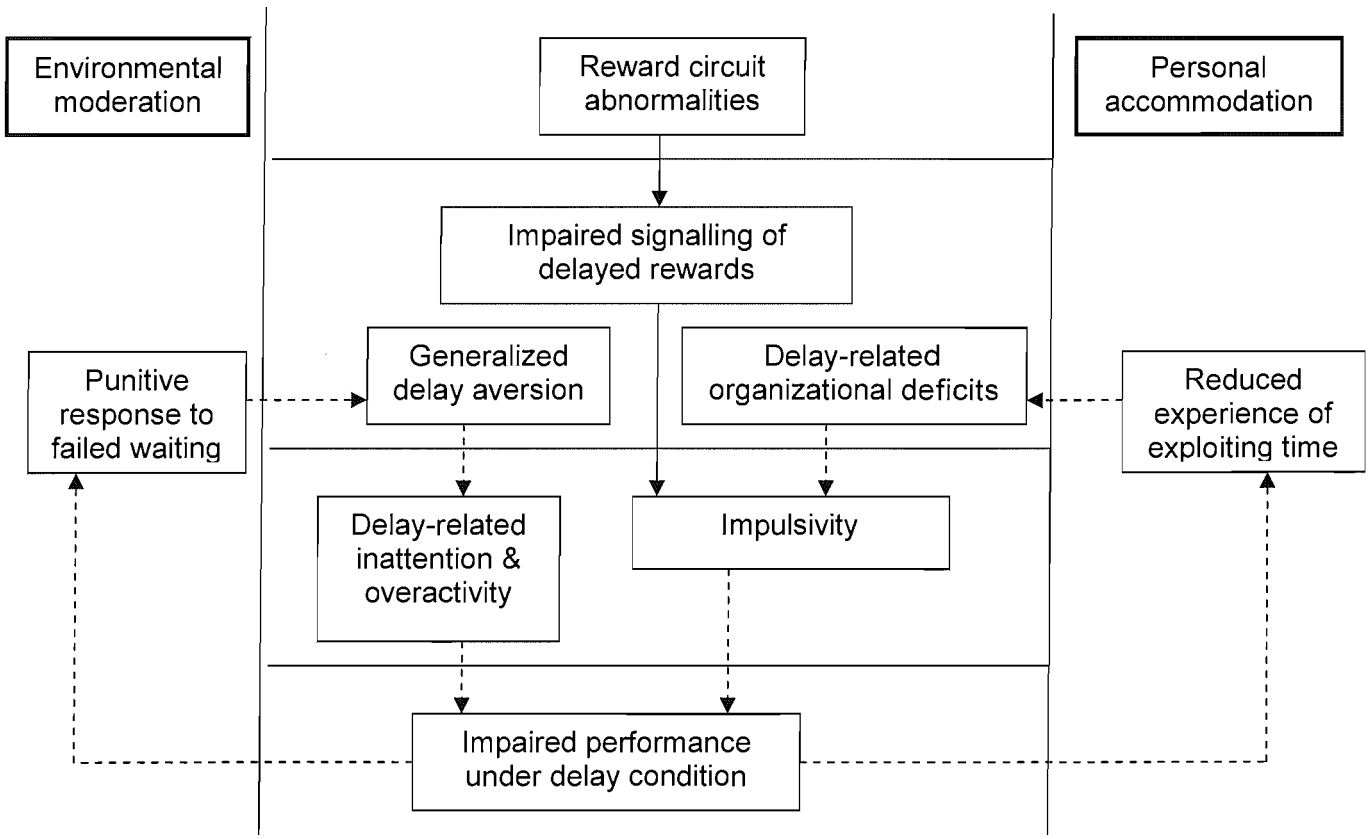


Figure 3.3.: Schematic representation of a hypothetical motivational developmental pathway for ADHD (cited by Sonuga-Barke, 2005).

3.4.2. The evidence: Is ADHD a delay aversion (DAV) disorder?

3.4.2.1. Neuropsychology

A comprehensive review of studies investigating response to reward in ADHD was recently provided by Luman, Oosterlaan, and Sergeant (2005). They argued that the mixed literature due to different designs, measurements, and sample size, makes it difficult to support any one formulation about the reinforcement effect in ADHD. However, the authors mainly concluded that ADHD is associated with increased preference of immediate small over delayed large rewards.

Evidence for the motivational model of ADHD and the delay aversion hypothesis comes primarily from choice studies. Pooled data of choice delay tasks indicate moderate effect sizes (ranging form .5 to .7; Sonuga-Barke et al., 2007). Children with ADHD are more likely to choose a small, immediate reward (1 point for 2sec) in order to reduce the overall trial and session length, rather than a larger, delayed reward (2 points after 30sec; Kuntsi et al., 2001a). However, in another condition, where choosing the small immediate reward led to a post-reward delay, such that the overall delay was the same as when choosing the large delayed reward, children with ADHD waited as well as the control children for the larger reward (Sonuga-Barke et al., 1992). Thus, children with ADHD were not impulsive in the sense that they were unable to wait; instead, it appeared that they preferred not to wait.

Further support for this view comes from a recent study illustrating that when children were provided with stimulation during large delayed rewards, they were more likely to choose the large delayed reward with the stimulation, than the immediate small reward without the stimulation (Antrop et al., 2006). According to these findings cognitive deficit in ADHD might also be motivational in nature. In order for these children to reduce the delay period, they show greater locomotor activity, resulting to inattentive and overactive behaviour, such as time off-task, fidgeting, talking and so on (Sonuga-Barke, 1994). However, Tripp and Alsop (2001) found contradictory results. They provided children with ADHD with two reward conditions. In the immediate reward condition, a correct identification of one stimulus produced an immediate reward and then a delay before the next trial. In the delayed reward condition, correct identification of another stimulus was associated with a delay before reward was delivered. Children with ADHD showed a greater bias toward immediate reward than the controls. Thus, although children with ADHD had to experience delay in both conditions, they showed sensitivity towards the immediate

reward. Age is an important factor in reward sensitivity, as Scheres and colleagues (2005) have reported young children with ADHD to be driven by reward immediacy and not by delay aversion, where the contrary was true for adolescence with ADHD.

Apart from the choice studies, researchers have focused on alternative measurements of delay aversion. Sonuga-Barke and Taylor (1992) introduced the Delay Reaction Time task, in which children were provided with three delay periods (i.e. 1, 15 or 30sec.) and had to give a response to a stimulus after the delay. It was found that the response given by the children with ADHD was slower than that of their counterparts and that the reaction time of their responses increased with the length of the pre-response delay. Moreover, a very interesting recent study has supported the delay aversion hypothesis in children with ADHD using the dot-probe paradigm (Sonuga-Barke, De Houwer, De Ruiter, Ajzenstzen, & Holland, 2003). According to the authors, if DAV hypothesis is true, and avoidance of delay is of motivational significance for children with ADHD, then the attention of these children should be captured more rapidly by cues related to delay experiences. The dot-probe paradigm was used to measure ADHD children's attention towards delay cues. The results indicated that children with ADHD displayed an attentional bias to cues for delay-related events, suggesting a motivational significance of the delay aversion for children with ADHD. Finally, the Delay Frustration task (DeFT) has recently been developed in order to measure delay intolerance/frustration. It was designed to be used in a similar form with adolescents and adults as well as children (Bitsakou, Antrop, Wierseman, & Sonuga-Barke, 2005). Delay frustration is indexed as the number and duration of responses made on a response key during a series of unpredictable and unsignalled delay periods that interrupt the completion of simple computer-based maths questions. Results indicated that young adults with high ADHD symptom scores appeared to be more sensitive to the imposition of unscheduled and unsignalled delay (i.e. higher frustration level during delay) compared to young adults with low ADHD symptom scores. This effect became more pronounced when anxiety was controlled.

3.4.2.2. Brain structure and function

The ability to wait for delayed rewards seems to be related to alternations in the thalamocortical-basal ganglia circuits (Alexander, Crutcher, & Delong, 1990). However, in the delay-related causal model the motivational or affective circuit plays the dominant role (Figure 3.4). This circuit links the ventral striatum, and in particular the nucleus accumbens, (Zink, Pagnoni, Martin-Skurski, Chappelow, & Berns, 2004)

to frontal regions (especially the anterior cingulate and orbitofrontal cortex), connections that are reciprocal via the ventral pallidum and related structures through the thalamus (Robbins & Everitt, 1996). The amygdala may also play a role in defining the motivational significance of incentives (Winstanley, Theobald, Cardinal, & Robbins, 2004).

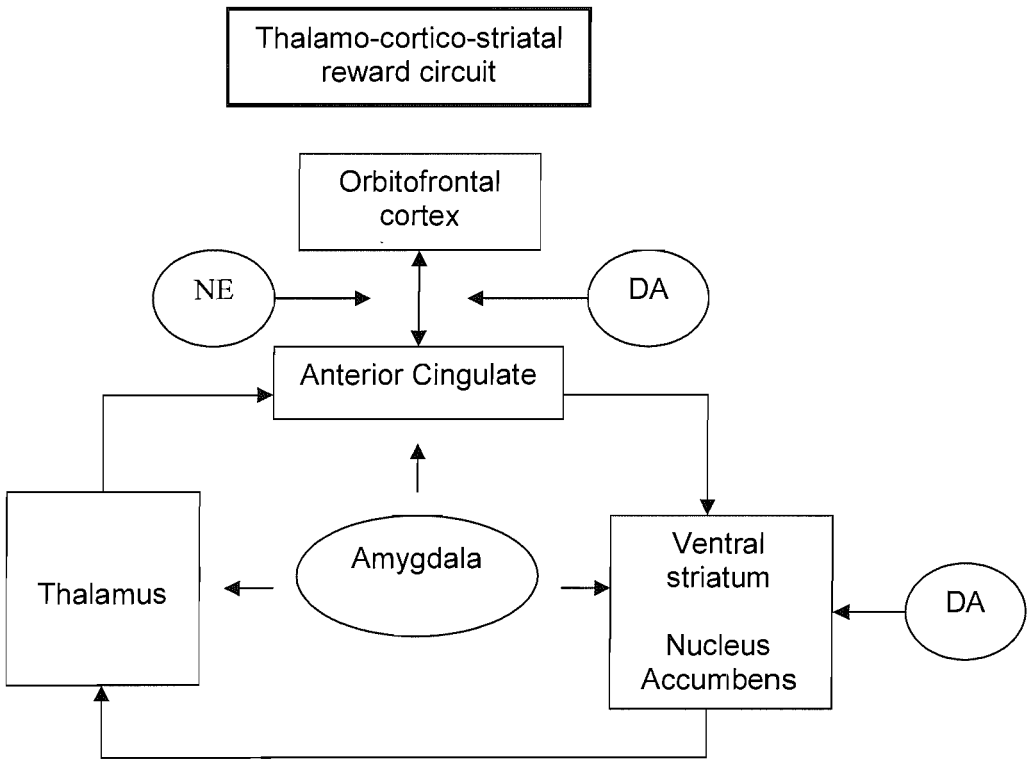


Figure 3.4: Schematic representation of a simplified account of the neurobiological function of the Motivational model (cited by Sonuga-Barke, 2005). DA = dopamine; NE = norepinephrine.

The specific role of the motivational circuit in signalling rewards has been investigated by studies using animal models (Burk & Mair, 2001; Wade, de Wit & Richards, 2000). Animal models of ADHD implicate abnormalities in mesolimbic reward circuits projecting from midbrain ventral tegmentum to subcortical areas including ventral striatum (Carboni, Silvagni, & Valentini, 2003; Johansen, Aase, Meyer, & Sagvolden, 2002; Viggiano, Vallone, & Sadile, 2004). Specifically, lesions in the core of the accumbens in rats have been shown to reduce their ability to wait for large delayed rewards in a self-control paradigm (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001).

Suggested alterations in striatal dopamine transporter density in patients with ADHD (Spencer et al., 2005) could also support the potential relevance of mesolimbic

reward circuitry. In one fMRI study the responsiveness of mesolimbic reward circuitry has been directly examined in patients with ADHD (Scheres, Milham, Knutson, & Castellanos, 2007). Results showed decreased ventral striatal activation in adolescents with ADHD during reward anticipation, which correlated with symptoms of hyperactivity/impulsivity. These results provide neural evidence to support the hypothesis that the salience of anticipated rewards is diminished in ADHD (Johansen et al 2002; Volkow et al 2004). Although ADHD may involve abnormalities in motivational neural pathways (alongside executive neural pathways) as shown by Scheres and colleagues (2007), further structural and functional MRI studies are required to replicate these findings.

3.4.2.3. Neurochemistry

The most prominent biochemical theory of ADHD has been based on a catecholamine hypothesis involving the dopamine (DA) and norepinephrine (NE) neurotransmitter systems (Pliszka, 2005; Pliszka et al., 1996). However, only animal studies have been used to investigate the relation of these biochemical systems and motivational processes. Moreover, the acetylcholine and serotonin system have also been associated with alertness, arousal, and delay discounting.

Castellanos (1997) have argued that dopaminergic neurons of the mesocortical system lie in the ventral tegmental area and provide a diffuse innervation to the forebrain, including the frontal and cingulate cortex and nucleus accumbens. DA underactivity in these cortical regions results in shorter delay gradient (e.g. Johansen et al., 2002; Johansen and Sagvolden, 2005). Interestingly, a neuro-computational model of fronto-striatal DA function has been used to understand motivational deficits in ADHD (Frank, Santamaria, O'Reilly, & Willcutt, 2007). The model predicts that low striatal DA levels in ADHD should lead to deficits in 'Go' learning from positive reinforcement, which should be alleviated by stimulant medications. Indeed, while non-medicated adult ADHD participants were impaired at both positive (Go) and negative (NoGo) reinforcement learning, only the former deficits were ameliorated by medication.

Brody and colleagues (2004) have shown that nicotine increases ventral striatal DA and they suggested that cholinergic agonists may work through catecholamine systems. Recent research indicates that smoking during pregnancy might increase the risk to the offspring for developing ADHD, even after controlling for parental ADHD (Mick, Biederman, Prince, Fischer, & Faraone, 2002b). Nicotine has also been

found to reduce ADHD symptoms in adults (Levin et al., 1996; Shytle, Silver, Wilkinson, & Sanberg, 2002; Willens et al., 1999) and to have significant effects on the Conner's continuous performance test of attention (Levin et al., 1996). However, this reduction was less robust than that of stimulants (Wilens et al., 1999). Finally, the rodent models show that the psychostimulant effect on improving delay discounting also depends on an intact serotonin system (Winstanley, Dalley, Theobald, & Robbins, 2003). However, further research is required to identify the specific role of cholinergic and serotonergic systems in ADHD and their association with other neurotransmitter systems.

3.4.2.4. Is DAV deficit in ADHD heritable, genetic, and familial?

Very limited research exists on the investigation of heritable, genetic and familial effects of DAV deficit, highlighting the need for further investigation on these important criteria for the validity of motivational causal model of ADHD.

Heritability: Only one twin study exists on heritability range of delay aversion measures (Kuntsi et al., 2006), where heritability estimate was quite small (h^2_g = .18). However, model fitting on the delay aversion data suggested significant shared environmental effects and less genetic influence. Further inspection of the data indicated that the model fitting had been affected by ceiling effects, which inflate twin similarity for both MZ and DZ twins, resulting in an overestimation of shared environmental influences and underestimation of genetic influences. Further twin studies are required in order to investigate heritability estimates of more delay aversion tasks.

Genes: The genetic liability of DAV deficit in ADHD has not been investigated yet.

Familiality: Up to date, only one study (Kuntsi & Stevenson, 2001) has examined the bivariate heritability of delay aversion measures in ADHD. According to this study, delay aversion did not show any evidence of genetic overlap with ADHD (h^2_g = -.06). However, this study used only one measure of delay aversion. Furthermore, DZ twin pairs discordant for ADHD and control DZ twin pairs were compared on their performance on two delay aversion measures in a recent twin study (Bidwell et al., 2007). It was found that both probands with ADHD and their unaffected co-twins were not significantly impaired in comparison with control twins on both delay aversion measures (Bidwell et al., 2007). Obviously, further family and twin studies on delay aversion measures are required, although findings so far indicate that delay

aversion might not co-segregate within families.

3.5. Partitioning the neuropsychological heterogeneity of ADHD

The issue of the heterogeneity of ADHD has been emphasized repeatedly throughout this thesis. The models reviewed above all make the assumption that ADHD is a homogeneous condition and that there is a core impairment that is common to all individuals with the condition. It is becoming increasingly clear that this position is not supported by the evidence from empirical studies. New theories have emphasized that ADHD can be reached through multiple pathways and that there are sub-groups of children with different and distinctive profiles of impairment.

Although there are many proposed neuropsychological pathways that could explain ADHD symptomatology, they do not allow a full aetiological description of the disorder because children with ADHD exhibit great sample variance, with some children performing poorly and other children performing in a comparable way with controls (Nigg, 2006). Meta-analytic studies have mainly focused on EF measures (including inhibitory control). Efforts to evaluate the predictive power of EF measures in relation to ADHD tend to show that these measures have worthwhile sensitivity but poor specificity (Doyle, Beiderman, Seidman, Weber, & Faraone, 2000; Hinshaw et al., 2002; Willcutt et al., 2005). In other words, individuals with poor performance are likely to have ADHD, but only a minority of children with ADHD exhibit a deficit on any specific test. Thus, group effects reported in the literature are apparently carried by a subset of the children with ADHD.

Two twin studies have provided evidence for neuropsychological heterogeneity, as in both studies bivariate heritability of ADHD was stronger for composite than individual scores of measures (Chhabildas et al., unpublished data, cited by Doyle at al., 2005b; Kuntsi & Stevenson, 2001). Specifically, a bivariate heritability estimate of .80 was obtained for a composite score that included measures of working memory, delay aversion, and reaction time performance (i.e. RT and RT variability; Kuntsi & Stevenson, 2001). In the other study, a composite score of processing speed, vigilance, working memory, and inhibition showed a bivariate heritability of .52 (Chhabildas et al., unpublished data; cited by Doyle at al., 2005b). Therefore, getting higher bivariate heritability estimates by combining measures tapping different neuropsychological constructs provides further evidence for the neuropsychological heterogeneity of ADHD.

Nigg and colleagues (2005) pooled EF data from three different sites in order to examine the proportion of children with ADHD-C, who have EF impairment. The authors defined EF impairment in terms of performance exceeding the 90th percentile cut-off (based on the control samples). They found that only 10% of children with ADHD-C showed deficits across all EF measures, and on any individual measure, between 16% and 51% of children with ADHD-C were classified as impaired. In other words, only half of the children with ADHD-C had deficit in at least one EF measure. Moreover, approximately 50% of children with ADHD-C have shown increased RT variability (Nigg et al., 2005). Thus, despite their strong association with the disorder, EF deficits and RT variability are not found universally in ADHD. Nigg and colleagues (2005) argued that if 30-50% of children with ADHD-C had an EF impairment, then the remaining 50-70% of those children would have some other aetiology, which may often be a different neuropsychological dysfunction, such as problems in motivation, state regulation, processing time or attention, or in a few instances, no dysfunction at all. These results do not rule out the importance of EF as a potential causal contributor to ADHD. On the contrary, they suggest that there may be multiple pathways to ADHD, with only one of those pathways involving impaired EF.

Based on the empirical evidence, it became quite clear that ADHD cannot be explained by a single neuropsychological deficit common to all cases and that it can be better understood as a multiple-pathway neuropsychological disorder. A number of multiple pathway or process models have been proposed in ADHD or general psychiatric literature (Nigg, Goldsmith, & Schachar, 2004b; Pennington, 2006; Swanson et al., 2007). However, the dual pathway model was the first attempt to partition heterogeneity of ADHD to propose that ADHD is a disorder with at least two neuropsychological pathways (Sonuga-Barke, 2002a).

3.5.1. The dual pathway hypothesis

Traditionally inhibitory control and delay aversion have been perceived as competitive neuropsychological functions in ADHD. However, Sonuga-Barke (2002a) has perceived these two models as complementary. Although the two models are most distinctive in terms of the presence of inhibitory deficits and impaired performance under delay conditions, Sonuga-Barke suggested that ADHD is a heterogeneous disorder and can be explained in terms of two different

neuropsychological pathways (i.e. dual pathway model; Figure 3.5). According to this hypothesis, alternations within the executive and the reward circuit represent dissociable neuropsychological processes leading to executive/inhibitory deficits and delay aversion respectively (Sonuga-Barke, 2005). In other words, the dual pathway suggests that either or both of the IC and DAV accounts are plausible to explain the structure of ADHD in terms of the three causal levels: biological, cognitive and behavioural.

The way of evaluating the existence of multiple pathways is to compare competing neuropsychological models. In a head-to-head study exploiting the distinctive underlying processes of the two models, school-age children with ADHD-C performed an IC and a DAV task (Solanto et al., 2001). The results indicated that there was no association between the performance on the two tasks, suggesting that inhibitory deficit and delay aversion were independent characteristics of ADHD. Furthermore, performance on both tasks was strongly and independently associated with ADHD, suggesting that inhibitory deficit and delay aversion are two possible neuropsychological pathways that can independently lead to ADHD symptomatology. When the performance of children with ADHD was categorized into 'impaired' and 'non-impaired' base on the 90th percentile cut-off of the control sample (Nigg et al., 2005), 23% had "pure" inhibitory deficit, 15% had "pure" delay aversion, and 23% had both deficits. 39% of children with ADHD had none of these two deficits, although this does not exclude the possibility that this percentage could be explained by other deficits. These results by Solanto and colleagues (2001) have been recently replicated in children with ADHD (Thorell, submitted) and have also been supported in another study with a younger population (3-5 years) at high- and low-ADHD symptoms (Sonuga-Barke et al., 2002), suggesting that 29% of high-ADHD children displayed both delay aversion and executive dysfunction, 27% "pure" delay aversion, 15% "pure" executive dysfunction, and 29% neither deficit. Finally, in a rat study it has shown that delay aversion and response inhibition are independent constructs, with aggressive behaviour positively correlated only with delay aversion (van der Bergh et al., 2006).

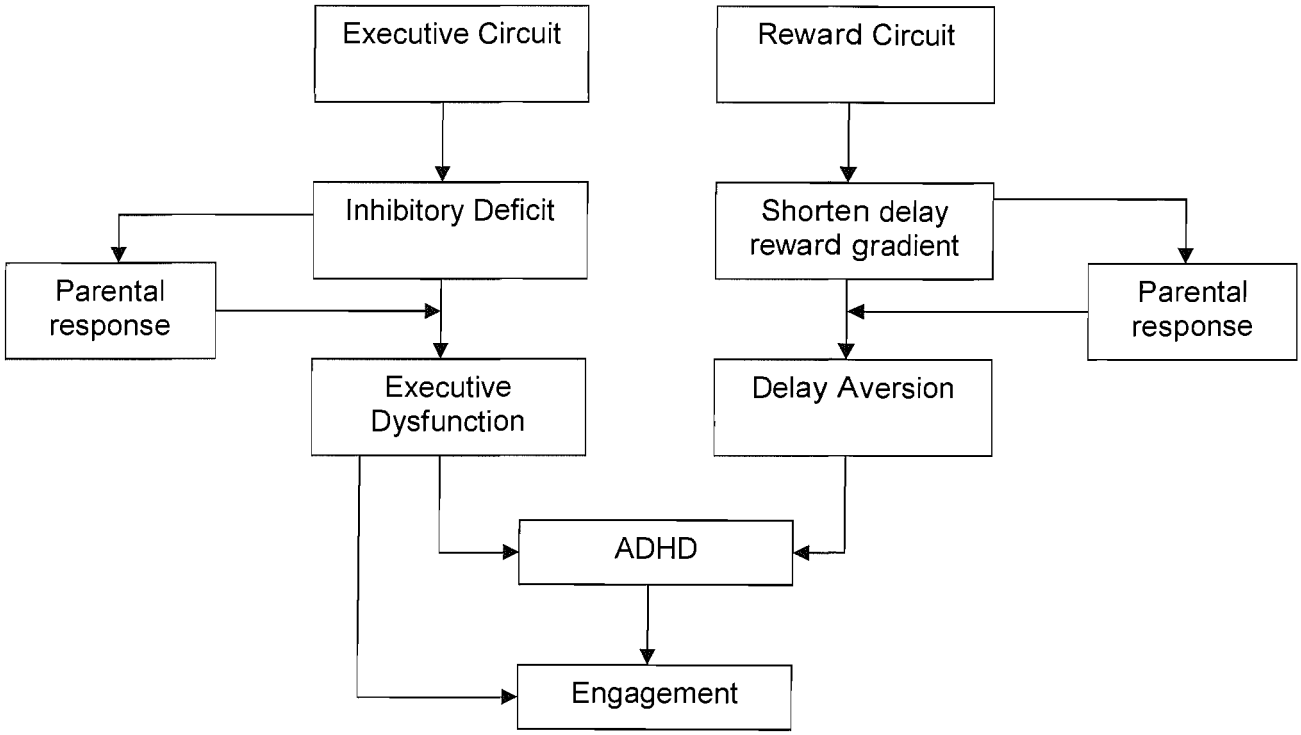


Figure 3.5: Schematic representation of the Dual Pathway Model of ADHD (cited by Sonuga-Barke, 2003).

At a neurobiological level, the dual pathway model can be understood within a common neurobiological theoretical account of the interplay between cortical and sub-cortical brain regions in the regulation of action, cognition and motivation. As mentioned earlier, IC involves the executive circuit and the DAV involves the reward circuit. However, in both pathways there are reciprocal excitatory connections to the cortical regions of each circuit via the dorso-medial sections of the thalamus and direct and indirect pathways within other subcortical brain regions, such as the globus pallidus, ventral pallidus, subthalamic nucleus and substantial nigra (Sonuga-Barke, 2003). Moreover, dopamine has been found to be a key neuro-modulator of both the executive and reward circuits (Robbins & Everitt, 2004; Williams et al., 2002), which provides further support for the neurobiological interplay between these two models of ADHD. On the other hand, each circuit is influenced by inputs from different branches of the dopamine system which confirms the heterogeneity of the pathways. The executive circuit is modulated by the mesocortical and nigrostriatal braches whereas the reward circuit is modulated by the mesolimbic branch of the dopamine system (Sonuga-Barke, 2003).

Although there is evidence that ADHD is a heterogeneous disorder, with both cognitive and motivational processes contributing independently to the phenotypic expression of ADHD (Sonuga-Barke, 2005, 2003, 2002a), the dual pathway hypothesis might not be exhaustive, and other pathways might be hypothesised. For instance, other neuropsychological mechanisms such as deficits in state-regulation (Sergeant, 2005) and temporal processing dysfunction (Castellanos and Tannock, 2002) have been proposed as candidate neuropsychological markers of ADHD.

3.6. Summary and hypotheses of the thesis

Emerging knowledge about the neuropsychological pathways of ADHD should lead to an improved understanding of the underlying causes of the disorder. Neuropsychological pathways could be associated with the previous knowledge on the neurobiological causality of ADHD, and could improve diagnostic and treatment strategies. However, none of the candidate neuropsychological markers identified so far have been proven to provide a substantial causal aetiology of the disorder. There is substantial empirical evidence suggesting that children with ADHD have impaired IC (and more generally EF) and DAV mechanisms. However, each deficit affects only a subset of children with ADHD, providing evidence for a neuropsychologically heterogeneous disorder.

One way to partition heterogeneity is to compare neuropsychological mechanisms and investigate the variation of each deficit in an ADHD population. Evidence exists that ADHD can be explained at two levels of neuropsychological functioning: inhibitory control and delay aversion. Despite the general shift from single to multiple causal pathways, only two studies with children and one study with pre-schoolers have investigated the existence of a dual pathway in ADHD. Even more important is that none of these studies have used an extensive neuropsychological battery to validly and reliably investigate the effect of the two constructs. Finally, due to the very limited evidence available, the ADHD literature is far from establishing whether IC and especially DAV impairments are heritable, are associated with specific genetic markers and are co-segregated within families.

In the present thesis, IC and DAV deficits of children with ADHD were investigated. In order to maximize construct validity for each domain (i.e. IC and DAV), three measurements were used per construct. Moreover, unaffected siblings of children with ADHD were also included in the study in order to examine the familial effect of

the two constructs. Therefore, the aim of the present thesis was threefold:

1. *To identify whether ADHD was associated with inhibitory control and delay aversion* (Chapters 5 and 6). Children with ADHD were expected to have impaired inhibitory control and increased aversion towards delay compared with control children.
2. *To replicate findings on dual pathway model* (Chapter 7). Inhibitory control and delay aversion measures were expected to form two independent constructs leading to ADHD in a principal component analysis.
3. *To examine the familial effect of inhibitory control and delay aversion deficits* (Chapter 8). Unaffected siblings of children with ADHD were expected to have an intermediate performance between their probands and controls. More specifically, it was expected that unaffected siblings of ADHD probands who had impaired IC and DAV would have worse neuropsychological performance compared to unaffected siblings of ADHD probands who did not have impaired IC and DAV performance.

CHAPTER FOUR: Measurement issues related to Inhibitory Control (IC) and Delay Aversion (DAV) measures

4.1. Introduction

In order to test the hypotheses set out in chapter 3, tasks were required that provided valid and reliable measures of inhibitory control (IC) and delay aversion (DAV). This chapter therefore has two aims:

(i) to describe the process of task selection for the thesis, by considering general measurement issues related to neuropsychological measures, and specifically to IC and DAV and

(ii) to report a pilot study, which examined the test-retest reliability of a number of selected tasks in a population sample of twelve children.

4.2. General measurement issues related to IC and DAV measures

There are a number of general measurement issues regarding neuropsychological measures and specifically IC and DAV. Before these measures can be used to test causal models of the disorder, it must be confirmed that tasks are measuring what they are intended to measure in a reliable and valid way. A reliable measure is measuring something consistently, while a valid measure is measuring what it is supposed to measure. If these two criteria are not fulfilled in any measure, then the results on group differences derived from the measures could be misleading. The issues of reliability, validity, and age appropriateness will be reviewed, although these issues are interrelated.

4.2.1. Reliability

In order for a measure to be reliable it should give consistent results over time. Reliability of measures may be assessed by correlating performance on the measure at two different testing sessions. Statistically, reliability is assessed by Pearson product-moment correlation coefficient, intra-class correlation, and Cronbach's α.

The utility of any measure is constrained by its reliability. However, few studies of ADHD have formally assessed the reliability of IC and DAV measures. In those studies that have considered reliability, measures of IC such as Stop Signal, Continuous Performance test, Stroop and Go/No-Go tasks have been shown to have adequate reliability, with intra-class correlations ranging from .5 - .9 (Gualtieri & Johnson, 2006; Kuntsi, Andreou, Ma, Börger, & van der Meere, 2005a; Lemay, Bertram, & Stelmach, 2004; Logan, Schachar & Tannock, 1997; Salinsky, Storzbach, Dodrill, & Binder, 2001). One study on psychometric properties of Stop Signal task (Kuntsi, Stevenson, Oosterlaan, & Sonuga-Barke, 2001b) showed that the SSRT was found to have low test-retest reliability (intra-class correlation = .11). In the same study, high test-retest reliability (intra-class correlation = .74) was found for a delay aversion measure, and moderate reliability (intra-class correlation = .5-.69) was found for working memory tasks (sentence span and counting span).

Therefore, ADHD studies investigating reliability of neuropsychological measures have shown variable results. This variability of results between studies could be due to several reasons. First, the energetic state of participants from one session to the other may impact their performance on IC (Doyle et al., 2005b) and delay-related motivational measures. For example, shorter sleep duration can affect performance on verbal executive tasks (Harrison & Horne, 1998), and abstract thinking can be influenced by even one night of sleep restriction (Randazzo, Muehlbach, Schweitzer, & Walsh, 1998). Second, studies testing the reliability of IC and DAV measures include different subtypes of ADHD sample. The subtype of ADHD could have a different impact on neuropsychological performance. For instance, children with ADHD-In are more sensitive to motivation compared to children with ADHD-C (Huang-Pollock, Mikami, Pfiffner, & McBurnett, 2007).

Third, the reliability of a task could also depend on testing situations. For instance, performance on CPT task (an inhibitory control task) deteriorated significantly in children with ADHD but not in control children when the examiner left the room (Draeger, Prior, & Sanson, 1986). Finally, reliability of IC and DAV measures may also be constrained by the lack of normative data and standardization across research labs. It is very common in the ADHD literature to use a specific task across studies with different stimuli, interval length, number of trials, modality, or scoring algorithm. Therefore, it is very difficult to draw conclusions about the reliability (as well as validity) of tasks, because different designs of the same task could require different effortful control and therefore neuropsychological function ability (e.g.

Babiloni et al., 2006; Wiersema et al., 2006). Thus, experimental tasks must be used cautiously and must be clearly described in publications until standardized neuropsychological batteries are developed (but see Gualtieri & Johnson, 2006; Moller et al., 1998; Sahakian & Owen, 1992).

4.2.2. Validity

In order for a task to be valid, it should measure what it is intended to. Validity may be assessed by correlating the measure in question with a criterion measure known to be valid (for example, validated questionnaire). A measure has construct validity if it is related to other measures as required by the theory, and has discriminant validity if it discriminates individuals with one disorder from individuals with another disorder or from the typical population.

There are a number of possible threats to the construct validity of IC and DAV tasks. They might, for instance, tap into other neuropsychological functions that could decrease their construct validity. One way of resolving this is by using control measures to parse out the IC and DAV component of tasks (Pennington & Ozonoff, 1996; Sergeant et al., 2002). Such procedures are often used clinically but are not regularly incorporated into research designs with traditional neuropsychological tasks. Children with ADHD perform poorly on tasks with little or no inhibitory demand (Rhodes, Coghill, & Matthew, 2006) and they are typically slower and more variable in simple RT paradigms (e.g. Andreou et al., 2007), indicating a deficit in basic processing efficiency. Therefore, in neuropsychological measures, where RT performance is assessed, there is the need to partial out confounding effects of basic processing efficiency deficits to increase the construct validity of the task.

The discriminant validity of a task can be increased when valid selection criteria, such as DSM-IV criteria and use of validated structured or semi-structured interviews, are used to identify ADHD cases. Moreover, inclusion of psychiatric comparison groups as well as better control of ADHD symptoms when examining deficits in other disorders could increase discriminant validity of the measure (Sergeant et al., 2002). The effect sizes of the measures between two groups could also provide a statistical way to assess discriminant validity. The higher the effect size, the more likely it is for the measure to discriminate two experimental groups. For instance, the effect sizes of IC measures between ADHD cases and controls range from .3 to .6, with the lower effect size shown by the Stroop interference task,

indicating that this might not be the best measure for discriminating ADHD from control cases (see review Sergeant, Willcutt and Nigg, in press). On the other hand, moderate to high pooled effect sizes have been found for two delay aversion measures – Maudsley's Index of Delay aversion, d = .57; Choice Delay task, d = .71; Sonuga-Barke et al., 2007), indicating that these measures might best discriminate between ADHD and controls cases on delay aversion.

Some neuropsychological measures might have higher discriminant validity than other measures of the same constructs, although both measures might show adequate construct validity. For instance, both Stop Signal and Stroop interference tasks are measuring an IC deficit. However, the SSRT is more likely to discriminate children with ADHD from controls than Stroop interference task, as SSRT has a higher effect size (Sergeant et al., in press). The same can be claimed for the Choice Delay task compared to Maudsley's Index of Delay Aversion (Sonuga-Barke et al., 2007). The variable effect sizes between the measures within each construct could also be an indication of inconsistent reliability across measures (more reliable measures yield larger effect sizes; Sergeant et al., in press). Therefore, some measures might have adequate construct validity, but reduced discriminant validity and inconsistent reliability. One way of resolving this issue is by using several tasks to measure the same construct and then use a latent variable for each construct. By combining multiple measures tapping into the same construct, it is more likely to obtain a broad picture of the construct, identify impairments in specific domains of the construct, and provide a more reliable and valid measure of that construct.

4.2.3. Age appropriateness

The validity and reliability of a task can be affected by whether it is age appropriate. The main issue to consider in relation to this issue is ceiling effects. Ceiling effects can be caused when participants are performing at or near the maximum possible score of the test, and as a result the scores are not variable and normally distributed. For example, adolescents tend to show ceiling effects when assessed on tasks developed for children as they find them quite easy. Ceiling effects on IC and DAV measures can be apparent for several reasons. For IC measures, the task might not be equivalent to neural maturation of the brain and task difficulty might not fluctuate to adjust on the mental and emotional abilities of different age groups. For DAV measures, the qualitative increase of motivational salience and social maturation during adolescence might reduce reward sensitivity and increase delay tolerance.

In relation to IC specifically, and EF more generally, the brain circuits implicated in EF show increasing specialization as the children develop from childhood to adolescence as a result of myelination, pruning, and specialization (Casey, Tottenham, Liston, & Durston, 2005). A study by Klenberg, Korkmand, and Lanti-Nouttila (2001) suggests that different components of EF mature at different ages. Therefore, tasks that are appropriate for children might be too easy for adolescents, causing ceiling effects. Ceiling effects could be minimized by developing tasks that are hard enough for both children and adolescents. Tasks that are adjusted to participant's performance (e.g. Stop signal tasks, tracking version) are useful tools to address this issue. Moreover, tasks with fast intervals can also increase the level of difficulty. However, this level of difficulty changes according to age, and therefore age should also be controlled for statistically.

While the developmental appropriateness and age-equivalence of neuropsychological tests relates to IC, it may be particularly marked in tasks incorporating motivational factors such as reward and delay. Patterns of motivational salience of outcomes undergo a qualitative change as people age across the life span, with small rewards becoming less salient as children grow into adolescence when access to reward in their every day life increases (Bjork et al., 2004). This is particularly so with regard to monetary rewards, which are often used in choice studies with children (Wulfert, Block, Santa, Rodriguez, & Colsman, 2002). At the same time the ability to tolerate delay prior to the delivery of reward seems to develop very rapidly across this period (Green, Fry, & Myerson, 1994; Green, Myerson, Lichtman, Rosen, & Fry, 1996). In the choice delay paradigms, typically employed with school-aged children with ADHD, ceiling effects are apparent for adolescents, as they show an increased preference for large rewards compared to controls. This preference might result from the adolescents' increased ability to tolerate delay to achieve a preferred outcome or because of their greater responsiveness to non-choice factors such as social desirability (Holtgraves, 2004; Zuckerman, Knee, Hodgins, & Miyake, 1995).

There are a number of possible ways to respond to the methodological challenge of ceiling effects of motivational tasks. First, one could simply change the delay and reward parameters so that they are more developmentally appropriate. However, the sheer impracticality of increasing reward amounts and delay lengths to suitable levels make this an unattractive option. Second, one could try to increase the sensitivity of

the measures by systematically reducing the pay-off for each additional unit of time waited so that, while the amount of reward increases as a function of delay, the additional unit of reward per additional unit of time gets progressively smaller over trials (Müller, Sonuga-Barke, Brandeis, & Steinhausen, 2006). Third, one could replace real choices between rewards and delays by hypothetical choices (e.g., £1 now or £1,000 in a year's time; Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Madden, et al., 2004). However, it is not clear that these decisions and those made between real rewards are equivalent (Green & Myerson, 2004). Finally, one can move away from the choice paradigms completely and try to develop other non-choice indices of delay sensitivity and intolerance. One approach of this type was used in a recent study of motivationally based attention biases to delay-related stimuli (Sonuga-Barke et al., 2003). A second approach is to use simple reaction time tasks with increased interval length (delay condition), where the participant has to respond after a delayed interval as quickly as possible (Sonuga-Barke & Taylor, 1992). Increased RT indicates increased aversion towards delay. Finally, one can use tasks measuring delay intolerance due to unexpected and unsignalled delays that are an obstacle to the completion of what is considered by the participant to be a primary task (Bitsakou et al., 2006). All these non-choice delay tasks do not reinforce socially desirable performance in relation to delay, as participants are unaware that their delay-related response is being monitored and they are not rewarded for more "patient" performance.

4.3. The neuropsychological battery used in the current thesis

The selection of neuropsychological measures for the present thesis was a challenge, as controversial or limited evidence exists for the reliability, validity and developmental appropriateness of IC and DAV measures. In order to overcome these measurement issues, a latent approach was used: multiple measures tapping into the same construct were selected to provide a more reliable and valid way of measuring IC and DAV constructs.

Two IC domains were examined: response inhibition and interference control (Nigg, 2006). Interference control was assessed by using a Modified version of the Stroop task (Hogan, Vergha-Khadem, Kirkham, & Baldeweg, 2005). Two response inhibition tasks were selected, as this domain has been reported to be most impaired in children with ADHD (Barkley, 1997): a) the tracking version of the Stop Signal task (Logan et al., 1997), as this scoring algorithm would prevent ceiling effects deriving

from the level of task difficulty for each age group, and b) a Go/No-Go task. To increase the cross-task consistency of design between interference control and response inhibition tasks, the Go/No-Go task was developed in our labs, based on the presentation stimuli of the Modified Stroop task. Therefore, the same presentation platform was used for the primary task in both Modified Stroop and Go/No-Go task. Moreover, the same stimuli were also used for a control measure (2 Choice Response task; Hogan et al., 2005), which was used to partial out any confounding effects of basic processing efficiency deficit that could influence the reliability and validity of IC tasks.

A smaller set of DAV measures are available in the literature to measure this construct. As already reviewed, the most widely used delay-related motivational tasks are the choice delay tasks. The Maudsley's Index of Delay Aversion task (Kuntsi et al., 2001b) was used in the present thesis as it was found to have good test-retest reliability (Kuntsi et al., 2001b). However, choice delay tasks have an increased risk for ceiling effects, if used with adolescents. Therefore, two more non-choice delay tasks were used to measure DAV deficit: the Delay Reaction Time (Sonuga-Barke & Taylor, 1992) and Delay Frustration tasks (Bitsakou et al., 2006).

In the following two subsections, the description of the tasks and their psychometric properties will be provided.

4.3.1. IC measures

Stop-Signal task (Logan et al., 1997):
The Stop-Signal task measures the IC mechanism in relation to pre-potent responses. The task has been found to have good reliability, adequate validity (Logan et al., 1997) and an adequate effect size of .6 (Willcutt et al., 2005). The Stop-Signal measure had two parallel elements: the 'go' and the 'stop' task. The visual stimuli for the go task were the uppercase letters "X" and "O", presented in the centre of the screen for 1000ms (Inter-stimulus interval – ISI – 2500ms). Each go-task stimulus was preceded by a 500ms fixation point, also presented in the centre of the screen. A 500ms, 1000Hz auditory tone (stop stimulus) was generated by the computer and was presented, after the 'go' stimulus, randomly on 25% of the trials. The task had 192 trials divided into six 32-trial blocks. The first two blocks were practice trials, thus they were not included in the analysis. There was an equal number of "X" and "O"s in each block. The stop signal was presented on 8 (i.e. 25%)

of the response execution trials and it was also presented on half of the time with an "X" and half of the time with an "O". Participants were instructed to respond to 'go' stimulus by pressing a response button and, whenever an auditory tone occurred, to inhibit their response to the 'go' stimulus. Moreover, they were instructed to respond as quickly as possible without making errors on the X/O discrimination, that they would be unable to stop every time, and that they should not wait for the beep. All the instructions were written on the computer screen at the beginning of the task, and they were read by the experimenter, who remained with each child throughout the task.

Adjusting procedure: The interval between the go signal and the stop tone was varied on the basis of the participants' performance to ensure that the probability of stopping successfully was thus maintained at approximately 50%. The stop signal delay was initially set at 250ms. If the child failed to inhibit their response when the tone sounded, on the subsequent trial the stop signal delay (i.e. the interval between the presentation of the go signal and the auditory tone, i.e. stop signal) was decreased by 50ms (making it easier to inhibit on the next stop-signal trial); if they inhibited successfully, the stop signal delay was increased by 50ms on the next trial (making it harder to stop next time). The stop signal reaction time (SSRT) was estimated by subtracting the mean stop signal latency from the mean of correct go response times in each block, and then averaging out the values across the four blocks (Figure 4.1). This was then taken as an estimate of the time required to complete the stopping of an initiated go response.

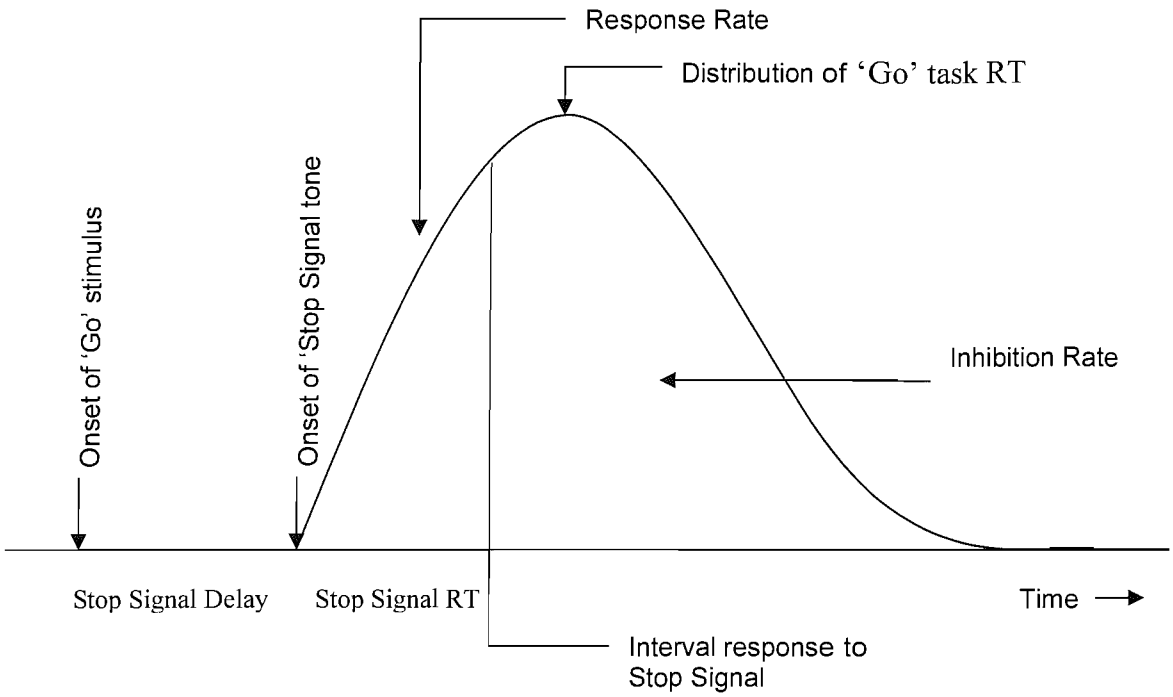


Figure 4.1.: Schematic representation of Stop Signal Task (cited by Band, van der Molen, & Logan, 2003).

Modified Stroop Task (MStroop; Hogan et al., 2005):

Two tasks have been widely used in the literature to measure interference control: Stroop Colour/Word and Flanker tasks. In the original Stroop Task (Stroop, 1935), participants have to read words of colours printed in incompatible colour as fast as they can, while resisting naming the colour of the letters. The RT of their reading speed is an index of interference control. Test retest reliability of Stroop task ranges from low to high (intra-class correlation = .2 - .9; Gualeti & Johnson, 2006; Lemay et al., 2004; Lowe & Rabbitt, 1998; Salinski et al., 2001). However, the interference control deficit found in children with ADHD might be mediated by their reading difficulties, as they need more time to process and read a word (van Mourik et al., 2005). On the other hand, in the original Eriksen Flanker task (Eriksen & Eriksen, 1974), the distracter/interfering stimuli are presented in parallel with the target stimulus, so participants have to disengage from the visual distractor and respond to the target. Hogan and colleagues (2005) have developed a task (MStroop task) that integrates the principle of both Stroop and Flanker tasks: it shares the same target stimulus like the one used in Flanker task (i.e. arrow), although the distractor factor is the colour of the stimulus (as in the Stroop task).

In the MStroop task children were presented with of 100 trials of compatible and interference stimuli. Compatible stimuli were green left- or right-pointing arrows ('go'

stimuli in Figure 4.2) and interference stimuli were red left- or right-pointing arrows (Figure 4.2). For the compatible stimuli (ISI 1500ms, stimulus duration 100ms) participants were instructed to press the left computer mouse button on presentation of a green left-pointing arrow, and the right mouse button on presentation of a green right-pointing arrow. On 25% of the trials a red arrow (interference stimulus; ISI 1500ms, stimulus duration 100msec), which was pointing either to the left or to the right, appeared on the screen. Participants were instructed to press the opposite mouse button in response to red arrows (i.e. if there was a red left-pointing arrow then the participant had to press the right button). They were also instructed to respond to the stimuli as fast and as accurate as possible.

The probability of correctly inhibiting responses to the interference stimulus (MStoopPI) is regarded as the main IC index derived from the task. The correct/error RT, RT variability, and the probability of omitted trials were also recorded for each participant. Test re-test reliability for this task can be found in section 4.4 of this chapter.

Go/No-Go task (GNG; Hogan, unpublished data):
This was a computer-based task specifically developed for this study and it was based on previously developed Go/No-Go tasks (e.g. Rubia et al., 2001). Previous findings have shown that Go/No-Go task has adequate test-retest reliability (intra-class correlation = .64; Kuntsi et al., 2005a). In the present GNG task, a motor response had to be selectively executed or inhibited depending on whether a 'go' (left/right green arrow) or 'no-go' (double-ended green arrow) stimulus appeared on the computer screen in 75% or 25% of trials, respectively. The ISI for all stimuli was 1500ms: stimulus duration was 100ms, followed by response duration (blank screen) of 1400ms (Figure 4.2). The task was administered in one block of 100 experimental trials. However, participants were provided with 10 practice trials before the experimental trials. Children were instructed to respond as fast and as accurately as they could to the 'go' stimuli by pressing the left or right computer mouse button indicating the direction of the green left or right-pointing arrow respectively, but not to respond to the 'no-go' stimuli.

The probability of a correctly inhibited response to the 'no go' stimulus is regarded as the main index of the GNG task (GNGPI). The correct/error RT, RT variability, and the probability of omitted trials were also recorded for each participant. Test re-test reliability for this task can be found in section 4.4 of this chapter.

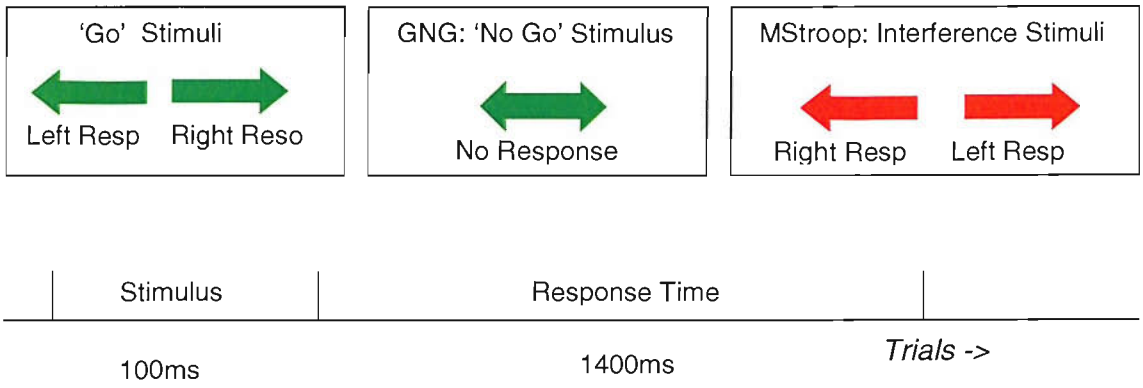


Figure 4.2.: Schematic representation of the 2CR, GNG and MStroop task. 'Go' stimuli are the same for all three tasks. For GNG task, the inhibitory stimulus is a double ended arrow, where children should avoid giving a response. On the MStroop task, the inhibitory stimuli are red arrows, where children have to give the opposite response from the direction of the arrow. For all tasks stimulus interval is 100ms and 1400ms response time.

4.3.2. DAV measures

The Maudsley's Index of Childhood Delay Aversion (MIDA; Kuntsi et al., 2001b): This is a computer-based choice delay task specifically designed to test delay aversion. The task measures preference towards a large reward after a long delay rather than a small immediate reward. MIDA has been found to have high reliability (intra-class correlation = .74; Kuntsi et al., 2001b) and adequate effect size (d = .57; Sonuga-Barke et al., 2007).

The task was presented as a space game, in which the child had to destroy enemy space-craft with their own spaceship, by using the computer mouse (Figure 4.3). The child chose between two options: either to wait for 2sec in order to destroy one spaceship and get 1 point as a reward, or to wait for 30sec in order to destroy two spaceships and get 2 points as a reward. Whenever the child made a response the computer was moving to the next mission (i.e. no-post reward delay). The task included 15 trials, which were counted to the child by placing 15 stars next to the computer. Every time the child completed a trial, a star was removed. Before the experimental trials, children were administered two practice trials to choose one of each of the rewards. After the practice session the researcher also asked the child questions about the game, to ensure that they had understood the rules and aims of the game correctly. Depending on the child's final score (max. 30 points) the child received a reward of either 1 pencil or 1 pencil and two extra small stationary items

(e.g. robber, ruler etc). The value of the reward was not revealed to the child until the end of the task. The percentage of selecting the large delayed reward (MIDA Prob DR) is perceived as the main index of the task.

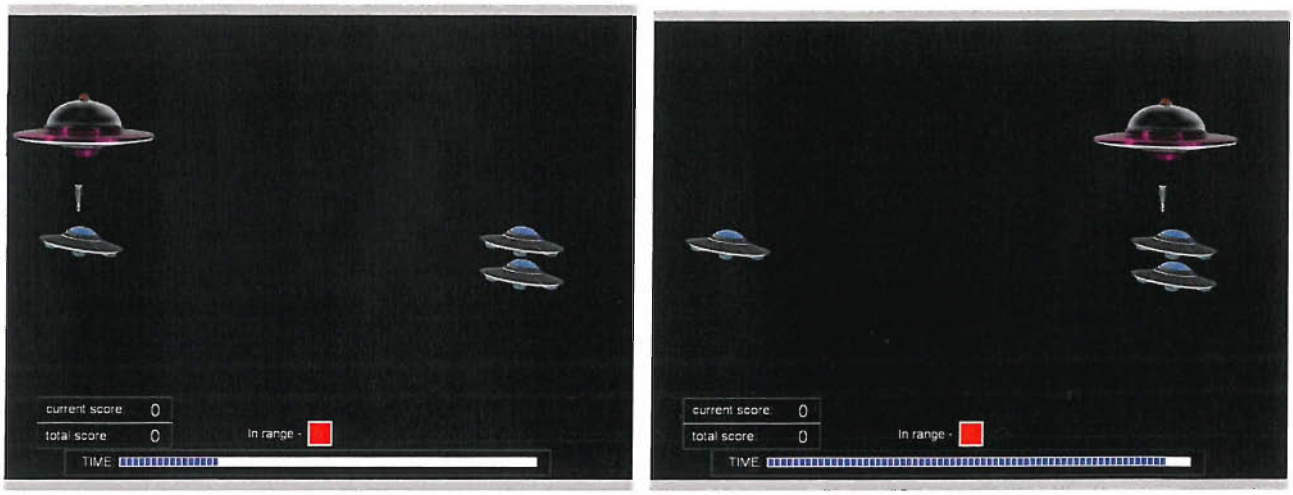


Figure 4.3.: Schematic representation of Maudsley's Index of Delay Aversion (MIDA), no post-delay reward condition (Kuntsi et al., 2001b). In each trial the child can choose out of two options; either to wait for 2sec and get 1 point (small reward; Left picture), or to wait for 30sec and get 2 points (large reward; Right picture).

Delay Frustration Task (DeFT; Bitsakou et al., 2006):

This task was based on the idea that people who are delay intolerant will be especially frustrated by unexpected and unsignalled delays during a series of activities, even when these delays are relatively short. This was expected to be especially the case when these delays represent an obstacle to the completion of what is considered by the participant to be an important primary task. In the Delay Frustration Task (DeFT), the 'primary task' involves a series of simple maths questions (55 trials; Appendix A.1) presented on a computer (Figure 4.4). The questions were presented separately one at a time with each question accompanied by four possible solutions. Participants were required to select the correct answer by pressing a button from a 4-button response box. On most trials ($N = 39$) as soon as the participant responded the program moved to the next trial (no post-response delay condition). However, on a minority of trials the access to the next question was delayed by 20sec (8 trials; post-delay condition). Moreover, 8 distractor trials were provided, where the delay period varied from 3 to 10 seconds. On the post-delay condition and distractor trials the response button was 'inactive' during the delay period and the responses were therefore ineffective at accessing the subsequent trial although all responses were recorded. At the end of the delay period the response box was 'reactivated' once again and the first response became effective in allowing

the participant to move on to the next trial. The sequencing of the post-response delay trials was presented in a pseudo-random order. For the first 10 trials there were no post-response delay trials. After that the placement of these trials was randomised across the remaining 45 trials.

This pattern of delay following responses was designed to create delay-related frustration leading to attempts by those delay averse participants to escape delay by pressing the button to move on to the next question. In order to reduce the possibility that participants would simply stop responding during these intervals on the grounds that the computer equipment was broken and/or contact the experimenter to complain that they were experiencing technical difficulties with the computer, the participants were 'warned' that the computer has given signs of malfunction and that if the computer appeared not to register their response they may need to respond again before they could move onto the next trial. No information was given about the nature of the length of the delays that might be experienced or how likely they would occur during a particular period in the experiment.

Total Duration (TD) of responding per second on the 20sec delay conditions was the main index of the task. TD was the product of the average response frequency (i.e. number of responses per second) and the average duration of each response (i.e. the total time of response per second) for each of the 20 seconds delay period. The overall mean of TD (i.e. DeFT MTD) was calculated, by averaging out the TD of the 19 second delay trials. The first second out of the 20 seconds delay was not included in the analysis, as this response was showing participants' reaction time to the arithmetic question and not delay aversion. Moreover, the 20sec delay period was also divided into four bin intervals (5 seconds per bin). Calculation of the effect sizes from the original paper, indicate that this task had high effect size (d = 1.42). Test-retest reliability of the task can be found in section 4.4 of this chapter.

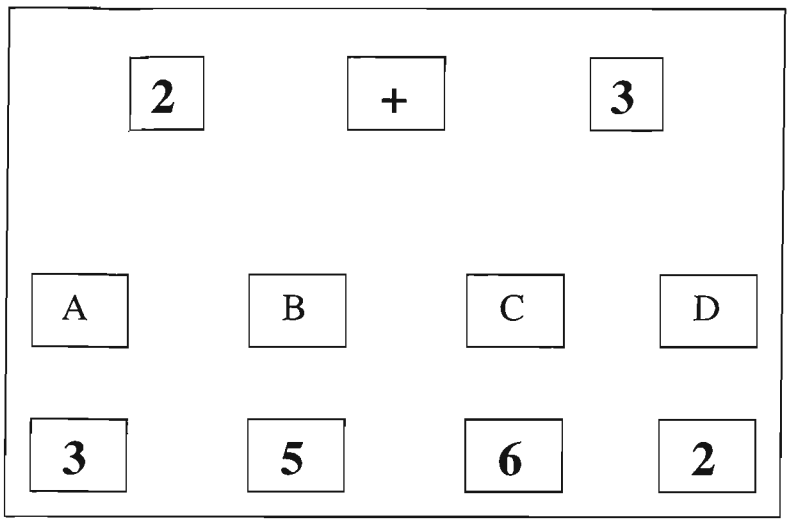


Figure 4.4.: Schematic representation of Delay Frustration Task (DeFT; Bitsakou et al., 2006). Children are presented with maths questions and four possible solutions to choose from. Questions are followed directly after the response, with the exception of some trials where the response initiates a delay period.

Delay Reaction Time task (DRT; Sonuga-Barke & Taylor, 1992):

This task is a modified version of the Delay Reaction Time task used by Sonuga-Barke and Taylor (1992), which was developed to measure aversion towards delay indicated by an increased RT to a delayed stimulus. The task used the same basic visual display elements of the GNG and the MStroop task. However, during this task a stimulus (either a left or a right green arrow) appeared on the centre of the computer screen for an extended period of delay (Figure 4.5). The screen then turned blank, at which point the participant was required to respond as quickly and accurately as possible to the disappearance of the stimulus, by pressing a left or right button according to the direction of the arrow. Each trial was indicated by a fixation tone of 500msec. Two delay periods were sampled a 3 second and a 20 second delay period. Participants were presented with 4 practice trials (2 trials for each delay condition) and then with 12 experimental trials (6 trials for each delay condition). The presentation of the left and right arrows was counterbalanced (i.e. in the 3 second delay condition, 3 trials involved the left arrow and 3 trials involved the right arrow; the same was true for the 20 second condition).

The main DRT index (i.e. DRT Delay Sensitivity – DRT DS) was based on an aggregated RT score for the two delay levels minus the RT on the 2 Choice Response task (see next section for details of this task). The 2CR measure, which had the same structure and visual components as the DRT, essentially had no delay (100 ms) prior to response being required and so represented a useful control against which to judge sensitivity to delay. Moreover, the RT and variability of

responses was recorded for each of the two delay conditions. Calculation of the effect sizes from the original paper, indicate that the task had moderate effect size for the delay conditions (15s: $d = .60$; 30sec: $d = .56$). Test-retest reliability of the task can be found in section 4.4 of this chapter.

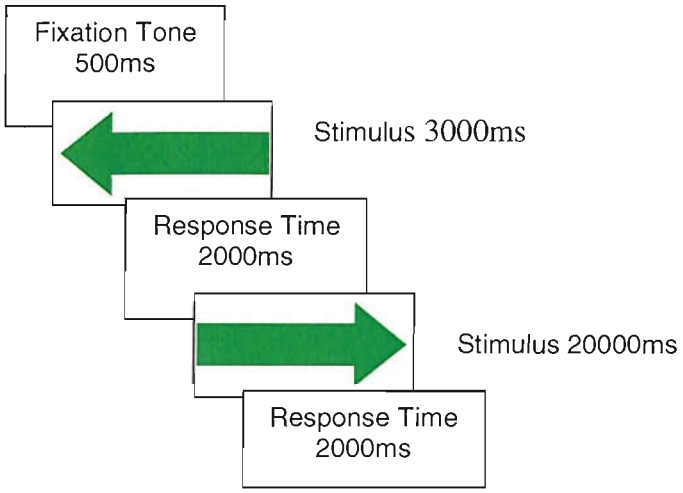


Figure 4.5.: Schematic representation of Delay Reaction Time (DRT; Sonuga-Barke & Taylor, 1992). Participants are presented with green arrows for either 3 or 20 seconds, and they were instructed to give a response after the disappearance of the stimulus.

4.3.3. Control measure

Basic Processing Efficiency – 2 Choice Response (2CR; Hogan et al., 2005):
This simple reaction time task was used to measure basic ability of processing fast event rate stimuli. This computer-based task included 100 green left- or right-pointing arrows (50% each; see Figure 4.2., 'Go' stimuli). ISI was 1500ms and stimulus duration was at 100ms. Children were instructed to respond as fast and as accurately as possible to the stimuli by pressing the left or right computer mouse button indicating the direction of the green left or right pointing arrow respectively. Correct RT and RT variability to the stimuli were the main indices for this task. Simple RT tasks have good reliability (intra-class correlation = .8; Lemay et al., 2004). Test-retest reliability results of this task are reported in section 4.4 of this chapter.

4.4. Pilot Study

Some of the tasks used in the current study did not have established psychometric properties. Therefore, a small pilot study was run to examine the reliability of the novel and untested measures.

4.4.1 Aims

All tasks, apart from Stop Signal task and MIDA, were either developed in our laboratory (e.g. GNG), or have never been tested for their reliability when used with children (MStroop, 2CR, DRT and DeFT tasks). Therefore, a small pilot study was conducted with 12 children recruited from the community, in order to investigate tasks' test-retest reliability. Due to the small number of cases the construct and discriminant validity of the tasks could not be investigated.

4.4.2. Methods

4.4.2.1. Participants

Twelve children from the community were recruited to the pilot study. Mean age was 12.14 years (*SD* = 2.70; age range: 7 – 15). Seven children were males, with mean age of 12.83 (*SD* = 2.00) and five were females, with mean age of 11.19 (*SD* = 3.49).

4.4.2.2. Materials

Test-retest reliability was examined for MStroop, GNG, 2CR, DeFT and DRT tasks. Description of the tasks can be found in section 4.3 of this chapter.

Parents also completed the *Strengths and Difficulties Questionnaire* (SDQ; Goodman, 1997). The SDQ (Appendix A.10) measures general childhood behavioural symptoms and includes five subscales: conduct symptoms scale, hyperactivity scale, emotional symptoms scale, peer problem scale and pro-social behaviour scale (30 items). As indicated in Table 4.1, children's behaviour was rated below the clinical cut-off point (Goodman, 1997) for all subscales.

Table 4.1.: Mean and Standard Deviation of parental SDQ rating and clinical cut-off point for each subscale

SDQ scales	*Mean*	*SD*	*Clinical cut-off*
Hyperactivity	3.50	2.97	> 6
Conduct problems	1.08	1.50	> 3
Emotionality	2.83	2.82	> 4
Peer problems	1.92	2.27	> 3
Pro-social behaviour	8.75	1.28	< 5
Total behaviour	9.33	6.77	> 14

4.4.2.3 Procedure

All tasks were presented in pseudo-counterbalanced order across participants. However, the 2CR task was always administered before the MStroop and GNG tasks. All children were re-tested 2 weeks after the initial testing. The order of the battery remained the same for each participant at Time 2 as at Time 1.

4.4.2.4. Initial data preparation

Impossible responses and outliers: Tests were run for outliers on all the dependent measures of each individual and each task. Reaction times that were less than 100ms were considered as impossible non-processed responses, and were replaced with the mean for the relevant cell for that person. Moreover, any score that lay outside of three standard deviations from the mean was considered an outlier. In those cases, outliers were replaced with the group mean for the relevant cell for that measure.

Omissions: High omission rate in IC tasks indicate high inattention level, and therefore children's responses could be invalid. Thus, the number of omissions of 3 SDs above group mean on all IC measures was perceived as inappropriate, and scores for that person were replaced with the group mean.

4.4.3. Results

To establish test-retest reliability, the intra-class correlations, inter-class Pearson product-moment correlations, and partial correlations - controlling for age – were calculated for each of the response variables (Table 4.2). Following previous research we focus on intra-class rather than inter-class correlations (e.g. Kuntsi et al., 2001b), although we report both to enable comparison with previous research.

Measures with intra-class correlations ranging from .4 to .6 are considered having a moderate reliability, whereas measures with intra-class correlations of .7 and higher are considered as highly reliable. In addition, to indicate whether participants' performance improved consistently across time, t-test results are also reported for the comparisons between mean scores at time 1 and time 2 for each variable (Table 4.2).

In general, all tasks had high reliability, with very few exceptions. GNG main index (GNGPI) showed moderate reliability, whereas Error responses had low reliability. All MStroop measures, including the main index MStroopPI, were highly reliable with the exception of Error RT variability. The basic processing efficiency measures and all DeFT measures were highly reliable. Finally, DRT reaction times showed moderate to high intra-class correlations, whereas RT variability in both delay conditions had low to moderate reliability. Most importantly though the main index of DRT (i.e. DRT DS) had high intra-class correlation.

Despite the wide age range used in this study, the Pearson's correlation results were in general similar for the main indices of the tasks, whether or not age was controlled, with only slight decreases in the size of the correlation for the partial correlations. Finally, t-test results were not significant for any of the measures, indicating that there were no learning effects.

Table 4.2.: Test-retest reliability results on 2CR, GNG, MStroop, DRT, and DeFT tasks

Measure	*Intra-class r*	*Inter-class r*	*Partial r*[a]	*Time 1 Mean (SD)*	*Time 2 Mean (SD)*	*t-value*	*df*	*p*
2 Choice Response								
RT (ms)	**.86**	**.79**	**.65**	**384 (95)**	**401 (72)**	**1.00**	**11**	**.33**
SD (ms)	**.78**	**.65**	**.31**	**88 (37)**	**101 (45)**	**1.26**	**11**	**.23**
Go/No-Go								
GNGPI (%)	**.61**	**.44**	**.45**	**83.33 (15.61)**	**84.66 (17.54)**	**0.26**	**11**	**.79**
Go RT (ms)	.89	.81	.67	451 (83)	457 (93)	0.34	11	.73
Go SD (ms)	.75	.64	.57	104 (35)	109 (51)	0.48	11	.63
Error RT (ms)	.45	.34	.03	352 (103)	324 (57)	0.84	8	.42
Error SD (ms)	.27	.70	.24	91 (38)	78 (49)	0.37	5	.72
Modified Stroop								
MStroopPI (%)	**.71**	**.56**	**.57**	**78.68 (12.21)**	**79.15 (10.05)**	**0.15**	**11**	**.88**
Go RT (ms)	.93	.89	.83	487 (114)	489 (100)	0.12	11	.90
Go SD (ms)	.94	.89	.85	142 (54)	138 (46)	0.62	11	.54
Error RT (ms)	.87	.82	.79	481 (149)	482 (107)	0.04	10	.96
Error SD (ms)	.30	.30	.29	114 (64)	164 (85)	1.28	9	.23
Delay Reaction Time								
DRT DS (ms)	**.79**	**.74**	**.72**	**178 (148)**	**155 (91)**	**0.75**	**11**	**.46**
RT 3s (ms)	.51	.35	.66	604 (157)	585 (119)	0.41	11	.68
SD 3s (ms)	.15	.08	.06	224 (148)	191 (108)	0.64	11	.53
RT 20s (ms)	.89	.80	.65	520 (151)	529 (149)	0.32	11	.75
SD 20 (ms)	.57	.40	.24	147 (104)	122 (94)	0.81	11	.43
Delay Frustration								
DeFT MTD (ms)	**.89**	**.81**	**.82**	**138 (154)**	**136 (140)**	**0.08**	**10**	**.93**
TD RT 2-5 (ms)	.90	.82	.82	118 (112)	139 (118)	1.04	10	.32
TD RT 6-10 (ms)	.79	.66	.72	134 (164)	148 (169)	0.33	10	.74
TD RT 11-15 (ms)	.88	.80	.81	132 (147)	135 (127)	0.14	10	.89
TD RT 16-20 (ms)	.88	.81	.81	165 (192)	122 (159)	1.26	10	.23

Note: DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go/No-Go Probability of Inhibition; MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; TD = Total Duration; [a] = control for age.

4.4.4. Discussion of pilot results

The main aim of the pilot study was to examine the test-retest reliability of the novel and untested measures to be used in this thesis.

The main indices of all measures showed high reliability, and only the main index of GNG task showed moderate, but adequate, reliability. Subsidiary measures also demonstrated good reliability. Exceptions were the error responses on the GNG and MStroop tasks, and RT variability on the short delay condition of the DRT tasks. These results are in line with previous reported reliabilities of IC and DAV measures (e.g. Gualtieri & Johnson, 2006; Kuntsi et al., 2005a; Kuntsi et al., 2001b; Lemay et al., 2004; Logan et al., 1997; Salinsky et al., 2001). Consistent with previous research (Kuntsi et al., 2005a), age did not have a significant effect on participants' performance. Finally, no effect of learning was found as participants' performance was consistent across time for all measures.

4.5. Summary

The psychometric properties of IC and DAV measures have not been documented extensively. Factors such as the energetic state or ADHD subtype of the participant, the tasks' various designs across research labs, their low effect size, ceiling effects, and the possibility of tapping into additional neuropsychological functions, can influence the psychometric properties of the tasks. Taking into account the so far known psychometric properties of various IC and DAV measures, a neuropsychological battery was selected for the present thesis.

Three tasks were selected for each construct, in order to increase consistency and construct validity. For inhibitory control, the Stop Signal, Go/No-Go and Modified Stroop tasks were selected. For delay aversion, the Maudsley's Index of Delay Aversion, Delay Frustration and Delay Reaction Time tasks were selected. Furthermore, a measure of basic processing efficiency was included in order to control for its effect on IC measures. All measures, except the Stop Signal task and MIDA were tested for their test retest reliability. The main indices of the measures showed moderate to high reliability. Therefore, the measures were adequate to be used in the main study. Because the

sample of this study was small, it was not possible to investigate the construct and discriminant validity of the tasks, as well as whether they were appropriate to be used across different age groups. However, issues of validity and age appropriateness of these tasks were explored in the main study.

CHAPTER FIVE: ADHD and impaired Inhibitory Control (IC)

5.1. Aim of the chapter

In Chapter 1 and 2, the clinical characteristics and the genetic and environmental aetiology of ADHD were presented. Causal models of ADHD were presented in Chapter 3 with an emphasis on inhibitory control (IC) and delay aversion (DAV) as neuropsychological markers. The dual pathway model of ADHD was also discussed. Finally, in chapter 4, methodological issues relating to the measurements of IC and DAV were highlighted.

The aim of this chapter was to investigate the association of ADHD with IC measures. Specifically, two main IC domains were investigated: motor response inhibition and interference control. In response inhibition measures, a pre-potent response should be inhibited. In interference control tasks, an automatic response should be inhibited and replaced by another contradictory response.

The four key predictions are:

(i) *Children with ADHD will have poor performance on both IC domains compared to control children.*
(ii) The ADHD-IC link will persist even when the relationship with basic processing efficiency is controlled.
(iii) The ADHD-IC link will persist even when age, gender, IQ, and comorbid ODD are controlled.
(iv) The main indices of IC measures will be correlated.

5.2. Methods

5.2.1. Participants

Seventy-one pairs of children with ADHD and their siblings and 50 typical control children were recruited to the study. Six siblings of ADHD probands were also affected with ADHD. For the purpose of the analyses in this chapter, only children affected with

ADHD (i.e. probands and affected siblings) as well as control children were included. Therefore, 77 children with ADHD combined type (M_{ADHD} = 11.82years, SD_{ADHD} = 2.39years) and 50 typical controls ($M_{controls}$ = 12.15years, $SD_{controls}$ = 2.25years) were included in the analysis of this chapter. Inclusion criteria were an estimated full IQ of at least 70 as measured by a short version of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), age range between 6 to 17, and no apparent other major mental health problems, such as autism, epilepsy, brain disorders, or known genetic disorders, such as Downs syndrome or Fragile X syndrome.

5.2.2. Recruitment and Procedure

ADHD cases: Families of children with ADHD who were registered at a clinic around the Hampshire area were contacted by phone and informed about the study. If the family was interested in participating, they were sent an information pack (Appendix A.2), consent forms (Appendix A.3-A.5), and a set of questionnaires to be completed by parents and children (see below for details). Moreover, the experimenter booked an appointment with the family, in order for the neuropsychological testing to take place either in the clinic or in their house. Parents were asked to provide the researcher with the complete set of questionnaires on the day of the appointment. For children with ADHD a set of questionnaires (see below) was also sent to their teacher to complete and return by post.

Controls: Two sources were used to recruit healthy control children – schools and churches. Information letters were sent to Head of Schools and Reverends of churches. If they agreed to take part, an information letter, consent forms and a set of questionnaires were sent to families (Appendix A.6 and A.7). If the family was interested in the study, they sent the consent forms and questionnaires back to the researcher, who then contacted the families to book an appointment for the neuropsychological testing at the family's house or at school. For healthy control children the teacher questionnaires were given to the parent, who passed them to the teacher of the child. Teachers returned the questionnaires by post.

Children with ADHD were off-drug at least for 48 hours before testing. During the children's neuropsychological testing, the parent completed the *Parental Account of*

Childhood Symptoms interview (PACS; Taylor et al., 1991). No PACS interview was taken from the healthy control children. Full testing time was approximately 2 to 2 1/2 hours. At the end of the testing all children received a £5 voucher for their participation.

5.2.3. Diagnostic Criteria

Children with ADHD were recruited from six clinics in the Hampshire area and have been diagnosed with the disorder by a child psychiatrist, based on the DSM-IV criteria following a thorough clinical evaluation. Rating scales used to quantify ADHD symptoms included in this study were the long version of *Conners' Parent Rating Scale* (CPRS-R:L; Conners, 1996), long version of *Conners' Teacher Rating Scale* (CTRS-R:L; Conners, 1996), parent and teacher versions of the *Strengths and Difficulties Questionnaire* (SDQ; Goodman, 1997), parent and teacher versions of the Swanson, Nolan, and Pelham questionnaire (*SNAP-IV;* Swanson, 1992), and Social Communication Questionnaire (Berument et al., 1999). Details about these psychometric scales are reported in section 5.2.4.2.

In addition to the clinical diagnosis, children with ADHD were assessed on the PACS (Taylor et al., 1991). PACS is a semistructured interview developed to provide an objective measure of child behaviour. A trained interviewer administered PACS with parents, who were asked for detailed description of the child's typical behaviour in a range of specified situations. Inter-rater reliability was high with product-moment correlations for pairs of interviewers ranging from .79 to .96 (Brookes et al., 2006). The Hyperactivity subscale was made up of attention span, restlessness, fidgetiness, and activity level, with other subscales covering defiant, emotional and other comorbid disorders including ODD and autistic spectrum disorder. A standardized algorithm was applied to PACS to derive each of the 18 DSM-IV ADHD items. These were combined with items that were scored 2 (pretty much true) or 3 (very much true) in the teacher-rated Conners ADHD subscales to generate the total number of hyperactive-impulsive and inattentive symptoms of the DSM-IV symptom list. Situational pervasiveness was defined as at least one symptom occurring in two or more situations and the age of onset of the symptoms needed to be before 7 years old.

Typical control children were recruited if they scored below the clinical cut-off of 5 on the hyperactivity/impulsivity subscale of the SDQ. In this analysis the parent and teacher SNAP-IV rating scale was used to quantify symptoms in this sample. Moreover, none of the typical control children had any diagnosed mental disorder according to parental reports. See Table 5.1 for background information on clinical cases and controls.

5.2.4. Materials

5.2.4.1. Inhibitory Control measures

As in Chapter 4, section 4.3.1.

5.2.4.2. Clinical and IQ evaluations

Wechsler Intelligence Scales for Children (WISC-III; Wechsler, 1991): The Vocabulary and Block Design subtests from the Wechsler Intelligence Scales for Children-III (WISC-III; Wechsler, 1991) were used to estimate IQ. In order to convert the scaled scores to deviation IQ scores, the formula by Sattler (1992) was used. According to Sattler (1992) this two-subtest short form IQ has reliability of .95 and validity of .86.

Parents and teachers of children with ADHD and control children completed a set of questionnaires to examine their clinical characteristics.

Conners' Parent Rating Scale – Revised (CPRS-R; Conners, 1996):
This is a well validated 80-item behavior rating scale that measures symptoms of ADHD (hyperactivity, impulsivity, and inattention) as well as comorbid behaviours such as oppositional behavior, anxiety, and somatic complaints (Appendix A.8). All 12 CPRS-R scales focus on behaviours central to a diagnosis of ADHD such as Cognitive Problems and Hyperactivity or measure behaviours that are commonly comorbid with inattention and hyperactivity, such as social problems. Behaviours are rated on a 4-point scale that ranges from 'Very True' to 'Not True'. A T-score is derived for each scale, based on a large age and gender specific normative sample. A T-score (M = 50, SD = 10) over 65 is considered to indicate moderate to severe clinical impairment. The Conners' Teacher Rating Scale – Revised (CTRS-R; Conners, 1996) has the same structure as the CPRS-

R, only that it includes 59 items instead of 80 (Appendix A.9). The CPRS-R and CTRS-R were only administered to parents and teachers of children with ADHD.

Parent & Teacher Strengths and Difficulties Questionnaire (SDQ; Goodman, 1997):
The SDQ (Appendix A.10 and A.11) measures general childhood behavioural symptoms and includes five subscales: conduct symptoms scale, hyperactivity scale, emotional symptoms scale, peer problem scale and pro-social behaviour scale (30 items). According to Goodman (1997) the questionnaire has good psychometric properties and has been shown to have high levels of both sensitivity and specificity when used to identify clinical cases. The questionnaire was administered to parents and teachers of both groups.

Parent and Teacher Swanson, Nolan, and Pelham questionnaire (SNAP-IV; Swanson, 1992):
The original version of this questionnaire included 43 items, which included DSM-IV symptoms of ADHD and ODD. However, in order to keep the questionnaires shorter only the inattentive (8 items) and impulsive/hyperactive items (10 items) of the SNAP-IV were included (Appendix A.12). This questionnaire was used in conjunction with the SDQ for a better measurement of the ADHD symptoms. This questionnaire was completed by parents and teachers of both groups. Table 5.1 provides the characteristics of the two groups.

Table 5.1.: Clinical Characteristics of ADHD cases and typical controls by age and by gender.

	ADHD Cases				Typical Controls					
	6 -12 years		13 – 17 years		6 -12 years		13 – 17 years			
	Male	Female	Male	Female	Male	Female	Male	Female	Status *F*	*p*
	N = 44	**N = 10**	**N = 19**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 5**		
Age	10.48 (1.48)	10.83 (1.41)	14.89 (1.06)	14.45 (1.36)	10.79 (2.16)	11.05 (2.14)	13.85 (.8)	13.99 (1.02)	0.62	.43
WISC-III	**N = 44**	**N = 10**	**N = 19**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 5**		
Vocabulary	9.11 (2.81)	7.8 (3.93)	8.26 (2.42)	10.25 (0.50)	10.82 (4.06)	9.58 (2.71)	8.50 (2.78)	11.2 (4.32)	3.31	.07
Block Design	9.59 (2.89)	8.2 (2.86)	9.05 (2.06)	9.50 (1.00)	10.82 (2.24)	11.17 (2.51)	9.38 (2.36)	11.2 (3.89)	6.45	< .05
Full	96.2 (13.77)	87.76 (18.88)	91.94 (9.90)	99.25 (4.50)	105.07 (16.91)	102.27 (10)	93.62 (13.76)	107.20 (18.8)	6.80	< .05
Parent SDQ	**N = 44**	**N = 10**	**N = 19**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 5**		
Hyperactivity	8.25 (1.76)	8.00 (1.76)	8.16 (2.00)	8.75 (2.50)	2.18 (1.74)	2.08 (1.78)	1.94 (1.61)	1.20 (1.78)	374.36	< .001
Conduct	5.84 (2.51)	5.8 (2.04)	5.37 (2.45)	5.00 (2.16)	1.88 (2.23)	0.75 (0.96)	1.38 (1.58)	0.60 (0.89)	123.98	< .001
Emotional	4.41 (2.59)	3.6 (3.2)	3.32 (2.26)	4.75 (2.36)	1.59 (2.23)	2.00 (1.90)	1.06 (1.28)	1.20 (1.3)	37.50	< .001
Peer Relation	4.59 (4.01)	4.3 (1.7)	3.47 (2.48)	3.50 (3.41)	1.24 (1.60)	1.5 (1.62)	2.56 (2.75)	2.00 (1.87)	20.23	< .001
Prosocial	5.64 (2.30)	5.2 (2.74)	5.37 (1.57)	5.25 (1.50)	7.94 (2.04)	9.25 (1.28)	8.69 (2.38)	-	71.91	< .001
Impact	5.48 (2.41)	4.8 (3.39)	5.05 (2.22)	4.27 (3.39)	0.35 (0.99)	0.17 (0.57)	0.25 (0.77)	0.20 (0.44)	176.32	< .001
Total	23.09 (6.75)	21.7 (6.43)	20.32 (5.46)	22.00 (7.39)	6.88 (5.21)	6.33 (4.31)	6.31 (4.19)	5.00 (3.00)	230.70	< .001
Teacher SDQ	**N = 34**	**N = 10**	**N = 15**	**N = 3**	**N = 14**	**N = 10**	**N = 10**	**N = 3**		
Hyperactivity	6.88 (2.76)	6.2 (3.88)	7.13 (2.56)	-	1.57 (1.65)	0.90 (1.28)	1.8 (.91)	0.33 (0.57)	120.30	< .001
Conduct	2.61 (2.43)	2.5 (2.36)	3.60 (2.13)	0.33 (0.57)	0.36 (0.63)	0.40 (0.96)	0.30 (0.67)	-	36.05	< .001
Emotional	2.09 (2.08)	2.8 (2.57)	2.53 (3.04)	4.00 (1.73)	0.71 (1.13)	1.00 (1.63)	0.60 (1.26)	1.33 (2.3)	13.61	< .001
Peer Relation	2.79 (2.52)	4.1 (3.81)	2.53 (1.99)	4.00 (3.60)	1.36 (1.59)	1.20 (1.13)	1.20 (1.47)	1.33 (2.33)	13.15	< .001
Prosocial	5.65 (2.78)	6.1 (2.47)	5.13 (2.5)	5.00 (2.00)	6.29 (2.92)	9.3 (1.05)	7.50 (2.46)	8.00 (2.00)	13.86	< .001
Impact	1.65 (1.49)	2.00 (1.88)	2.07 (1.9)	1.33 (1.15)	0.21 (0.42)	0.10 (0.31)	0	0	38.35	< .001
Total	14.33 (6.99)	15.6 (9.95)	15.8 (7.7)	14.33 (5.50)	3.71 (3.56)	3.50 (3.89)	3.90 (2.72)	3.00 (3.00)	74.38	< .001

Note: SDQ = Strengths and Difficulties Questionnaire; WISC = Wechsler Intelligence Scales for Children

Table 5.1.: Clinical Characteristics of ADHD cases and typical controls by age and by gender (continued)

	ADHD Cases				Typical Controls					
	6 -12 years		13 – 17 years		6 -12 years		13 – 17 years			
	Male	Female	Male	Female	Male	Female	Male	Female	Status *F*	*p*
Parent SNAP	**N = 44**	**N = 10**	**N = 19**	**N = 4**	**N = 17**	**N = 12**	**N = 15**	**N = 5**		
Hyperactivity	2.27 (0.79)	1.96 (.62)	2.09 (0.70)	1.50 (0.84)	0.55 (0.60)	0.40 (0.35)	0.14 (0.09)	0.36 (0.37)	218.43	< .001
Inattention	2.26 (0.70)	2.17 (.61)	2.28 (0.55)	2.56 (0.42)	0.55 (0.44)	0.42 (0.43)	0.35 (0.40)	0.32 (0.41)	313.32	< .001
Total	2.27 (0.64)	2.05 (.52)	2.17 (0.52)	1.97 (0.65)	0.54 (0.47)	0.40 (0.34)	0.23 (0.19)	0.34 (0.36)	358.23	< .001
Teacher SNAP	**N = 33**	**N = 10**	**N = 14**	**N = 3**	**N = 14**	**N = 10**	**N = 10**	**N = 3**		
Hyperactivity	1.29 (0.83)	0.79 (0.69)	1.44 (0.78)	0	0.23 (0.33)	0.14 (0.24)	0.24 (0.24)	0	48.79	< .001
Inattention	1.44 (0.85)	1.19 (0.81)	1.43 (0.77)	2.08 (0.94)	0.47 (0.44)	0.17 (0.27)	0.46 (0.41)	0	55.32	< .001
Total	1.35 (0.75)	0.96 (0.72)	1.43 (0.74)	0.97 (0.41)	0.33 (0.34)	0.15 (0.22)	0.33 (0.23)	0	65.59	< .001
Parent Conners	**N = 43**	**N = 10**	**N = 19**	**N = 4**	**N/A[a]**	**N/A[a]**	**N/A[a]**	**N/A[a]**	**N/A[a]**	**N/A[a]**
Hyperactivity	81.95 (9.70)	86.8 (6.69)	85.05 (7.85)	75.5 (17.69)						
Inattention	72.16 (7.22)	78.2 (13.4)	73.58 (7.68)	82.5 (13.07)						
Total	79.07 (7.78)	85.4 (8.52)	82.32 (7.69)	82.50 (15.00)						
Teacher Conners	**N = 35**	**N = 10**	**N = 16**	**N = 3**	**N/A[a]**	**N/A[a]**	**N/A[a]**	**N/A[a]**	**N/A[a]**	**N/A[a]**
Hyperactivity	62.43 (13.38)	67.2 (20.32)	72.50 (15.74)	46.00 (1.73)						
Inattention	59.09 (11.87)	68.3 (17.78)	68.38 (13.52)	80.67 (6.42)						
Total	61.74 (13.06)	68.7 (19.45)	72.44 (14.74)	69.33 (3.21)						
Comorbid Disorder	**N = 39**	**N = 10**	**N = 19**	**N = 4**	**N/A[b]**	**N/A[b]**	**N/A[b]**	**N/A[b]**	**N/A[b]**	**N/A[b]**
CD	13	5	4	0						
ODD	32	9	14	3						
Autism	0	0	0	0						
Mood	1	3	2	1						
Bipolar	1	0	0	0						
Anxiety	20	3	8	3						
Tourett's	1	0	0	0						
Substance Use	0	0	2	0						
OCD	5	1	2	0						
Attachment	0	0	0	0						
Schizophrenia	0	0	0	0						

Note: CD = Conduct Disorder; OCD = Obsessive Compulsive Disorder; ODD = Oppositional Defiant Disorder; SNAP = Swanson, Nolan, and Pelham Questionnaire (Swanson, 1992)

a = Typical controls did not complete parent and teacher Conners' questionnaire.

b = Typical controls were not administered the PACS in order to assess for comorbid disorders

5.2.5. Data preparation and analysis

5.2.5.1. Initial data preparation

Impossible responses and outliers: Tests were run for outliers on all the depended measures of each individual and each task. Reaction times that were less than 100ms were considered as impossible non-processed responses, and were replaced with the mean for the relevant cell for that person. Moreover, any score that lay outside of three standard deviations from the mean was considered an outlier. In those cases, outliers were replaced with the group mean for the relevant cell for that measure.

Omissions: High omission rate in IC tasks indicate high inattention level, and therefore children's responses could be invalid. Thus, the number of omissions of 3 SDs above group mean on all IC measures was perceived as inappropriate, and scores for that person were replaced with the group mean (1 child with ADHD on MStroop and Stop Signal task tasks, and 1 control child on GNG and MStroop tasks).

5.2.5.2. Data analysis

Analysis: Multivariate analysis of variance (MANOVA) was performed for all dependent variables with status (ADHD vs. controls) and age (6-12 years vs. 13-17 years) as independent between subject variables. Initial analyses suggested that gender was not a significant factor in any analysis and was therefore excluded from the models reported in this chapter in order to increase numbers of participants per cells (Appendix B.1).

Confounders: If the dependent variables correlated with estimated IQ, then ANCOVA was used controlling for IQ. In a further analysis, RT and RT variability on 2CR task were controlled for in ANCOVA to identify whether basic processing efficiency was likely to contribute to Status main effects on inhibitory control.

Comorbidity: As ODD is the most frequent comorbid disorder with ADHD, its effect on IC performance was also investigated. ADHD cases were categorized into 'pure' ADHD cases and ADHD+ODD cases based on the PACS. MANOVA was repeated by

introducing three status groups (ADHD, ADHD+ODD, and controls) into the analysis, alongside age.

Distribution of data: Parametric tests were used for the first analysis for all measures. However, all dependent variables were checked for normal distribution (Kolmogorov-Smimov test for normality). If the data from any measure was not normally distributed, it was log transformed and checked again for normality. If test of normality was not significant, MANOVA was performed with the log transformed measures. If however, log transformed measures were still not normally distributed, then non-parametric test (Mann-Whitney U-test) was used in addition to MANOVA. Any differences between parametric tests and log transformation and non-parametric tests are reported.

5.3. Results

5.3.1. Clinical characteristics

Table 5.1 displays the clinical characteristics for each group by age and gender. The groups did not differ in age ($F(1,125) = .62$, ns) but a gender difference was found between the two groups, with ADHD group having a higher proportion of males ($\chi^2(1) = 9.37$, $p < .01$). The response rate for teachers was 80.5% for ADHD cases and 78% for healthy controls ($U = 1799$, $p > .05$). Moreover, both parents and teachers reported more ADHD symptoms for ADHD cases compared to typical controls, according to the SDQ and SNAP questionnaires. In addition, control cases had higher estimated full IQ compared to ADHD cases ($F(1,125) = 6.80$, $p < .05$). Finally, 75% of ADHD cases had comorbid ODD, 44% had anxiety disorder and 26% had comorbid CD.

5.3.2. Stop Signal task

Correlation Analysis

In the literature, SSRT has been used as the main index of response inhibition for the Stop Signal task. In the current study response inhibition performance, as indicated by SSRT, was not affected by Go and Error RT (see Table 5.2). However, the more variable children were in their Go and Error responses, the slower their SSRT. Moreover, variability on SSRT was associated with all task measures. Go and Error RT

and SD were found to correlate. Finally, children's IQ was not associated with any of the measures. However, age and basic processing efficiency, as indicated by 2 CR RT and RT variability, were associated with response inhibition ability.

Table 5.2.: Correlation table of Stop Signal task measures and Basic processing efficiency, age and IQ

		1	2	3	4	5	6	7	8	9
1	SSRT (ms)									
2	SSRT SD (ms)	**.47****								
3	Go RT (ms)	-.01	**.51****							
4	Go SD (ms)	**.42****	**.94****	**.56****						
5	Error RT (ms)	-.10	**.34****	**.88****	**.37****					
6	Error SD (ms)	**.41****	**.49****	**.34****	**.49****	**.26****				
7	2CR RT (ms)	**.25****	**.50****	**.42****	**.46****	**.36****	**.28****			
8	2CR SD (ms)	**.29****	**.52****	.11	**.47****	.07	**.27****	**.37****		
9	Age	**-.24***	**-.37****	**-.26****	**-.36****	**-.24****	**-.22***	**-.50****	**-.29****	
10	IQ	.06	-.14	-.17	-.10	-.10	.01	.13	**-.19***	-.12

Note: 2CR = 2 Choice Response; RT = Reaction Time; SD = Standard Deviation, SSRT = Stop Signal Reaction Time; * = $p < .05$; ** = $p < .01$.

Analysis of Variance

A two-way MANOVA was used with two independent factors: status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years). Table 5.4 reports the MANOVA main effects and two-way interactions between independent factors and dependent measures. ADHD cases were significantly slower in SSRT compared to controls, indicating that they have deficient response inhibition (Figure 5.1). No significant difference was found on SSRT between the two age groups (Table 5.4). However, the status x age interaction on SSRT was not significant. In general ADHD cases had significantly worse performance in all Stop Signal measures compared to their counterparts, except for Go RT. Moreover, the main effect of age was significant, with the young age group having slower Go RT and SD, SSRT SD and faster Error RT compared to older children.

Log Transformation and Non-parametric Tests

The Kolmogorov-Smimov test of normality indicated that only Go RT was normally distributed. After log transformation of the remaining measures, only log transformed Go SD, Error SD and SSRT SD were normally distributed. The two-way MANOVA was performed for the log transformed measures. Log transformation did not alter the results of the analysis, with the significant main and interaction effects remaining significant. No significant differences were added.

The remaining two Stop Signal measures – Error RT and SSRT– that were not normally distributed even after log transformation were inserted into non-parametric tests (i.e. Mann-Whitney U-test). Even after non-parametric test was used, the main effects that MANOVA generated remained the same (Appendix B.2). Most importantly, the Status main effect on SSRT remained significant (U = 1273, p < .01).

Analysis of confounding factors

Children's IQ was not associated with any Stop Signal measure (Table 5.2.) and therefore no further action was taken to control for its effect.

Performance on response inhibition, as indicated by the SSRT, can be confounded by basic processing ability (see Table 5.2 for pattern of correlations). After 2CR RT was controlled for in ANCOVA, status (ADHD vs. control) main effect on SSRT remained significant (F(1,117) = 9.74, p = .002). After controlling for 2CR RT variability, the status main effect on SSRT was reduced, but remained significant (F(1,117) = 4.45, p = .037; Figure 5.1). Finally, the status main effect on SSRT was still significant even after controlling for SSRT SD (F(1,113) = 4.64, p = .033).

Table 5.3.: Group by Age by Gender Means (Standard Deviation) on Stop Signal task measures

	ADHD Cases				Controls			
	6 – 12 years		13 – 17 years		6 – 12 years		13 – 17 years	
	Male	Female	Male	Female	Male	Female	Male	Female
	N = 41	**N = 10**	**N = 19**	**N = 4**	**N = 16**	**N = 11**	**N = 16**	**N = 4**
SSRT (ms)	276 (94)	337 (149)	307 (166)	265 (67)	268 (112)	234 (73)	204 (38)	191 (117)
SSRT SD (ms)	119 (58)	151 (73)	121 (86)	53 (16)	106 (53)	109 (55)	54 (22)	71 (21)
Go RT (ms)	614 (110)	616 (153)	572 (133)	421 (86)	629 (111)	704 (170)	562 (135)	546 (144)
Go SD (ms)	175 (57)	206 (99)	172 (73)	98 (22)	161 (51)	163 (60)	111 (25)	120 (30)
Error RT (ms)	502 (85)	480 (121)	460 (108)	369 (68)	551 (95)	584 (131)	473 (111)	453 (124)
Error SD (ms)	122 (31)	128 (29)	134 (47)	94 (22)	123 (44)	109 (36)	100 (29)	100 (21)

Note: RT = Reaction Time; SD = Standard Deviation, SSRT = Stop Signal Reaction Time.

Table 5.4.: Main and interaction effects on Stop Signal task measures

	Status (S)			Age (A)			S x A		
	df	*F*	*P*	*df*	*F*	*p*	*df*	*F*	*p*
SSRT (ms)	117	9.33	.003	117	0.83	.363	117	2.44	.12
SSRT SD (ms)	117	8.77	.004	117	7.62	.007	117	2.17	.14
Go RT (ms)	117	1.29	.257	117	11.38	.001	117	.41	.52
Go SD (ms)	117	7.70	.006	117	8.79	.004	117	1.32	.25
Error RT (ms)	117	5.31	.023	117	14.00	.001	117	1.11	.29
Error SD (ms)	117	5.93	.016	117	0.94	.334	117	2.30	.13

Note: RT = Reaction Time; SD = Standard Deviation, SSRT = Stop Signal Reaction Time;

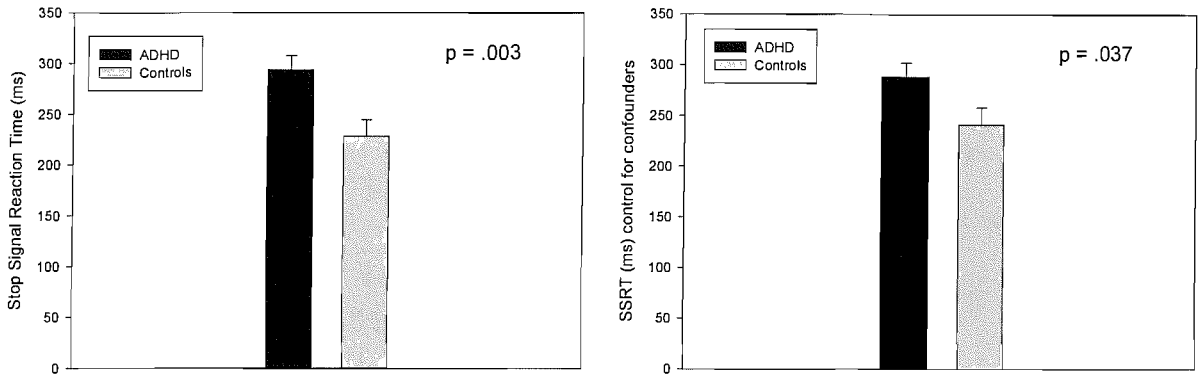


Figure 5.1.: Left: SSRT (SE) by Status; Right: SSRT (SE) by Status after controlling for 2CR SD.

Comorbidity

In order to examine the effects of comorbid ODD on Stop Signal performance, MANOVA was used with two independent factors: status (ADHD, ADHD+ODD, and Controls) and age (6-12 years vs. 13-17 years). Table 5.5 reports main and interaction effects of the analysis, as well as Bonferroni analysis results on Status differences. Most importantly, a significant main effect of Status was found on SSRT ($F(2,115) = 5.05$, $p = .008$). Bonferroni post-hoc analysis indicated that only ADHD+ODD cases had significantly worse performance on SSRT compared to controls ($p < .01$; Figure 5.2). 'Pure' ADHD cases were not different from either control or ADHD+ODD cases.

Table 5.5.: Main and interaction effects on Stop Signal task measures by comorbid group

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
SSRT (ms)	115	5.05	.008[a]	115	0.66	.416	115	1.81	.16
SSRT SD (ms)	115	4.59	.012[b]	115	3.34	.070	115	1.19	.30
Go RT (ms)	115	0.65	.521	115	5.21	.024	115	1.06	.34
Go SD (ms)	115	3.82	.025[a]	115	4.51	.036	115	0.74	.47
Error RT (ms)	115	2.64	.075	115	7.01	.009	115	0.97	.38
Error SD (ms)	115	4.16	.018[a]	115	0.74	.390	115	1.71	.18

Note: RT = Reaction Time; SD = Standard Deviation, SSRT = Stop Signal Reaction Time;
a = ADHD+ODD > CTR
b = ADHD, ADHD+ODD > CTR
> the group on the left of the symbol has worse performance

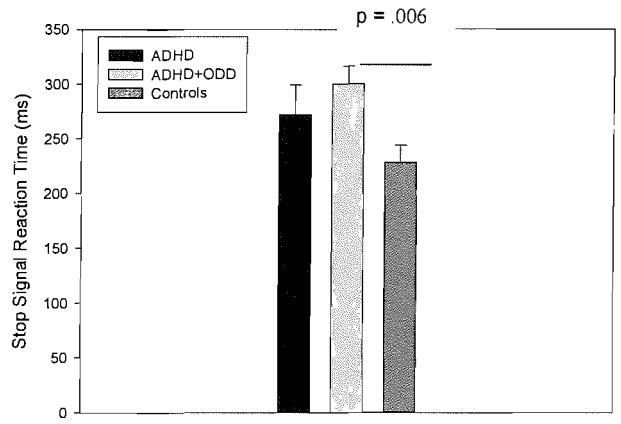


Figure 5.2.: SSRT (SE) by Comorbid group

5.3.3. Go-No-Go task (GNG)

Correlation Analysis

Probability of Inhibition has been used in the literature as the dependent variable most indicative of response inhibition on the Go-No-Go task (i.e. GNGPI). Response inhibition performance in the GNG task, as indicated by GNGPI, was not affected by slow Go RT (see Table 5.6). However, the higher the Go SD, Error RT and Error SD were, the lower the GNGPI. Moreover, the probability of omitting a trial was negatively correlated with GNGPI. Finally, children's IQ was not associated with any of the dependent measures of the task, whereas age and basic processing efficiency were associated with most of the GNG measures.

Table 5.6.: Correlation table of GNG task measures and Basic Processing efficiency, Age and IQ

		1	2	3	4	5	6	7	8	9
1	GNGPI (%)									
2	Go RT (ms)	-.006								
3	Go SD (ms)	**-.56****	**.51****							
4	Error RT (ms)	**-.24****	**.58****	**.56****						
5	Error SD (ms)	**-.52****	**.42****	**.63****	**.77****					
6	% Omission	**-.44****	**.37****	**.61****	**.37****	**.55****				
7	2CR RT (ms)	.13	**.58****	**.24****	**.27****	.08	.01			
8	2CR SD (ms)	**-.50****	**.50****	**.72****	**.47****	**.57****	**.52****	**.37****		
9	Age	**.18***	**-.42****	**-.26****	**-.29****	**-.19***	-.06	**-.50****	**-.29****	
10	IQ	-.04	.02	-.07	.03	-.03	-.17	.13	**-.19***	-.12

Note: 2CR = 2 Choice Response; GNGPI = Go No Go Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; * = $p < .05$; ** = $p < .01$.

Analysis of Variance

A two-way MANOVA was used with two independent factors: status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years). Main effects and two-way interactions between independent factors and dependent measures are reported in Tables 5.8. ADHD cases had lower GNGPI compared to control children (Figure 5.3). No age main effect or status x age interaction was found for GNGPI. Moreover, ADHD cases had worse performance in all GNG measures compared to controls, except for Error RT. Finally, young children showed slower Go RT and faster Error RT compared to adolescents (see Table 5.7). No two-way interactions were significant.

Log Transformation and Non-parametric Tests

None of the GNG dependent measures were normally distributed. In order to recover normality, log transformation was performed. The Kolmogorov-Smimov test of normality indicated that only log transformed Go RT was normalized. A two-way ANOVA (status and age) was performed for the log transformed Go RT. Log transformation did not alter the previous results reported on Go RT.

The remaining GNG dependent measures that were not normally distributed even after log transformation were entered into non-parametric tests (Mann-Whitney U-test). The main effects that MANOVA generated remained the same after non-parametric test was used (Appendix B.2). More interestingly, Status main effect on GNGPI remained significant ($U = 1005$, $p < .001$).

Analysis of confounding factors

Children's IQ was not associated with any GNG measures (Table 5.6.) and therefore no further action was taken to control for its effect.

Performance on response inhibition, as indicated by the GNGPI, can be confounded by basic processing efficiency (see Table 5.6 for pattern of correlations). After 2CR RT was controlled for in ANCOVA, status (ADHD vs. control) main effect on GNGPI increased ($F(1,120) = 14.07$, $p = .001$). After controlling for 2CR RT variability status main effect on GNGPI was marginally significant ($F(1,120) = 3.21$, $p = .075$; Figure 5.3) indicating that RT variability may be mediating inhibitory control performance in GNG task.

Table 5.7.: Group by Age by Gender Means (Standard Deviation) on GNG task measures

	ADHD Cases				Controls			
	6 – 12 years		13 – 17 years		6 – 12 years		13 – 17 years	
	Male	Female	Male	Female	Male	Female	Male	Female
	N = 44	**N = 10**	**N = 18**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 5**
GNGPI (%)	59.4 (21.82)	58 (25.59)	67.64 (22.17)	69 (24.95)	74.11 (23.28)	87.66 (10.01)	75.73 (21.45)	81.6 (19.51)
Go RT (ms)	468 (70)	473 (117)	441 (108)	376 (18)	444 (81)	476 (68)	368 (46)	381 (26)
Go SD (ms)	166 (88)	211 (135)	138 (83)	81 (16)	103 (43)	99 (26)	80 (41)	72 (24)
Error RT (ms)	375 (107)	389 (152)	331 (124)	297 (67)	265 (68)	340 (53)	323 (73)	288 (25)
Error SD (ms)	194 (164)	193 (190)	147 (175)	138 (145)	154 (141)	63 (29)	65 (21)	47 (9)
% Omission	5.96 (6.8)	7.86 (8.67)	8.35 (9.07)	1 (1.27)	1.31 (2)	1.66 (2.55)	.81 (1.17)	.8 (1.19)

Note: GNGPI = Go No Go Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation.

Table 5.8.: Main and interaction effects on GNG task measures

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*Df*	*F*	*p*
GNGPI (%)	99	4.83	.030	99	0.01	.921	99	2.31	.13
Go RT (ms)	99	4.92	.029	99	11.40	.001	99	3.16	.07
Go SD (ms)	99	9.11	.003	99	2.67	.105	99	.45	.50
Error RT (ms)	99	0.44	.508	99	4.37	.039	99	.008	.92
Error SD (ms)	99	6.37	.013	99	2.56	.112	99	.015	.90
% Omission	99	16.08	.001	99	0.04	.840	99	.72	.39

Note: GNGPI = Go No Go Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation.

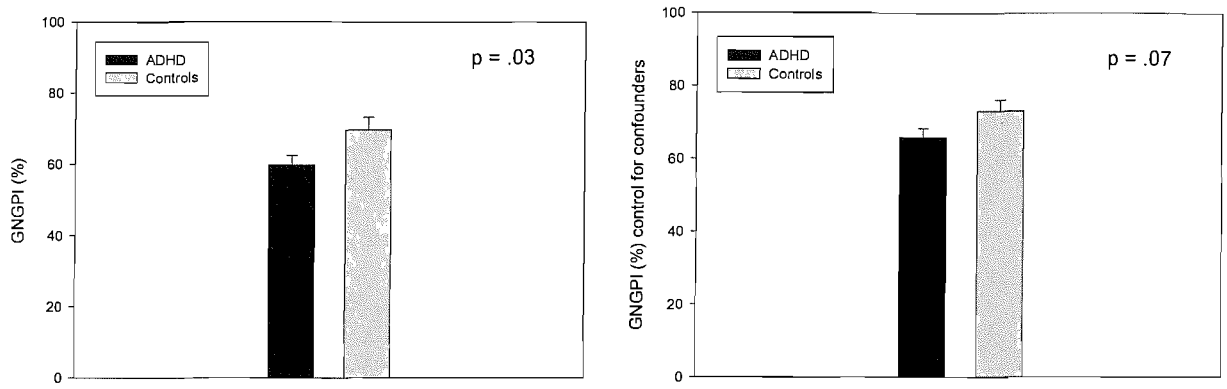


Figure 5.3.: Left: GNGPI (SE) by Status; Right: GNGPI (SE) by Status after controlling for 2CR SD.

Comorbidity

In order to examine the effects of comorbid ODD on GNG performance, MANOVA was used with two independent factors: status (ADHD, ADHD+ODD, and Controls) and age (6-12 years vs. 13-17 years). Table 5.9 reports main and interaction effects of the analysis, as well as Bonferroni analysis results on status differences. Most importantly, status main effect on GNGPI did not remain significant ($F(2,97) = 2.47$, $p = .09$; Figure 5.4).

Table 5.9.: Main and interaction effects on GNG measures by comorbid group

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
GNGPI (%)	97	2.47	.090	97	1.03	.31	97	1.70	.18
Go RT (ms)	97	2.52	.085	97	4.47	.03	97	2.22	.11
Go SD (ms)	97	4.66	.012[b]	97	1.20	.27	97	1.40	.25
Error RT (ms)	97	0.39	.676	97	2.72	.10	97	0.27	.75
Error SD (ms)	97	3.63	.030[a]	97	1.84	.17	97	0.02	.97
% Omission	97	8.34	.001[a]	97	0.56	.45	97	0.58	.55

Note: GNGPI = Go No Go Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation.
a = ADHD+ODD > CTR
b = ADHD, ADHD+ODD > CTR
> the group on the left of the symbol has worse performance

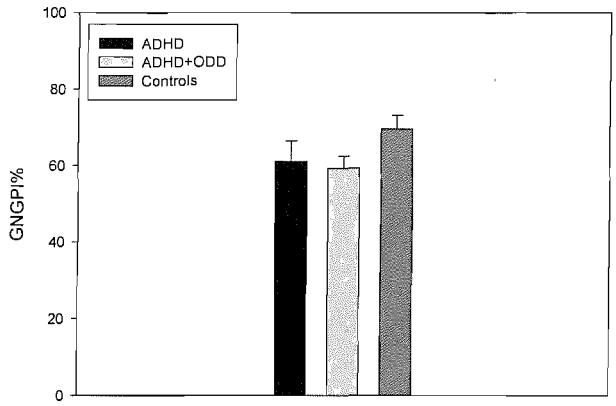


Figure 5.4.: GNGPI (SE) by Comorbid group

5.3.4. MStroop

Correlation Analysis

The MStroop task has many dependent measures. However, Probability of Inhibition (MStroopPI) has been regarded in the literature as the most indicative dependent variable of response inhibition on this interference control task. Response inhibition performance, as indicated by MStroopPI, was associated with Go and Error RT and Go and Error variability (see Table 5.10). Moreover, the probability of omitting a trial was negatively correlated with MStroopPI. Children's IQ was not associated with any of the dependent measures of the task. Finally, basic processing efficiency and age seems to play an important role in all MStroop task measures.

Table 5.10.: Correlation table of MStroop task measures and basic processing efficiency, age and IQ

		1	2	3	4	5	6	7	8	9
1	MStroopPI (%)									
2	Go RT (ms)	**.22***								
3	Go SD (ms)	**-.33****	**.51****							
4	Error RT (ms)	**.20***	**.64****	**.26****						
5	Error SD (ms)	**-.28****	**.41****	**.66****	**.47****					
6	% Omissions	**-.44****	.16	**.57****	-.05	**.39****				
9	2CR RT (ms)	.12	**.66****	**.31****	**.46****	**.25****				
10	2CR SD (ms)	**-.42****	**.36****	**.73****	.12	**.51****	**.66****	**.37****		
7	Age	**.18***	**-.39****	**-.31****	**-.25****	**-.18***	**-.30****	**-.50****	**-.29****	
8	IQ	.17	.06	-.14	.15	-.01	-.15	.13	**-.19***	-.12

Note: 2CR = 2 Choice Response; MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; * = $p < .05$; ** = $p < .01$.

Analysis of Variance

A two-way MANOVA was used with two independent factors: status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years). Tables 5.12 reports main effects as well as two- way interaction between independent factors and dependent measures of the task. Results showed a main effect of status on MStroopPI, with ADHD cases being less likely to inhibit themselves compared to typical controls (Figure 5.5). Moreover, children with ADHD were more variable on their Go and Error RT responses compared to their counterparts (Table 5.11 and 5.12). There was also a main effect of age in all measures apart from MStroopPI and Error variability (Table 5.11 and 5.12). Finally, status x age interaction on Error RT was also significant. No other two-way interactions were found.

Log Transformation and Non-parametric Tests

The Kolmogorov-Smimov test of normality indicated that only Go RT was normally distributed. In order to recover normality for the remaining measures, log transformation was performed. The Kolmogorov-Smimov test of normality indicated that log transformed Go and Error SD were normally distributed. The two-way MANOVA was performed for the log transformed measures. Log transformation did not alter the results of the analysis, with the main and interaction effects remaining significant. No significant differences were added.

The remaining MStroop dependent measures that were not normally distributed even after log transformation were inserted into non-parametric tests (Mann-Whitney U-test). In general, the main effects that MANOVA generated remained the same (Appendix B.2). Most importantly, status main effect on MStroopPI remained significant ($U = 927$, $p < .001$). However, with non-parametric analysis ADHD cases made more omissions compared to controls ($U = 1179$, $p < .001$) and age main effect on percentage of omissions did not remain significant ($U = 1360$, $p = .10$).

Analysis of confounding factors

Children's IQ was not associated with MStroopPI (Table 5.10) and therefore no further action was taken to control for its effect.

Performance on response inhibition, as indicated by the MStroopPI, was correlated with basic processing efficiency (see Table 5.10 for pattern of correlation). After 2CR RT was

controlled for in ANCOVA, status (ADHD vs. control) main effect on MStroopPI remained significant ($F(1,120) = 20.75$, $p < .001$). Similarly, after controlling for 2CR RT variability, status main effect on MStroopPI also remained significant ($F(1,120) = 8.97$, $p < .001$; Figure 5.5). However, status x age interaction on MStroopPI also became significant ($F(1,120) = 5.54$, $p = .02$), as adolescents with ADHD had the same response inhibition processing as control adolescents.

Table 5.11.: Group by Age by Gender Means (Standard Deviation) on MStroop task measures

	ADHD Cases				Controls			
	6 – 12 years		13 – 17 years		6 – 12 years		13 – 17 years	
	Male	Female	Male	Female	Male	Female	Male	Female
	N = 44	**N = 10**	**N = 18**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 5**
MStroopPI (%)	60.88 (15.27)	56.4 (10.94)	65.49 (12.13)	67 (29.46)	74.28 (16.04)	86.93 (9.57)	71.41 (20.67)	78.4 (8.29)
Go RT (ms)	490 (106)	506 (133)	456 (85)	415 (73)	492 (101)	542 (100)	385 (74)	423 (34)
Go SD (ms)	204 (104)	235 (108)	197 (113)	95 (12)	148 (56)	140 (54)	102 (57)	95 (15)
Error RT (ms)	426 (91)	421 (98)	434 (128)	355 (55)	466 (138)	486 (108)	369 (108)	405 (46)
Error SD (ms)	164 (104)	246 (199)	196 (162)	101 (45)	148 (100)	125 (94)	80 (62)	87 (38)
% Omissions	5.61 (7.39)	4.25 (4.49)	8.80 (7.72)	0	5.88 (9.91)	1.06 (2.37)	.33 (1.15)	0

Note: MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; * = $p < .05$; ** = $p < .001$.

Table 5.12.: Main and interaction effects on MStroop task measures

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*P*
MStroopPI (%)	109	11.91	.001	109	0.05	.809	109	2.77	.09
Go RT (ms)	109	1.44	.232	109	14.57	.001	109	2.05	.15
Go SD (ms)	109	15.74	.001	109	4.76	.031	109	0.48	.48
Error RT (ms)	109	.001	.979	109	4.99	.027	109	4.28	.04
Error SD (ms)	109	8.87	.004	109	1.30	.256	109	1.58	.21
% Omissions	109	2.70	.103	109	4.77	.031	109	0.08	.77

Note: MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation.

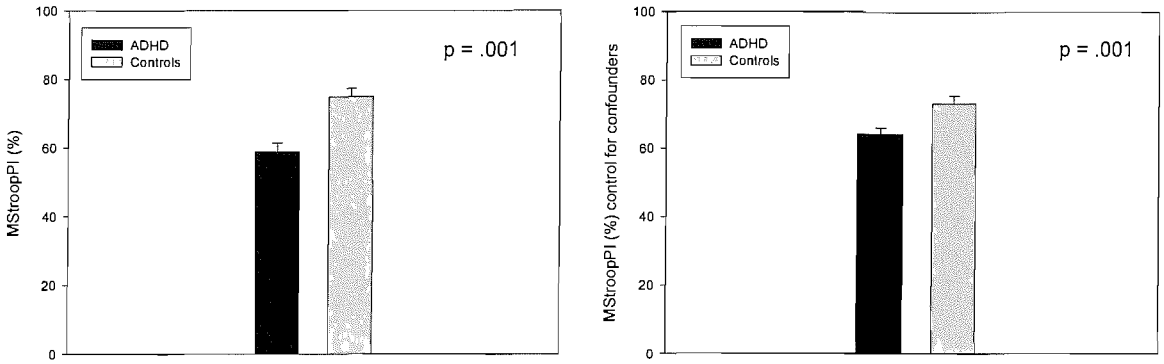


Figure 5.5.: Left: MStroopPI (SE) by Status; Right: MStroopPI (SE) by Status after controlling for 2CR SD.

Comorbidity

In order to examine the effects of comorbid ODD on MStroop performance, MANOVA was used with two independent factors: status (ADHD, ADHD+ODD, and Controls) and age (6-12 years vs. 13-17 years). Table 5.13 reports main and interaction effects of the analysis, as well as Bonferroni analysis results on status differences. Most importantly, a significant status main effect on MStroopPI was found ($F(2,107) = 6.85$, $p < .01$). Bonferroni post-hoc analysis indicated that both ADHD and ADHD+ODD groups differed significantly from controls on MStroopPI ($p < .05$ and $p < .001$ respectively; Figure 5.6). Interestingly, status X age interaction on MStroopPI was also significant (see Table 5.13).

Table 5.13.: Main and interaction effects on MStroop task measures by comorbid group

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
MStroopPI (%)	107	6.85	.002[a]	107	1.16	.28	107	3.14	.04
Go RT (ms)	107	0.78	.458	107	5.45	.02	107	2.25	.10
Go SD (ms)	107	8.13	.001[b]	107	3.96	.04	107	0.42	.65
Error RT (ms)	107	.005	.995	107	1.95	.16	107	2.10	.12
Error SD (ms)	107	5.10	.008[b]	107	1.46	.22	107	1.67	.19
% Omissions	107	1.41	.246	107	5.11	.02	107	0.45	.63

Note: MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation.
a = ADHD, ADHD+ODD > CTR
b = ADHD+ODD > CTR
> the group on the left of the symbol has worse performance

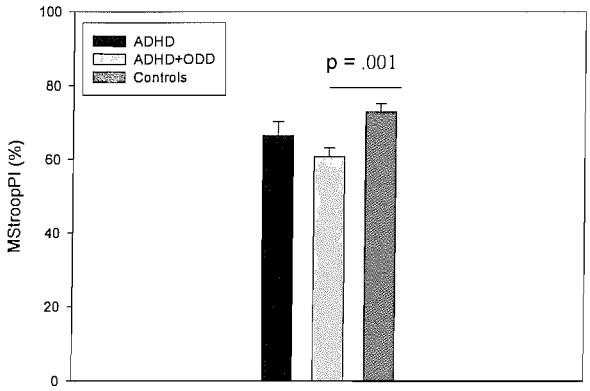


Figure 5.6.: MStroopPI (SE) by Comorbid group

5.3.5. Effect sizes of IC measures

The main indices of each task, suggested in the literature, showed moderate to high effect sizes as indicated in Table 5.14. It is worth noting though that measures of variability also show high effect sizes.

Table 5.14: Effect sizes of the three Inhibitory Control measures

Task	*Measures*	*d*
Stop Signal Task	**SSRT RT**	**.56**
	SSRT SD	.59
	Go RT	.17
	Go SD	.54
	Error RT	.39
	Error SD	.41
Go-No-Go Task	**GNGPI**	**.80**
	Go RT	.45
	Go SD	.95
	Error RT	.25
	Error SD	.64
	% Omission	.97
Modified Stroop task	**MStroopPI**	**.95**
	Go RT	.17
	Go SD	.87
	Error RT	.08
	Error SD	.63
	% Omissions	.46
Basic Processing Efficiency	2CR RT	.06
	2CR SD	**.91**

Note: 2CR = 2 Choice Response; GNGPI = Go-No-Go Probability of Inhibition; MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; SSRT = Stop Signal Reaction Time.

5.3.6. Associations between Key IC Indicators

Pearson correlation indicated that the main indices of the three tasks under investigation are correlated with each other (Table 5.15). Therefore, it can be assumed that these tasks tap the same neuropsychological function, hence Inhibitory Control. Moreover, basic processing efficiency, and especially variability, is associated with all IC indices.

Table 5.15.: Inter-correlation of IC indices and basic processing efficiency

		1	2	3	4
1	SSRT RT				
2	GNGPI	-.33**			
3	MStroopPI	-.26**	.59**		
4	2CR RT	.25**	.13	.12	
5	2CR SD	.29**	-.50**	-.42**	.37**

Note: 2CR = 2 Choice Response; GNGPI = Go-No-Go Probability of Inhibition; MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; SSRT = Stop Signal Reaction Time; * = p <. 05; ** = p < .01.

5.4. Discussion

The main aim in this chapter was to examine the association between three inhibitory control measures that tap different aspects of the construct (i.e. response inhibition and interference control) and each of their relationships with ADHD. Inhibitory control in ADHD cases was deficient compared to controls across all measures, and main indices of IC measures were interrelated, indicating that the measures tap into the same neuropsychological construct.

Both response inhibition and interference control deficits were found in ADHD cases, with differences between the two groups being more pronounced in the MStroopPI and SSRT. This result partly contradicts recent evidence suggesting that inhibitory deficit in children with ADHD is more consistent when the deficit involves suppression of a pre-potent motor response (e.g. on the Stop or GNG task) than when the deficit involves suppression of a conflicting, secondary response (e.g. interference control on Stroop task; Nigg, 2001). Moreover, in the literature higher effect sizes have been reported for

response inhibition compared to interference control in ADHD (van Mourik et al., 2005; Oosterlaan et al., 1998; Willcutt et al., 2005). In the present study, SSRT effect size was similar to those reported in a recent meta-analysis (pooled d = .61; Willcutt et al., 2005). In contrast, higher effect sizes were found for MStroop and GNG tasks compared to the literature. Pooled data from three scientific sites indicated that the original Stroop Colour/Word task has an average effect size of .65 (Nigg et al., 2005). However, reading difficulties that are highly associated with ADHD could be the reason of interference control deficit, as children with ADHD who have increased reading difficulties might need more time to process and read a word (van Mourik et al., 2005). The Modified Stroop task used in the present study was measuring interference control without the confounding effect of reading ability, which might explain the high effect sizes of the task.

Kuntsi and colleagues (2001a) argued that slower and more variable inhibitory processes could account for the slow SSRT on the stop signal task. This finding, together with the association between inhibitory control and RT variability, opens up the possibility that the deficits in inhibitory control displayed in this study could be accounted for by deficits in basic non-executive processing that underpin performance on most laboratory tasks of higher order function. This was, on the whole, not the case. Controlling for RT variability, reduced, but did not eliminate the significant group differences on the SSRT and MStroopPI. However, controlling for RT variability reduced the group differences to non-significant, but still substantial, levels on poor inhibitory control in GNG task. This general pattern of results suggests that while inhibitory deficits are in part due to processing deficits in non-executive processes, such deficits cannot fully account for the established patterns of inhibitory control.

Other confounding effects such as IQ, age and gender were not associated with IC deficit. Contrary to previous research supporting a mediating effect of IQ on executive functioning in ADHD (e.g. Hishaw et al., 2007; Riccio et al., 2006; Polderman et al., 2006), the present results showed that IQ was not associated with any of the inhibitory controls measures. Furthermore, no gender effects were found in any of the tasks that were associated with ADHD. However, the proportion of males in the ADHD group was much higher than that of controls, restricting the analysis on gender effects. Finally, age had a general effect on IC deficit with children having worse performance in most

measures (except the main indices) compared to adolescents. However, this effect was not specific to ADHD cases, indicating that IC deficits persist in this group. Although this finding contradicts previous evidence that response disinhibition is more pronounced in childhood (Drechsler et al., 2005; Nichelli et al., 2005), it is important to recognize that the current study was cross sectional in design and that longitudinal studies have shown that executive deficits in children with ADHD persist even into early adolescence (Hinshaw et al., 2007).

Previous research has suggested that executive functioning is not unique to the disorder (Oosterlaan et al., 1998) and that executive functioning deficit has been identified to other comorbid disorders. On the other hand, Oosterlaan and colleagues (2005) argued that executive functioning deficits are associated only with ADHD, and that the presence of comorbid ADHD accounts for the executive functioning deficits in children with ADHD+CD or ADHD+ODD. In the present study, inhibitory control deficit that has been the most widely associated executive function deficit in ADHD (Barkley, 1997) was differentially associated with comorbidity. "Pure" ADHD cases were only found to differentiate from controls on the interference control measure. This is in line with interference control studies where children with ADHD have been found to be deficient in interference control, alongside other clinical groups such as ODD and CD (Sergeant et al., 2002). However, the lack of significant differences between 'pure' ADHD and control cases on the response inhibition measures could be influenced by the small number of cases within the "pure" ADHD group (N = 19). The group that showed consistent inhibitory control deficit in all tasks was that of ADHD+ODD. This could indicate that comorbid ODD might account for inhibitory control deficits in children with ADHD. However, this conclusion should be interpreted with caution for two main reasons. First, the sample size of the groups could reduce the power of the analysis (ADHD = 19; ADHD+ODD = 58). Second, no difference between the two ADHD groups was found in any of the IC measures indicating again a possible lack of power.

In sum, children with ADHD were found to be impaired in all IC measures (both response inhibition and interference control measures), with moderate effect sizes at group level. Moreover, inhibitory control measures were inter-correlated indicating that different response inhibition and interference control measures share some common elements – but also have some non-shared features. IQ was not related to task performance.

Furthermore, non-executive task variability, although associated with all tasks, did not, in general, account for group differences. Longitudinal studies with larger samples are required to adequately test for age-related changes in inhibitory deficits as children move from childhood to adolescence. Finally, "pure" ADHD cases were only associated with interference control deficit, and comorbid ODD seems to account for the IC deficit in ADHD. However, results on comorbidity should be perceived with caution due to the small sample size of the "pure" ADHD group.

CHAPTER SIX: ADHD and impaired Delay Aversion (DAV)

6.1. Aim of the chapter

In chapter 5, the association between ADHD and three measures of IC was investigated. In this chapter we conduct a similar analysis for the measures we selected to tap delay aversion (DAV).

The aim in this chapter was to investigate the association of ADHD with delay-related motivational measures. Specifically, DAV was investigated under three conditions; the impact of delay on reward choice (Maudsley's Index of Delay Aversion - MIDA; Kuntsi et al., 2001), frustration during unexpected delay (Delay Frustration Task – DeFT; Bitsakou et al., 2006), and the impact of delay on response times (Delay Reaction Time – DRT; Sonuga-Barke & Taylor, 1992).

The three key predictions were:

(v) *Children with ADHD will have poor performance on all DAV conditions compared to control children.*

(vi) The ADHD-DAV link will persist even when age, gender, IQ, and comorbid ODD are controlled.

(vii) The main indices of DAV measures will be correlated.

6.2. Methods

6.2.1. Participants, Recruitment Procedure, Diagnostic Criteria

As in Chapter 5, sections 5.2.1-5.2.3.

6.2.2. Materials

6.2.2.1. Delay Aversion measures

As in Chapter 4, section 4.3.2.

6.2.2.2. Clinical and IQ evaluation

As in Chapter 5, section 5.2.4.2.

6.2.3. Data preparation and analysis

As in Chapter 5, section 5.2.5.

6.3. Results

6.3.1. Maudsley's Index of Delay Aversion (MIDA)

Correlation Analysis

In the literature, the probability of selecting the high reward (i.e. Probability of Delayed Reward) has been used as the main index of delay aversion for the MIDA. Probability of Delayed Reward (Probability of DR) was positively associated with Age and IQ (see Table 6.1). Measures of basic processing abilities were not included in the analyses in this chapter for the MIDA or the DeFT as these were essentially not performance measures. Finally, initial analyses showed no effects of gender (Appendix B.1) and so this variable was not included in the subsequent analyses for all DAV tasks.

Table 6.1.: Correlation table of MIDA measures and age and IQ

		1	2	3
1	% DR			
2	% Omission	-.006		
3	Age	**.41****	-.15	
4	IQ	**.21***	.14	-.12

Note: DR = Delayed Reward; * = $p < .05$; ** = $p < .01$.

Analysis of Variance

A two-way MANOVA was used with two independent factors: status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years). Table 6.3 reports main effects as well as two-way interaction between independent factors and dependent measures. ADHD cases were less likely to wait for the delayed large reward compared to control cases (Figure 6.1). The same effect was true for young children compared to adolescents (Table 6.3). No two -way interaction was found.

Log Transformation and Non-parametric Tests

The Kolmogorov-Smimov test of normality indicated that all dependent measures were not normally distributed even after log transformation. Non-parametric tests were used to justify the results from MANOVA. Specifically the Mann-Whitney U-test was used. With non-parametric test, status main effect on Probability of DR was considerably stronger (U = 1332, p = .004; Appendix B.2).

Analysis of confounding factors

Since IQ was associated with preference on delayed reward (Table 6.1), IQ was controlled for in ANCOVA. The effect of status (ADHD vs. control) was no longer significant ($F(1,121) = 2.51$, ns; Figure 6.1). However, the age main effect remained significant ($F(1,121) = 9.59$, p = .002), with children showing a lower probability of choosing the large delayed reward compared to adolescents.

Table 6.2.: Group by Age by Gender Means (Standard Deviation) on MIDA task measures

	ADHD Cases				Controls			
	6 – 12 years		13 – 17 years		6 – 12 years		13 – 17 years	
	Male	Female	Male	Female	Male	Female	Male	Female
	N = 44	**N = 10**	**N = 19**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 4**
% DR	62.93 (29.4)	51.79 (32.04)	83.15 (23.03)	72.74 (35.01)	81.14 (29.45)	72.62 (34.74)	85.82 (29)	93.32 (13.35)
% Omission	0.91 (2.72)	0.67 (2.11)	0	1.67 (3.35)	0.39 (1.62)	0.55 (1.93)	0.41 (1.67)	0

Note: DR = Delayed Reward; * = $p < .05$; ** = $p < .01$.

Table 6.3.: Main and interaction effects on MIDA task measures

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
% DR	122	4.21	.04	122	7.43	.007	122	0.94	.33
% Omission	122	0.20	.65	122	0.77	.380	122	0.31	.57

Note: DR = Delayed Reward.

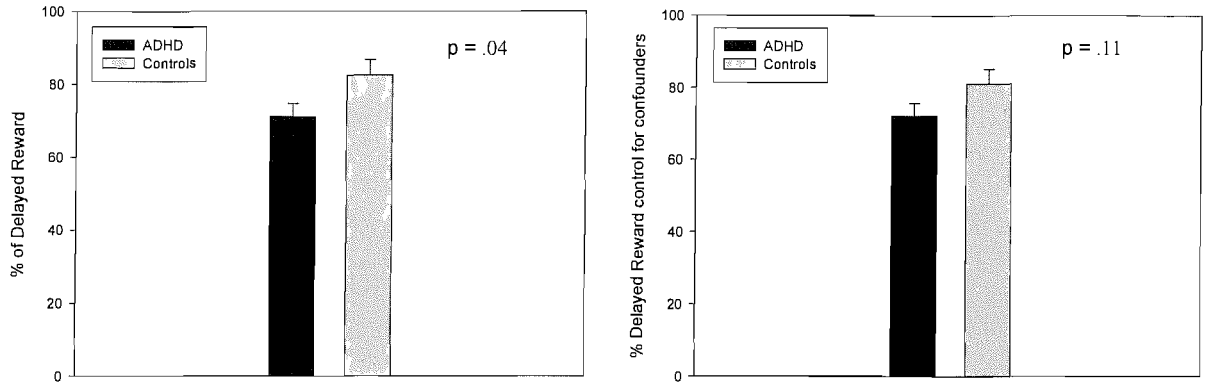


Figure 6.1.: Left: MIDA Probability of Delayed Reward (SE) by Status; Right: MIDA Probability of Delayed Reward (SE) by Status after controlling for IQ.

Comorbidity

In order to examine the effects of comorbid ODD on MIDA performance, MANOVA was used with two independent factors: status (ADHD, ADHD+ODD, and Controls) and age (6-12 years vs. 13-17 years). Table 6.4 reports main and interaction effects, as well as Bonferroni analysis results on status differences. The status main effect on probability of choosing the large reward was marginally significant ($F(1,120) = 3.00$, $p = .053$). Bonferroni post-hoc analysis indicated that only ADHD+ODD cases were significantly less likely to prefer the delayed reward compared to controls ($p < .01$; Figure 6.2). 'Pure' ADHD cases were not different from either control or ADHD+ODD cases. Finally, the age main effect, although reduced, remained significant. No status x age interaction was evident.

Table 6.4.: Main and interaction effects on MIDA task measures by comorbid group

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
% DR	122	3.00	.053[a]	122	5.09	.02	122	1.04	.35
% Omission	122	0.72	.48	122	0.40	.52	122	0.44	.64

Note: DR = Delayed Reward
a = ADHD+ODD < CTR

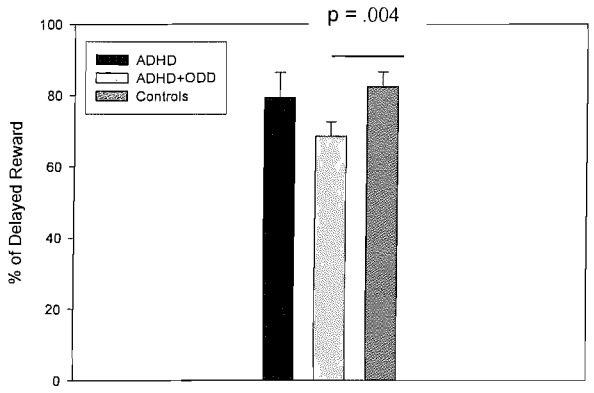


Figure 6.2.: MIDA Probability of Delayed Reward (SE) by Comorbid group

6.3.2. Delay Frustration Task (DeFT)

Correlation Analysis

Total Duration (TD) is the main index of DeFT. The 20sec delay period was divided into four bin intervals (5 seconds per bin). The first second out of the 20 seconds delay was not included in the analysis, as this response was showing participants' reaction time to the arithmetic question and not delay aversion. All bin intervals' reaction times were inter-correlated (Table 6.5.). Age and IQ were not associated with any of the measures of this task.

Table 6.5.: Correlation table of MIDA measures and age and IQ

		1	2	3	4	9
1	TD RT 2-5					
2	TD RT 6-10	**.81****				
3	TD RT 11-15	**.82****	**.83****			
4	TD RT 16-20	**.81****	**.79****	**.89****		
9	Age	-.10	.01	-.01	.003	
10	IQ	-.04	-.10	-.03	-.02	-.12

Note: RT = Reaction Time; TD = Total Duration; ** = $p < .001$.

Repeated Measures ANOVA

Repeated Measures ANOVA was used with Bin Interval (TD RT 2-5, TD RT 6-10, TD RT 11-15, TD RT 16-20) as within-subject factor and status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years) as between-subject factors. Main effects and two- and three-way interactions between independent factors and dependent measures are

reported in Tables 6.7. ADHD cases showed increased TD RT, suggesting an increased frustration levels, compared to control cases (Figure 6.3). Bin Interval main effect was also significant (Table 6.7). Moreover, no status x bin interval interaction was found, a finding consistent with the view that ADHD cases were more frustrated than controls throughout the delay period.

Since the two groups differ across all four Bin Intervals, a composite score was calculated by taking the mean TD (i.e. DeFT MTD) from all Bin Intervals. Univariate ANOVA with status (ADHD vs. Controls) and age (6-12 years vs. 13-17 years) as between-subject factors, indicated that status main effect was still significant on the DeFT MTD ($F(1,116) = 7.56$, $p = .007$). Age main effect and status x age interaction were not significant ($F(1,116) = 0.39$, $p = .53$; $F(1,116) = 0.59$, $p = .44$ respectively).

Log Transformation and Non-parametric Tests

The Kolmogorov-Smimov test of normality indicated that all dependent measures were not normally distributed even after log transformation. Non-parametric tests were used to justify the results from repeated measures ANOVA. The Mann-Whitney U-test showed same results as repeated measures ANOVA and Univariate analysis of variance (Appendix B.2).

Analysis of confounding factors

Children's IQ was not associated with DeFT TD (Table 6.5.) and therefore no further action was taken to control for its effect.

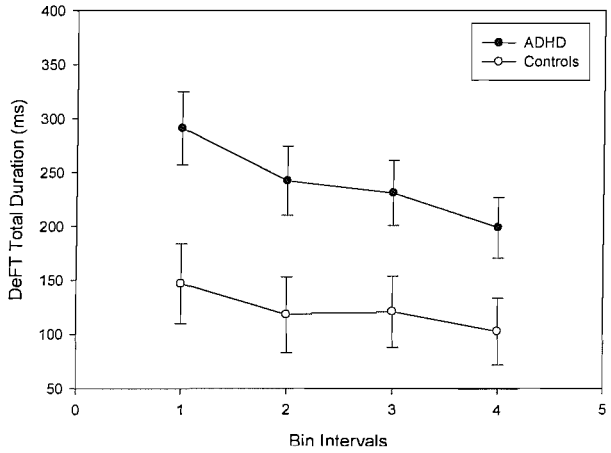
Table 6.6.: Group by Age by Gender Means (Standard Deviation) on DeFT Total Duration measures

	ADHD Cases				Controls			
	6 – 12 years		13 – 17 years		6 – 12 years		13 – 17 years	
	Male	Female	Male	Female	Male	Female	Male	Female
	N = 41	**N = 10**	**N = 16**	**N = 4**	**N = 16**	**N = 12**	**N = 16**	**N = 5**
TD RT 2-5	360 (344)	273 (257)	279 (277)	75 (80)	128 (144)	157 (148)	165 (190)	116 (109)
TD RT 6-10	274 (309)	222 (284)	267 (268)	30 (42)	77 (95)	142 (165)	145 (185)	85 (39)
TD RT 11-15	254 (256)	261 (366)	250 (286)	33 (32)	90 (133)	125 (126)	157 (196)	72 (45)
TD RT 16-20	229 (267)	173 (199)	222 (279)	15 (18)	54 (59)	131 (133)	136 (193)	59 (22)

Note: RT = Reaction Time; TD = Total Duration.

Table 6.7.: Main and interaction effects on DeFT task measures

	Repeated Measures ANOVA		
	df	*F*	*p*
Status (S)	116	7.53	.007
Age (A)	116	0.15	.698
Bin Interval (BI)	348	7.62	.001
S x BI	348	0.96	.411
A x BI	348	0.92	.428
S x A	116	0.95	.331
S x A x BI	348	0.32	.808



BI: p = .001; Status: p = .007; BI x S: p = .41

Figure 6.3.: DeFT Total Duration (SE) by Status

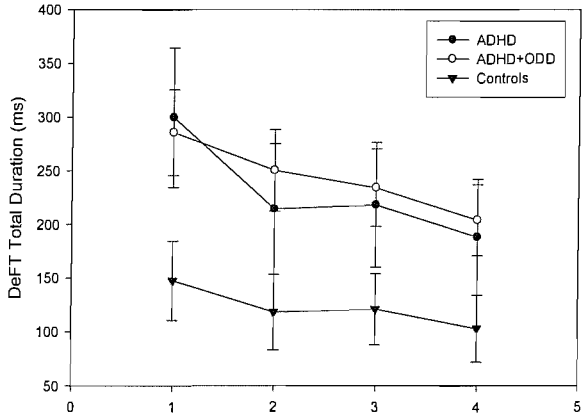
Comorbidity

In order to examine the effects of comorbid ODD on DeFT performance, a repeated measures ANOVA was used with bin interval (TD RT 2-5, TD RT 6-10, TD RT 11-15, TD RT 16-20) as within-subject factor and status (ADHD, ADHD+ODD, and Controls) and age (6-12 years vs. 13-17 years) as between-subject factors. Table 6.8 reports main and interaction effects, as well as Bonferroni analysis results on status differences. The status main effect was significant ($F(2,114) = 3.65$, $p = .029$). Bonferroni post-hoc analysis indicated that ADHD+ODD cases had increased TD RT during unexpected delay compared to controls ($p < .01$; Figure 6.4). 'Pure' ADHD cases were not different from control or ADHD+ODD cases.

Table 6.8.: Main and interaction effects on DeFT task measures by comorbid group

	Repeated Measures ANOVA		
	df	*F*	*p*
Status (S)	114	3.65	.029[a]
Age (A)	114	0.19	.659
Bin Interval (BI)	342	8.35	.001
S x BI	342	0.66	.681
A x BI	342	0.79	.499
S x A	114	0.54	.583
S x A x BI	342	0.84	.534

Note: a = ADHD+ODD > CTR



BI: p = .001; Comorbid Status: p = .02; BI x S: p = .68

Figure 6.4: DeFT Total Duration (SE) by comorbid group

6.3.3. Delay Reaction Time (DRT)

Correlation Analysis

Initially the RT and SD of the two delay conditions in the DRT task and the control condition in the 2CR task were generated. Reaction time and variability of the three delay conditions were inter-correlated (Table 6.9). Age, but not IQ, was negatively associated with all measures, except with SD at 3 second interval.

Table 6.9.: Correlation table of DRT and 2CR measures, Age and IQ

		1	2	3	4	5	6	7
1	RT 3s							
2	SD 3s	**.59****						
3	RT 20s	**.52****	**.31***					
4	SD 20	**.45****	**.27***	**.64****				
5	RT 100ms	**.28****	.17	**.44****	**.27****			
6	SD 100ms	**.43****	**.30****	**.33****	**.39****	**.37****		
7	Age	**-.32****	-.14	**-.40****	**-.31****	**-50****	**-.29****	
8	IQ	-.16	-.12	-.03	-.04	.13	-.19	-.12

Note: RT= Reaction Time; SD = Standard Deviation; * = $p < .05$; ** = $p < .01$.

Repeated Measures ANOVA for Reaction Time

Repeated Measures ANOVA was used with delay condition RT (100ms, 3s and 20s) as within-subject factor and status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years) as between-subject factors. Table 6.11 reports main and interaction effects on RT of the three delay conditions. ADHD cases had slower RT after a delay compared to

control children (Table 6.11). Moreover, status x delay condition RT interaction was also significant, with ADHD cases having the same performance as control cases at the 100ms, but had increased RT at 3 and 20 seconds delay condition (Figure 6.5). Younger children were also significantly slower on their RT during delay compared to adolescents (Table 6.11). Delay condition RT main effect was also significant. No further interaction effects were evident.

Repeated Measures ANOVA for RT Variability

Repeated Measures ANOVA was used with delay condition SD (100ms, 3s and 20s) as within-subject factor and status (ADHD cases vs. Controls) and age (6-12 years vs. 13-17 years) as between-subject factors. Table 6.12 reports main and interaction effects on SD of the three delay conditions. ADHD cases had higher SD in all a delay conditions compared to controls (Table 6.12). Status x delay condition SD interaction was not significant, a finding suggesting that ADHD cases were more variable than controls throughout the three delay conditions (Figure 6.5). Younger children had also significantly higher SD during delay compared to adolescents (Table 6.12). Delay condition SD main effect was also significant. No interaction effects were evident.

Table 6.10.: Group by Age by Gender Means (Standard Deviation) on DRT and 2CR measures

	ADHD Cases				Controls			
	6 – 12 years		13 – 17 years		6 – 12 years		13 – 17 years	
	Male	Female	Male	Female	Male	Female	Male	Female
	N = 41	**N = 10**	**N = 16**	**N = 4**	**N = 17**	**N = 12**	**N = 16**	**N = 5**
RT 3s	686 (249)	766 (221)	630 (178)	579 (41)	615 (151)	617 (154)	503 (78)	550 (164)
SD 3s	234 (105)	238 (125)	232 (119)	263 (99)	190 (108)	225 (123)	166 (63)	194 (174)
RT 20s	673 (176)	628 (138)	553 (176)	552 (52)	606 (211)	537 (108)	422 (107)	450 (132)
SD 20	237 (111)	177 (71)	203 (74)	156 (68)	149 (102)	139 (71)	100 (64)	142 (115)
RT 100ms	381 (74)	382 (75)	336 (80)	324 (29)	392 (71)	419 (64)	312 (51)	311 (45)
SD 100ms	176 (89)	235 (93)	166 (82)	88 (19)	143 (79)	106 (39)	79 (22)	96 (67)
DS RT	680 (194)	697 (161)	592 (142)	565 (42)	583 (129)	577 (124)	462 (65)	500 (132)
DS SD	235 (86)	207 (78)	218 (80)	209 (45)	155 (69)	182 (88)	133 (26)	168 (75)

Note: DRT Delay Reaction Time; RT = Reaction Time; SD = Standard Deviation.

Table 6.11.: Main and interaction effects on DRT and 2CR RT measures

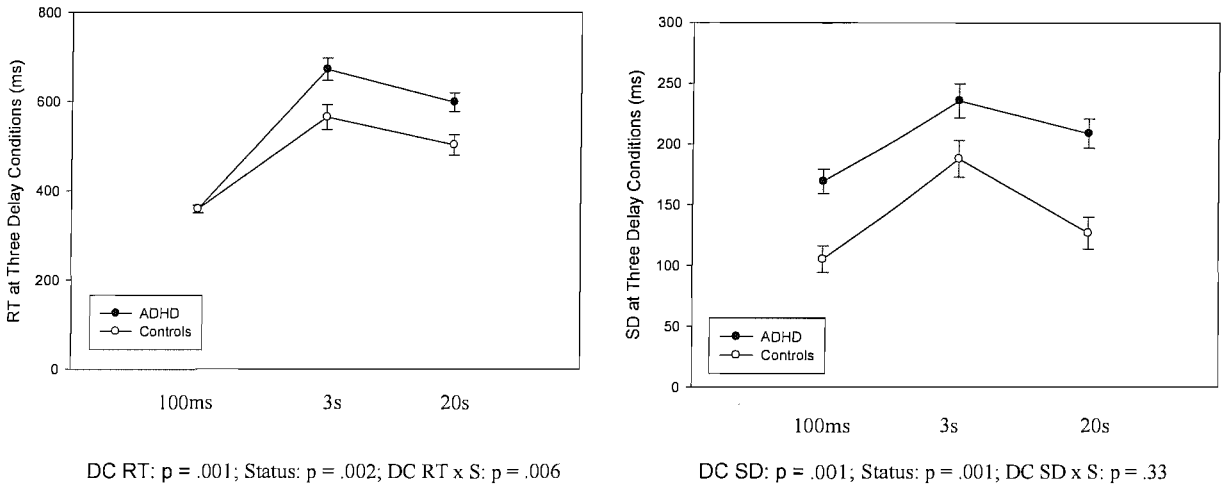
	Repeated Measures ANOVA		
	Df	*F*	*p*
Status (S)	119	9.84	.002
Age (A)	119	20.41	.001
Delay Condition RT (DC RT)	238	116.89	.001
S x DC RT	238	5.30	.006
A x DC RT	238	1.74	.176
S x A	119	0.52	.471
S x A x DC RT	238	0.10	.905

Note: RT = Reaction Time.

Table 6.12.: Main and interaction effects on DRT and 2CR SD measures

	Repeated Measures ANOVA		
	df	*F*	*p*
Status (S)	117	25.34	.001
Age (A)	117	5.27	.023
Delay Condition SD (DC SD)	234	22.01	.001
S x DC SD	234	1.11	.331
A x DC SD	234	0.72	.484
S x A	117	0.37	.541
S x A x DC SD	234	0.29	.752

Note: SD = Standard Deviation.



DC RT: p = .001; Status: p = .002; DC RT x S: p = .006

DC SD: p = .001; Status: p = .001; DC SD x S: p = .33

Figure 6.5.: Left: DRT and 2CR Reaction Time (SE) by Status; Right: DRT and 2CR Standard Deviation (SE) by Status

DRT Delay Sensitivity Index

Based on the RT performance, it is evident that children with ADHD were sensitive to long (3 and 20 seconds) compared to short intervals (100ms). In order to investigate the extent of delay sensitivity in the DRT task, 2CR RT was used as a control condition to compare performance during a delay condition. An aggregated RT score was calculated for the two delayed trial intervals (3 and 20 seconds). To calculate the index of delay sensitivity in DRT task (i.e. DRT DS), the 2CR RT score (control condition) was subtracted from the aggregated DRT RT score.

A two-way ANOVA was used to examine the extent of delay sensitivity in DRT task with two independent factors: status (ADHD cases vs. Controls) and age (6-12 years vs. 13-

17 years). The status main effect on DS RT was significant ($F(1,119) = 12.16$, $p < .001$), with ADHD cases showing slower RT, as an indication of their delay sensitivity (Figure 6.6). The age main effect and status x age interaction were not significant ($F(1,119) = 2.55$, $p > .05$; $F(1,119) = .19$, $p > .05$ respectively).

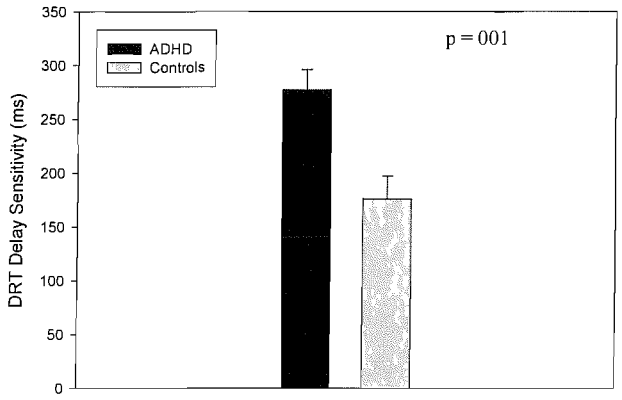


Figure 6.6.: DRT Delay Sensitivity (SE) by Status

Log Transformation and Non-parametric Tests

The Kolmogorov-Smimov test of normality indicated that all dependent measures were not normally distributed. Distribution was normalized after log transformation for all measures except for DRT DS. Non-parametric tests were used to justify the results from MANOVA. Specifically the Mann-Whitney U-test was used. With non-parametric test, status main effect on DRT DS was still significant ($U = 1019$, $p < .001$; Appendix B.2).

Analysis of confounding factors

Children's IQ was not associated with DRT or 2CR measures (Table 6.9 for pattern of correlations) and therefore no further action was taken to control for its effect.

Comorbidity

In order to examine the comorbid effects of ODD on DRT DS, ANOVA was used with two independent factors: status (ADHD, ADHD+ODD, and Controls) and age (6-12 years vs. 13-17 years). The status main effect on DS RT was significant ($F(1,117) = 6.22$, $p < .01$), Figure 6.7). Bonferroni post-hoc analysis indicated that both ADHD groups were significantly more sensitive to delay compared to control ($p < .01$). No further main or interaction effects were significant.

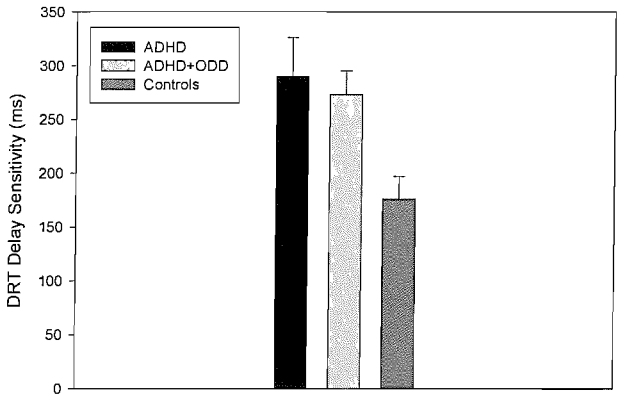


Figure 6.7.: Left: DRT Delay Sensitivity (SE) by Comorbid group

6.3.4. Effect size of DAV measures

All DAV main indices had moderate effect sizes (Table 6.13).

Table 6.13: Effect sizes of the three DA measures

Task	*Measure*	*d*
MIDA	**% DR**	**.48**
	TD RT 2-5	.67
	TD RT 6-10	.59
DeFT	TD RT 11-15	.55
	TD RT 16-20	.52
	MTD	**.60**
DRT	**DS**	**.76**

Note: DeFT = Delay Frustration Task; DR = Delayed Reward; DRT = Delay Reaction Time; DS = Delay Sensitivity; MIDA = Maudsley's Index of Delay Aversion; MTD = Mean Total Duration; RT = Reaction Time; TD = Total Duration.

6.3.5. Associations between Key DAV indicators

The main indices of DAV measures (MIDA Prob of DR, DeFT MTD and DRT DS) were entered in Pearson correlation (Table 6.14). The analysis indicated that DRT DS was associated with the other two DAV measures. Moreover, the main index of MIDA was not correlated with DeFT MTD.

Table 6.14.: Pearson correlations of DAV measures

		1	2	3
1	MIDA % DR			
2	DeFT MTD	-.15		
3	DRT DS	**-.26****	**.20***	

Note: DeFT = Delay Frustration Task; DR = Delayed Reward; DRT = Delay Reaction Time; DS = Delay Sensitivity; MIDA = Maudsley's Index of Delay Aversion; MTD = Mean Total Duration; * = $p < .05$; ** = $p < .01$.

Since IQ was found to have a significant effect on MIDA Probability of Delayed Reward, its effect was controlled for in partial correlation (Table 6.15). The significant levels of the association of the three DAV indices remained the same.

Table 6.15.: Partial correlations of DAV measures, controlling for IQ.

		1	2	3
1	MIDA % DR			
2	DeFT MTD	-.16		
3	DRT DS	**-.19***	**.19***	

Note: DeFT = Delay Frustration Task; DR = Delayed Reward; DRT = Delay Reaction Time; DS = Delay Sensitivity; MIDA = Maudsley's Index of Delay Aversion; MTD = Mean Total Duration; * = $p < .05$; ** = $p < .01$.

6.4. Discussion

The main aim of this chapter was to examine the association between three delay aversion measures that tap different aspects of the construct (i.e. impact of delay on reward choice, on reaction times and delay-related frustration) and each of their relationships with ADHD. Delay aversion in ADHD cases was deficient compared to controls across all measures and DAV measures were partly inter-correlated. In fact, MIDA was not associated with the DeFT task.

Delay aversion deficit was found in ADHD cases, with differences between the two experimental groups being more pronounced in the DeFT (i.e. delay frustration) and DRT (delay response sensitivity). In the literature of ADHD, frustration has been examined as an indication of reward sensitivity (e.g. Douglas & Parry, 1994). Children with ADHD experience higher levels of frustration compared to controls when a reward is partially provided or is terminated (i.e. extinction). If children with ADHD have an

aversion towards delay, then immediacy could be perceived as a reward for those children. In the present study, by withholding this reward (i.e. introducing unexpected delay periods), children with ADHD were experiencing higher levels of frustration compared to controls throughout the delay period. This finding is in line with Amsel's (1958) theory that individuals with ADHD may show increased frustration because their excessive focus on reward tips the balance of reward expectancy and frustration towards frustration. Moreover, the present results on delay-related frustration are also consistent with the adult literature on frustration levels during an unexpected and unsignaled delay (Bitsakou et al., 2006).

Delay response sensitivity had been investigated in the past by using three delay intervals (1, 15 and 30sec; Sonuga-Barke & Taylor, 1992). It was found that children with ADHD had slower reaction times after a delayed period compared to controls. Sonuga-Barke and Taylor (1992) found that the reaction time of children with ADHD increased with the length of the pre-response delay, indicating that children with ADHD were more sensitive to increased delay. In the present study, reaction time performance of children with ADHD was comparable to that of their counterparts in a no pre-response delay (100ms interval). However, comparing reaction time performance at longer intervals (3 and 20 second) to that of short intervals, ADHD cases were found to be more sensitive to delay compared with controls. On the other hand, variability was not found to be related to delay. Although ADHD cases were more variable than controls in all delay conditions, the increase of variability from no pre-response delay to long pre-response delay was the same for both groups. However, results on variability as an indication of delay sensitivity should be perceived with caution due to the low effect size of this measure.

Replicating previous findings (e.g. Kuntsi et al., 2001a), the impact of delay on reward choice (i.e. MIDA task) was also significant, as ADHD cases showed a preference towards a small immediate over a large, delayed reward. However, IQ was found to moderate this effect. In the beginning of the task, the researcher made sure that children understood the benefit of selecting the delayed reward, although they were not specifically informed about the maximum points that they could earn by the end of the game. Therefore, in principle children may have understood the aim of the game, but in real practice it could have been difficult for them to calculate the possible maximum

score to achieve their goal. Another possible explanation might be the moderate effect size of the task, which is lower than that reported in the literature (d = .57; Sonuga-Barke et al., 2007). Moreover, there is a debate on whether MIDA is sensitive enough to measure reward preference under delay across different ages. Based on the present study, age had a significant main effect on the probability of selecting the delayed reward, with adolescents being more tolerant to delay.

Confounding factors such as IQ, age, and gender had a moderator effect on each DAV measure. In line with previous studies on delay aversion (e.g. Carlson & Tamm, 2000), gender was not found to be associated with DAV deficits. As already mentioned, IQ had a moderating effect for delay-related reward preference, with lower IQ leading to lower preference to delayed large reward. Contrary to results from a recent review (Luman et al., 2005), age in the present study, had a significant effect on delay-related reward preference, as young children seem to be less sensitive to delayed large rewards compared to adolescents. However, age effect on preference to reward immediacy was not specific to ADHD. This result contradicts previous findings that young children with ADHD are more driven by reward immediacy compared to adolescents with ADHD (Scheres et al., 2005).

Approximately 40-70% of children with ADHD (Faraone & Biederman, 1994) and 25-75% of adolescents with ADHD (Barkley, 1998) have also comorbid ODD/CD. Two studies have included a comorbid ODD group when task performance was studied in children with ADHD under different reinforcement contingencies (Antrop et al., 2006; van der Meer, Marzocchi, & de Meo, 2005). These studies have provided inconclusive results. In one study, reinforcement contingency improved task performance in children with ADHD alone, but not in children with ADHD+ODD (van der Meer et al., 2005). In a second study, where delay aversion was measured directly by using the MIDA task, both ADHD and ADHD+ODD groups displayed a stronger preference than control children for the small immediate reward (Antrop et al., 2006). However, in the present study, the impact of delay on reward preference was more pronounced in the ADHD+ODD group, as children with ADHD alone did not differ from controls. The effect of comorbidity on other delay-related measures has not been investigated. Results from the present study suggest that delay-related frustration level is significantly elevated only in children with ADHD+ODD compared to control children. Moreover, reaction time delay sensitivity was

increased in both ADHD and ADHD+ODD groups compared to control children. However, conclusions on comorbid ODD should be interpreted with caution because the sample size of the groups is likely to reduce the power of the analysis (ADHD = 19; ADHD+ODD = 58).

In sum, ADHD cases were found to be impaired in all DAV measures. DAV seemed to be sensitive to IQ and age. Gender on the other hand showed no effect on DAV impairment. Moreover, main measures of the delay aversion tasks were partly associated with DeFT not being correlated with MIDA. Finally, "pure" ADHD cases were only impaired on reaction time delay sensitivity, and comorbid ODD seems to account for the DAV deficit in ADHD. However, results on comorbidity should be perceived with caution due to the small sample size of the "pure" ADHD group.

CHAPTER SEVEN: Evaluating the Dual Pathway model

7.1. Aim of the chapter

In the present thesis so far an association between ADHD and IC and DAV measures has been supported (see Chapters 5 and 6). ADHD cases were found to have poor performance on response inhibition and interference control tasks and they also displayed heightened sensitivity to delay as shown by their increased RT and variability, decreased preference towards a large delayed reward and increased frustration level during unexpectedly imposed delay.

Sonuga-Barke (2002) proposed that although IC and DAV are both associated with ADHD, they might be different and independent constructs associated with different pathways leading to the disorder. He suggested that children with ADHD might be affected by none, either or both deficits (i.e. Dual Pathway; see also Chapter 3). IC deficits and DAV have been shown to contribute independently to ADHD symptoms in both clinical and community-based samples (Solanto et al., 2001; Sonuga-Barke et al., 2003; Thorell, in press). However, in these studies a limited number of tasks were used to test each construct. The present study is the first to employ multiple measures of IC and DAV, which increases the power of the tests of the dual pathway hypothesis.

The four key predictions tested in this chapter, derived from the dual pathway hypothesis, are:

(i) *Measures within each construct (i.e. IC) will be independent of measures within the other construct (i.e. DAV).*

(ii) *IC and DAV measures will form two independent components in a principal component analysis.*

(iii) *ADHD cases will have poor performance on the overall IC and DAV components compared with control cases.*

(iv) *Different subgroups of ADHD cases will have 'pure' IC deficit, 'pure' DAV deficit, both IC and DAV deficit, and some cases will show no IC and DAV deficit.*

7.2. Methods

7.2.1. Participants, Diagnostic Criteria, Recruitment Procedure

As in Chapter 5, sections 5.2.1-5.2.3.

7.2.2. Materials

7.2.2.1. IC Tasks

As in Chapter 4, section 4.3.1.

7.2.2.2. DAV tasks

As in Chapter 4, section 4.3.2.

7.2.3. Data Analysis

In Chapters 5 and 6 the main indices of IC and DAV tasks respectively were selected. In sum, three IC indices (Stop Signal Reaction Time - SSRT, Modified Stroop Probability of Inhibition - MStroopPI, and Go-No-Go Probability of Inhibition - GNGPI) and three DAV indices (Maudsley's Index of Delay Aversion Probability of Delayed Reward - MIDA Probability of DR, Delay Frustration Task Mean Total Duration - DeFT MTD, Delay Reaction Time Delay Sensitivity - DRT DS) were selected.

7.3. Results

7.3.1. Intra- and inter-construct correlations

Pearson correlations with pairwise case exclusion were performed in order to investigate the relationship of the selected indices. Table 7.1 displays summary of the results. The following number of cases was entered for the dependent measures: 126 cases for MIDA Prob DR, 123 cases for DRT DS, 120 cases for DeFT MTD, 125 cases for MStroop PI, 125 cases for GNG PI, and 122 cases for SSRT.

In Chapter 5 and 6, the correlation between measures within each contract was presented and discussed. In this analysis some IC measures were found to be significantly associated with DAV measures. GNGPI was negatively associated with both DeFT and DRT, whereas the MStroop main index was associated with all DAV measures. Only SSRT was not associated with any DAV main indices.

Table 7.1.: Correlations between main IC and DAV indices

		1	2	3	4	5
1	MIDA % DR					
2	DeFT MTD	-.15				
3	DRT DS	-.26**	.20*			
4	SSRT	-.16	.11	.13		
5	GNGPI	.10	**-.26****	**-.20***	-.33**	
6	MStroopPI	**.24****	**-.33****	**-.18***	-.26**	.59**

Note: DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; SSRT = Stop Signal Reaction Time; * = $p < .05$; ** = $p < .01$.

7.3.2. Are there discernable principal components representing DAV and IC?

All the selected indices of IC and DAV constructs were entered into a Principal Component Analysis (PCA), with a Varimax rotation to an orthogonal solution. This rotation was selected so as to produce dimensions that would be independent of one another so that any associations with ADHD would also be independent. The Kaiser measure of sampling adequacy was .66 and the Bartlett's test of sphericity was significant, $\chi^2(15) = 99.98$, $p < .001$, indicating that the analysis was appropriate to the data set. Based on the criterion of eigenvalue higher than one, two components were extracted (Table 7.2). In the first component, all IC measures were loaded (i.e. Inhibitory Control component). The IC component explained 32% of the variance. In the second component (i.e. Delay Aversion component), all DAV measures were loaded. The DAV component explained 27% of the variance. The DeFT MTD was cross-loading on both components suggesting that it shared elements with both constructs, although the loading was stronger for IC.

Table 7.2: Component Structure of Inhibitory Control and Delay Aversion measures

		Component	
		Inhibitory Control	Delay Aversion
Delay Aversion	MIDA % DR	.08	**-.78**
	DRT DS	-.13	**.75**
	DeFT MTD	**-.46**	**.32**
Inhibitory Control	SSRT	**-.56**	.08
	GNG PI	**.85**	-.01
	MStroop PI	**.81**	-.16
	Eigenvalue	1.95	1.33
	% Variance Explained	32.57	22.20

Note: DeFT MTTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; SSRT = Stop Signal Reaction Time; * = $p < .05$;** = $p < .01$.

7.3.3. ADHD association with factor scores

A factor score was calculated using the item to factor loadings as the weights in the calculation. In order to examine group differences on the two factor scores, MANOVA was used, with status (ADHD vs. Controls) and age (6-12 and 13-17 years) as independent factors. Initial analysis indicated that gender did not have any effect on status and therefore was removed from the analysis (Appendix B.1). The status main effect on the IC and DAV factor scores was significant (Table 7.3) with ADHD cases having worse performance than controls (d = .87; d = .65, respectively). Moreover, the age main effect was only significant on DAV component score (Table 7.3). The status x age interaction was not significant for any of the two factor scores.

Table 7.3.: Main and interaction effects on IC and DAV factor scores

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*df*	*F*	*p*	*df*	*F*	*p*
IC Component	106	14.42	.001	106	0.64	.42	106	2.30	.13
DAV Component	106	7.55	.007	106	5.07	.02	106	0.70	.40

Note: DAV = Delay Aversion; IC = Inhibitory Control.

7.3.4. Effect of comorbid ODD on factor scores

In order to investigate the effect of ODD on the IC and DAV factor scores, MANOVA was used, with status (ADHD, ADHD+ODD and Controls) and age (6-12 and 13-17 years) as independent factors. The status main effect on the IC and DAV factor scores was significant (Table 7.4). However, Bonferroni post-hoc analysis indicated that both ADHD groups had IC deficit, whereas only ADHD+ODD cases had DAV deficit. Moreover, age main effect was only significant on DAV component score (Table 7.4). The status x age interaction was not significant for any of the two factor scores.

Table 7.4.: Main and interaction effects on IC and DAV factor scores by comorbid group

	Status (S)			Age (A)			S x A		
	df	*F*	*p*	*Df*	*F*	*p*	*df*	*F*	*p*
IC Component	104	7.28	.001[a]	104	2.05	.15	104	1.37	.25
DAV Component	104	3.69	.02[b]	104	4.03	.04	104	0.50	.60

Note: DAV = Delay Aversion; IC = Inhibitory Control
a = ADHD, ADHD+ODD > Controls
b = ADHD+ODD > Controls

7.3.5. Proportion of IC and DAV deficit in ADHD cases

In order to investigate the proportion of cases with ADHD, who had neuropsychological deficits in either DAV or IC, cases were categorised into 'impaired' and 'unimpaired' using the worse 10% performance on the control's factor scores of both the IC and DAV components as a cut off point. Based on this cut off score, 25% had IC deficits only, 15% of ADHD cases had DAV deficits only, 11% had deficit on both IC and DAV, and 49% did not have either DAV or IC deficits (Figure 7.1). A one-way ANOVA was used to compare the clinical characteristics of the four neuropsychologically impaired ADHD groups. As shown in Table 7.5, ADHD cases with 'pure' IC deficit had better vocabulary and estimated IQ compared to the other groups. However, the groups did not differ on parent and teacher reports on general behaviour, ADHD symptoms and on comorbid disorders.

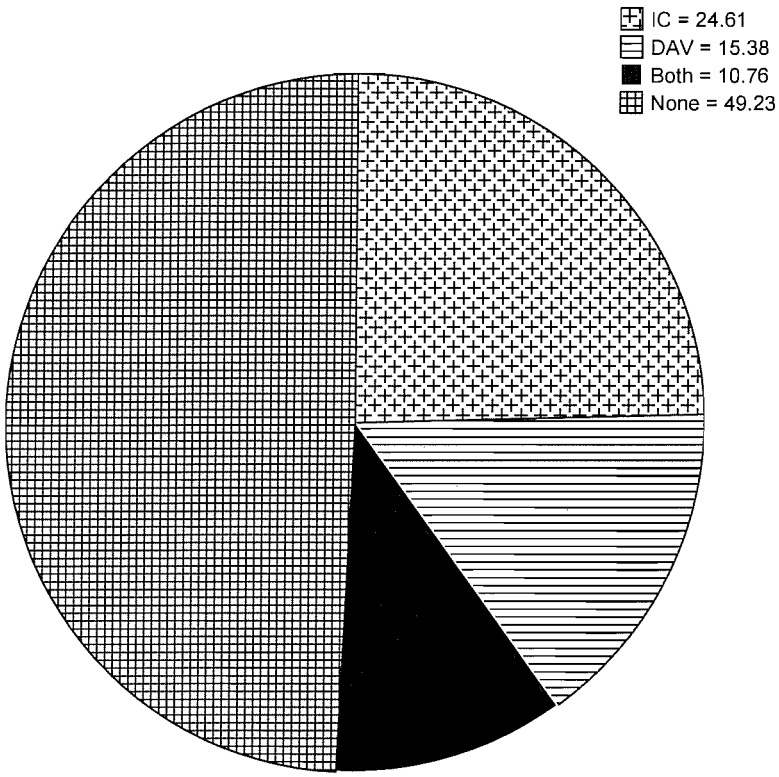


Figure 7.1: Pie chart of proportion of IC and DAV deficit in ADHD cases

Table 7.5.: Clinical characteristics (mean and standard deviation) of ADHD cases by neuropsychological deficit

	1: 'Pure' IC	2: 'Pure' DAV	3: Both	4: None	*F- value*
WISC-III					
Vocabulary	11.0 (2.9)	7.8 (1.9)	7.2 (2.5)	8.4 (2.8)	4.65** (1>2,3,4)
Block Design	10.4 (2.3)	9.4 (3.9)	8.5 (2.1)	9.2 (2.3)	0.96
Full	104.3 (14.7)	91.4 (16.0)	87.3 (7.3)	93.1 (11.5)	4.03* (1>3,4)
Parent SDQ					
Hyperactivity	7.8 (2.1)	7.7 (1.7)	8.7 (1.9)	8.2 (1.8)	0.48
Conduct	4.9 (2.6)	5.3 (1.4)	7.5 (1.9)	5.3 (2.3)	2.25
Emotional	3.4 (2.5)	3.9 (3.1)	3.8 (2.6)	4.3 (2.5)	0.45
Peer Relation	3.9 (2.8)	2.8 (1.8)	5.4 (2.7)	4.6 (4.4)	0.95
Prosocial	5.4 (2.1)	5.4 (2.7)	5.1 (2.1)	5.7 (2.0)	0.17
Total	20.2 (5.4)	19.7 (6.0)	25.5 (5.6)	22.6 (7.3)	0.20
Teacher SDQ					
Hyperactivity	6.0 (2.5)	7.1 (3.7)	6.0 (2.8)	7.1 (2.5)	0.76
Conduct	1.6 (2.3)	3.5 (2.4)	2.1 (1.1)	2.7 (2.2)	0.24
Emotional	2.1 (1.9)	2.4 (2.5)	1.5 (1.9)	2.5 (2.5)	0.33
Peer Relation	3.6 (2.5)	2.4 (2.8)	4.3 (4.1)	2.5 (2.3)	1.17
Prosocial	6.0 (3.2)	5.3 (3.0)	4.6 (2.1)	5.5 (2.2)	0.42
Total	13.5 (6.6)	15.5 (9.5)	14.0 (8.8)	15.0 (6.5)	0.17
Parent Conners					
Hyperactivity	79.1 (12.3)	79.2 (10.7)	86.5 (7.7)	84.1 (8.8)	1.62
Inattention	74.9 (9.3)	69.3 (9.4)	72.0 (11.7)	74.1 (8.8)	0.88
Total	80.2 (8.8)	75.9 (9.6)	81.0 (9.5)	81.5 (8.2)	1.06
Teacher Conners					
Hyperactivity	61.5 (16.7)	64.8 (17.6)	62.0 (14.9)	66.6 (15.4)	0.34
Inattention	63.7 (13.9)	65.6 (15.7)	60.6 (12.3)	65.2 (14.2)	0.20
Total	64.5 (15.5)	66.6 (17.1)	62.0 (13.8)	67.5 (14.1)	0.28
Comorbid Disorder[a]					χ^2-*value*
CD	4	3	2	9	0.11
ODD	9	9	6	24	1.30
Autism	0	0	0	0	0.00
Mood	1	3	1	8	2.20
Bipolar	0	0	0	1	2.32
Anxiety	6	4	2	17	0.87
Tourett's	0	0	0	1	1.71
Substance Use	0	0	0	2	1.71
OCD	0	0	0	1	1.63
Attachment	0	0	0	0	0.00
Schizophrenia	0	0	0	0	0.00

Note: CD = Conduct Disorder; DAV = Delay Aversion; IC = Inhibitory Control; OCD = Obsessive Compulsive Disorder; ODD = Oppositional Defiant Disorder; SDQ = Strengths and Difficulties Questionnaire; WISC = Wechsler Intelligence Scales for Children

[a] = Number of cases;

* $p < .05$; ** $p < .001$

7.4. Discussion

The dual pathway hypothesis was first proposed five years ago (Sonuga-Barke, 2002). Since then, many researchers have accepted this causal model as a possible theoretical aetiology of ADHD, but only few studies have investigated whether ADHD has independent associations with IC and DAV deficits. This is the first study to examine the dual pathway hypothesis using multiple measures for each construct.

Like Solanto and her colleagues (2001) and Thorell (in press), results from the present study suggest that ADHD is a heterogeneous disorder, with at least two causal neuropsychological pathways. Although measures across domains seem to show weak but significant association, principal component analysis indicated that these two constructs are independent pathways leading to ADHD. However, one DAV measure (i.e. DeFT MTD) was found to cross load between the two constructs indicating that this task might have some inhibitory control component. The frustration caused by unexpected delay in this task increases impulsivity (i.e. pressing the response key more often and for longer time), a behavioural reaction that is possibly hard to suppress (lack of inhibition).

As it was also hypothesised, ADHD cases had worse performance on the overall IC and DAV components compared to controls. Children were also found to have worse performance on the overall DAV component compared to adolescents, although this was not specific to any experimental group. This might be because patterns of motivational salience of outcomes undergo a qualitative change as people age across the life span (Green et al., 1994; Green et al., 1996) and adolescents' ability to tolerate delay to achieve a preferred outcome or to respond to a socially desirable manner increases (Zuckerman et al., 1995; Holtgraves, 2004).

The comorbid effect of ODD on DAV performance has been examined in two studies and the results were inclusive (Antrop et al., 2006; van der Meer, Marzocchi, and de Meo, 2005). In the first study, both ADHD and ADHD+ODD groups have shown deficits on a delay aversion measure. In the second study, only children with ADHD+ODD were found to have impaired reinforcement contingency. The present study is the first one to investigate comorbid effects on an overall DAV component constructed by multiple DAV

measures. As in van der Meer and colleagues (2005) study, only ADHD+ODD cases had worse performance on the overall DAV component compared to controls, indicating that ODD might account for DAV deficit in ADHD. On the other hand, Oosterlaan and colleagues (2005) argued that executive functioning deficits are associated only with ADHD, and that the presence of comorbid ADHD accounts for the executive functioning deficits in children with ADHD+CD or ADHD+ODD. The present results are in line with these findings, as both ADHD and ADHD+ODD cases had worse performance than controls on the overall IC score.

The final aim of the study was to identify the different subgroups of ADHD cases based on their neuropsychological impairment. It was found that 25% of ADHD cases had IC deficit, 15% had DAV deficit, 11% had deficit on both neuropsychological functions, and 49% did not have any of the two neuropsychological deficits. Proportions on 'pure' IC and 'pure' DAV deficit are similar with those reported by Nigg and colleagues (2005; based on the study by Solanto et al., 2001). However, a higher proportion of non-affected individuals and a lower proportion of dual-deficit individuals were found compared to the literature. These discrepancies might be due to the increased amount of measures used in the present study. Compared to Solanto et al. (2001), the number of measures tapping into each construct was increased here in order to increase construct validity. Moreover, the four neuropsychologically impaired ADHD groups did not have different clinical characteristics, with the exception of vocabulary and estimated IQ performance, where the IC deficit group showed better performance compared to their counterparts. Considering that this is the third study examining the dual pathway hypothesis in ADHD cases, and the second to estimate proportion of children with neuropsychological impairments, there is a strong need of further research on the issue.

Finally, the dual pathway hypothesis is not an exhaustive causal model (Sonuga-Barke, 2005). Evidence for this claim comes from present data (see also Nigg et al., 2005) showing that approximately 49% of ADHD cases do not have either IC or DAV deficit. Therefore, a significant proportion of ADHD cases might be affected by other neuropsychological deficits reported in the literature, such as state regulation (Sergeant, 2005), temporal processing, and working memory (Castellanos & Tannock, 2002). Furthermore, environmental factors can have a significant effect on the expression of neuropsychological deficits (Sonuga-Barke, 2005); therefore further research is required

on identifying the effect of external factors on IC and DAV deficits, as well as on investigating other neuropsychological dysfunctions associated with ADHD-related IC and DAV deficits.

CHAPTER EIGHT: What is the role of Inhibitory Control (IC) and Delay Aversion (DAV) deficits in the causal chain between family factors and ADHD?

8.1. Aim of the chapter

ADHD cases were shown to have IC and DAV deficits compared to controls (Chapters 5 and 6 respectively). Moreover, IC and DAV constructs have been found to be independent pathways leading to ADHD (Chapter 7).

ADHD is a highly familial disorder and genetic and possibly other environmental factors have been shown to be causally important to the outcome of the disorder. We have reviewed elsewhere the literature of genetic and other aetiological factors and the potential role that neuropsychological deficits might play in mediating the effects of these factors. In this chapter we move from describing the relationship between ADHD and IC and DAV to examining the potential role of these neuropsychological deficits in the causal chain between family factors and the disorder. In short, if IC and DAV mediate these familial effects we would predict the following:

(i) *Proband-sibling correlations on IC and DAV measures and on each construct's composite score would be significant.*

(ii) *Control cases will show better performance compared to ADHD probands and their unaffected siblings in all individual measures and their composite score.* Moreover, the data will have a linear and non-quadratic trend in such a way so that ADHD proband siblings' neuropsychological performance will be intermediate between their ADHD probands and controls.

(iii) *Siblings of neuropsychologically impaired probands will show worse neuropsychological performance compared to siblings of neuropsychologically unimpaired probands.* In other words DAV and IC deficits would co-segregate within families of ADHD.

8.2. Methods

8.2.1. Participants

The ADHD cases used for the present analysis were the same as the ones reported in previous chapters. However, from the 77 ADHD cases used previously, six cases were affected siblings of ADHD probands. For the present analysis, these six sibling cases (and their matched ADHD probands) were excluded. Therefore, 65 pairs of ADHD cases combined type (M_{ADHD} = 12.12 years, SD_{ADHD} = 2.32 years), their unaffected siblings ($M_{Sibling}$ = 11.46 years, $SD_{Sibling}$ = 3.19 years) and 50 typical controls ($M_{Controls}$ = 12.15 years, $SD_{Controls}$ = 2.25 years) were included for this study (Table 8.1 displays sample and clinical characteristics of the three groups). Inclusion criteria were an estimated full IQ of at least 70 as measured by a short version of the Wechsler Intelligence Scale for Children (WISC-III; Wechsler, 1991), age range between 6 to 17, and no apparent other mental health problems, such as autism, epilepsy, brain disorders, or known genetic disorders, such as Downs syndrome or Fragile X syndrome.

8.2.2. Recruitment Procedure

The procedure of recruitment of ADHD and control cases was the same as described in Chapter 5. Siblings were recruited in the same way as their probands. Both probands and siblings were tested on the same day and time by two different researchers to reduce family's time engagement to the study, and avoid information exchange between probands and siblings. Researchers were not blind to children's experimental status. To control for potential researcher bias effects, the researchers were randomly counterbalanced during testing.

8.2.3. Diagnostic Criteria

Diagnostic criteria for ADHD and control cases were the same as described in Chapter 5.

Parents and teachers of unaffected siblings completed the same rating scales as for ADHD probands. Rating scales used to quantify ADHD symptoms in siblings included

CPRS-R:L, CTRS-R:L, parent and teacher version SDQ, and parent and teacher version of SNAP-IV (description of the scales can be found in Chapter 5). If siblings scored above the clinical cut-off at CPRS-R:L and CTRS-R:L (i.e. T-score > 65), then they were also assessed on the PACS (description of the PACS can be found in Chapter 5). Six siblings were found to be affected with ADHD, according to the PACS, and these probands-sibling pairs were excluded from the analysis.

8.2.4. Materials

8.2.4.1. IC measures

As in Chapter 4, section 4.3.1.

8.2.4.2. DAV measures

As in Chapter 4, section 4.3.2.

8.2.4.3. Clinical and IQ evaluation

As in Chapter 5, section 5.2.4.2.

8.2.5. Data analysis

Analysis was based on performance on individual tasks and on the overall composite score of IC and DAV measures. Due to limited space and for better clarity, only results on the main indices of each task are reported. Furthermore, in order to be able to interpret the results universally, a composite score for each of the two constructs was calculated (i.e. IC and DAV), by aggregating the standardized scores of the three main indices of each construct.

Exploratory analysis of the data was carried out to investigate any indications of familiality of IC and DAV measures. First, Pearson correlation between siblings' and probands' performance on IC and DAV measures and constructs was conducted (Nigg et al., 2004). This was based on the assumption that if unaffected siblings were to have

a similar neuropsychological profile as their ADHD probands, then it would be expected that probands-sibling correlations on task performance and on construct composite score would be significant. Second, differences on neuropsychological performance between ADHD probands, their unaffected siblings and typical controls were investigated by using a univariate ANOVA. Age (6-12 years vs. 13-17 years) was also included as an independent factor. Bonferroni post-hoc analysis was used to identify specific differences between the three groups. Analysis was also carried out to investigate the linear and non-quadratic trend of the data, as was used by Waldman and colleagues (2006). Finally, a univariate ANOVA was used with status (ADHD, siblings and controls) as an independent factor and family number as a random effect in order to investigate whether shared family variance influenced the results. Each control child was assigned to one family. Probands and siblings of the same family were also assigned to one family. Therefore, there were 50 control families, and 65 proband-sibling families. Age was not included in this analysis as there were not enough numbers of participants per cell.

The last section of results focused on familial co-segregation and therefore it was investigated whether IC and DAV deficits found in ADHD probands could be mediating the familial causes of ADHD. ADHD probands were defined by neuropsychological risk status; impaired and unimpaired. This categorization has been previously used by Nigg and colleagues (2004a, 2005). Impairment on neuropsychological tasks and construct was defined as worse than the 10^{th} or 90^{th} percentile (depending on the task) in the control group. However, because of tie scores, the actual cut points varied from the 10^{th} to the 13^{th} (or 88^{th} to 90^{th}) percentile. Then siblings were categorised into those who had a task-impaired ADHD proband (i.e. siblings of impaired probands) and those who had a task-unimpaired ADHD proband (i.e. siblings of unimpaired probands). Further analysis was performed using the median score of controls' performance in order to increase power for each group, but no significant changes of the results were found. Univariate ANOVA was used to identify any differences between siblings of impaired probands and siblings of unimpaired probands. Age (6-12 years vs. 13-17 years) was also used as an independent factor.

Table 8.1.: Sample and clinical characteristics of ADHD probands, their unaffected siblings and typical controls by age

	ADHD		Siblings		Controls			
	6-12 years	13-17 years	6-12 years	13-17 years	6-12 years	13-17 years	Status *F*	*p*
	N = 43	**N = 22**	**N = 40**	**N = 25**	**N = 29**	**N = 21**		
Age	10.72 (1.32)	14.81 (1.09)	9.45 (2.23)	14.68 (1.22)	10.90 (2.12)	13.89 (0.83)	1.31	.27
Male %	90.69	86.36	55	48	58.62	76.19	21.15[e]	< .001[c]
WISC-III	**N = 43**	**N = 22**	**N = 40**	**N = 25**	**N = 29**	**N = 21**		
Vocabulary	8.91 (2.80)	8.55 (2.36)	9.00 (2.78)	8.68 (2.61)	10.31 (3.56)	9.14 (3.30)	2.09	.12
Block Design	9.44 (2.51)	9.14 (1.95)	9.85 (3.15)	9.40 (2.21)	10.97 (2.32)	9.81 (2.80)	2.84	.06
Full	95.13 (12.23)	93.04 (9.72)	96.51 (14.42)	94.24 (11.45)	103.91 (14.31)	96.85 (15.74)	3.74	< .05[b]
Parent SDQ	**N = 43**	**N = 22**	**N = 40**	**N = 25**	**N = 29**	**N = 21**		
Hyperactivity	8.49 (1.71)	8.41 (1.96)	3.13 (3.05)	2.20 (2.04)	2.14 (1.72)	1.76 (1.64)	165.02	< .001[c]
Conduct	5.91 (2.47)	5.41 (2.36)	2.55 (2.34)	2.60 (2.70)	1.41 (1..88)	1.19 (1.47)	59.85	< .001[c,d]
Emotional	4.70 (2.71)	3.59 (2.34)	3.03 (2.98)	1.76 (1.89)	1.76 (2.08)	1.10 (1.26)	20.13	< .001[c]
Peer Relation	4.67 (4.02)	3.55 (2.61)	1.83 (2.01)	2.08 (2.30)	1.34 (1.58)	2.43 (2.54)	16.07	< .001[c]
Prosocial	5.65 (2.14)	5.41 (1.53)	8.53 (3.44)	7.52 (2.14)	8.48 (1.86)	9.00 (2.14)	29.11	< .001[c]
Impact	5.58 (2.32)	5.09 (2.40)	1.60 (2.84)	1.32 (2.49)	0.28 (0.84)	0.24 (0.70)	90.68	< .001[c,d]
Total	23.77 (6.70)	20.95 (5.56)	10.53 (8.71)	8.64 (7.59)	6.66 (4.79)	6.00 (3.91)	100.20	< .001[c,d]
Teacher SDQ	**N = 33**	**N = 17**	**N = 36**	**N = 16**	**N = 24**	**N = 13**		
Hyperactivity	6.55 (2.58)	7.00 (2.42)	3.11 (2.42)	4.50 (2.73)	1.29 (1.51)	1.46 (1.05)	62.17	< .001[c,d]
Conduct	2.36 (2.28)	3.24 (2.25)	1.06 (1.89)	2.13 (1.89)	0.38 (0.77)	0.23 (0.59)	17.29	< .001[c,d]
Emotional	2.12 (2.19)	2.76 (2.96)	1.28 (1.44)	2.25 (2.79)	0.83 (1.34)	0.77 (1.48)	5.90	< .01[b]
Peer Relation	2.91 (2.83)	2.94 (2.22)	1.19 (1.67)	2.44 (2.65)	1.29 (1.39)	1.23 (1.42)	7.88	< .001[c]
Prosocial	5.85 (2.64)	5.00 (2.39)	7.00 (2.66)	6.25 (2.38)	7.54 (2.75)	7.62 (2.29)	6.98	< .001[c]
Impact	1.42 (1.43)	2.06 (1.78)	0.28 (.70)	0.88 (1.36)	0.17 (0.38)	0	24.01	< .001[c]
Total	13.94 (6.87)	15.94 (7.29)	6.64 (5.48)	11.31 (8.17)	3.63 (3.62)	3.69 (2.68)	35.95	< .001[c,d]

Note: SDQ = Strengths and Difficulties Questionnaire; WISC = Wechsler Intelligence Scales for Children.
a = Typical controls did not complete parent and teacher Conners' questionnaire.
b = ADHD probands were significantly different from Controls
c = ADHD probands were significantly different from Siblings and Controls
d = Siblings were significantly different from Controls
e = χ^2

Table 8.1.: Sample and clinical characteristics of ADHD probands, their unaffected siblings and typical controls by age (continued)

	ADHD		Siblings		Controls			
	6-12 years	13-17 years	6-12 years	13-17 years	6-12 years	13-17 years	Status *F*	*p*
Parent SNAP	**N = 43**	**N = 22**	**N = 40**	**N = 25**	**N = 29**	**N = 20**		
Hyperactivity	2.26 (0.73)	2.06 (0.67)	0.63 (0.71)	0.36 (0.53)	0.48 (0.51)	0.20 (0.21)	149.24	< .001[c]
Inattention	2.29 (0.68)	2.34 (0.54)	0.74 (0.77)	0.53 (0.71)	0.50 (0.43)	0.34 (0.39)	159.10	< .001[c]
Total	2.27 (0.58)	2.18 (0.50)	0.68 (0.73)	0.44 (0.60)	0.49 (0.42)	0.26 (0.24)	193.78	< .001[c]
Teacher SNAP	**N = 33**	**N = 16**	**N = 35**	**N = 17**	**N = 24**	**N = 13**		
Hyperactivity	1.14 (0.79)	1.27 (0.86)	0.36 (0.41)	0.54 (0.71)	0.19 (0.29)	0.18 (0.23)	34.11	< .001[c]
Inattention	1.34 (0.80)	1.58 (0.83)	0.63 (0.59)	0.80 (0.64)	0.34 (0.40)	0.35 (0.33)	32.42	< .001[c,d]
Total	1.23 (0.70)	1.40 (0.70)	0.48 (0.41)	0.67 (0.64)	0.26 (0.31)	0.25 (0.25)	42.57	< .001[c]
Parent Conners	**N = 43**	**N = 22**	**N = 39**	**N = 24**	**N/A[a]**	**N/A[a]**		
Hyperactivity	83.02 (9.39)	84.73 (8.30)	55.59 (14.82)	54.29 (12.57)			174.03	< .001
Inattention	73.58 (8.34)	75.68 (8.95)	53.08 (12.80)	51.13 (8.20)			138.97	< .001
Total	80.30 (7.98)	83.36 (7.61)	54.59 (14.41)	52.58 (10.64)			187.83	< .001
Teacher Conners	**N = 35**	**N = 18**	**N = 35**	**N = 18**	**N/A[a]**	**N/A[a]**		
Hyperactivity	61.83 (13.73)	69.44 (17.25)	49.80 (6.46)	60.17 (14.22)			18.53	< .001
Inattention	59.80 (12.12)	69.89 (13.60)	52.29 (8.90)	59 (8.52)			14.95	< .001
Total	61.86 (13.45)	72.17 (13.91)	51.46 (7.42)	60.61 (10.83)			20.60	< .001

Note: SNAP = Swanson, Nolan, and Pelham questionnaire (Swanson, 1992)

a = Typical controls did not complete parent and teacher Conners' questionnaire.

b = ADHD probands were significantly different from Controls

c = ADHD probands were significantly different from Siblings and Controls

d = Siblings were significantly different from Controls

8.3. Results

8.3.1. Clinical characteristics

Table 8.1 displays the clinical characteristics for each group by age. The groups did not differ in age ($F(2,177) = 1.31$, ns) but gender difference was found between the three groups ($\chi^2(2) = 21.15$, $p < .001$). The ADHD group had more males than both the sibling group ($U = 1332$, $p < .001$) and the control group ($U = 1247$, $p < .01$). However, no gender differences were found between siblings and controls ($U = 1402$, ns). In addition, the three groups differed on estimated IQ ($F(2,177) = 3.74$, $p < .05$). Post-hoc analysis indicated that ADHD cases had lower estimated IQ compared to controls ($p < .05$).

The response rate for teachers was approximately 80% for ADHD cases, 83% for siblings and 78% for healthy control children ($\chi^2(2) = .62$, $p > .05$). In general, children with ADHD had higher parental and teacher report scores on the SDQ and the SNAP compared to their siblings and controls. Moreover, in some SDQ and SNAP subscales siblings were found to have higher scores compared to controls (e.g. SDQ conduct, impact and total subscales, teacher SNAP Inattention; see Table 8.1). The Conners' questionnaire was only completed by parents and teachers for children with ADHD and their siblings. Based on these rating scales ADHD cases had higher hyperactivity/impulsivity and attention symptoms compared to their siblings (see Table 8.1).

8.3.2. Exploratory analysis for familiality

Proband-Sibling Correlations

Proband-sibling correlations for the IC measures were not significant, although in the right direction to suggest some level of familiality (Table 8.2). On the other hand, sibling correlations for the DAV measures were of modest to moderate magnitude, with correlation on MIDA task being significant. Finally, overall IC and DAV performance, as indicated by the composite score of each construct, did not show proband-sibling correlation. Controlling for the effect of age did not change the results (Appendix B.3).

Table 8.2.: One-diagonal correlation of probands and siblings on IC and DAV measures

	Proband-Sibling *r*
SSRT (ms)	.24
MStroopPI (%)	.18
GNGPI (%)	.17
MIDA % DR	.35**
DeFT MTD (ms)	.26
DRT DS (ms)	.14
IC composite	.15
DAV composite	..21

Note: DAV = Delay Aversion; DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; IC = Inhibitory Control; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; SSRT = Stop Signal Reaction Time;
* = $p < .05$; ** = $p < .01$

Group differences on neuropsychological performance

A univariate ANOVA was used with two independent factors: status (ADHD, siblings, and controls) and age (6-12 years vs. 13-17 years). Table 8.4 reports ANOVA main and interaction effects. The status main effect was significant for all measures, indicating that there was a difference between the three groups (Figure 8.1.I-VI and Figure 8.2.II) with only differences on IC composite score showing marginal significance difference between ADHD and control cases (Figure 8.2.I). The age main effect was significant on SSRT, MIDA, and DRT DS, with children having worse performance than adolescents (Table 8.3). The status x age interaction was significant for SSRT, MStroopPI and IC composite score (Table 8.4).

Bonferroni post-hoc analysis was used to identify specific difference between groups (Table 8.4). First, control cases showed significantly better performance compared to ADHD probands in all neuropsychological measures and composite scores. Only in the MIDA task the difference, although in the expected direction, was not significant. Second, control cases demonstrated better performance compared to unaffected siblings on the MStroop and DRT task. Finally, unaffected siblings and their ADHD probands did not show any differences on tasks, except for the GNG and DAV

composite score, where siblings showed significantly better performance than their probands.

In order to statistically test whether siblings' neuropsychological performance was intermediate to that of their ADHD probands and control cases, the linear and non-quadratic trend of data was tested. Results as displayed in Table 8.4 indicated that the group means increased proportionally for all neuropsychological measures, with ADHD probands having increased deficits than unaffected siblings who had, in turn, worse performance than typical controls. Only performance in MIDA did not show a linear trend, as unaffected siblings had worse performance than ADHD probands (Figure 8.1.IV). Quadratic trend analysis also confirmed the linear trend of all data. Quadratic tests on MIDA performance was significant, indicating that siblings' neuropsychological performance on that task deviates from being intermediate to performance of ADHD probands and typical controls (Figure 8.1.IV).

Finally, a univariate ANOVA was used with status (ADHD, siblings and controls) as between subject factor and family number as a random effect in order to control for shared family variance between probands and siblings. The status main effects remained the same or were slightly increased for most of the measures. In fact, the status main effect on IC composite score became significant. However, the status main effect on SSRT did not remain significant after controlling for shared family variance.

Table 8.3.: Mean (standard deviation) of ADHD probands, unaffected siblings and typical controls

	ADHD probands		*Unaffected Siblings*		*Controls*	
	6 - 12 yrs	*13 - 17yrs*	*6 - 12 yrs*	*13 - 17yrs*	*6 - 12 yrs*	*13 - 17yrs*
SSRT (ms)	275 (94)	299 (157)	300 (128)	214 (69)	254 (98)	201 (57)
MStroopPI (%)	61.13 (15.28)	66.33 (15.80)	65.14 (14.59)	72.68 (14.57)	79.51 (14.94)	70.74 (20.97)
GNGPI (%)	59.50 (21.97)	69.72 (21.28)	70.06 (19.83)	79.23 (14.17)	79.72 (19.88)	74.66 (23.23)
MIDA % DR	63.84 (29.61)	83.82 (22.32)	54.91 (34.03)	71.46 (30.33)	77.61 (31.43)	87.32 (26.49)
DeFT MTD (ms)	307 (311)	332 (563)	223 (359)	144 (272)	150 (239)	156 (212)
DRT DS (ms)	293 (175)	247 (135)	292 (134)	196 (96)	192 (125)	159 (102)
IC composite	-0.86 (1.56)	0.15 (2.23)	0.09 (1.63)	0.21 (1.32)	1.00 (1.53)	-0.20 (1.93)
DAV composite	0.37 (1.56)	0.74 (2.13)	-0.18 (1.79)	-0.45 (1.30)	-0.30 (1.47)	-0.24 (0.96)

Note: DAV = Delay Aversion; DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; IC = Inhibitory Control; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; SSRT = Stop Signal Reaction Time.

Table 8.4.: ANOVA Main and interaction effects, post-hoc analysis, status main effect after controlling for shared family variance and linear and quadratic trend of data.

	Analysis of Variance					*ANOVA*[a]	*Trend*	
	df	*Status (S) (F-value)*	*Age (A) (F-value)*	*S x A (F-value)*	*Post-hoc*[b] *(p-value)*	*Status (F-value)*	*Linear (p-value)*	*Quadratic (p-value)*
SSRT (ms)	164	3.87*	5.02*	3.92*	A>C	2.30	.006	.98
MStroopPI (%)	169	6.76**	0.28	3.99*	A,S>C	8.36**	.001	.84
GNGPI (%)	171	5.80**	2.24	2.25	A>C,S	6.37**	.002	.26
MIDA % DR	173	5.64**	10.89**	0.39	S>C	10.08**	.143	.002
DeFT MTD (ms)	158	3.58*	0.09	0.36	A>C	3.95*	.01	.35
DRT DS (ms)	160	6.32**	6.93**	0.76	A,S>C	6.54**	.001	.37
IC composite	174	2.81[c]	0.008	5.79**	A>C	4.66*	.021	.62
DAV composite	174	5.59**	0.04	0.60	A>C,S	5.89**	.007	.07

Note: A = ADHD; C = Controls; DAV = Delay Aversion; DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; IC = Inhibitory Control; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; S = Siblings; SSRT = Stop Signal Reaction Time.

* $p < .05$; ** $p < .01$;

[a] After controlling for shared family variance; [b] > indicates that the group(s) on the left of the symbol had worse performance; [c] $p = .06$

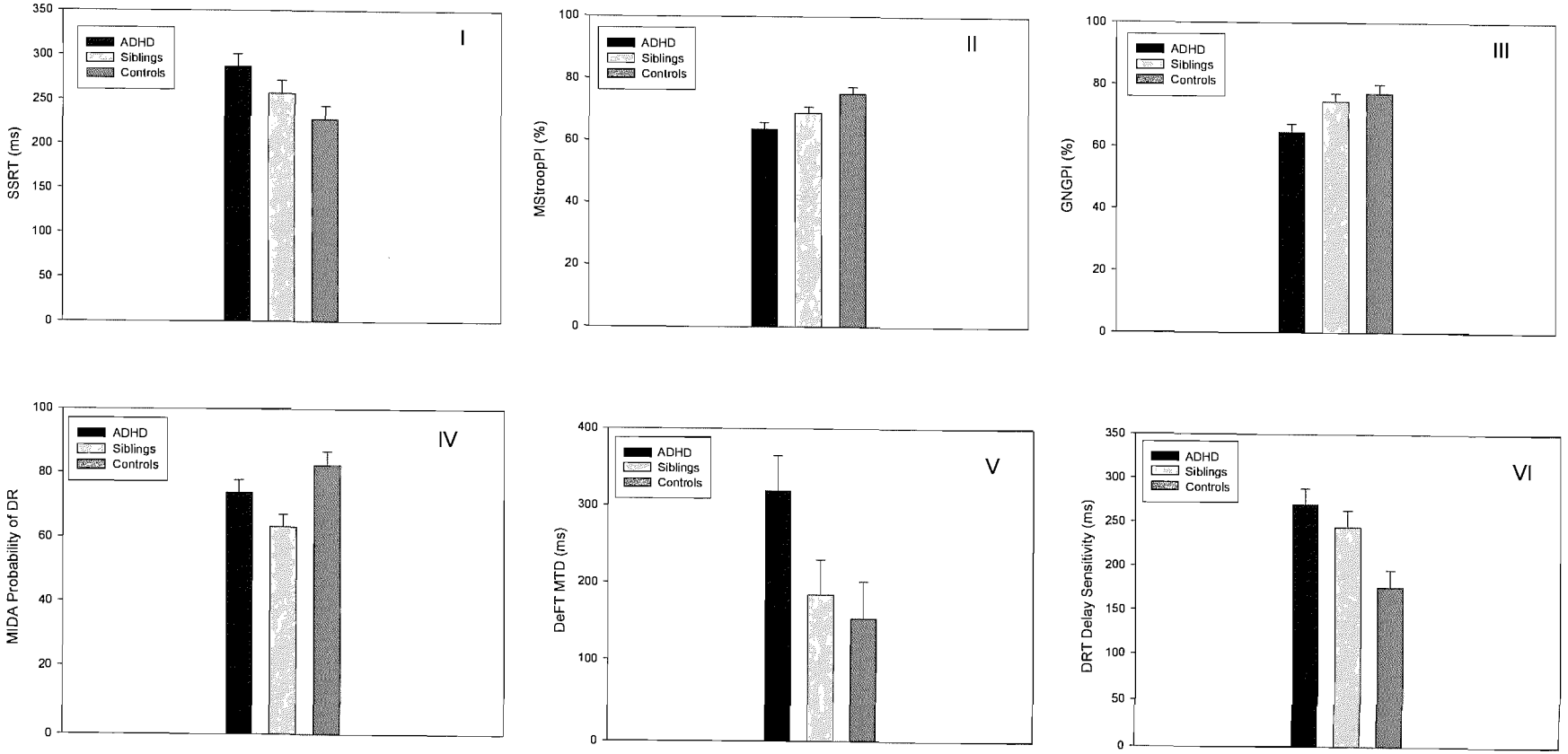


Figure 8.1.: Status performance on neuropsychological measures (error bars indicate SE; age controlled).
I. Stop Signal Reaction Time. II. Modified Stroop Task Probability of Inhibition. III. Go/No-Go Probability of inhibition. IV. Maudsley's Index of Delay Aversion Probability of Delayed Reward. V. Delay Frustration Mean Total Duration. VI. Delay Reaction Time Delay Sensitivity.

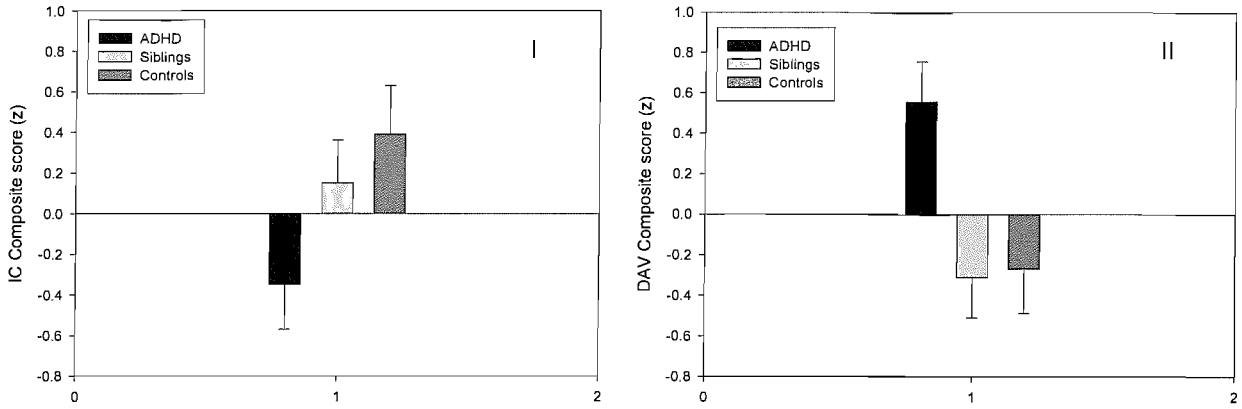


Figure 8.2.: Status performance on composite scores (error bars indicate SE; age controlled) I. Inhibitory Control composite score. II. Delay Aversion composite score.

8.3.3. Do IC and DAV performance co-segregate with ADHD within families?

A univariate ANOVA was used with two independent factors: status (siblings of impaired probands vs. siblings of unimpaired probands) and age (6-12 years vs. 13-17 years). Table 8.5 reports ANOVA main and interaction effects. The status main effect was not significant for all individual measures and the two composite scores. The age main effect was significant for SSRT, GNGPI and DRT DS with children showing worse performance in all three measures compared to adolescents. Finally, status x age interaction was not significant for any of the measures.

Table 8.5.: Siblings' means (standard deviation) by age and ANOVA main and interaction effects

	Siblings of Impaired probands		*Siblings of Unimpaired probands*		*Analysis of Variance*			
	6 - 12 yrs	*13 - 17yrs*	*6 - 12 yrs*	*13 - 17yrs*	*df*	*Status (S)*	*Age (A)*	*S x A*
SSRT (ms)	342 (136)	235 (103)	293 (127)	205 (50)	54	1.46	8.84**	0.09
MStroopPI (%)	62.10 (13.4)	71.33 (8.9)	66.71 (15.4)	73.13 (16.2)	56	0.53	3.19	0.10
GNGPI (%)	62.70 (22.9)	77.00 (14.4)	72.16 (19.1)	80.35 (14.3)	57	1.45	4.47*	0.33
MIDA % DR	42.66 (36.0)	66.65 (26.1)	56.66 (33.9)	72.37 (31.5)	61	0.68	2.75	0.12
DeFT MTD (ms)	403 (639)	162 (137)	157 (195)	131 (315)	46	1.59	1.47	0.95
DRT DS (ms)	295 (137)	217 (86)	298 (142)	185 (102)	49	0.15	6.83*	0.21
IC composite	-0.25 (1.58)	0.15 (.94)	0.19 (1.66)	0.24 (1.47)	61	0.35	0.25	0.15
DAV composite	0.56 (2.16)	-0.35 (1.26)	-0.62 (1.38)	-0.49 (1.35)	61	2.32	0.79	1.43

Note: DAV = Delay Aversion; DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition;
IC = Inhibitory Control; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed
Reward; MStroopPI = Modified Stroop Probability of Inhibition; SSRT = Stop Signal Reaction Time.
* $p < .05$; ** $p < .01$;

8.4. Discussion

The main aim of the present study was to investigate whether IC and DAV deficits found in ADHD probands could be mediating the familial causes of ADHD (i.e. they showed familial co-segregation with ADHD symptoms). Studies assessing neuropsychological function of unaffected ADHD relatives are far from definitive. Most studies have focused on executive function processing, and specifically inhibitory control (Bidwell et al., 2007; Chhabildas et al., unpublished data, cited by Doyle et al., 2005b; Doyle et al., 2005a; Kuntsi & Stevenson, 2001; Nigg et al., 2004a; Schachar et al., 2005; Slaats-Willemse et al., 2003; Waldman et al., 2006). Delay aversion impairment has been investigated in only two studies (Bidwell et al., 2007; Kuntsi & Stevenson, 2001). Results from these studies suggest that inhibitory control performance of unaffected ADHD relatives may index familial vulnerability to the disorder, as bivariate heritability of IC was high (Chhabildas et al., unpublished data, cited by Doyle et al., 2005b; Kuntsi & Stevenson, 2001) and unaffected relatives of ADHD probands showed subtle deficits in response inhibition and interference control measures compared with control children (Bidwell et al., 2007; Doyle et al., 2005a; Nigg et al., 2004a; Schachar et al., 2005; Slaats-Willemse et al., 2003; Waldman et al., 2006). However, this was not the case for delay aversion. Bidwell and colleagues (2007) failed to find any differences between siblings of ADHD probands and controls on a delay aversion measure. Similarly, Kuntsi and Stevenson (2001) showed that the bivariate heritability of delay aversion in ADHD was very low.

As the interest in investigating familiality of neuropsychological functions in ADHD is fairly recent, there are no definitive and universally agreed methodological and statistical ways to test familial liability in family studies. Some researchers have used proband-sibling correlations as an indication of associated performance (Nigg et al., 2004a). Others have hypothesised that unaffected relatives would have worse performance than typical controls but not from ADHD probands (Doyle et al., 2005a; Schachar et al., 2005; Slaats-Willemsel et al., 2003). Further studies have investigated whether unaffected siblings' performance would be intermediate to that of ADHD probands and siblings (Waldman et al., 2006). All these statistical methods could provide an exploratory analysis for indications of familial liability. However, the most direct way to investigate whether IC and DAV deficits mediate the familial causes of ADHD is the analysis of the familial co-segregation of neuropsychological

deficits and ADHD within families. For this analysis, unaffected relatives are categorized into those who have a task-impaired ADHD proband and those who have a task-unimpaired ADHD proband (Nigg et al., 2004a) and then the two sibling groups are compared. The prediction is that siblings of impaired probands would have worse performance than siblings of unimpaired probands. In the present thesis, we first explored the data with correlation and group comparison analyses, before running the familial co-segregation analysis.

Exploratory analyses to identify any indications for IC and DAV deficits mediating familial liability in ADHD gave inconclusive results. First, proband-sibling correlation analysis indicated that from all IC and DAV measures and their composite scores only MIDA could mediate familial liability. In the second exploratory analysis the three experimental groups (i.e. ADHD probands, unaffected siblings, and controls) were compared on their neuropsychological performance. From this analysis, performance on MStroop and DRT tasks provided some evidence of familiality, because siblings had significantly worse performance than control cases. Unexpectedly, unaffected siblings were found to have worse performance in the MIDA task. Although unaffected siblings on most cases did not differ in their performance from typical controls, they were found to be intermediate between their probands and control cases. Therefore, exploratory analysis of the data provided inconclusive evidence on which individual tasks or overall constructs could serve as the mediating neuropsychological factor of the causal chain of ADHD. The following analysis aimed to directly examine familial co-segregation, by comparing siblings of impaired and unimpaired ADHD probands.

As already reviewed earlier in this thesis, several familial factors (i.e. genetic and environmental) can contribute to the outcome of ADHD. For instance, genetic markers such as DAT1 and DRD4, alongside several other genes, have been associated with ADHD (e.g. Brookes et al., 2006; Faraone et al., 2005). Moreover, environmental factors such as prenatal nicotine and alcohol exposure, low birth weight, family adversity and parental psychopathology have been proven to be risk factors for ADHD (Linnet et al., 2003; Mick et al., 2002a; 2002b; Pressman et al., 2006; Romano et al., 2006). Neuropsychological markers have been conceptualized as an expression of familial liability to the disorder, and therefore, neuropsychological deficits should appear in unaffected relatives of ADHD probands as they share a high percentage of genetic (Doyle et al., 2005b) and other family influences with their proband. Specifically, it would be expected that unaffected siblings of

neuropsychologically impaired ADHD probands would have worse performance than siblings of ADHD probands, who did not have the deficit (i.e. third hypothesis). Familial co-segregation results failed to support this hypothesis, as there was no difference between the two sibling groups in any individual task or the overall IC and DAV deficit. So, could it be claimed that IC and DAV deficits are not mediating familial liability in ADHD? And if so, then why did unaffected siblings have an intermediate performance between ADHD probands and controls?

The main aim of the present study was the investigation of the role of neuropsychological markers as mediators of familial factors. The main limitation of the present study in investigating such a hypothesis was that basic familial factors of the causal chain of ADHD were not assessed directly; such as genetic, common and non-shared environmental factors. To be able to claim that IC and DAV deficits are not co-segregated within ADHD families, twin studies would be necessary, where genetic and environmental factors would be assessed alongside neuropsychological deficits. On the other hand, family studies could also be used, where several familial as well as neuropsychological factors would be assessed and the mediating effect of neuropsychological deficits between familial factors and ADHD would be examined with structural equation modelling. Therefore, the present results on familial co-segregation can lead us to several assumptions that would need to be further examined in twin or family studies.

Exploratory analysis indicated that there might be some level of familiality on MIDA, MStroop and DRT performance. However, familial co-segregation analysis showed that siblings of neuropsychologically impaired ADHD probands did not have a significantly worse performance compared to siblings of unimpaired ADHD probands, as it would be expected based on the causal model theory of ADHD. Therefore, IC and DAV deficits found in ADHD might not be mediators of familial factors in ADHD. Interestingly though, siblings' performance was found to be intermediate to ADHD probands and controls. The justification for this intermediate performance could lie in the possibility that unaffected siblings have intermediate symptoms of ADHD (as reported by parents and teachers) between ADHD probands and controls. However, this was not the case as unaffected siblings were found to be rated as controls on ADHD symptoms.

Factors such as genetic liability, common and non-shared environment could be the reason for siblings' intermediate performance. Unaffected siblings share 50% of their

genes with their ADHD proband, so siblings might not carry genes that are associated with the disorder. On the other hand, siblings might carry protective genes that could restrain to some level the expression of the disorder. Regarding the environmental factors, since the proband-sibling pairs live in the same family environment, one could rule out the possibility that common environmental factors are affecting siblings' performance to a different degree from ADHD probands' performance. In fact, Nigg (2006) reported that shared environment main effects for ADHD are small. Non-shared environmental factors, on the other hand, could explain why siblings do not perform as their ADHD probands. There is evidence that non-shared environmental main effects account for approximately 20% of variance in ADHD symptoms (Nigg, 2006) and that non-shared environmental effects increase from childhood to early adolescence, perhaps because of less influence from parenting (Kuntsi, Rijsdijk, Ronald, Asherson, & Plomin, 2005b; Larsson et al., 2004). Moreover, non-shared environmental factors, such as low birth weight, and prenatal exposure to toxicants such as lead, nicotine and alcohol (Braun, Kahn, Froehich, Auinger, & Lanphear, 2006; Linnet et al., 2003; Mick et al., 2002a; 2002b; Pressman et al., 2006; Romano et al., 2006) are associated risk factors leading to ADHD. ADHD probands are more likely to be exposed to non-share environmental factors compared to their siblings. However, all these are speculations, and twin and family studies are required to investigate the association of genetic and environmental effects with neuropsychological performance of ADHD relatives.

In sum, exploratory analysis on familial liability gave contradictory results, with MIDA, MStroop and DRT showing some evidence of familiality. However, familial co-segregation analysis indicated that IC and DAV deficits found in ADHD, might not be familial. Although the level of neuropsychological impairment of ADHD probands (i.e. impaired and unimpaired) did not differentiate performance between their siblings, the results were in the expected direction and unaffected siblings were found to have an intermediate performance between ADHD probands and controls. Several possibilities might account for this effect, but twin and family studies are needed to examine the association between familial effects and neuropsychological performance.

CHAPTED NINE: General discussion

9.1. Introduction

The high prevalence of impulsive, hyperactive and attention problems in the population, is a concern in our society and highlights the importance of identifying the aetiological factors that contribute to ADHD. The clinical characteristics of the disorder are not consistent in providing a clear picture of the outcome of an individual with ADHD. The discontinuity or change of the expression of ADHD symptomatology from childhood to adulthood and between males and females, as well as the high rate of co-occurrence of ADHD with other psychopathological disorders, give a complex symptomatic picture, which leads many researchers to highlight that ADHD is a clinically heterogeneous disorder. Therefore, researchers have directed their attention to more implicit aetiologies of the disorder, such as biological, neurophysiological and neuropsychological factors. At a neuropsychological level, ADHD is also heterogeneous in nature, as several neuropsychological deficits are associated with the disorder and these may be present in some, but not all children with ADHD. The aim of the present thesis was to identify the role of neuropsychological dysfunction in children and adolescents with ADHD as a possible causal factor of the disorder. Specifically, the aims of the present thesis were threefold:

1. *To identify whether ADHD is associated with IC and DAV* deficits.
2. *To replicate findings on dual pathway model from a multivariate perspective* (Sonuga-Barke, 2002).
3. *To examine the familial basis of IC and DAV deficits.*

This final chapter of the thesis sums up the findings relating to IC and DAV deficits in ADHD, the potential role of dual pathway in partitioning the heterogeneity of the disorder, and the familial co-segregation of these neuropsychological dysfunctions as further support of their important role in the aetiological pathways to the disorder. The role of age, gender, non-executive processes and comorbid ODD on neuropsychological function are also discussed. The chapter also considers the value of neuropsychological markers as candidate endophenotypes of the disorder and the contribution of the findings of the present thesis to the concept of neuropsychological subtypes of ADHD. Finally, at the end of this chapter the

methodological limitations of the study and suggestions on overcoming them in future studies are reported.

9.2. Summary results of the main three hypotheses

9.2.1. ADHD association with Inhibitory Control (IC) and Delay Aversion (DAV)

Executive function, and specifically IC deficits, are probably the most well-established and well-examined neuropsychological dysfunction in ADHD. However, fewer studies have investigated delay-related motivation and ADHD (i.e. delay aversion; DAV). In order to investigate these two neuropsychological constructs in depth, multiple tasks were included per construct. Two inhibitory control domains (i.e. response inhibition and interference control) and three delay-related motivation conditions (i.e. impact of delay on reward choice, frustration during unexpected delay and the impact of delay on response times) were examined for their association with each other and with ADHD.

In the present thesis children and adolescents with ADHD were shown to have motor inhibition and interference control deficits, a finding that is in line with previous research on the relationship between ADHD and IC deficits (see for review Doyle et al., 2005b). To identify the magnitude of group effects, the effect sizes for each measure were calculated. These effect sizes were similar or slightly higher than that reported in the literature (Nigg et al., 2005; Willcutt et al., 2005). For research purposes, the group effects for ADHD versus healthy control participants were generally modest to high in size, ranging from d = .58 to .95. However, these effect sizes are not sufficiently high to use these measures for diagnostic purposes. In fact, to have 80% discrimination between ADHD and controls at the individual level, an effect size of 2.0 is required (Sergeant et al., in press). Moreover, Nigg and colleagues (2005) reported that although effect sizes of EF measures ranged from d = .50 to 1.0, there was still 30-50% overlap of the ADHD and normal score distributions on most EF tasks. Therefore, tasks such as Stop Signal, GNG, and Stroop are not adequate to be used for diagnostic purposes, but they give a clear picture of IC deficit in ADHD cases. Finally, the main indices of IC measures showed high construct validity as they were found to interrelate.

The second construct under study, delay-related motivation, was found to be deficient in ADHD cases. Although most research has been focused on the choice between rewards with different delay conditions (see for review Luman et al., 2005),

interestingly in the present thesis, the most pronounced differences between ADHD cases and controls were found for frustration during unexpected delay and for the impact of delay on response times. First, following previous results (Douglas & Parry, 1994), ADHD cases were found to experience higher levels of frustration compared to controls during an unexpected and unsignaled delay. Second, replicating Sonuga-Barke and Taylor's (1992) results, ADHD cases were found to be more sensitive to delay compared to controls, as indicated by their increased reaction time during long delays. Third, ADHD cases showed a preference towards a small immediate over a large, delayed reward, a finding that is in line with several choice delay studies (e.g. Kuntsi et al., 2001a). As in the case of IC, DAV measures are not adequate for diagnostic purposes. However, the effect sizes of DAV measures for research purposes were moderate to high, ranging from d = .48 to .76. Finally, DAV measures were only partly inter-correlated, as the impact of delay on reward choice was not associated with frustration during unexpected delay.

9.2.2. Dual pathway model

Although Barkley (1997) has suggested that ADHD is an inhibitory-based executive dysfunction disorder, more recent accounts reject this version of the inhibitory deficit model (Willcutt et al., 2005). Rather they emphasize the neuropsychologically heterogeneous nature of the condition, where inhibitory deficits are presented as affecting only a subgroup of children with ADHD, while other groups of children with ADHD will have other patterns of impairment in non-inhibitory domains (Nigg, 2006; Sonuga-Barke, 2002; 2003; 2005). Sonuga-Barke (2002) was first to suggest that ADHD might be explained by a dual causal pathway of neuropsychological deficits: inhibitory control and delay aversion. The dual pathway hypothesis was first proposed five years ago. Since then, many researchers have considered this model as a possible theoretical basis for the causal aetiology of ADHD, but only a few studies have investigated the various neuropsychological mechanisms together in the same sample, to evaluate whether children with ADHD tend to have diffuse problems in all areas or whether there are discrete neuropsychological groups.

This is the third study examining the dual pathway hypothesis and whether children and adolescents with ADHD have deficits in IC and/or DAV. Like Solanto and her colleagues (2001) and Thorell (in press), results from the present thesis suggest that ADHD is a heterogeneous disorder, with at least two independent causal neuropsychological pathways leading to ADHD and with ADHD cases having worse performance on the overall IC and DAV components compared to controls. In

addition, four neuropsychological subgroups of ADHD cases were identified based on their neuropsychological dysfunction. It was found that 25% of ADHD cases had 'pure' IC deficit, 15% had 'pure' DAV deficit, 11% had a deficit on both neuropsychological functions, and 49% did not have any of the two neuropsychological deficits. Proportions on 'pure' IC and 'pure' DAV deficit are similar with those reported by Nigg and colleagues (2005; based on the study by Solanto et al., 2001). However, a higher proportion of non-affected individuals and a lower proportion of dual-deficit individuals were found compared to the literature. One possible explanation for this discrepancy might be the increased measures per construct used in the present study. However, considering that this is the second study providing proportions of neuropsychological subgroups, it is important to approach these numbers with caution.

Finally, the dual pathway hypothesis is not an exhaustive causal model (Sonuga-Barke, 2005). Evidence for this claim comes from present data (see also Nigg et al., 2005) showing that approximately 49% of ADHD cases do not have either IC or DAV deficit. Therefore, a significant proportion of ADHD cases might be affected by other neuropsychological deficits reported in the literature, such as state regulation (Sergeant, 2005), temporal processing, and working memory (Castellanos and Tannock, 2002). Furthermore, environmental factors can have a significant effect on the expression of neuropsychological deficits (Sonuga-Barke, 2005); therefore further research is required to identify the effect of external factors on IC and DAV deficits, as well as to investigate other neuropsychological dysfunctions associated with ADHD-related IC and DAV deficits.

9.2.3. Familial co-segregation of IC and DAV deficits

Neuropsychological markers have been conceptualized as an expression of familial liability to the disorder (Doyle et al., 2005b). A causal neuropsychological marker should appear in some unaffected relatives because it presumably combines with other factors in only some family members to cause the full disorder. Failing this test, the neuropsychological marker might only be another symptom of the disorder but not causal or at least not related to the genetic causal processes (Nigg, 2005). Few studies exist, examining this prediction, and this is the reason why there are no definitive and universally agreed methodological and statistical ways to test familial liability in family studies.

Exploratory analysis in the present thesis initially indicated that performance on interference control and delay sensitivity provided some evidence of familiality, as unaffected siblings had significantly worse performance than control cases. However, familial co-segregation analysis indicated that there was no difference between siblings of impaired and unimpaired probands in any individual task or the overall IC and DAV scores. In other words, IC and DAV deficits found in ADHD probands were not found to mediate the familial causes of ADHD, and therefore, they showed no familial co-segregation with ADHD symptoms. These results contradict findings suggesting that inhibitory control performance of unaffected ADHD relatives may index familial vulnerability to the disorder (Bidwell et al., 2007; Chhabildas et al., unpublished data, cited by Doyle et al., 2005b; Doyle et al., 2005a; Kuntsi & Stevenson, 2001; Nigg et al., 2004a; Schachar et al., 2005; Slaats-Willemse et al., 2003; Waldman et al., 2006). In addition, they are in line with findings suggesting that delay aversion does not mediate the familial causes of ADHD (Bidwell et al., 2007; Kuntsi & Stevenson, 2001).

Although the results of familial co-segregation indicate that IC and DAV deficits do not mediate familial causes of ADHD, there are two reasons why this result should be interpreted with caution. First, siblings' performance on all measures was found to be intermediate to ADHD probands and controls (see also Waldman et al., 2006). If IC and DAV deficits did not show familial co-segregation and they were only symptoms of the disorder, then we would also expect that unaffected siblings would have intermediate ADHD symptoms in order to explain their intermediate neuropsychological performance. Based on parental and teacher reports however, unaffected siblings were not different from controls on their ADHD symptomatology. This leads us to the second explanation, that the sample of the two unaffected siblings groups could be too small to indicate any differences. In fact, in a study with a larger sample (Nigg et al., 2004a), performance on motor inhibition and variability, but not interference control, was found to be different between relatives (i.e. parent and sibling composite score) of children with ADHD with impaired neuropsychological scores and relatives of control children and of children with ADHD with normal cognitive scores, which supports the familial co-segregation hypothesis. This is the first study directly comparing neuropsychological performance on unaffected siblings of impaired and unimpaired ADHD probands, and therefore, further research is required to replicate the present results.

9.3. Summary results: controlling for confounding effects

9.3.1.. Gender and age effects

Epidemiological studies indicate that ADHD is more commonly diagnosed among boys than girls (for reviews, see Lahey, Miller, Gordon, & Riley, 1999; Rowland, Lesesne, & Abramowitz, 2002). This was also true in the present study, whereas the proportion of males in the ADHD group was much higher than that of controls. Although this disproportion weakened the power for examining gender differences, it was found that there was no difference between males and females on both IC and DAV performance. This is in line with other researchers' suggestion that girls with ADHD have similar executive functioning as compared with boys with ADHD (Carlson & Tamm, 2000; Houghton et al., 1999; Rucklidge & Tannock, 2002; Seidman et al., 2005a). No evidence exists on gender differences and DAV deficit.

The developmental maturation of the neural circuits involved in IC and DAV is evident from the toddler years and continues as late as early adulthood, due to continued myelination, pruning, and specialization of circuity (e.g. Casey, Tottenham, Liston, & Durston, 2005; Nigg and Casey, 2005; Sowell, Thompson, Leonard, Welcome, Kan, & Tonga, 2004). Although the present study was not longitudinal, by comparing children and adolescents, one could observe the behavioural maturation of neuropsychological deficits. No age effects were found for any IC and DAV main indices, with the exception of the MIDA task. Results indicated that adolescents had improved performance compared to children. This result was also true for RT and RT variability of most of the measures. In both IC and DAV tasks normal developmental maturation was apparent in both ADHD and control cases. Therefore, although ADHD cases follow the normal maturational curve at the same pace as their counterparts, the starting point of their neuropsychological performance is lower than that of the controls, indicating that IC and DAV deficits in ADHD cases are evident in childhood and adolescence. These findings contradict previous evidence that response disinhibition is more pronounced in childhood (Drechsler et al., 2005; Nichelli et al., 2005), but is in line with evidence from the few motivational studies (see for review Luman et al., 2005).

9.3.2.. Effects of non-executive processes

Contrary to previous research supporting a mediating effect of IQ on executive functioning in ADHD (e.g. Hinshaw et al., 2007; Riccio et al., 2006; Polderman et al., 2006), the present results show that IQ was not associated with any of the IC

measures, despite the usually reported difference in IQ between ADHD cases and controls. This was also the case for delay-related frustration and delay sensitivity ability. However, IQ moderated the effect of ADHD on delay-related reward preference, with lower IQ leading to lower preference to delayed large reward. The MIDA task is a choice delay task, where decision-making processes take place. Disadvantageous decision-making has been described as major behavioural characteristic of patients with ADHD (Drechsler, Rizzo, & Steinhausen, 2007) and the overall cognitive ability of individuals with ADHD has been found to be significantly lower than controls (Frazier, Demaree, & Youngstrom, 2004). Although no studies exist on the moderating role of IQ between decision making and ADHD, in a study of healthy participants, higher IQ was associated with faster decision making and greater modulation of risk-taking (Deakin, Aitken, Robbins, & Sahakian, 2004). Therefore, the choice of reward in MIDA task might not be purely associated with delay aversion but also with disadvantageous decision-making, which can be modulated by IQ. However, these assumptions need to be further investigated in future studies.

Other non-executive processes, such as basic processing efficiency, were examined for their effect on IC. Kuntsi and colleagues (2001a) argued that slow inhibitory processes in an IC task could be associated with slow and variable responding. This finding, together with the association between inhibitory control and RT variability, opens up the possibility that the deficits in inhibitory control displayed in this study could be accounted for by deficits in basic non-executive processing that underpin performance on most laboratory tasks of higher order function. In the present study, a simple RT task was used to measure children's basic processing efficiency. Controlling for RT variability, reduced, but did not eliminate the significant group differences on the SSRT and MStroopPI. However, controlling for RT variability reduced the group differences to non-significant, but still substantial, levels on poor inhibitory control in GNG task. This general pattern of results suggests that while inhibitory deficits are in part due to deficits in non-executive processes, such deficits cannot fully account for the established patterns of inhibitory control.

9.3.3. Comorbid effects

Several studies have incorporated the comorbidity effect on executive function and specifically inhibitory control, but less information exists as to how comorbid disorders can influence delay-related motivation. Approximately 40-70% of children with ADHD (Faraone & Biederman, 1994) and 25-75% of adolescents with ADHD

(Barkley, 1998) have also comorbid ODD/CD. Executive functioning deficits have been identified in other comorbid disorders (Oosterlaan et al., 1998), although more recently this finding has been contradicted (Oosterlaan et al., 2005). Inconclusive results also exist from motivational studies, whereas in one study reinforcement contingency improved task performance in children with ADHD alone, but not in children with ADHD+ODD (van der Meer et al., 2005), and in another study both ADHD and ADHD+ODD groups displayed a stronger preference than control children for a small immediate reward (Antrop et al., 2006).

The most consistent result in the present thesis was that ADHD+ODD cases had worse performance in all IC and DAV measures compared to controls. "Pure" ADHD cases were found to have worse performance than controls only on interference control and delay sensitivity. These results could indicate that comorbid ODD might account for response inhibition and delay-related motivational deficits in children with ADHD. However, this conclusion should be interpreted with caution as this is a clinically referral sample. In fact, most ADHD cases (75%) had comorbid ODD. Previous research has shown that comorbidity and parental practices discriminate clinic-referred and non-referred children who are hyperactive (Woodward, Dowdney, & Taylor, 1997) and that clinical referral is more likely when the child is experiencing a comorbid disorder. A comorbid disorder might increase parental problems in coping with the child's behaviour, which would in turn increase the likelihood of clinical referral. This suggests that clinical samples are more likely to have a more severe disorder or even a comorbid disorder, and it has been suggested that clinical and community samples of children with ADHD might not be comparable, highlighting the need to consider referral biases in research (Woodward et al., 1997). Furthermore, conclusions on comorbid ODD should also be interpreted with caution because the sample size of the groups is likely to reduce the power of the analysis (ADHD = 19; ADHD+ODD = 58).

9.4. Are IC and DAV neuropsychological markers useful endophenotypes?

As already reviewed in the introductory chapters of this thesis, ADHD is a heterogeneous disorder at multiple levels: clinical, genetic, environmental, and neuropsychological. This heterogeneity represents a significant barrier to the study of aetiology in ADHD and recently researchers have proposed several ways to partition this causal heterogeneity of the disorder. The most influential and increasingly popular approach to address the challenge of isolating more aetiologically

homogeneous ADHD entities is the identification and investigation of candidate endophenotypes (e.g. Almasy & Blangero, 2001; Bearden & Freimer, 2006; Coghill et al., 2005; Gottesman & Gould, 2003). Endophenotypes are the intermediate causal factor linking the pathway between genes and behaviour, with environment playing a significant role on the expression of those endophenotypes (Gottesman & Gould, 2003). Several markers, such as neurophysiological, neuroanatomical, and neuropsychological markers could be potential endophenotypes of the disorder, as long as they fulfil four criteria (Doyle et al., 2005c): a) endophenotypes should be associated with the disorder; b) endophenotypic measures should have good psychometric properties; c) the endophenotype should show evidence of heritability; and d) it should also show familial-genetic overlap (i.e. familial co-segregation) with the disorder.

One aim of the present thesis was to explore the causal role of two neuropsychological markers of ADHD; inhibitory control and delay aversion. Although the present thesis was not focused on the endophenotype hypothesis and was not specifically designed to validate the role of these neuropsychological markers as candidate endophenotypes, some of the criteria set out for candidate endophenotypes (Doyle et al., 2005c) were studied, with the exception of heritability.

Table 9.1.: Putting head-to-head evidence from the literature and the present thesis on the four criteria for IC and DAV candidate endophenotypes

	Associated with ADHD		*Good psychometrics*		*Heritability*		*Familial co-segregation*	
	Literature	Thesis	Literature	Thesis	Literature	Thesis	Literature	Thesis
IC	✓	✓	✓	✓	✓	N/A	✓	**X**
DAV	✓	✓	✓	~	**X***	N/A	**X***	**X**

Note: DAV = Delay Aversion; IC = Inhibitory Control; * Evidence comes from less than 3 studies.

In table 9.1 the evidence from the literature on the four criteria for IC and DAV candidate endophenotypes are put head-to-head with the results from this thesis. Based on the literature, IC seems to fulfil the four criteria, indicating that this neuropsychological marker could be a valid causal link between genes and behaviour. In the present thesis evidence showed that IC was associated with ADHD and the IC measures used had good test-retest reliability and construct validity. However, results from the present thesis failed to support the idea that the IC neuropsychological marker is mediating the familial causes of ADHD, although the effects were in the expected direction. A possible explanation might be the different

statistical approach to investigating familial co-segregation. The investigation of familial co-segregation is in its infancy and, therefore, no standardized methodological and statistical approaches exist. Sibling-proband correlation, or group mean differences, that have been used in the past could serve as a starting point to explore the data, but it does not directly tell us about the relationship between siblings' and probands' neuropsychological function. One direct way to do this is by categorizing unaffected siblings into those with a neuropsychologically impaired proband and those with a neuropsychological unimpaired proband. If a neuropsychological marker is mediating the familial cause of ADHD, then it would be expected that unaffected relatives of impaired probands would have worse neuropsychological performance than unaffected relatives of unimpaired probands. In this way, we are able to investigate the neuropsychological deficit of unaffected relatives, by also taking into consideration the neuropsychological function of the proband. However, this is the first study following this approach, and future studies are required to replicate these findings and the significance of this approach. In sum, there is some evidence that the IC neuropsychological marker is a valid neuropsychological endophenotype of ADHD, although more in depth investigation is required in relation to familiality.

Results on the role of the DAV neuropsychological marker on ADHD provide more consistent evidence. As in the literature, so this thesis found an association of ADHD with DAV deficit. Moreover, some, but not all, DAV measures have been tested for their psychometric properties in the literature. In the present study, delay-related motivational measures showed adequate test-retest reliability, but their construct validity could be questioned as two of those measures were not inter-correlated (i.e. MIDA and DeFT). Finally, only two studies (i.e. one twin and one family study) have investigated familial co-segregation of DAV (Bidwell et al., .2007; Kuntsi & Stevenson, 2001). Consistent with this limited evidence, in the present study DAV deficit was not found to mediate familial causes of ADHD, although differences between the two sibling groups were in the expected direction. Therefore, it could be claimed that DAV deficit could be a symptom, rather than an aetiological factor and a valid endophenotype of the disorder. However, further research is required, especially on investigating the familial co-segregation of DAV deficit on ADHD, as the evidence up to now is very limited.

9.5. Clinical and research implications of neuropsychological subtypes

It is evident that a proportion of children with ADHD have one or more neuropsychological deficits. These subgroups could formulate potential subtypes, each of which could be represented by the specific neuropsychological dysfunction. In the present thesis results showed that 25% of ADHD cases had 'pure' IC deficit, 15% had 'pure' DAV deficit, 11% had a deficit on both neuropsychological functions. However, 49% of ADHD cases did not have either of the two neuropsychological deficits. This could indicate that IC and DAV neuropsychological subtypes are not exclusive causal pathways and that other neuropsychological subtypes could be identified, such as state regulation (Sergeant, 2005), temporal processing, and working memory (Castellanos and Tannock, 2002). However, even if there are a number of cases that could be categorized into subtypes based on their neuropsychological deficit, a question remains as to whether such a categorization is profitable for clinical and research use.

9.5.1. Clinical implications

The fact that a subgroup of children with ADHD has IC and DAV deficits supports the re-examination of the assumptions that underpin current clinical practices. Formal adoption of neuropsychological subtype definition in DSM is premature, because it has not yet been fully validated. In fact, although several studies exist on the association between ADHD and IC and DAV deficits, the present study is the second in identifying neuropsychological subtypes of ADHD (see also Nigg et al., 2005), and the first in comparing clinical characteristics of these subgroups. However, such subtypes might prove productive for research purposes that would eventually help clinical practice. For instance, the presence of cases of ADHD with and without IC and/or DAV impairment might indicate the need for therapies targeted at IC and DAV deficits. However, these therapies should be supplementary to core therapies and not replace them (Nigg et al., 2005).

In order to include neuropsychological subtypes in clinical practice, it should be demonstrated that, for at least a subgroup of children, the disorder is caused by the neuropsychological dysfunction in question and that this neuropsychological impairment is fundamentally different from other neuropsychological deficits associated with ADHD. Evidence from very few studies (Solanto et al., 2001; Sonuga-Barke et al., 2003; Thorell, in press) and from the present thesis indicates that IC and DAV neuropsychological dysfunctions are independent and are not

associated with each other. In addition Nigg and colleagues (2005) argued that neuropsychological subtypes should be validated for their clinical significance, such as worse outcome. From the present thesis, the IC subtype was found to have worse vocabulary ability and lower IQ than the other three neuropsychological subtypes, indicating that IQ performance might only be linked to IC and not DAV deficits. However, ADHD symptomatology and comorbidity as reported by parents and teachers did not distinguish between IC and DAV subtypes. Therefore, although these subgroups have difficulties at a cognitive level (i.e. inhibition and motivation), the symptomatic outcome of each subtype is similar. However, this result does not necessarily mean that IC and DAV subtypes do not differ on other characteristics, such as academic performance. Therefore, once a conceptual basis for partitioning heterogeneity is established (e.g. Sonuga-Barke, 2002), neuropsychologic testing may become a more valuable and viable element in assessment and potentially in treatment planning to address their particular dysfunction (Nigg et al., 2005).

9.5.2. Research implications

As already mentioned several times throughout this thesis, neuropsychological function of ADHD is complex. For instance, EF is a construct with several domains (Pennington & Ozonoff, 1996), each of which has been found to be impaired in ADHD. Neuropsychological subtypes could help researchers to partition within and between neuropsychologic heterogeneity of ADHD. Identifying neuropsychological subtypes, such as IC subtype, allows for study of additional heterogeneity within EF overall (e.g. versus children with working memory, planning, and set-shifting problems; Nigg et al., 2005). Researchers could also study children with ADHD who do not have neuropsychological deficits versus those with any neuropsychological deficit, such as IC and/or DAV, as we did in the present thesis. However, in order to use neuropsychological subtypes in the design of future studies, certain methodological issues should first be overcome and addressed by all research teams.

Nigg and colleagues (2005) have proposed three ways to validate the use of neuropsychological subtypes in research. First, normative data are required in order to identify the point to which children who do not have any psychiatric problems exhibit an 'abnormal' score on any given neuropsychological test. This process would enable the formulation of empirical groups of children based on their neuropsychological dysfunction and would also contribute to clinical assessment. Of course this implies that normative data should be collected for the most commonly

used and easily accessible neuropsychological tests in the literature. Second, in studies investigating neuropsychological function of ADHD it should become the norm to report score ranges, mean and variance of the control and ADHD samples, and most importantly to report the proportion of participants in each group with significant impairment on the measure. If normative data on the measures do not exist, then the identification of this proportion could be based on a reasonable clinical cut-off on the measure. At the moment, the 90th percentile of controls' performance has been used as a cut-off, but this cut-off should be tested for its sensitivity. Third, once these neuropsychological subtypes have been defined in a sample, researchers should compare behavioural, academic, and social characteristics of these subgroups. Finally, if valid neuropsychological subtypes can be identified, then researchers could focus their interest on samples based on their neuropsychological function rather than their behavioural outcome. In other words, rather than using a bottom-up design to recruit participants (i.e. recruitment based on behavioural outcome in order to identify aetiology), researchers could use a top-down design by recruiting children who have and do not have impaired neuropsychological function and identify similarities or differences on psychiatric and behavioural outcome, environmental input, and genetic liability.

9.5.3. Taxonomic issues in relation to neuropsychological subtypes

The use of neuropsychological subtypes as a way of partitioning within disorder heterogeneity should be pursued with caution. At the moment, the phenomenologically based categorical approach in ADHD and other psychiatric disorders (i.e. DSM diagnosis based on behavioural outcome) is commonly used in clinical and research practice. However, this approach has been found to have two main shortcomings: high levels of comorbidity between and heterogeneity within disorders (Clarke et al., 1995). Sonuga-Barke (1998) has suggested that within disorder heterogeneity could be reduced by using more subcategories. Therefore, neuropsychological subtypes could be the solution to heterogeneity within the disorder. However, increasing the number of subcategories is likely to increase the levels of comorbidity (Sonuga-Barke, 1998). So far, there is evidence of IC deficit in other psychiatric disorders, such as CD, ODD, autism and Tourette syndrome (Crawford, Channon, & Robertson, 2005; Herba, Tranah, Rubia, & Yule, 2006; Kana, Keller, Minshew, & Just, 2007).

There is a suggestion that the shortcomings of the categorical approach might rely on the phenomenological basis of the system. One solution to the problem would be to

focus on more theoretically based systems of classification, such as aetiology-based categories (Andreasen & Carpenter, 1993). This would mean that where symptoms share the same cause they should be seen as indicating the same disorder (Sonuga-Barke, 1998). Neuropsychological markers may represent intermediate aetiological factors linking the path between genes and behaviour. Therefore, neuropsychological dysfunction could serve as an aetiology-based category. However, given the current lack of knowledge about the aetiological basis of disorders, the feasibility of such a model is under question (Sonuga-Barke, 1998).

9.6. Limitations and future directions

Although every effort was made to carry out a well-designed study, there were some sampling and measurement limitations that should be noted. Possible suggestions to overcome these issues in future research will be discussed in the following sections. Finally, based on the theoretical background and the present results, a number of future studies are suggested.

9.6.1. Sample characteristics and design of the study

Limitations on sample characteristics and design of the study could be summarized as follows:

1. *Limited number of females:* Some evidence suggests that girls with ADHD may be less vulnerable to the executive deficits compared to boys (e.g. Seidman et al., 1997). Although other researchers have suggested that girls with ADHD have similar executive functioning compared with boys with ADHD (e.g. Houghton et al., 1999; Rucklidge & Tannock, 2002; Seidman et al., 2005). Gender differences on DAV deficits have not yet been identified. Therefore, the initial goal in the present thesis was to match ADHD and control cases for gender. However, in line with the male to female ratios in clinic-referred samples (i.e. 9:1 to 6:1; Biederman et al., 2002; Lahey et al., 1994; Sandberg, 1996), ADHD cases had more males than females. In addition, due to practical issues, recruitment of more male controls was not feasible. One way of resolving the problem would be to remove females from the analysis. However, this would reduce the sample size, which would then affect statistical power, especially in principal component analysis. Since there is controversy or lack of evidence on gender differences and neuropsychological function, it becomes essential for future studies to have gender-matched comparable samples.

2. *ADHD cases were only recruited from psychiatric clinics.* Woodward and colleagues (1997) have argued that clinic and community samples of children who are hyperactive are not comparable, since clinic-referred samples tend to be associated with higher comorbidity and more problematic parenting practices compared to non-referred children with ADHD. Therefore, one could claim that the present results could only be generalized for clinic-referred ADHD samples. Although this might be true, there is already evidence indicating that children with ADHD that were recruited from community samples have neuropsychological deficits (e.g. Lawrence et al., 2004). A comparison of clinic referred and non-referred ADHD cases on neuropsychological function could provide further evidence on the severity of impairment of the disorder and might provide evidence on factors affecting cognitive function.
3. *ADHD subtypes:* It is quite common in ADHD research to recruit cases with Combined subtype (ADHD-C). In fact, ADHD-C cases have been found to have impairment in both IC and DAV (e.g. Huang-Pollock et al., 2007; Nigg et al., 2002). Less is known about the neuropsychological function of the Predominantly Inattentive subtype and Hyperactive-Impulsive subtype. Evidence suggests that Inattentive subtype is more strongly associated with the IC deficits (Chhabildas et al., 2001), although results from a recent study supported the association between ADHD-I and reward-based motivation (Huang-Pollock et al., 2007). It would be interesting in future studies to investigate whether the dual pathway that is found in ADHD-C subtype, is also evident in ADHD-I and ADHD-H/I subtypes.
4. *Insufficient power to fully explore comorbidity:* CD, ODD, and anxiety are the most common comorbid disorders of ADHD (Bird et al., 1993; Faraone & Biederman, 1994). This was also apparent in the present thesis as 80% of ADHD cases had ODD (83% males and 74% females), 47% had anxiety disorder (47% males and 48% females), and 30% of ADHD cases had CD (37% males and 17% females). Unfortunately, due to the small sample size it was not possible to investigate anxiety comorbid effects. Moreover, it was not feasible to examine the comorbid effects of CD as all ADHD cases with comorbid CD also had comorbid ODD. Further research is required in ADHD literature to investigate the association of comorbid effects and neuropsychological deficits.
5. *Cross-sectional data:* The variables assessed were all measured at one point in time and the cross-sectional nature of the design precluded the possibility of determining the developmental aspect of neuropsychological functioning. Longitudinal research would make an invaluable and unique contribution to the understanding of the development of neuropsychological functions in ADHD.

9.6.2. Measurement issues

Measurement limitations and statistical issues could be summarized as follows:

1. *Effect sizes and heterogeneity:* The modest and variable effect sizes of measures in the literature, as well as in the present thesis, raise serious questions as to the ability of any one neuropsychologic hypothesis to fully account for ADHD. Moreover, the construct validity of the various neuropsychological measures has not been fully validated. One way of reducing the possible effects of variable reliability and lack of construct validity of measures is to use the multiple-measure approach. By combining multiple measures tapping into the same construct, there is a greater chance of obtaining a broad picture of the construct, of identifying impairments in specific domains of the construct, and providing a more reliable and valid measures of that construct. In fact, results from the present thesis indicate that differences between the experimental groups are stronger when the measures are combined into one composite score, especially in the case of DAV deficit. Thus, researchers using multiple measures to assess the same sample, not only have to report differences on individual tasks, but should also investigate group effects on composite scores.
2. *Delay Aversion construct validity:* One could question the construct validity of the delay frustration measure (i.e. DeFT), as it was not associated with the delay-related reward choice task (i.e. MIDA) and was also cross-loading to IC component, indicating that this task might tap into IC. Influenced by Gray (1982), Nigg (2005) identified reactive behavioural inhibition as an interruption of behaviour due to events that are unfamiliar or unexpected (novel, unexpected, or signal potential loss of reward or punishment), and distinguished it from strategic interruption of prepotent response (i.e. inhibitory control). Moreover, Nigg (2001) has argued that reactive behavioural inhibition is likely to be impaired in cases with comorbid conduct disorder or aggression, but not otherwise. Theoretically, DeFT could be perceived as a reactive behavioural inhibition measure, as the delayed events were unexpected and children with ADHD did not inhibit their reaction during the unexpected event. Even more interestingly, present results showed that only ADHD+ODD cases show deficits in delay frustration that support even further Nigg's (2001) argument. Although DeFT has been used elsewhere as a 'hot' measure of IC (i.e. measure of regulation of affect and motivation; Huijbregts et al., in press), it is a new measure that needs to be validated for its association with DAV construct.

9.6.3. Theoretical considerations and future directions

Plenty of studies have examined IC deficit in ADHD, which is relatively well established and might not need further replications. However, there are several theoretical questions that still need to be answered to be able to fully understand the aetiological factors of ADHD at a neuropsychological level:

1. Although considerable evidence exists about the association of ADHD with IC deficit, there is still the need to further our knowledge in relation to the association of ADHD with DAV deficits.
2. Not only further research is required to replicate the dual pathway hypothesis, but researchers should take into consideration the causal effect of other neuropsychological dysfunctions associated with the disorder, such as temporal processing (Castellanos & Tannock, 2002) and state regulation (Sergeant, 2005).
3. Neuropsychological deficits are not the only potential causes of the disorder. In fact, they may be the intermediate link between genes and behaviour. Therefore, molecular genetic studies are needed to investigate the association of neuropsychological markers with specific genes. Moreover, the effect of environmental factors (i.e. parental practices, parental psychopathology, pre- and post-natal risk factors) on neuropsychological markers still needs to be investigated.
4. Statistical modeling techniques, such as latent variable and confirmatory factor models, might be more regularly applied to evaluate the relationships among the measures, constructs, and levels of analysis at issue across interrelated theories that have been described herein.
5. In future studies investigating the effect of neuropsychological markers in ADHD, researchers should routinely report the proportion of participants with ADHD with neuropsychological impairment. Therefore, in meta-analytic studies, one would be able to recognize (or not) the importance of specific neuropsychological deficits. Moreover, these neuropsychologic subgroups should be compared in their clinical characteristics, academic performance, and social ability to identify whether neuropsychological subtypes have any clinical value.
6. Familial co-segregation and the investigation into whether specific neuropsychological markers are mediating the causal effects of ADHD is fairly recent, and there is a need to establish a universal statistical method to investigate it. One approach is to compare unaffected ADHD relatives with controls and expect them to have a significant difference. However, this approach

does not tell us whether these relatives have or do not have a neuropsychologically impaired ADHD proband. In the present study we compared neuropsychological performance of unaffected siblings of impaired and unimpaired ADHD probands, with the expectation that relatives of impaired ADHD probands would have worse performance than relatives of unimpaired ADHD probands. Findings from this analysis did not support the hypothesis of familiality of IC and DAV deficits in ADHD families. Further research is required using this statistical and methodological approach to replicate the present result.

7. Only one brain imaging study (Scheres et al., 2007) exists so far on the investigation of brain regions associated with DAV deficit. Further neuroimaging studies are required to enrich our knowledge not only on the neuroanatomical structure of DAV deficit, but also to understand the possible associations and/or disassociations of IC and DAV deficits at the neuroanatomical level.

9.7. Concluding remark

The aim of the present thesis was to partition the neuropsychological heterogeneity of ADHD. First, IC and DAV deficits were found to be associated with the disorder. Second, IC and DAV deficits were independent constructs leading to ADHD. Third, from familial co-segregation analysis IC and DAV deficits were not found to mediate familial effect in ADHD. However, the fact that unaffected ADHD relatives had intermediate neuropsychological performance to ADHD probands and typical controls and the use of a new statistical approach to consider the issue of familial co-segregation leaves an open window to the possibility that IC and DAV deficits might be familial. Neuropsychological constructs of interest in ADHD are multifaceted and need to be examined with the view that performance on any one task may have multiple determinants. Therefore, in order to establish a differential deficit affecting a particular ability, one must control for possible artifacts and demonstrate that effects converge across different measures of the same ability (Nigg, 2005). In addition, results need to be evaluated within a developmental context and in consideration of gender influences. Comparison groups beside the "typical control" would be useful. One strategy to address the known heterogeneity of current DSM-IV defined subtypes of ADHD in experimental designs is to utilize comorbid disorders to facilitate sub-grouping and reduce within group heterogeneity. An alternative strategy would be to separate groups on the basis of poor performance on a particular set of neuropsychological measures, and then examine the external correlates of these so divided groups.By identifying the underlying internal factors that contribute to the

symptoms of ADHD, it would be possible to classify children with ADHD who have specific behavioural problems (e.g. inattention) that derive from specific genetic, neuropsychological and environmental factors.

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Abbreviations

5-HT	Serotonin Transporter
ADHD	Attention Deficit Hyperactivity Disorder
ADHD-IA	Attention Deficit Hyperactivity Disorder – Inattention
ADHD-C	Attention Deficit Hyperactivity Disorder – Combined
ADHD-HI	Attention Deficit Hyperactivity Disorder – Hyperactive/Impulsive
ADRA1A	Alpha-1A Adrenergic Receptor
ADRA1C	Alpha-1C Adrenergic Receptor
ADRA2C	Alpha-2C Adrenergic Receptor
ADRA2A	Alpha-2A Adrenergic Receptor
ADRB2	Beta 2 Adrenergic Receptor, surface
APA	American Psychiatry Association
ARRB2	Arrestin Beta 2
AUD	Alcohol Use Disorder
CBCL	Child Behavior Checklist
CD	Conduct Disorder
CHRNA4	Nicotine Cholinergic Receptor Alpha 4
CHRNA7	Nicotine Cholinergic Receptor Alpha 7
COMT	Catechol-*O*-methyl-transferase
CPT	Continuous Performance Task
DA	Dopamine
DAT	Dopamine Transporter
DAV	Delay Aversion
DB	Digit Span
DBH	Dopamine Beta-Hydroxylase
DDC	Dopa Decarboxylase
DeFT	Delay Frustration Task
DeFT MTD	Delay Frustration task Mean Total Duration
DLPFC	Dorsolateral Prefrontal Cortex
DRD1	Dopamine D1 Receptor
DRD2	Dopamine D2 Receptor
DRD3	Dopamine D3 Receptor
DRD4	Dopamine D4 Receptor
DRD5	Dopamine D5 Receptor
DRT	Delay Reaction Time
DRT DS	Delay Reaction Time Delay Sensitivity
DSM	Diagnostic and Statistical Manual
DZ	Dizygotic
EEG	Electroencephalography
EF	Executive Function
ERP	Event-Related Potentials
FADS2	Fatty Acid Desaturase 2
fMRI	functional Magnetic Resonance Imaging
G x E	Gene-Environment interaction
GNG	Go/No-Go
GNGPI	Go/No-Go Probability of Inhibition
HES1	Hairy and Enhancer of Split1 (Drosophila)
HKD	Hyperkinetic Disorder
HTR1B	5-Hydroxytryptamine Serotonin Receptor 1B
HTR1E	5-Hydroxytryptamine Serotonin Receptor 1E
IC	Inhibitory Control
ICD	International Classification of Disease
ISI	Interstimulus Interval
KCNJ6	Potassium Inwardly-Rectifying Channel, Subfamily J, member 6
LBW	Low Birth Weight

MAOA	Monoamine Oxidase A
MIDA	Maudsley's Index of Delay Aversion
MIDA Prob DR	Maudsley's Index of Delay Aversion Probability of Delayed Reward
MRI	Magnetic Resonance Imaging
MStroop	Modified Stroop task
MStroopPI	Modified Stroop task Probability of Inhibition
MZ	Monozygotic
NE	Norepinephrine
NET	Norepinephrine Transporter
OCD	Obsessive Compulsive Disorder
ODD	Oppositional Defiant Disorder
OR	Odds Ration
PCA	Principal Component Analysis
PFC	Prefrontal Cortex
PNMT	Phenylothenolamine N-Methyltransferase
PRE2	Period Homolog 2 (Drosophila)
RD	Reading Disorder
rGE	Gene-Environment correlation
ROCFT	Rey-Osterreith Complex Figure
RT	Reaction Time
SD	Standard Deviation
SLC9A9	Solute Carrier family 9 (sodium/hydrogen exchanger), member 9
SNAP-25	synaptosomal-associated protein 25
SSRT	Stop Signal Reaction Time
SWM	Spatial Working Memory
SYP	Synaptophysin
TD	Total Duration
TH	Tyrosine Hydroxylase
TPH	Tryptophan Hydroxylase
WCST	Wisconsin Card Sorting Test
WHO	World Health Organisation
WM	Working Memory

Appendix A: Task and recruitment materials and questionnaires used in the study

Appendix A.1.: Maths questions used in the DeFT task.

Trial	Maths exercise	A	B	C	D	Delay type	Position of correct answer
1	3 + 7	10	13	11	9	ND	A
2	3 + 12	17	8	15	5	ND	C
3	4 + 8	15	17	8	12	ND	D
4	2 + 1	2	4	9	3	ND	D
5	4 + 4	8	4	9	6	ND	A
6	4 + 3	1	5	9	7	ND	D
7	6 + 6	4	6	12	8	ND	C
8	10 + 7	17	10	6	7	ND	A
9	9 + 2	10	9	3	11	ND	D
10	2 + 3	3	5	6	2	3sec +	B
11	4 + 5	5	8	9	7	ND	C
12	3 + 6	15	2	6	9	20sec	D
13	4 + 7	7	11	9	10	ND	B
14	9 + 3	9	14	15	12	ND	D
15	0 + 10	0	1	10	3	7sec +	C
16	1 + 2	5	3	1	2	ND	B
17	0 + 2	2	12	4	10	ND	A
18	5 + 1	5	18	15	6	20sec	D
19	2 + 4	9	1	6	12	ND	C
20	9 + 5	4	7	11	14	ND	D
21	6 + 1	11	7	13	8	ND	B
22	5 + 5	5	3	10	8	4sec +	C
23	6 + 5	1	9	11	7	ND	C
24	8 + 2	2	10	11	3	ND	B
25	2 + 6	6	8	4	1	ND	B
26	2 + 4	10	1	6	3	20sec	C
27	1 + 1	2	6	4	1	ND	A
28	2 + 2	4	2	6	10	5sec +	A
29	8 + 0	8	9	6	5	2sec +	A
30	9 + 1	1	5	10	6	ND	C
31	7 + 5	7	12	9	2	ND	B
32	4 + 1	4	5	8	3	ND	B
33	5 + 1	6	3	9	1	ND	A
34	2 + 5	9	7	5	8	20sec	B
35	10 + 3	5	10	13	3	ND	C
36	5 + 9	5	9	14	1	6sec +	C
37	0 + 9	2	9	6	1	ND	B
38	8 + 1	2	9	0	7	ND	B
39	7 + 3	10	13	8	5	20sec	A
40	7 + 1	10	9	4	8	ND	D
41	3 + 0	3	5	6	2	20sec	A
42	2 + 7	12	9	5	10	ND	B
43	7 + 7	10	14	12	7	8sec +	B
44	10 + 2	12	8	10	15	ND	A
45	3 + 3	6	9	2	7	ND	A

46	1 + 3	3	5	9	4	20sec	D
47	5 + 0	6	5	10	8	ND	B
48	1 + 4	10	9	7	5	ND	D
49	1 + 9	10	12	6	7	10sec +	A
50	1 + 6	8	17	7	12	ND	C
51	2 + 9	9	13	15	11	ND	D
52	5 + 3	10	14	5	8	ND	D
53	6 + 3	12	11	9	13	ND	C
54	3 + 4	7	4	5	8	20sec	A
55	6 + 4	8	12	10	11	ND	C

ND = No Delay
+ = Distractor

Appendix A.2.: Information pack of parents of children with ADHD and their siblings

Parent information sheet

The IMAGE Project
Institute of Psychiatry
Social Genetic and Developmental Psychiatry Centre and Department of Child and Adolescent Psychiatry

Dr. Philip Asherson
Prof. Eric Taylor

The International Multi-centre ADHD Genetics project (IMAGE)
An International Resource For The Study Of ADHD Genetics

Information sheet for parents

We would like to invite you to take part in this project that is designed to find out about the genetic causes of attention deficit hyperactivity disorder (ADHD). We would be grateful if you would read this information sheet and, if you agree to take part in this study, sign the enclosed consent forms.

PURPOSE OF THE IMAGE PROJECT

The IMAGE project aims to identify the genetic causes of attention deficit hyperactivity disorder (ADHD). This study will use modern genetic techniques, and match the findings to a detailed clinical examination, to try to find out which genes are contributing to the symptoms of ADHD.

The National Institute of Mental Health (NIMH), the main government research funding body for mental health in the United States, funds the IMAGE project. NIMH would like to help scientists learn more about how genes effect the development of ADHD. They are therefore funding the IMAGE Project, to gather medical information and genetic material (DNA), from individuals who seem to have ADHD, as well as from their brothers, sisters and parents. In order to make this research possible, NIMH will store the medical information and DNA in a central place in New Jersey, called a repository.

NIMH will fund this initial study and will also make the medical information and DNA available to other scientists who want to help in the search for genes that influence ADHD. Use of these materials in the future will require full scientific review by NIMH to ensure that only recognised scientists gain access to the clinical data and DNA. Access to materials will also require review by one or more independent ethical committees to ensure that your DNA and clinical information will only be used to benefit individuals who have ADHD. The clinical data and DNA will be kept indefinitely until the work required to find the genes involved in the development of ADHD has been completed.

Since you or a member of your family have received a diagnosis of ADHD, we are contacting you to see if you and other members of your family are willing to contribute medical information and blood samples to the repository for use in genetic studies of ADHD.

IMPORTANCE OF THE IMAGE PROJECT

ADHD is a common behaviour that affects many children. ADHD is recognised as a major cause of childhood problems with schoolwork and relationships with friends and family, and may go on to have long-term consequences in adulthood. In order to develop the best and most effective treatments for ADHD, we need to have a very detailed understanding of what the causes are. Research has shown that genetic influences are particularly important in the development of ADHD, although this does not mean that the behaviour is caused by genetic factors alone. Our research program is designed to look for the genes involved.

WHO CAN TAKE PART IN THE IMAGE PROJECT

We are asking children aged between 5 and 17 years of age who are thought to have ADHD, their siblings (brothers and sisters) and both parents, to take part in this study. We require at least one sibling to take part in addition to your child who is being treated for ADHD.

PROCEDURES

If you agree to participate, we will ask you to complete a booklet of questionnaires for each sibling aged 5-17 who takes part in the study. We will also request the name and address of their teachers who will be sent a similar set of questionnaires to complete.

Finally, we would like to refer to clinical notes provided by your doctor at the child clinic.

PARENT INTERVIEWS

Following these initial assessments, we will also need to interview you to gather a detailed description of your child, who is thought to have ADHD. This interview about your child usually takes between 2 to 3 hours.

We would like to tape the interview although you do not have to agree to this if you do not want to. The tapes will enable us to check the quality and consistency of the information being gathered by different interviewers. These tapes will be kept securely and destroyed after 5-years.

DNA SAMPLING

We will require a blood sample from each individual taking part in this study. Although this study is designed to find the genes that increase risk for ADHD, we also require blood samples from brothers and sisters of children with ADHD so that we can look for differences between those with high and low levels of ADHD-symptoms. The information from children without ADHD is as important for this study as information from children with ADHD. Blood samples are needed from parents so that we can tell which of your genes your children are sharing and which of your genes your children are not sharing.

If you agree to participate, we will draw a small sample of blood (about 20 mls. or four tablespoons full) from each person. The sample will be sent to the cell repository in the United States and to the laboratory in the Institute of Psychiatry. The blood samples that are sent to the repository will be used to create cell lines. By storing blood cells in this way, we will be creating a permanent resource of DNA for the study of genes involved in ADHD.

COMPUTER TASKS

In addition to the main part of the study we also wish to find out more about how genes give rise to ADHD symptoms. We can do this by investigating the way that genes affect the performance of individuals on tests of attention and response to tasks that are faster or more rewarding. This will help us to understand the way in which genes contribute to difficulties in concentrating and in keeping-to-task and may be important for the development of the most effective treatments for ADHD.

For this part of the study you and your children will need to attend the Research Clinic for a 3-hour assessment session. This can be done at the same time as the parent interview or you can come at any other time that is convenient.

During the session we will ask your children to complete a variety of tasks and computer-based games. We also wish to gather information by videotaping your children during the computer session. The tapes will be identified by a code number, kept securely in our research institute and only used for research. We would like to keep the tapes for around 10 years, until the research is completed.

With your agreement your children will earn small prizes and thank you gifts during some of the tasks.

RISKS

There are no more than minimal medical or psychological risks associated with this research. Prior to taking the bloods A local anesthetic cream can be used (if requested) to numb the skin which will reduce any mild discomfort. You may experience bruising, and/or other bleeding at the site where the needle is inserted. Sometimes people get dizzy or feel faint when their blood is drawn.

BENEFITS

DNA from your sample will be used to look for the genes involved in ADHD and related behaviours. Although you personally will not receive any direct benefit from this project, individuals who develop ADHD in the future, their family members, and future generations may benefit if we can locate the genes involved.

Because the meaning of research results are not usually fully understood results on individual families will not be made available to subjects or their doctors. If later on, diagnostic tests or new ways to treat ADHD are discovered, this information should be obtained from your own doctor or ADHD clinic. We do not expect to discover any information of direct clinical relevance to the condition or treatment of your child during the next few years.

COSTS AND COMPENSATION

There are no costs to subjects in this research project. In line with current UK practice on the collection of samples for research, we are asking you to donate the information and blood samples as a gift. We will however be able to reimburse you for reasonable costs incurred with your travel.

Some scientists who obtain your DNA and medical information in the future may work with a private company. However all data produced from these materials will be made public and available in the public domain. Some companies may have a financial interest in using information found from studying DNA. This includes developing commercial products that may later help others by improving the diagnosis and treatment of ADHD. These companies may patent products or sell discoveries based on this research. Some of the scientists who study your DNA and medical information may get some financial benefit from this work. There are no plans to provide any compensation to you or your heirs should this occur.

CONFIDENTIALITY

We will keep confidential your name and any other personal information we learn about you. This information will not be sent to the repository in the United States, or known to other scientists in Europe or elsewhere.

We will take the following steps to ensure confidentiality. A research number will be assigned to you and your name will not be used. DNA and medical information collected will be stored at the repository in a coded way, to keep your identity a secret. The only people who will have access to your individual identity are the research team at the Institute of Psychiatry (Dr. Philip Asherson, Prof. Eric Taylor and their research staff). The results from the analysis of your DNA will not be released or shared in any way with your relatives, with insurance companies, or any third party not involved in research. When results of this study are published, your name will not be used.

WITHDRAWAL FROM THE RESEARCH PROJECT

You have the right to leave the study at any time without giving any reason, and without penalty. If you wish to leave the study, contact any member of the research team on our free phone number 0800 092 3392. We will tell the repository to remove your medical information and genetic material. We will keep your identity a secret by using a code number. The repository can use this code number to remove your medical information and genetic material, without ever knowing your name or other personal information.

PARTICIPATION IS VOLUNTARY

You do not have to take part in this study if you do not wish to. Signing the consent form does not commit you or any member of your family to participate in this research. You will not lose any benefits or access to treatment that you are otherwise entitled to if you do not want to be in this study.

WHAT DO I DO NOW ?

If you wish to take part in the IMAGE project would you please sign the enclosed consent forms, returning two copies per set and keeping one copy for your records. These can be returned together with the questionnaires for each child in the FREEPOST envelop provided.

If your children are able to understand what the study involves they should read or have explained to them the child information sheet. If they wish to take part they should sign their own consent forms, which are enclosed. We will also ask you to confirm that you are willing for them to take part, which you can do by signing the child consent form as well. if any of your children are not able to understand what is involved, we will only require your consent for them to participate.

ANY QUESTIONS?

If you have any questions about IMAGE project please feel free to contact the team on our FREE PHONE number 0800 092 3392. you may also contact us by mail The Image Project, Institute of Psychiatry, Social, Genetic and Developmental Psychiatry Centre, Box Number P080, De Crespigny Park, Denmark Hill, London, SE5 8AF.

Appendix A.3.: Consent form for parents of children with ADHD

Parent consent form

The IMAGE Project
Institute of Psychiatry
Social Genetic and Developmental Psychiatry Centre and Department of Child and Adolescent Psychiatry

Dr. Philip Asherson
Prof. Eric Taylor

Consent form for the IMAGE Project

Please tick the boxes below then sign the consent form:

	YES	NO
• I have read (or been read to) the information about the IMAGE project. I understand what I have read and have been able to ask questions.	☐	☐
• I do not feel that I have to take part in the study if I do not want to. I understand that I can withdraw from the study at any stage without giving a reason. This will not affect my medical care or legal rights.	☐	☐
• I give permission for the interview about my child with ADHD to be recorded	☐	☐
• I give permission for my child to take part in the optional task and computer games session (optional)	☐	☐
• I agree to provide a blood sample that will be stored in the DNA bank in Rutgers, USA. DNA from this sample will only be used to look for genes that influence ADHD.	☐	☐
• I agree to take part in the IMAGE project.	☐	☐

Name of Parent	Date	Signature
Name of Parent	Date	Signature

Appendix A.4.: Consent form for children with ADHD

Child with ADHD 12-15 consent form

The IMAGE Project
Institute of Psychiatry
Social Genetic and Developmental Psychiatry Centre and Department of Child and Adolescent Psychiatry

Dr. Philip Asherson
Prof. Eric Taylor

Consent form for the IMAGE Project

Please tick the boxes below then sign the consent form:

	YES	NO
• I have read (or been read to) the information about the IMAGE project. I understand what I have read and have been able to ask questions.	☐	☐
• I do not feel that I have to take part in the study if I do not want to. I understand that I can withdraw from the study at any stage without giving a reason. This will not affect my medical care or legal rights.	☐	☐
• I give permission for the interview with my parents to be recorded.	☐	☐
• I understand that members of the IMAGE project research team may look at sections of my medical records where it is relevant to my taking part in this project. I give permission for these individuals to have access to my records.	☐	☐
• I agree to provide a blood sample that will be stored in the DNA bank in Rutgers, USA. DNA from this sample will only be used to look for genes that influence ADHD.	☐	☐
• I wish to take part in the computer task/game session.	☐	☐
• I agree to take part in the IMAGE project.	☐	☐

Name of Patient	Date	Signature
Name of Parent	Date	Signature
Name of Researcher	Date	Signature

Appendix A.5.: Consent form for siblings of children with ADHD

Sibling 12-15 consent form

The IMAGE Project
Institute of Psychiatry
Social Genetic and Developmental Psychiatry Centre and Department of Child and Adolescent Psychiatry

Dr. Philip Asherson
Prof. Eric Taylor

Consent form for the IMAGE Project

Please tick the boxes below then sign the consent form:	**YES**	**NO**
• I have read (or been read to) the information about the IMAGE project. I understand what I have read and have been able to ask questions.	☐	☐
• I do not feel that I have to take part in the study if I do not want to. I understand that I can withdraw from the study at any stage without giving a reason. This will not affect my medical care or legal rights.	☐	☐
• I agree to provide a blood sample that will be stored in the DNA bank in Rutgers, USA. DNA from this sample will only be used to look for genes that influence ADHD.	☐	☐
• I wish to take part in the computer task/game session.	☐	☐
• I agree to take part in the IMAGE project.	☐	☐

Name of Sibling	Date	Signature
Name of parent	Date	Signature
Name of researcher	Date	Signature

Appendix A.6.: Information pack for parents of healthy control children

Dear Parent/Guardian

My name is Paraskevi Bitsakou and I am a PhD student in the School of Psychology at the University of Southampton, under the supervision of Prof. E. Sonuga-Barke. I am writing to ask you to participate in a study to help us to further our research examining children's ability to focus their attention while playing a game over a period of time.

In this study we will investigate children's ability to sustain attention and concentrate during a period of time as well as to estimate time. In order to observe children's behaviour (8 to 17 years old), computerised games will be used. Some games include arrows and the child will have to indicate the direction of the arrow by using a computer mouse. Some other games have spaceships and the child will have to save them by giving them oxygen at specific times. Although the study takes about 2 hours to complete, including breaks for the child to relax, each computer game is not very long (ranging from 3 to 15 minutes). Moreover, because all the games are computerized children usually enjoy them. In one of the tasks the child will also be rewarded with small stationary items (e.g. pencils, rulers, erasers, pens etc.). Finally, at the end of the assessment, children will also receive a £5 voucher from Woolworths as a reward for their participation.

Together with this letter you will find attached three questionnaires (1 copy of the Strengths and Difficulties questionnaire, 1 copy of the Parent rating of reading difficulties and 1 copy of the Behavioural Questionnaire). If you are willing for your child to participate in the study, then we would appreciate it if you could send us back the section "Statement of consent for parents", which follows, together with the three attached questionnaires. In order to send back the questionnaires and the consent forms please use the pre-paid return envelop, which is attached with this letter.

Moreover, we are aware that children would feel more comfortable and relaxed if they were at their home during the study. Thus, we would like to ask for your consent for the study to take place in your house, whenever is convenient for you. Finally, we are also interested in teachers' opinion about children's behaviour. So, we would also like to ask for your permission to gather some information about your child's behaviour from his/her teacher. You will be able to see the questionnaire before handing it to the teacher.

Personal information will not be released to or viewed by anyone other than researchers involved in this project. Results of this study will not include your name or any other identifying characteristics. Your participation is voluntary and you may withdraw your participation at any time. If you have any questions please do not hesitate to contact me Paraskevi Bitsakou at (023) 8059 4586 or pb@soton.ac.uk.

Thank you for reading this information sheet. We hope to hear from you soon.

Yours sincerely,

Paraskevi Bitsakou
PhD student
DBBU School of Psychology
University of Southampton
Highfield, Southampton
SO17 1BJ

Appendix A.7.: Consent form for parents of healthy control children

Statement of Consent for parents

I _____ have read the above informed consent form.
[Parent's name]

I understand that my child may withdraw my consent and discontinue participation at any time without penalty or loss of benefit. I understand that data collected as part of this research project will be treated confidentially, and that published results of this research project will maintain my child's confidentially. In signing this consent letter, I am not waiving my child's legal claims, rights, or remedies. A copy of this consent letter will be offered to me.

(Circle Yes or No)

I give consent for my child to participate in the above study. Yes No

I give consent for my child's teacher to be contacted. Yes No

Will you be willing to be contacted about future studies? Yes No

Is your child's first language English? Yes No

Has your child being diagnosed with any psychiatric disorder? Yes No

If yes, please state_____

Please state your address and phone number*:

Address _____

_____

Post Code _____

Telephone Number _____

Time of contact _____

Signature Date

Name

I understand that if I have questions about my child's rights as a participant in this research, or if I feel that I or my child have been placed at risk, I can contact the Chair of the Ethics Committee, Department of Psychology, University of Southampton, Southampton, SO17 1BJ. Phone: (023) 8059 3995.

* The phone number and the address will only be used if you are willing to participate and in order to arrange an appointment for the study to take place. The researchers will not use your personal details for any other purposes.

Appendix A.8.: Conners' Parent Rating Scale

Conners' Parent Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

Child's Name:_____ Gender: M F
(Circle One)

Birthdate:_____/_____/_____ Age:_____ School Grade:_____
Month Day Year

Parent's Name:_____ Today's Date:_____/_____/_____
Month Day Year

Instructions: Below are a number of common problems that children have. Please rate each item according to your child's behavior in the last month. For each item, ask yourself "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1. Angry and resentful	0	1	2	3
2. Difficulty doing or completing homework	0	1	2	3
3. Is always "on the go" or acts as if driven by a motor	0	1	2	3
4. Timid, easily frightened	0	1	2	3
5. Everything must be just so	0	1	2	3
6. Has no friends	0	1	2	3
7. Stomach aches	0	1	2	3
8. Fights	0	1	2	3
9. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework)	0	1	2	3
10. Has difficulty sustaining attention in tasks or play activities	0	1	2	3
11. Argues with adults	0	1	2	3
12. Fails to complete assignments	0	1	2	3
13. Hard to control in malls or while grocery shopping	0	1	2	3
14. Afraid of people	0	1	2	3
15. Keeps checking things over again and again	0	1	2	3
16. Loses friends quickly	0	1	2	3
17. Aches and pains	0	1	2	3
18. Restless or overactive	0	1	2	3
19. Has trouble concentrating in class	0	1	2	3
20. Does not seem to listen to what is being said to him/her	0	1	2	3
21. Loses temper	0	1	2	3
22. Needs close supervision to get through assignments	0	1	2	3
23. Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
24. Afraid of new situations	0	1	2	3
25. Fussy about cleanliness	0	1	2	3
26. Does not know how to make friends	0	1	2	3
27. Gets aches and pains or stomachaches before school	0	1	2	3
28. Excitable, impulsive	0	1	2	3
29. Does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
30. Has difficulty organizing tasks and activities	0	1	2	3
31. Irritable	0	1	2	3
32. Restless in the "squirmy sense"	0	1	2	3
33. Afraid of being alone	0	1	2	3
34. Things must be done the same way every time	0	1	2	3
35. Does not get invited over to friends' houses	0	1	2	3
36. Headaches	0	1	2	3
37. Fails to finish things he/she starts	0	1	2	3

Items continued on back page...

Conners' Parent Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
38. Inattentive, easily distracted	0	1	2	3
39. Talks excessively	0	1	2	3
40. Actively defies or refuses to comply with adults' requests	0	1	2	3
41. Fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	0	1	2	3
42. Has difficulty waiting in lines or awaiting turn in games or group situations	0	1	2	3
43. Has a lot of fears	0	1	2	3
44. Has rituals that he/she must go through	0	1	2	3
45. Distractibility or attention span a problem	0	1	2	3
46. Complains about being sick even when nothing is wrong	0	1	2	3
47. Temper outbursts	0	1	2	3
48. Gets distracted when given instructions to do something	0	1	2	3
49. Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
50. Forgetful in daily activities	0	1	2	3
51. Cannot grasp arithmetic	0	1	2	3
52. Will run around between mouthfuls at meals	0	1	2	3
53. Afraid of the dark, animals, or bugs	0	1	2	3
54. Sets very high goals for self	0	1	2	3
55. Fidgets with hands or feet or squirms in seat	0	1	2	3
56. Short attention span	0	1	2	3
57. Touchy or easily annoyed by others	0	1	2	3
58. Has sloppy handwriting	0	1	2	3
59. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
60. Shy, withdrawn	0	1	2	3
61. Blames others for his/her mistakes or misbehavior	0	1	2	3
62. Fidgeting	0	1	2	3
63. Messy or disorganized at home or school	0	1	2	3
64. Gets upset if someone rearranges his/her things	0	1	2	3
65. Clings to parents or other adults	0	1	2	3
66. Disturbs other children	0	1	2	3
67. Deliberately does things that annoy other people	0	1	2	3
68. Demands must be met immediately — easily frustrated	0	1	2	3
69. Only attends if it is something he/she is very interested in	0	1	2	3
70. Spiteful or vindictive	0	1	2	3
71. Loses things necessary for tasks or activities (e.g., school assignments, pencils, books, tools or toys)	0	1	2	3
72. Feels inferior to others	0	1	2	3
73. Seems tired or slowed down all the time	0	1	2	3
74. Spelling is poor	0	1	2	3
75. Cries often and easily	0	1	2	3
76. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
77. Mood changes quickly and drastically	0	1	2	3
78. Easily frustrated in efforts	0	1	2	3
79. Easily distracted by extraneous stimuli	0	1	2	3
80. Blurts out answers to questions before the questions have been completed	0	1	2	3

Appendix A.9.: Conners' Teacher Rating Scale

Conners' Teacher Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

Student's Name:_____ Gender: M F
(Circle One)

Birthdate:_____/_____/_____ Age:_____ School Grade:_____
Month Day Year

Teacher's Name:_____ Today's Date:_____/_____/_____
Month Day Year

Instructions: Below are a number of common problems that children have in school. Please rate each item according to how much of a problem it has been in the last month. For each item, ask yourself "How much of a problem has this been in the last month?", and circle the best answer for each one. If none, not at all, seldom, or very infrequently, you would circle 0. If very much true, or it occurs very often or frequently, you would circle 3. You would circle 1 or 2 for ratings in between. Please respond to all the items.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
1. Defiant	0	1	2	3
2. Restless in the "squirmy" sense	0	1	2	3
3. Forgets things he/she has already learned	0	1	2	3
4. Appears to be unaccepted by group	0	1	2	3
5. Feelings easily hurt	0	1	2	3
6. Is a perfectionist	0	1	2	3
7. Temper outbursts; explosive, unpredictable behavior	0	1	2	3
8. Excitable, impulsive	0	1	2	3
9. Fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities	0	1	2	3
10. Sassy	0	1	2	3
11. Is always "on the go" or acts as if driven by a motor	0	1	2	3
12. Avoids, expresses reluctance about, or has difficulties engaging in tasks that require sustained mental effort (such as schoolwork or homework)	0	1	2	3
13. Is one of the last to be picked for teams or games	0	1	2	3
14. Is an emotional child	0	1	2	3
15. Everything must be just so	0	1	2	3
16. Restless or overactive	0	1	2	3
17. Fails to finish things he/she starts	0	1	2	3
18. Does not seem to listen to what is being said to him/her	0	1	2	3
19. Actively defies or refuses to comply with adults' requests	0	1	2	3
20. Leaves seat in classroom or in other situations in which remaining seated is expected	0	1	2	3
21. Poor in spelling	0	1	2	3
22. Has no friends	0	1	2	3
23. Timid, easily frightened	0	1	2	3
24. Keeps checking things over and over	0	1	2	3
25. Cries often and easily	0	1	2	3
26. Inattentive, easily distracted	0	1	2	3
27. Has difficulty organizing tasks or activities	0	1	2	3
28. Has difficulty sustaining attention in tasks or play activities	0	1	2	3
29. Has difficulty waiting his/her turn	0	1	2	3
30. Not reading up to par	0	1	2	3

Items continued on back page...

Conners' Teacher Rating Scale - Revised (L)

by C. Keith Conners, Ph.D.

	NOT TRUE AT ALL (Never, Seldom)	JUST A LITTLE TRUE (Occasionally)	PRETTY MUCH TRUE (Often, Quite a Bit)	VERY MUCH TRUE (Very Often, Very Frequent)
31. Does not know how to make friends	0	1	2	3
32. Sensitive to criticism	0	1	2	3
33. Seems over-focused on details	0	1	2	3
34. Fidgeting	0	1	2	3
35. Disturbs other children	0	1	2	3
36. Talks excessively	0	1	2	3
37. Argues with adults	0	1	2	3
38. Cannot remain still	0	1	2	3
39. Runs about or climbs excessively in situations where it is inappropriate	0	1	2	3
40. Lacks interest in schoolwork	0	1	2	3
41. Has poor social skills	0	1	2	3
42. Has difficulty playing or engaging in leisure activities quietly	0	1	2	3
43. Likes everything neat and clean	0	1	2	3
44. Fidgets with hands or feet or squirms in seat	0	1	2	3
45. Demands must be met immediately—easily frustrated	0	1	2	3
46. Blurts out answers to questions before the questions have been completed	0	1	2	3
47. Spiteful or vindictive	0	1	2	3
48. Short attention span	0	1	2	3
49. Loses things necessary for tasks or activities (e.g., school assignments, pencils, books, tools, or toys)	0	1	2	3
50. Only pays attention to things he/she is really interested in	0	1	2	3
51. Shy, withdrawn	0	1	2	3
52. Distractibility or attention span a problem	0	1	2	3
53. Things must be done the same way every time	0	1	2	3
54. Mood changes quickly and drastically	0	1	2	3
55. Interrupts or intrudes on others (e.g., butts into others' conversations or games)	0	1	2	3
56. Poor in arithmetic	0	1	2	3
57. Does not follow through on instructions and fails to finish schoolwork (not due to oppositional behavior or failure to understand instructions)	0	1	2	3
58. Easily distracted by extraneous stimuli	0	1	2	3
59. Restless, always up and on the go	0	1	2	3

Appendix A.10.: Strengths and Difficulties Questionnaire – Parent report for 4 – 16 years old children.

Strengths and Difficulties Questionnaire

P4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months.

Child's Name ..... Male/Female

Date of Birth .....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Overall, do you think that your child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes - minor difficulties	Yes - definite difficulties	Yes - severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress your child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with your child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
HOME LIFE	☐	☐	☐	☐
FRIENDSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐
LEISURE ACTIVITIES	☐	☐	☐	☐

- Do the difficulties put a burden on you or the family as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Mother/Father/Other (please specify:)

Thank you very much for your help

Appendix A.11.: Strengths and Difficulties Questionnaire – Teacher report for 4 – 16 years old children.

Strengths and Difficulties Questionnaire T4-16

For each item, please mark the box for Not True, Somewhat True or Certainly True. It would help us if you answered all items as best you can even if you are not absolutely certain or the item seems daft! Please give your answers on the basis of the child's behaviour over the last six months or this school year.

Child's Name ..... Male/Female

Date of Birth .....

	Not True	Somewhat True	Certainly True
Considerate of other people's feelings	☐	☐	☐
Restless, overactive, cannot stay still for long	☐	☐	☐
Often complains of headaches, stomach-aches or sickness	☐	☐	☐
Shares readily with other children (treats, toys, pencils etc.)	☐	☐	☐
Often has temper tantrums or hot tempers	☐	☐	☐
Rather solitary, tends to play alone	☐	☐	☐
Generally obedient, usually does what adults request	☐	☐	☐
Many worries, often seems worried	☐	☐	☐
Helpful if someone is hurt, upset or feeling ill	☐	☐	☐
Constantly fidgeting or squirming	☐	☐	☐
Has at least one good friend	☐	☐	☐
Often fights with other children or bullies them	☐	☐	☐
Often unhappy, down-hearted or tearful	☐	☐	☐
Generally liked by other children	☐	☐	☐
Easily distracted, concentration wanders	☐	☐	☐
Nervous or clingy in new situations, easily loses confidence	☐	☐	☐
Kind to younger children	☐	☐	☐
Often lies or cheats	☐	☐	☐
Picked on or bullied by other children	☐	☐	☐
Often volunteers to help others (parents, teachers, other children)	☐	☐	☐
Thinks things out before acting	☐	☐	☐
Steals from home, school or elsewhere	☐	☐	☐
Gets on better with adults than with other children	☐	☐	☐
Many fears, easily scared	☐	☐	☐
Sees tasks through to the end, good attention span	☐	☐	☐

Do you have any other comments or concerns?

Overall, do you think that this child has difficulties in one or more of the following areas: emotions, concentration, behaviour or being able to get on with other people?

No	Yes - minor difficulties	Yes - definite difficulties	Yes - severe difficulties
☐	☐	☐	☐

If you have answered "Yes", please answer the following questions about these difficulties:

- How long have these difficulties been present?

Less than a month	1-5 months	6-12 months	Over a year
☐	☐	☐	☐

- Do the difficulties upset or distress the child?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

- Do the difficulties interfere with the child's everyday life in the following areas?

	Not at all	Only a little	Quite a lot	A great deal
PEER RELATIONSHIPS	☐	☐	☐	☐
CLASSROOM LEARNING	☐	☐	☐	☐

- Do the difficulties put a burden on you or the class as a whole?

Not at all	Only a little	Quite a lot	A great deal
☐	☐	☐	☐

Signature ..... Date .....

Class Teacher/Form Tutor/Head of Year/Other (please specify:)

Thank you very much for your help

Appendix A.12.: SNAP-IV

BEHAVIOURAL RATING SCALE

Name of Child_____Date of Birth_____
Grade_____Gender_____Date_____
Completed by: Teacher___Aide___Mother___Father___Other_____

Please check each column which best describes the child

	Not at all	Just a little	Pretty much	Very much
1. Is often easily distracted by extraneous stimuli				
2. In absence of close supervision, often has difficulty following through on instructions				
3. Often has difficulty sustaining attention in tasks or play activities				
4. Often does not seem to listen to what is being said to him or her				
5. Often loses things necessary for tasks or activities at school or at home				
6, Often fails to give close attention to details on schoolwork or other activities				
7. Often has difficulty organizing goal-directed activities				
8. Often shifts from one uncompleted activity to another				
9. Often leaves seat in classroom or in other situations in which remaining seared is expected				
10. Often acts before thinking				
11. Often has difficulty awaiting turn in games or group situations				
12. Often blurts out answers to questions before the questions have been completed				
13. Often has difficulty playing quietly				
14. Often runs about or climbs excessively in situations where it is inappropriate				
15. Often engages in physically dangerous activities without considering possible consequences				
16. Often fidgets with hands or feet or squirms in seat				
17. Often interrupts or intrudes on others				
18. Often talks excessively				

Thank you very much for your help

Appendix B: Additional statistical analyses

Appendix B.1.: Gender main effects on all IC and DAV measures

	MANOVA (including gender)		
	df	*F-value*	*p*
Stop-Signal Task			
SSRT (ms)	113	.06	.80
SSRT SD (ms)	113	.07	.78
Go RT (ms)	113	.56	.45
Go SD (ms)	113	.31	.57
Error RT (ms)	113	1.05	.30
Error SD (ms)	113	1.91	.16
Go/No-Go			
GNGPI (%)	95	.58	.44
Go RT (ms)	95	.06	.80
Go SD (ms)	95	.07	.78
Error RT (ms)	95	.07	.78
Error SD (ms)	95	.52	.47
Modified Stroop			
MStroopPI (%)	105	.38	.53
Go RT (ms)	105	.09	.76
Go SD (ms)	105	.84	.36
Error RT (ms)	105	.10	.74
Error SD (ms)	105	.09	.76
Maudsley's Index of Delay Aversion			
% DR	118	.68	.41
% Omissions	118	.35	.55
Delay Frustration			
DeFT MTD (ms)	112	1.69	.19
Delay Reaction Time			
DRT DS (ms)	115	.01	.92
PCA			
IC component	102	1.10	.29
DAV component	102	.58	.44

Note: DAV = Delay Aversion; DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; IC = Inhibitory Control; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; PCA = Principal Component Analysis; RT = Reaction Time; SD = Standard Deviation; SSRT = Stop Signal Reaction Time;
* = $p < .05$; ** = $p < .01$

Appendix B.2.: Non-parametric tests for not normally distributed IC and DAV measures

	Status (S)			Age (A)		
	U	*z*	*p*	*U*	*z*	*p*
Stop-Signal task						
SSRT	1273	-2.57	.01*	1414	-1.52	.12
Error RT	1352	-2.05	..04*	1123	-3.00	.003**
Go/No-Go						
GNGPI (%)	1005	-4.34	.000**	1494	-1.30	.19
Go SD (ms)	745	-5.75	.000**	985	-4.11	.000**
Error RT (ms)	1535	-.51	..60	1032	-3.00	.003**
Error SD (ms)	857	-2.40	.01*	804	-2.56	.01*
% Omission	867	-5.28	.000**	1561	-1.18	.23
Modified Stroop task						
MStroopPI	927	-4.77	.000**	1608	-.80	.42
Error RT	1647	-.41	.67	1218	-2.21	.02*
% Omissions	1179	-3.48	.000**	1360	-1.61	.10
Maudsley's Index of Delay Aversion						
% DR	1332	-2.88	.004**	1237	-2.93	.003**
% Omissions	1829	-.61	.53	1694	-.98	.32
Delay Frustration						
DeFT MTD (ms)	1151	-3.14	.002	1437	-1.00	.31
Delay Reaction Time						
DRT DS (ms)	1019	-4.14	.000	1244	-2.43	.01

Note: DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; RT = Reaction Time; SD = Standard Deviation; SSRT = Stop Signal Reaction Time;
* = $p < .05$; ** = $p < .01$

Appendix B.3.: On-diagonal correlation of probands and siblings on IC and DAV measures, controlling for age

	Proband-Sibling *r*
SSRT (ms)	.05
MStroopPI (%)	.17
GNGPI (%)	.17
MIDA % DR	.32*
DeFT MTD (ms)	.26
DRT DS (ms)	-.15
IC composite	.14
DAV composite	..19

Note: DAV = Delay Aversion; DeFT MTD = Delay Frustration Task Mean Total Duration; DRT DS = Delay Reaction Time Delay Sensitivity; GNGPI = Go-No-Go Probability of Inhibition; IC = Inhibitory Control; MIDA % DR = Maudsley's Index of Delay Aversion Probability of Delayed Reward; MStroopPI = Modified Stroop Probability of Inhibition; SSRT = Stop Signal Reaction Time;
* = $p < .05$; ** = $p < .01$