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'Time estimation deficits in Attention Deficit Hyperactivity Disorder'

by

Celine M. Mullins

A dissertation submitted for the degree of Doctor of Philosophy of the University of Dublin, Trinity College, Dublin 2, Ireland.

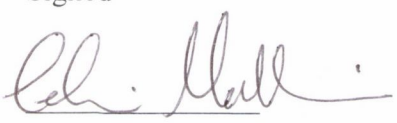
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Celine Mullins

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Summary

The main aim of this thesis was to examine whether a time deficit exists in children diagnosed with Attention Deficit Hyperactivity Disorder (ADHD) and to try to determine the nature and basis for such a deficit if it is established.

Chapter one provides an overview of ADHD and the clinical subtypes. Chapter two presents a summary of what is known about time perception in humans, and more specifically in those diagnosed with ADHD. Chapter 3 is the first experimental chapter. It investigates test-retest reliability on a time reproduction task, a time reproduction with distraction task, and a control Onset-Offset Detection task. The findings of this study suggest that the three tasks have considerable reliability. Chapter 4 investigates ADHD (ADHD-Combined and ADHD-Inattentive subtypes) compared to controls on the measure of time reproduction. The two subtypes of ADHD (combined and inattentive) show deficit in time reproduction and are distinguishable from each other on the basis of variability in time reproductions. When controlling for factors such as IQ the significant group time reproduction difference remains. Distraction makes the time reproductions errors larger. Chapter 5 compares ADHD-C children on and off methylphenidate (MPH) on the time reproduction tasks. MPH makes no difference to their performance on the time reproduction task but it does make the children less distractible on the time reproduction with distraction task. Chapter 6 examines the performance of ADHD subtypes and controls on tasks measuring executive functioning (Fixed SART, Random SART and TEA-Ch) and investigates the results in relation to time reproduction. The findings demonstrate that both sustained attention and response inhibition are involved in

performing a time reproduction task. Chapter 7 explores spatial neglect and temporal order judgement in relation to time reproduction, sustained attention and response inhibition in ADHD children / adolescents, revealing an association between all domains. The eighth and final chapter consists of a discussion of issues raised by the experiments, with suggestions for future research.

The most important findings in this thesis are that 1) there appears to be a very real deficit of time perception in ADHD, regardless of subtype and 2) these subtypes can be distinguished on various tasks based on their intra-individual variability, with the combined subtype performing significantly more variably than the inattentive subtype 3) time reproduction error is linked to sustained attention, a relationship which has previously been inferred from common right-lateralised neural circuitry that is thought to subserve these processes.

.

List of Publications

Refereed Published Journal Article:

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Bellgrove MA, Domschke K, Hawi Z, Kirley A, Mullins C, Robertson IH, Gill M. The methionine allele of the COMT polymorphism impairs prefrontal cognition in children and adolescents with ADHD. Exp Brain Res. 2005 Jan 15; [Epub ahead of print].

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Kirley A, Hawi Z, Daly G, McCarron M, Mullins C, Millar N, Waldman I, Fitzgerald M, Gill M. (2002) Dopaminergic System Genes in ADHD: - Towards a Biological Hypothesis, *Neuropsychopharmacology*, 27(4):607-19.

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Hawi Z, Kirley A, Mullins C, Fitzgerald M, Gill M. (2000). No association of serotonin transporter gene polymorphisms with Attention Deficit Hyperactivity Disorder. *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 96(4): 490.

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List Of Abbreviations

ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
ADHD-C	Attention deficit hyperactivity disorder combined type
ADHD-H	Attention deficit hyperactivity disorder hyperactive-impulsive type
ADHD-I	Attention deficit hyperactivity disorder inattentive type
ANOVA	Analysis of variance
CAPA	The Child and Adolescent Psychiatric Assessment
CBT	Cognitive behavioural training
CD	Conduct Disorder
CNS	Central nervous system
CPRS-R	Conners Parent Rating Scale
CPT	Continuous performance task
DA	Dopamine
DAT	Dopamine transporter
DBH	Dopamine ß-hydroxylase
DLPF	Dorsal lateral prefrontal cortex
DOPA	Dopamine decarboxylase
DRD	Dopamine receptor
DSM-II	Diagnostic and Statistical Manual of Mental Disorders, second edition
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, third edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
EEG	Electroencephalogram
EF	Executive functions
fMRI	Functional magnetic resonance imaging
IQ	Intelligence quotient
LD	Learning Disorder
LN	Lenticular nucleus
MPH	Methylphenidate

MRI	Magnetic resonance imaging
MTA	Multimodal Treatment Study
NAA/ Cr	N-acetylaspartate/ creatine-phosphocreatine
NE	Norepinephrine
ODD	Oppositional Defiant Disorder
PD	Parkinsons Disease
PPS	Perceived Point of Simultaneity (PPS)
RD	Reading Disability
RT	Reaction time
$SART_{Fixed}$	Fixed sequence SART
$SART_{Random}$	Random sequence SART
SCT	Sluggish cognitive tempo
SHR	Spontaneously hypertensive rat SHR
SMA	Supplementary motor area
TBI	Traumatic brain injury
TEA-Ch	Test of Everyday Attention for Children
TMS	Transcranial magnetic stimulation
WISC-III	Wechsler Intelligence Scale for Children – III

Chapter 1

ADHD: An Overview

1.1 ADHD

Attention-deficit hyperactivity disorder (ADHD) is a common heritable behavioural disorder of childhood (Brown et al., 2001), associated with cognitive impairments of response inhibition, sustained attention and working memory among others (e.g., Shallice et al., 2002). It is one of the most commonly studied and frequently diagnosed psychiatric disorders in children (Barkley, 1991; Shue & Douglas, 1992). Areas of interest include the disorder's affect on children and adolescents, comorbidity with learning disabilities, and other psychiatric disorders. Current research indicates that the majority of children diagnosed with ADHD continue to exhibit significant symptoms into adulthood, particularly symptoms of inattention (Gingerich et al.,1998; Roy-Byrne et al, 1997). Nonetheless, the severity of symptoms of the disorder appear to reduce by adulthood (Klein & Mannuzza, 1991).

ADHD is currently characterized in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) as a persistent pattern of inattention and/or hyperactivity-impulsivity that is inconsistent with developmental age appropriateness (American Psychiatric Association, 1994). The DSM-IV diagnostic criteria present multiple symptoms in both inattention and hyperactivity-impulsivity. Six or more

symptoms from either or both diagnostic categories must persist for six months and be inconsistent with appropriate developmental level. This differentiation allows for three alternative subtypes; Combined type (ADHD-C), primarily inattentive type (ADHD-I), and primarily Hyperactive-impulsive type (ADHD-H).

The classification of Attention-Deficit/ Hyperactivity Disorder (ADHD) has changed numerous times since its first appearance in the DSM-II (American Psychiatric Association, 1968). There has been an emphasis on different symptoms underlying the disorder with each edition. In DSM-II, the emphasis was on hyperactivity, whereas in DSM-III (American Psychiatric Association, 1980), it was on attention. The most recent version of DSM-IV (American Psychiatric Association, 1994) emphasizes both attention and hyperactive/ impulsive behaviours, and a child can be diagnosed as either of three types of ADHD, based on two symptom domains: (1) inattention-disorganization and (2) hyperactivity-impulsivity. Children are classified into one of three subtypes according to the cluster of symptoms they exhibit. They can be classified as Primarily Inattentive subtype (ADHD-I), Primarily Hyperactive subtype (ADHD-H), or Combined subtype (ADHD-C), the latter meaning they exceed thresholds for symptoms of both inattention and hyperactivity. The inattentive subtype child must be below threshold on hyperactivity/ impulsivity, and the hyperactive subtype must be below threshold on inattention symptoms.

1.2 ADHD and Comorbidity

In addition to their problems with inattention, impulsivity and overactivity, people with ADHD may present with a variety of other difficulties. These include an increased likelihood of having other medical, developmental, behavioural, emotional and/or academic problems. Co-morbidity of psychiatric disorders include mood disorders (Cantwell & Baker, 1992), Tourette's syndrome (Knell & Comings, 1993), Conduct Disorder and Oppositional Defiant Disorder (Cantwell & Baker, 1992; Eiraldi et al., 1997).

Studies have repeatedly found higher rates of learning disability co-morbidity with ADHD, particularly reading disorders and written language problems (August & Garfinkel, 1989; Aust, 1994; Cantwell & Baker, 1992; Resta & Eliot, 1994; Riccio et al., 1994), and central auditory processing problems (Riccio et al, 1994). Recent findings revealed 69.8% children that were evaluated had combined ADHD and learning disabilities, a significantly greater prevalence of learning disorders than children without ADHD. (Mayes et al., 2000). However, it is not as yet clear whether these differences represent real intellectual differences or merely differences in test-taking behaviour, as inattentiveness to task would naturally produce lower test scores. Other investigators have examined the IQs in children with ADHD, both with and without learning disabilities, and noted that children with ADHD can fall into the entire intellectual spectrum, ranging from giftedness to mental disabilities. In other words they are most likely normally distributed in intellectual capacity (Barkley, 1998; Kaplan et al., 2000).

1.3 Neuropsychological Profiles of ADHD

As with some other psychiatric disorders, objective psychological or biological tests with adequate sensitivity have not yet been established to replace a careful clinical history as the primary source of information for diagnosis. As a result, different approaches to characterising the precise nature of a core deficit associated with ADHD have emerged. Two contrasting theoretical accounts of attentional deficits are outlined below.

1.3.1 Barkley's Unified Theory of ADHD

On the basis of existing theories of language and frontal lobe function, Barkley (1997) has proposed that poor behavioural inhibition is the primary deficit of ADHD while attention deficits are secondary. In other words, deficient behavioural inhibition disrupts executive functions by not allowing adequate opportunity for them to occur. Barkley (1997) was not the first to suggest that impaired response inhibition is a distinguishing characteristic of ADHD. Still (1902), Douglas (1972), Quay (1988), and Sonuga-Barke et al. (1992) have all identified impulsivity as an important feature of ADHD. Barkley (1997) attempts to account for much of the existing data on the cognitive underpinnings of ADHD, to integrate what is currently known about the psychobiology of ADHD, and to explain how the underlying dysfunction relates to the behaviours and symptoms that characterize children with ADHD. This model applies only to children with ADHD-Hyperactive and ADHD-Combined, and not to those with ADHD-Inattentive (see Clinical Subtypes section (1.6) below pg 30). Barkley (1997) draws from four

neuropsychological models of pre-frontal lobe function (those of Bronowski, 1976; Dimasio, 1984; Fuster; 1989; and Goldman-Rakic, 1995;) to construct what he calls a 'Hybrid Model of Executive Functions'. In this model, behavioural inhibition is an executive function that allows for the occurrence of four other classes of executive functions: non-verbal working memory and sense of time, internalization of speech (verbal working memory), self-regulation (of affect, motivation, and arousal), and reconstitution. All are necessary for motor control, fluency, and syntax. Within this model, a primary deficit in behavioural inhibition would set the stage for secondary impairments in each of the four 'intermediate' executive functions, which in turn, would lead to deficits in motor programming, response execution, and goal-directed action. Primary deficits in behavioural inhibition could also lead directly to deficits in motor control.

1.3.2 Posner and Petersons' neuropsychological model of attention

On the basis of a neuroanatomical network theory of attention, Swanson et al. (1998), have characterized the core deficit of ADHD as a combination of alerting and executive control deficits. According to this framework, state and behavioural deficits would be considered as attentional deficits. This theory stems from the work of Posner and Peterson (1990), who proposed that on the basis of both lesion and functional imaging studies, there was good evidence for at least three attentional systems within the brain; selective, sustained and spatial attention. Posner and Raichle (1994), further proposed a neuroanatomical network theory of attention based on the working hypothesis that three distinct neural networks accomplish component processes of Alerting (suppressing

background neural noise to establish readiness to react by inhibiting ongoing activity and mental effort), Orienting (mobilizing specific neural resources to prepare for expected type of input by facilitation of one specialized process and inhibition of others), and Executive control (coordinating multiple specialized neural processes to direct behaviour toward a goal by detecting the presence of a target, starting and stopping mental operations, and ordering multiple responses). Based on brain imaging work, Posner and Raichle (1994) linked the neural network for Alerting to connected brain regions centred in the right frontal lobe, for Orienting to connected brain regions centred in the posterior parietal, and for Executive control to connected brain regions centred in the anterior cingulate gyrus and including the basal ganglia.

The terms used by Posner and Raichle (1994) as technical descriptions of cognitive and neural networks can be related to other traditional terms used to describe attention (Swanson, Posner et al., 1998). The alerting process and right frontal network operate to establish sustained attention (e.g. by maintaining a state of readiness to process non-specific or repetitive stimuli). The orienting process and posterior parietal network operate to establish selective attention (e.g. by covertly disengaging, moving and engaging an internal spotlight in response to internal or external cues signalling the type of processing required). The executive control process and anterior cingulate network operate to establish divided attention (e.g. by resolving conflict among multiple processes and responses in competition for execution in a co-ordinated fashion to regulate self-directed behaviour).

Another type of attention linked to ADHD is lateralised spatial attention, namely the bias of attention to right versus left hemispace. There is some debate as to whether spatial selection can be considered as a supramodal control system, a feature of the selection system or an emergent property of competing lower level perceptual systems (Robertson & Manly, 1999). Posner and Raichle (1993) suggested that the right hemisphere arousal system may directly and specifically modulate the spatial selection system. The contribution of the posterior parietal network in spatial selection, has been documented by Corbetta et al. (1995). Studies have also shown that spatial attention may be closely allied to bottom-up (exogenous) and top down (endogenous) systems of sustained attention, (Heilman et al., 1987; Robertson et al., 1997b).

1.3.3 Neuropsychological Deficits

Many neuropsychological batteries have been used to assess attention deficits in ADHD, and the consistent finding across studies has been that children with ADHD do not have generalized cognitive impairment, but that they do manifest specific deficits (Swanson et al., 1998). Neuropsychological tests are free of the potential biases of self-reported symptoms (Groth-Marnat, 2003). Given that inattention is one of the defining clinical features of ADHD and has been associated with a frontal lobe (anterior) dysfunction (Benson, 1991; Pennington & Ozonoff, 1996), many neuropsychological studies of the disorder have assessed attention in children diagnosed with ADHD. These children also perform poorly on tasks requiring inhibition of motor responses, organization of cognitive information, planning, complex problem solving, and the learning and recall of

verbal material (Barkley et al., 1992). The most commonly used measure of attention is the continuous performance (Vigilance) test (CPT) (Rosvold et al., 1956). This test requires participants to sustain their attention to subtle sensory signals, avoid distraction by irrelevant stimuli, and maintain alertness for the duration of the session. Most of these studies find ADHD children to be impaired on this measure (e.g. Carte et al., 1995; Okazaki et al., 2004; Raggio et al., 1995; van Leeuwen et al., 1998).

Neurocognitive profiles of ADHD adults are similar to those of ADHD children. Studies have shown ADHD adults to be impaired in functions known to affect ADHD children such as measures of vigilance using the CPT (Barkley et al., 1996; Seidman et al., 1998); perceptual-motor speed as assessed by the digit symbol/coding tests (Buchsbaum et al., 1985; Gualtieri et al., 1985, Murphy et al., 2001); working memory as assessed by digit span test (Barkley et al., 1996; Holdnack et al., 1995) and response inhibition as assessed by the Stroop Color-Word Test (Corbett et al., 1999; Lovejoy et al., 1999).

1.3.4 Intra-Individual Variability

Perhaps the most striking clinical characteristics of ADHD include the transient but frequent lapses of intention and attention, along with the moment-to-moment variability and inconsistency in performance, which are described by parents, teachers, spouses and those who receive a diagnosis of ADHD (Castellanos & Tannock, 2002). In conjunction with the observation that children and adults with ADHD often make more errors than controls, the most consistent finding in the ADHD cognitive literature is that the overall response times of ADHD people are reported to be more variable than control

participants on both behavioural and physiological measures (Douglas, 1972; Hynd et al., 1999; Silverstein, 1995).

Abnormal variability in reaction times (RT) across a variety of cognitive tasks may signify executive problems in top-down allocation of attention (Leth-Steensen et al, 2000), which may also explain poor control of motor timing (Rubia et al., 2003).

Performance variability has been observed in other disorders connected to frontal pathology. In Traumatic Brain Injury (TBI), impaired top-down regulation of attention has been accompanied by increased variability (Stuss et al., 1989). Intra-individual variability has also been connected to visual sustained attention deficits (Manly et al., 2000) and impaired response inhibition (Bellgrove et al., 2004), with lower variability correlating with better performance on tests of both. It has been argued that performance variability is not just a reflection of uninteresting random noise, but may actually tell us something about brain behaviour and how efficiently cognitive control is instantiated within the brain (Bellgrove et al., 2004).

In her recent review of the empirical ADHD findings, Douglas (1999) points out that the high degree of variability in ADHD performance on many cognitive tasks seems to signify a pervasive manifestation of regulatory problems involving the inconsistent allocation of effort. Methylphenidate (a mild central nervous system stimulant) has been shown to decrease within subject variability of response in cognitive domains such as response inhibition (Tannock et al., 1995a, 1995b), selective attention (Kiorman et al., 1991; Thurston et al., 1991), and sustained attention (Sonneville et al., 1991).

Such variability could be adaptive in some situations (Saldana & Neuringer, 1998). For example, recent studies have shown that it is possible to reinforce variability, i.e. variability is significantly higher when reinforcement is contingent upon it than when reinforcers are provided non-contingently (Machado, 1989; Page & Neuringer, 1985). Variability may be adaptive in real-world situations as well, e.g. when trying to elude an antagonist in a game or war situation, when trying to solve a novel problem, or when engaging in creative activities (Saldana & Neuringer, 1998). In support of the hypothesis, behavioural variability has been shown to be characteristic of an hypothesized animal model of ADHD, namely the spontaneously hypertensive rat (SHR) (Sagvolden et al., 1992). The acquisition of a better understanding of the nature of this variability represents an essential step towards a determination of the precise role of this aspect of regulatory or control processing in ADHD.

1.3.5 Neuroimaging of ADHD

Imaging studies link the cognitive impairments of response inhibition, sustained attention and working memory to dysfunction within dopamine-rich areas such as the prefrontal cortex, basal ganglia and the neocerebellum (Bush et al., 1999; Casey et al., 1997; Castellanos et al., 2001), with possible additional parietal involvement (Sowell et al., 2003).

The neuropsychological findings in ADHD provide an abundant resource for speculations about the role of subcortical structures. The attentional problems of ADHD children implicate a wide distribution of neural networks. Tomographic and morphometric MRI

studies that examine brain structure have demonstrated abnormalities in specific regions of the brain in children with ADHD-C (Peterson, 1995). They have a smaller anterior frontal lobe region (Filipek et al., 1997; Giedd et al., 1994; Hynd et al., 1991; Oades, 1998), a smaller corpus callosum, prefrontal cortex, and globus pallidus (Casey et al., 1997; Faraone & Biederman, 1998; Hynd et al., 1991; Lyoo et al., 1996; Semrud-Clikeman et al., 1994). The reductions tend to be lateralized to the right hemisphere (Casey et al., 1997). They have basal ganglia abnormalities (Aylward et al., 1996; Mataro et al., 1997), primarily a right greater than left asymmetry in size of caudate nucleus (Pueyo et al., 2000; Semrud-Clikeman et al., 2000). They have cerebellar abnormalities (Berquin et al., 1998; Mostofsky et al., 2003), and a larger posterior lateral ventricle (Lyoo et al., 1996). Additionally, children with ADHD have 3–4% smaller total cerebral volume (Castellanos et al., 2002)

Anterior cingulate cortex (ACC), lying on the medial surface of the frontal lobe, has strong connections to the dorsolateral prefrontal cortex. Bush et al. (1999) used a Stroop task to compare ACC activation in ADHD and non-ADHD adults. In contrast to controls, ADHD adults failed to activate the ACC.

These findings have not always been replicated (Castellanos et al., 1996; Mataro et al., 1997) and the laterality of the caudate findings have varied (Castellanos et al., 2001; Filipek, 1997; Mataro, 1997). Castellanos et al. (2001) reported no asymmetry in the caudate nucleus whereas Pineda et al. (2002) reported left greater than right asymmetry in size of caudate nucleus.

Although there are inconsistencies in the literature, it is notable that the pattern of deficits that has emerged is similar to what has been found among adults with frontal lobe damage. Among these, difficulties in attention and concentration (Wilkins et al., 1987; Whyte et al., 1995), memory (Levin et al., 1982; Schacter et al., 1977), executive skills (Hart & Jacobs, 1993), and social skills are particularly problematic. Thus the neuropsychological data tend to support the hypothesis that the frontal cortex or regions projecting to the frontal cortex are dysfunctional in at least some ADHD children. Interestingly, right hemisphere deficit has also been associated with ADHD-C (Ben-Artsy et al., 1996), indicating abnormal lateral differences in these children.

Hypofunctioning of the cortex has been proposed to explain impaired attention and increased impulsiveness (Dinn et al., 2001), and is improved by stimulant pharmacotherapy (Solanto, 1998). Hyperfunctioning of the striatum underlies increased motor activity (Teicher et al., 2000) and also benefits from drug treatment (Vaidya et al., 1998). The cerebellar vermis also plays a role in the pathophysiology of ADHD (Anderson et al., 2002a; Anderson et al., 2002b; Berquin et al., 1998; Castellanos et al., 2002; Houk & Wise, 1995).

Orbital frontal lesions predict social disinhibition and impulsivity and dorsolateral lesions affect organizational abilities, planning, working memory, and attention. Studies of ADHD children find impairment in all of these neuropsychological domains. Thus the neuropsychological test data, along with the clinical features of the disorder, implicate both orbito frontal and dorsolateral prefrontal dysfunction in ADHD. Overall, the functional studies are consistent with the structural studies in implicating fronto-

subcortical system in the pathophsiology of ADHD. Taken together, the brain imaging studies fit well with the idea that dysfunction in fronto-subcortical pathways occurs in ADHD. Notably, the fronto-subcortical systems that control attention and motor behaviour are rich in catecholamines, which have been implicated in ADHD by the mechanism of action of stimulants (Faraone & Biederman, 1998).

Very little is known about when ADHD related brain abnormalities emerge. To address this issue, Nopoulos et al. (2000) assayed four brain abnormalities believed to occur prior to birth: neural migration anomalies, corpus callosum agenesis or partial agenesis, enlarged cavum septi pellucidi and malformations of the posterior fossa. Neural migration anomalies and malformations of the posterior fossa were more common among ADHD compared with control subjects. Both of these abnormalities were rare. But given that several other studies show partial agenesis of the corpus callosum or anomalies of the cerebellar vermis (also formed prior to birth), it seems reasonable to conclude that at least a subset of ADHD children have a very early onset of brain abnormalities (Nopoulos et al., 2000).

1.4 Genetics of ADHD

Based on twin studies, Faraone and Biederman (1998) have determined that the heritability of ADHD-C is in the range of .80. They suggested that three dopamine receptor genes (D4, D2 and dopamine transporter genes) may be involved in the susceptibility to ADHD-C. Malone et al. (1994) hypothesized that both dopamine (DA) and noradrenergic (norepinephrine) (NE) systems may be impaired in ADHD-C children.

The noradrenergic system is known to be involved in arousal and sustained attention while the dopaminergic system is an essential component of executive control and possibly of sustained attention (Castellanos, 1997; Malone et al., 1994). The dopamine transporter (DAT) is a plasma membrane transport protein expressed exclusively within a small subset of CNS neurons. It plays a crucial role in controlling dopamine-mediated neurotransmission and a number of associated behaviours (Bannon, 2004).

Genetic research has not been very successful in its search for 'static' causative inherited deficits. Family, twin and adoption studies in ADHD have so far not been able to rule out psychosocial factors as potential cause for the clustering of ADHD symptoms in families or in monozygotic twins and genetic evidence in the strictest sense is therefore not given (Joseph, 2000). Attempts to localise single causative genes have not yet been successful in ADHD. Nevertheless, ADHD appears to be a complex genetic disorder, with many susceptibility genes each of small effect (Suarez et al., 1994; Tannock, 1998). Noradrenergic, serotoninergic and dopaminergic systems all appear to be involved to some degree.

Dopamine transmission has been extensively studied, as methylphenidate (the most commonly used treatment for ADHD), has as its site of action the dopamine transporter gene (DAT1), where it blocks the reuptake of dopamine from the synaptic cleft. Swanson et al. (1998) speculated that specific alleles of these dopamine genes may alter dopamine transmission in the neural networks implicated in ADHD (e.g. that the 10-repeat allele of the DAT1 gene may be associated with hyperactive re-uptake of dopamine (Swanson et

al., 2000) or that the 7-repeat allele of the DRD4 gene may be associated with a subsensitive postsynaptic receptor). The DAT1 10 repeat allele is considered to be the high-risk allele in ADHD and it is suggested that individuals with this allele have increased transporter density, which may lead to a depletion of dopamine from critical synaptic regions (Cook et al., 1995; Gill et al., 1997; Waldman et al., 1998).

DAT1 knockout mice have increased extracellular dopamine but reduced striatal dopamine and tyrosine hydroxylase activity (Jaber et al., 1999) and may suggest that feedback mechanisms lead to reduced striatal dopamine. DAT1 knockout mice have hyperactivity as part of their phenotype (Gainetdinov et al., 1999; Giros et al., 1996), and neuroimaging studies suggest frontostriatal dysfunction in ADHD patients. Overall the evidence for DAT1 suggests relative hypodopaminergic transmission in critical areas such as the striatum and the possible influence of excess dopamine neurotransmission from higher cortical areas.

An association between the 7-repeat Allele of the DRD4 genotype in ADHD has received the strongest genetic evidence so far (Faraone et al., 2001; Maher et al., 2002). The D4 receptor is known to mediate the postsynaptic action of dopamine. Although some research has failed to find an association between the two (Kirley et al., 2002; Todd et al., 2001), most studies have discovered that this relationship exists when ADHD children with severe combined type ADHD and comorbid Oppositional Defiant Disorder or Conduct Disorder are examined (Holmes et al., 2002, Kirley et al., 2004; La Hoste et al., 1996; Swanson et al., 1998). It has been suggested that the relationship between ADHD

and DRD 4 is related to clinical severity (Kirley et al., 2002). ADHD co-morbidity with Conduct Disorder results in a clinically more severe condition with worse outcome than ADHD alone (Barkley et al., 1990). Hence, the DRD4 gene is implicated as a gene of minor effect for ADHD. Other dopaminergic genes that have been associated positively with the disorder are DRD5 (Daly et al., 1999; Tahir et al., 2000a), DBH (Daly et al., 1999; Comings, 1996), DRD2 and DOPA (Kirley et al., 2002).

Swanson et al. (1998) assert that the association between the effect of dopamine genes and ADHD imply the involvement of the two attentional networks (the Altering Network and the Executive Control Network) as proposed by Posner and Raichle (1994). These include brain regions which are rich in dopamine receptors and may be involved in the "attentional deficit" that defines this disorder. The relationship might explain why Dopamine agonists drugs, such as methylphenidate, have clinical benefits when used to treat ADHD children by operating to correct dopamine deficit and thus normalize attention and behavior that is governed by activity in brain regions that are rich in dopamine receptors (e.g. the basal ganglia and anterior cingulated gyrus).

1.5 Treatment of ADHD

Methylphenidate (MPH) is the most well known and most prescribed example of effective pharmacological rehabilitation in the treatment of attention in ADHD (Elia et al., 1999). It is a central nervous system (CNS) stimulant. It has a notably calming and focusing effect on those with ADHD, and has generally been shown to improve the core

symptoms of the disorder (inattention, hyperactivity and impulsivity), as well as improving oppositional behaviour, impulsive aggression and social interactions.

MPH has been shown to increase metabolism in the dorsolateral prefrontal cortex, the cerebellum, the basal ganglia (Volkow et al., 1997) and the striatum (Wolraich & Doffing, 2004). It appears to operate by inhibiting dopamine transporter and stimulate release of dopamine from presynaptic stores increasing extracellular levels (Bellgrove et al., 2004, Loo et al., 2003).

The main positive effects of this medication are that it reduces disruptive behaviour and increases concentration. However, clinically significant benefits are found in only 70 – 80% of cases (Loo et al., 1999) and adverse reactions are reported, such as flat affect, mood changes, sleep disturbance, loss of appetite and sometimes even paradoxical worsening of behaviour (Chabot et al., 1999). Stimulants are contraindicated in people presenting with a psychotic illness or with a history of psychotic illness, as they can precipitate psychosis or indeed cause deterioration in a pre-existing psychosis (Lucas et al., 1971). Furthermore, stimulants are only effective while in the system (Chabot et al., 1999). There is little research on long-term effects (positive or negative), although reports of growth retardation following exposure in preschoolers are emerging (Swanson & Volkow, 2003).

Another drug that is used in the treatment of ADHD is also a stimulant called Dexamphetamine. The third choice of drug treatment is generally Clonidine (an anti-hypertensive drug), commonly prescribed when there is poor response to stimulant drugs

or there are tic disorders in addition to ADHD; there is often an increase in pre-existing tics as a result of Methylphenidate or Dexamphetamine (Castellanos et al., 1997).

There are many non-medicated approaches to dealing with ADHD. Cognitive-Behavioural Therapy is the most common and usually consists of a system of rewards and punishments, time outs, and changes in interpersonal response to the child. It is really the systematic application of common sense. If both parents apply it systematically, it can be very helpful. It is as effective as low dosages of medication, but when combined with low dose it is as effective as high dose (Root & Resnick, 2003).

A combination of methylphenidate, and cognitive-behavioral therapy is proving to be the best option for treatment of children with ADHD. In 1999, a large study, the Multimodal Treatment Study (MTA) compared medication, behavior therapy, a combination of both, and standard community care. While all four groups improved, medication, when carefully monitored, was more effective than behavior therapy, and its effects were similar to combination therapy. The combined approach, however, allowed lower doses of medication and also improved academic performance and family relations. In addition, it was more helpful for children who also had mood disorders (such as depression or anxiety) or oppositional-defiant disorder. A 2001 study further suggested that 80% of adolescents with ADHD who were treated with a combined approach showed an improvement in academic performance. Currently most professionals advocate the combination of pharmacological and behaviour management in the treatment of ADHD.

1.6 Clinical Subtypes of ADHD

Substantial evidence from studies of demographics and epidemiology, comorbidity, social functioning, and treatment response, indicates that the subtypes differ in ways other than hyperactivity. Different demographics and associated features have been identified between the inattentive and combined subtypes of ADHD. Studies using both epidemiological and clinic-referred samples as well as DSM-III and DSM-IV subtype distinctions provide generally consistent evidence. Compared to ADHD-C, children with ADHD-I tend to have a later age of onset and later age of clinic referral. The DSM-IV field trials found that only 57% of the ADHD-I group met the symptom criteria before age seven while 82% of the ADHD-C group met symptom criteria at the specified age of onset criterion for diagnosis. (Lahey et al., 1994; Milich et al., 2001). Gender ratios are generally found to represent a higher proportion of females in the inattentive type than in the combined type. The DSM-IV field trials reported ratios of M:F 2.7:1 for the ADHD-I group and M:F 7.4:1 for the ADHD-C group. Different rates of prevalence have been found between the groups although the direction of this difference depends on the type of sample studied. The inattentive type is more prevalent than the combined type in community samples whereas prevalence favours the combined type in clinical samples (Baumgaertel et al., 1995; Carlson & Mann, 2000). The nature of the subtypes is such that children with ADHD-C are referred much more frequently than children with ADHD-I, probably due to the discrepancy in prevalence of co-occurring externalizing problems.

The attentional problems of children with the ADHD Inattentive subtype are general and non-specific, related to poor focused or selective attention and less accurate information processing, and have been associated with reduced IQ. The more specific attention problems, i.e. distractibility and reduced persistence, of children with ADHD Hyperactive/Impulsive subtype are still present after correcting for IQ (Taylor et al., 1991). Thus, the ADHD Inattentive subtype may have a different aetiology than the ADHD Hyperactive/Impulsive subtype. Further, the aetiology of inattention in general may be quite heterogeneous and therefore difficult to disentangle. There is little or no data on medical treatment of ADHD Inattentive subtype although there is a common clinical notion that methylphenidate also helps these children. However, response to medication is not a diagnostic criterion, as practically all children will function better when given central stimulants (Carey, 2000). Also, most explanatory models of ADHD are assumed to apply exclusively to the ADHD Combined subtype or the Hyperactive/Impulsive subtype (Tannock, 1998).

Although ADHD appears to be a neurological condition, the relationship between the observable features of the disorder and the underlying neurocognitive impairment is not clear. Many studies have demonstrated similarity between symptoms of ADHD and impairment associated with the dysfunction of particular brain regions. Hyperactivity and the executive control of behaviour in ADHD has been predominantly linked to frontal lobe (anterior) functioning, whereas inattention in ADHD has been linked to the frontal lobes as well as to the right parietal (posterior) and midline subcortical regions involved

in the regulation of attention and arousal (Swanson et al., 1998), but these relationships have not been established in the subtypes. Attempts to identify a core deficit in ADHD are complicated by the existence of multiple neural networks of attention associated with various cognitive processes and clinical manifestations. A neurocognitive explanation of the impairment in this disorder must take into account the heterogeneity of symptoms encompassed both within and between subtype diagnoses.

As described above, attentional networks within the brain can be broadly categorized into anterior, posterior, and alerting systems, each with different yet interrelated function (Posner & Raichle, 1994). The anterior system involves regions of the pre-frontal cortex and basal ganglia and is responsible for the executive control of attention, an aspect of self-regulation that appears to be deficient in ADHD-C. This system has been the target for investigation of neuropsychological impairment in ADHD and has yielded substantial findings for populations with hyperactivity (Castellanos, 1999). Descriptors used to describe the inattention of the ADHD-I subtype (i.e. sluggish cognitive tempo, slow processing, 'spacey', and lethargic), however, are not typical features of executive function deficit and have not been clearly identified on neuropsychological tests of frontal lobe functions (Lahey et al., 1994; Milich et al., 2001). Alternatively, the posterior system has anatomical foci in the parietal lobes, parts of the midbrain and thalamus, and is responsible for visual orienting and shifting attention. In contrast to the executive mechanisms described above, this system is presumed to facilitate automatic processes associated with visual-spatial processing and the disengaging and reengaging of attention (Posner & Raichle, 1994). The third system of attention proposed by Posner & Raichle,

1994), the alerting system, involves the locus coeruleus nucleus of the midbrain and its connections to the frontal and parietal lobes of the right hemisphere and is believed to be involved in the regulation of vigilance and arousal. Cognitive processes associated with the posterior and alerting systems of attention may have relevance for the dysfunction in ADHD-I, and for negotiating the differences that mark the subtypes.

Barkley et al. (1990) examined the qualitative differences between ADHD subtypes. The researchers found that children with the added component of hyperactivity tended to be more active and persistent in their demands. ADHD children exhibited more impulsive behaviours, less self-control, as well as increased internalized and externalized problems. Children with the added criterion of hyperactivity ranked higher in areas of pervasiveness, conduct problems, self-destructive behaviours and aggression and tended to exhibit more difficulty in social and peer interactions than the children without hyperactivity.

However, debate continues as to the primary symptoms of the disorder, and to the validity of the inattentive subtype of ADHD, which was introduced in the DSM-III. Numerous studies have examined the validity of the inattentive subtype of ADHD, and some have attempted to categorize similarities and disparities between this and the combined subtype. There are a number of reviews arguing for the validity of the inattentive subtype (Carlson, 1996; Carlson & Mann, 2000; Lahey & Wilcutt, 1998). Alternatively, some argue that this subtype is actually a completely distinct diagnostic disorder, stating that there is an earlier age-at-onset for the Combined subtype, gender

differences in prevalence rates, with more males being diagnosed as Combined type than Inattentive type, and different rates of comorbid disorders associated with each subtype (e.g. Milich et al., 2001).

Studies that find some differences between the combined type and the inattentive type make an argument against combining all subtypes of the disorder as one group, when investigating the disorder (Carlson & Mann, 2000; Lahey & Wilcutt, 1998). ADHD children exhibit such a variety of symptoms that they are difficult to examine as a homogenous group, yet they are often studied as a single group of participants. Most investigators have a tendency to combine all subtypes and it is therefore possible that we are drawing conclusions that all ADHD participants exhibit behaviour that actually only applies to one subtype or alternatively to null findings across ADHD when a symptom/ difficulty does in fact exist in one subtype of the disorder (but not necessarily all subtypes). Viewing the inattentive subtype as a distinct separate disorder or even examining it as a separate subtype in all general research of ADHD, would allow investigators to explore alternative ways of treating the disorder.

It is also debated as to whether the nature of the attention deficit is inherently different when found alone, as with ADHD-I, or versus when paired with the presence of hyperactivity/ impulsivity, as with ADHD-C. The diagnostic labels imply that one can either have a problem with attention or a problem with attention in addition to a separate problem with hyperactivity/ impulsivity. It is still unclear what the effects of impairment in the domain of hyperactivity/ impulsivity may have on the expression of an attention

deficit. Predictions about the role of specific cognitive processes of inattention in the subtypes, both those that are primary to attention and those that may act more indirectly to regulate attention, depend on the relationship of symptoms across and within the two domains. For example, disruption of neural pathways associated with the various symptoms of hyperactivity and impulsivity can result in problems with the control of attentional resources. This component of attention can be distinguished functionally from among others (e.g. sensory or automatic processes of attention and arousal). In consideration of hyperactive behaviour, a child could have difficulty attending to an academic task due to a problem inhibiting pre-potent motor responses to fidget excessively, rather than a unique problem with inattention. Even though inattention usually accompanies hyperactivity, it has not been empirically confirmed that the associated attention problems are themselves etiologically distinct and not a result of the behavioural disruption caused by hyperactivity and/or impulsivity symptoms, such as the inability to inhibit behaviours that disrupt the maintenance of attention on a task or activity. If such an overlap exists between symptoms of attention and hyperactivity in ADHD-C, then the origin of the attention deficit in this group is likely different from that of the inattentive subtype.

A neurocognitive theory might consider ADHD-C in terms of a single domain of symptoms that stem from common underlying neurological dysfunction that is different from the neurological dysfunction in ADHD-I. Barkley's (1997) model of deficiency in the ADHD-C subtype provides a well-substantiated unifying explanation for the range of symptoms displayed in this particular group (Barkley, 1997). He proposes that the

attentional components of the two subtypes are different in cognitive function and neurological origin (Barkley, 1997). It has been argued that if the attention deficits of the inattentive and combined subtypes are different in nature, then the groups are not variants of the same disorder but are essentially distinct disorders altogether (Milich et al., 2001).

Some studies examining differences in the two groups (combined subtype and inattentive subtype) attention styles using parent and teacher ratings have consistently found that the ADHD-I group tends to be rated as more sluggish, slow, apathetic and lost in thought, while the ADHD-C group tends to be rated as more impulsive and distractible. For example, Lahey et al. (1985) examined a school sample of ADHD-C, ADHD-I and control children using teacher ratings on the Revised Behaviour Problem Checklist. Groups were compared on teacher responses to items on the Attention Problem-Immaturity factor of the checklist. Both ADHD groups were rated as exhibiting greater attention problems than controls on 12 of the 16 factor items. However, the two ADHD groups differed from each other on seven of the items. Children with ADHD-C were rated higher on the irresponsibility, distractibility, impulsivity, sloppiness, and answering without thinking items. The children with ADHD-I were rated higher on the sluggishness and slowness items. Lahey et al. (1985) and Barkley (1997) suggest that the patterns of behaviour for the two groups may differ so markedly that ADHD-I could be described as a separate internalizing disorder.

In another study examining differences in cognitive tempo among ADHD groups, Schaughency et al. (1987) compared children with ADHD-C and ADHD-I using teacher

ratings. On the Conners Behaviour Rating Scale, teachers rated children with ADHD-I as having a more sluggish tempo than children with ADHD-C. Barkley et al. (1990) also used teacher rating scales to examine differences in patterns of attention among ADHD-C, ADHD-I, LD and normal controls groups. On the Teacher Rating Form, children with ADHD-I were rated higher than children with ADHD-C on items 'lost in fog', 'daydreaming or getting lost in thought' and 'apathetic or unmotivated'. McBurnett et al. (2001) assessed the relationship between sluggish cognitive tempo (SCT) and DSM-IV symptoms of ADHD. Using factor analyses, they found that sluggish cognitive tempo items (forgetful, daydreams, sluggish/ drowsy) formed a factor separate from an inattention factor when hyperactivity/ impulsivity symptoms were removed from the analyses. They found that the ADHD-I group was elevated on the Sluggish Cognitive Tempo factor compared with the ADHD-C group. The sluggish cognitive tempo items showed good symptom utility when the ADHD-I group was examined but not when both groups were included in analyses. In other words, these items demonstrated more predictive power for the ADHD-I group than for the ADHD-C group. Todd et al. (2004) on the other hand, failed to replicate these findings, and claimed that the inclusion of SCT symptoms does not support the presence of additional discrete subtypes of ADHD. In this study 'Low energy' was more frequently associated with ADHD-I than with ADHD-C. Todd et al. (2004) associated this to Generalized Anxiety Disorder and social phobia symptoms.

Different patterns of comorbidity have been found depending on the presence or absence of hyperactivity. The most common externalizing disorders associated with ADHD are

Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) (Biederman et al., 1991; Jensen et al., 2001), with ADHD-C children more likely to be diagnosed with either of the disorders than ADHD-I (Barkley et al., 1990; Lalonde et al., 1998). Internalizing disorders (anxiety and depressive disorders) also frequently co-occur with ADHD. Barkley et al. (1990), and Cantwell and Baker (1992) found that children with ADHD-I were more likely to have Major Depressive Disorder compared to controls and to children with ADHD-C. More recently, Cody et al. (1997) found that children with ADHD-C exhibit significantly more symptoms of depression, anxiety, and internalizing behaviours compared to ADHD-I and controls, confusing matters further.

Studies examining neuropsychological features of ADHD-C and ADHD-I subtypes have yielded mixed results. Nigg et al. (2002) examined neuropsychological executive functions in the domain of output speed. On a measure of behaviour inhibition, differences between subtypes were dependent on gender effects: boys with ADHD-C obtained lower scores than boys with ADHD-I, while there was no differences between girls with ADHD-C and ADHD-I. Chhabildas et al. (2001) compared the performance of children diagnosed with ADHD-C, ADHD-H and ADHD-I in the areas of processing speed, vigilance, and inhibition, but found no difference in performance between the ADHD-C and ADHD-I subtypes. The results suggested that symptoms of inattention, rather than symptoms of hyperactivity/impulsivity, are associated with neuropsychological impairment in both subtypes, as children with ADHD-HI were not significantly impaired on any dependent measures once subclinical symptoms of

inattention were controlled. Faraone et al. (1998) found no differences between the ADHD subtypes on IQ and academic measures.

On the other hand, Houghton (1999) found that ADHD-I and ADHD-C type children differed from Controls on several neuropsychological tests of executive function, concluding that the combined type had larger deficits. ADHD-C children made the most errors on the Wisconsin Card Sorting Test and performed more poorly than the ADHD-I children and the controls for the Stroop Color-Word Test. Others find that ADHD-I have greater deficits in information retrieval and processing, lower levels of alertness, and more problems with memory/orientation (Barkley et al., 1990; Lahey et al., 1985; Lahey et al., 1987).

Very recently, the ADHD-C and ADHD-I subtypes have been compared using Magnetic resonance spectroscopy (MRS), a non-invasive functional imaging technique, which can detect metabolic changes in the brain (Sun et al., in press). N-acetylaspartate/ creatine-phosphocreatine (NAA/ Cr) was significantly decreased in the right lenticular nucleus (LN) of the ADHD-C group as compared with the ADHD-I and control groups. There was also significantly decreased NAA/ Cr in the left lenticular nucleus (LN) of the ADHD-C group as compared with the control groups and a trend towards significantly decreased NAA/ Cr in the left lenticular nucleus (LN) of the ADHD-C group as compared with the ADHD-I group. NAA reductions have been interpreted as strong evidence for neuron loss or dysfunction in a brain region of interest. The lenticular nucleus denotes a composite substructure of the basal ganglia that consists of the globus

pallidus and the putamen. The basal ganglia is involved in emotional, motivational and cognitive functions and has consistently been associated with the dysfunction in ADHD (Aylward et al., 1996; Mataro et al., 1997). The basal ganglia have extensive connections with diverse regions of the prefrontal cortex that have been considered to be particularly important in mediating executive functions (Barkley, 1998). Hence, this study indicates that decreased NAA in the lenticular nucleus is associated with dysfunction of the basal ganglia and perhaps executive function deficit. As the ADHD-C subtype show more neural dysfunction than do the ADHD-I subtype, this might explain why externalizing and aggressive behaviour is more predominant in ADHD-C.

Investigation of the Genetics of ADHD subtypes is rare and inconclusive. Rowe et al. (1998) found association between the DRD4 7-repeat allele and ADHD predominantly inattentive subtype as well as with dimensional measures of inattentive symptoms, but not with combined type or hyperactive-impulsive symptoms. However, the DRD4 7-repeat allele has also been found to occur significantly more frequently in ADHD combined type than in controls (La Hoste et al., 1996; Swanson et al., 1998), and in children with ADHD and comorbid conduct problems (Holmes et al., 2002).

Although some studies suggest that the subtypes may have different cognitive deficits, they do not allow for definitive conclusions. Most studies finding differences reveal that ADHD-C have a larger executive dysfunction than ADHD-I. The mixed findings among and within studies highlight the ambiguity of the validity of the current distinction

between the subtypes, and underscore the need for additional data to shed light on the extent to which these ADHD subtypes are closely related or distinct.

Chapter 2

Time Perception

Perception of time is affected in those suffering from ADHD (Barkley et al., 1997; Kerns et al., 2001). This has not, however, been examined amongst the ADHD subtypes to investigate whether there are group differences.

2.1What do we know about time perception?

The neural systems underlying subjective perception of time are of increasing interest for neuroscientists (Koch et al., 2002). Various factors may influence perceived passage of time, such as age, boredom, working memory loads, time of day, body temperature, mood, and the pharmacological action of many drugs (Greenson, 1953; Kuriyama et al., 2003).

There are many theories of the multiple processes involved in determining how subjective perception of time is mediated. The majority of theories of prospective timing comprise similar components, including an internal timekeeper, attention and memory (e.g.Gibbon et al., 1984; Matell & Meck, 2000).

The most popular theoretical model of timing uses a clock metaphor, namely the temporal information-processing model proposed by Gibbon et al. (1984). This model was expressed within the framework of the scalar timing theory and had initial success in the area of animal timing. It has more recently been used to explain human timing in different temporal tasks (Allan & Gibbon, 1991; Weardon & Grinrod, 2003). The theory proposes that the temporal processor, also called the timer, relies on four interrelated devices: a clock, a working-memory store, a reference memory store, and a comparator. The clock consists of a pacemaker, which emits pulses during the temporal interval, and a switch, which is driven by external stimuli (i.e. through attention to something) and with a certain latency controls access to an accumulator, which sums the pulses. The pacemaker continuously emits pulses at regular intervals and is hypothesized to determine clock speed. The emitted pulses are accumulated and can be used to determine the amount of time that has passed. If the rate of accumulation of these pulses is increased, the organism will overestimate the passage of time and under-produce a target interval. If the rate of accumulation of these pulses is decreased, the organism will underestimate the passage of time and overproduce a target interval. A comparator contrasts the value stored on the current trial in the accumulator, which is transmitted to working memory (within this short-term repository interval representations are maintained and manipulated in accord with current goals; for example, comparing two intervals of time)(Baddeley, 1986), with the values stored in reference memory on previous trials. The response is determined on the basis of this comparison, i.e. the temporal judgement relies on a comparison between the content of working memory (Short Term Memory) and a representation of the duration store in reference memory

(Long Term Memory). Instability in reference memory is hypothesized to lead to decreased precision (greater variability in timing responses and, hence, a less defined distribution of timing responses) by generating random errors in timing ability across the range of possible timing responses (Meck, 1983). Furthermore, Perbal et al. (2003) conclude that episodic memory could be involved in the reproduction of durations that exceed the short-term capacity.

The importance of attentional factors in adults' time perception is well established (e.g. Brown, 1985; Curton & Lordahl, 1974; Underwood & Swain, 1973; Zakay & Tsal, 1989). The attentional model views time estimation as a direct function of the amount of attention that is allocated for processing the passage of time. The less we attend to the temporal properties of a stimulus, the more likely we are to misperceive its duration (Coull, 2004). The less attentional resources resources are directed towards time, the shorter the perceived duration can appear (Brown, 1997; Hicks et al., 1976; Macar et al., 1994). Increased attentional allocation, to either a particular moment in time or to the time dimension in general, enhances behavioural performance (Coull, 2004). When attention is diverted, a systematic shortening of subjective duration occurs, implying that pulses from the timekeeper may be lost (Rao et al., 2001). Attention may also mediate the flexible starting and stopping of pulses from the timekeeper, which enables anticipation of predictable events (Zakay & Block, 1996). The effect of distraction on time reproduction has met with varying results with children. In one study it caused a shortening of the reproductions in control children (Zakay, 1992), yet in another it did not

affect the accuracy of control children, and resulted in longer reproductions by ADHD children (Barkley et al., 1997).

It is asserted therefore that the subjective perception of time emerges from the combination of the various component processes of timekeeping, attention mechanisms and memory functions. Support for these mechanisms comes from diverse areas of research, yet the issue of the number and 'location' of internal timekeeping processes is still widely debated.

2.2 Neuropsychology of Time Perception

Fuster (1997) states that the prefrontal cortex is critical for the temporal organization of goal-directed actions. Temporal organization is associated with three cognitive functions: attention; short-term memory, and motor set (i.e. planning). All three are interrelated and widely distributed in the brain, and therefore non-localizable. All three, however, have a prefrontal component that serves prospective action. Patients who have suffered orbital prefrontal lesions exhibit distractibility, i.e. attention is abnormally attracted by irrelevant sensory stimuli, relevant stimuli are neglected, while attention to background stimuli is enhanced (e.g. Chao & Knight, 1996). This implies failure of an inhibitory control mechanism. One of the most consistent and characteristic of all attention disorders from prefrontal damage is the inability to maintain concentration on any given trend of action or thought. Because the maturation of perceptual and motor attention are eminently prefrontal processes, it is logical to suppose that their failure in childhood is attributable

to a deficit in the normal development of the prefrontal cortex. Accordingly, the attention deficit in ADHD is due to abnormal neural development, more specifically, a lag in the development of the prefrontal cortex (Chelune et al., 1986; Kinsbourne, 1973).

Single-unit recording studies done with monkeys provide evidence of a role of prefrontal cortex in timing (Niki & Watanabe, 1979). Nichelli et al. (1995) argue that a reference memory system for time intervals is positioned in the dorsolateral frontal cortex. Research by Koch (2002) indicates that the right dorsolateral prefrontal cortex could be involved in the evaluation of long time intervals. Patients with lesions of the frontal lobe are impaired in discriminating time durations (Nichelli et al., 1995). The difficulties that these patients have in temporal integration of behavioural sequences have been demonstrated by a large number of neuropsychological tests (Shallice, 1982). It is most apparent in tests that require internal programming of new behaviour (Shallice, 1982). The Tower of London has been considered a test of planning and as such, used on frontal patients. (Shallice, 1982) Patients with such lesions also perform poorly on the Porteus Maze Test (Porteus, 1950) - a test of planning and impulsivity. These measures have been used as tests of inhibition in ADHD children (Carte et al., 1995) along with other measures such as the Matching Familiar Figures Test (Kagan et al., 1964) - a test of impulsivity.

The basal ganglia and lateral cerebellum have been logical candidates for hypothetical timekeeping operations, as damage to these brain regions commonly disrupts behaviours that depend upon precise timing, such as rhythmic movements in Parkinson's disease

(PD) (Yokochi et al., 1985) and regulation of agonist-antagonistic muscle activity (for example, dysmetria) in cerebellar damage (Manto, 1996). Although these movement abnormalities could be attributed to disruption of more generalized motor execution functions, the basal ganglia and cerebellum do seem to mediate time perception. Studies of PD patients (Artieda et al., 1992; Harrington et al., 1998) and pharmacological investigations in animals have argued that timekeeping operations are regulated through dopamine neurotransmission in the striatum. Time estimation 'the internal clock' is abnormally slow in PD (Pastor et al., 1992). The hypothetical internal clock is running at a slower rate than that set by the external tempo, leading to large errors in production of the time intervals by patients with PD. Following administration of levodopa / carbidopa, a significant improvement in time estimation and reproduction has been observed by these patients (Pastor et al., 1992). Animal research has further led to the conclusion that dopamine antagonists, such as haloperidol, and agonists, such as methamphetamine, respectively decrease and increase the speed of the internal clock (Pastor, 1992). Whal and Sieg (1980) and Tysk (1983) have reported that chronic sufferers of schizophrenia (also a disorder of the frontostriatal system) overestimate the duration of short time intervals, and that this overestimation can be reversed by treatment with neuroleptics.

Rao et al. (2001) provide evidence for the involvement of the basal ganglia in formulating representations of time. Activation in the right putamen and caudate were uniquely associated with encoding time intervals. These results corroborate studies in PD showing that dopaminergic treatment improves motor timing and time perception. The results are in agreement with converging avenues of research implicating a perceptual

system in which the basal ganglia acts as a timekeeper that is tightly coupled with an attention system in the right inferior parietal cortex. The distinct evolution of activation in the bilateral premotor and right DLPF (dorsal lateral prefrontal cortex) systems, together with previous neuroimaging studies, provides evidence for different working memory functions underlying time perception.

Human lesion studies indicate that the lateral cerebellar hemisphere and its primary output, the dentate nucleus (Casini & Ivry, 1999; Ivry et al., 1988; Ivry & Keele, 1989; Malapani et al., 1998; Mangels et al., 1998), are also involved in timekeeping mechanisms. Focal lesion investigations in animals and humans have shown that the frontal and parietal lobes are also essential for accurate time perception, perhaps due to their purported attention and working memory functions (Casini & Ivry, 1999; Harrington et al., 1998; Meck et al., 1987). Frontal patients have difficulty in reconstructing the time sequence of a series of events or in making judgements concerning the temporal order of a series of consecutive stimuli (Mangels et al., 1997). The level of activation over dorsolateral prefrontal regions has been found to be predictive of performance on a time reproduction task; activity level was inversely related to the accuracy of the produced interval (Casini & Macar, 1996a)

Further evidence that estimation of time depends strongly on memory mechanisms, is indicated by several reports revealing a severe distortion of temporal processing in amnesic patients (Kinsbourne & Hicks, 1990; Richards, 1973; Shaw & Aggleton, 1994; Williams et al., 1989). Amnesic patients can judge short durations precisely, but

consistently underestimate long durations. These results have been mainly interpreted as being due to memory dysfunction. Initially, underestimation of long durations was explained by a failure in a 'long-term temporal integrator' (Richards, 1973) or an inability to evaluate accurately durations exceeding the span of short-term memory (Williams et al., 1989).

2.3 Variability in Time Perception

Instability in reference memory is hypothesized to lead to decreased precision (greater variability in timing responses and, hence, a less defined distribution of timing responses) by generating random errors in timing ability across the range of possible timing responses (Meck, 1983). Shaw and Aggleton (1994) have suggested that impaired temporal performance is not only due to long-term memory, but also the result of frontal dysfunction, which is common in Korsakoff patients. These patients exhibit an important variability in temporal judgements, which is consistent with the assumed relationship between frontal functions and attentional capacity (Baddeley, 1986). This variability or fluctuation in performance in such individuals is not simply 'noise' but rather an important measure of impairment (Stuss et al., 2003).

TBI patients generally exhibit frontal dysfunctions (Stuss et al., 1989). Pouthas and Perbal (2004) have found that TBI patients are more variable in both time reproduction and time production tasks than controls. Further, variability in time reproduction correlated with working memory and processing speed measures (reaction time). Variability in time production correlated with processing speed measures only. I.e. there

is a relationship between temporal variability, processing speed and working memory. TBI patients time reproductions and productions were not less accurate than those of controls. Therefore the authors suggested that the pattern of variability found in TBI patients might not reflect deficits specifically related to timing but rather to generalized attention, working memory and processing speed problems, functions commonly thought to be controlled by the frontal cortex and hence this temporal variability is related to defective frontal lesions.

Stuss et al. (2003) found that intra-individual variability is significantly increased in patients with focal frontal lesions compared to controls and patients with non-frontal lesions. It is increased particularly in those with left and right dorsolateral frontal lesions and those with superior medial frontal lesions. Patients with inferior medial lesions, however, have normal levels on Intra-individual variability, indicating that increased Intra-individual variability is not simply due to brain damage. Stuss et al. (2003) asserts that variability is related to executive control of the deployment of attentional resources.

2.4 Time and Attention

A functional magnetic resonance imaging (fMRI) (Coull et al., 2004) study found that increasing attention to time improved timing performance and this coincided with increased activation of the anterior portion of the SMA (preSMA), right premotor and prefrontal cortices, right temporal cortex, bilateral intraparietal sulcus, and putamen. Coull (2004) found that the frontal operculum (ventrolateral premotor cortex) plays a pivotal role in the interaction between time and attention. This area was activated while

orienting attention to specific moments in time, selectively attending to, and estimating time. It was also activated when attentional resources were limited by time itself. Coull et al. (2004) suggest that increased attention to time allows more accurate processing of temporal pulses throughout the stimulus duration by enhanced neural activity in functionally specialised areas.

2.5 Development of Time Perception

Droit-Volet & Wearden, (2002) assert that developmental changes in timed behaviour are caused by changes elsewhere than in the internal clock, for example at the level of processing of the temporal information, such as attention to time, or memory for temporal information--processes that have previously been shown to exhibit developmental changes (Droit-Volet & Rattat, 1999; Gautier & Droit-Volet, 2002; Rattat & Droit-Volet, 2001). They assert this because children as young as three appear to have a functioning internal clock, which can be 'speeded up' in the same way as has been demonstrated in previous studies with both humans and animals. The operation of the presumed internal clock appears to be independent of age. Studies have examined the influence of age on the ability of children to time events (Droit-Volet, 1998; McCormack et al., 1999) with mixed results. Droit-Volet (1998) demonstrated that 3-year-old children made a significantly smaller percentage of correct responses than 5-year-old children did when required to press a lever and hold it down for either 5 or 10 seconds. In another study (Droit-Volet, 2001) young children as young as 3 years old were able to discriminate durations from hundreds of millisecondss up to 8 seconds in either temporal

generalization tasks or bisection tasks, and children's temporal sensitivity tended to increase as they got older. Research on the ability of 4.5-, 7-, and 11-year-old children to make a response that was between 2.5 and 7.5 seconds in duration found a small increase in the number of successful responses for 11-year-old children compared with 4.5-year-old children (Pouthas et al., 1990).

There has been very little research regarding the association of sex or intelligence with timing ability in children. One study found no significant differences between preschool-aged boys and girls when they were required to produce a 15 second interval (Friedman, 1977) Research on sex differences in timing ability in adults has produced conflicting results. Typically, no effect of sex is found in timing ability (Carlson & Feinberg, 1970; Marmaras et al., 1995). However, when sex differences are found, males typically are more accurate than females (Tracy et al., 1998). In humans, there are significant correlations between simple and choice reaction times and measures of IQ (Sen et al., 1983). In addition, response latencies for a variety of operant behavioral tasks also correlate significantly with measures of IQ (Paule, Chelonis, et al., 1999). It has also been demonstrated that there is a significant positive correlation between the number of correct timing responses in a time production task and intelligence in children; however, the magnitude of this correlation was only .26 (Paule, Meck, et al., 1999).

2.6 Assessment of Time Perception

A variety of approaches have been developed in attempts to assess the ability of humans and nonhumans to time events in the seconds-to-minutes range. These approaches

normally fall into one of three categories: time production, time estimation, or time reproduction.

Time production procedures have been used to assess the ability of humans and nonhumans to time events. In these procedures, participants are told or trained to make a response for a specified duration or to refrain from making a response for a specified duration. Variations of fixed interval schedules of reinforcement and differential reinforcement of low rate (DRL) schedules are often used to assess time production in nonhuman subjects (Dietrich et al., 1998; Jaldow et al., 1990; Stein, 1977). These procedures have been used extensively to assess timing ability in children (Cappella et al., 1977; Droit-Volet et al., 1998; Paule, Meck, et al., 1999) and adults (Bauer et al., 2001; Marmaras et al., 1995).

In time estimation procedures, an auditory or visual stimulus is presented for a specific duration. The participant is asked to attend to the stimulus and to verbally report his or her perceived duration of the stimulus. Given that this type of task requires a verbal response, it has been used only with human participants. However, discrimination procedures for assessing time estimation have been developed for use in both human and nonhuman subjects (Barnes et al., 2000). In time discrimination procedures used in humans, a target stimulus of fixed duration is presented, after which the participant must determine whether the duration of a comparison stimulus is the same as or different from that of the target stimulus (Barnes et al., 2000). Discrimination procedures used for measuring time estimation in nonhuman subjects involve training the subjects to make one response after the presentation of a short-duration stimulus and another response after

presentation of a long-duration stimulus. After successful training under this procedure, the stimuli of intermediate durations (probe or test stimuli) are presented, along with the original two stimuli (training stimuli). The subjects are then to indicate whether the test stimulus was more like the short or the long training stimulus (Meck, 1983; Wada, 1997).

The third type of procedure used to assess timing ability involves time reproduction (Barkley et al., 1997; Zakay et al., 1984). This procedure is a combination of time estimation and time production. Specifically, a target stimulus is presented for a fixed amount of time after which the subject is supposed to make a response of the same, or nearly the same, duration. This procedure has been used to assess timing ability in children with and without behavioral disorders (Barkley et al., 1997; McCormack et al., 1999) and in adults (Zakay, 1984). It has also been used to examine the effects of stimulant medication on timing ability in children (Barkley et al., 1997; Meaux et al., 2003).

2.7 Time Perception and ADHD

Deficits have been found in children with Attention Deficit Hyperactivity Disorder (ADHD) on tasks of time reproduction, time production and motor timing, implicating a deficit in temporal processing abilities (Barkley et al, 1997; Cappella et al., 1977; Dooling-Liftin, 1997; Kerns et al., 2001; Meaux & Chelonis, 2003; Senior et al., 1979; White et al., 1979). In addition to time perception, neuropsychological studies have identified a wide range of cognitive deficits in ADHD, including impairments on measures of response inhibition, sustained attention, working memory, and conceptual

reasoning. These deficits, like time perception, have been associated with abnormal functioning of the prefrontal cortex, basal ganglia, neocerebellum (Bush et al., 1999; Casey et al., 1997; Castellanos et al., 2001), and parietal cortex (Sowell et al., 2003).

Investigators have noted a trend in which children with ADHD tend to overestimate the target time duration at smaller intervals, and underestimate it at larger intervals. What constitutes a small or large duration fluctuates between studies, as a variety of intervals have been used across studies. For example, Barkley et al. (1997) found that ADHD children significantly overestimated at 12 and 24 second intervals, but underestimated at 36, 48 and 60 second intervals. More recently McInerney et al. (2003) discovered that ADHD children tend to over-produce significantly more than controls between 2 and 9 second intervals but underproduce 12 and 17 seconds intervals. Nevertheless, all studies consistently find that ADHD groups display significantly more variability (over-and under-estimations) in their performance than controls.

Impaired time estimation in hyperactive children was initially tested by way of a simple time estimation task (Cappella et al, 1977). This involved the experimenter dropping a ball to indicate the start of the interval and asking the child to drop another ball after a certain amount of time had elapsed (15-, 30- or 60-sec intervals). Both hyperactive and control children made larger errors (longer estimations) the longer the interval to be estimated, but the hyperactive children made significantly larger time estimations than the control group. This test was followed up by another time estimation task using a timer, where the child was instructed to press a button switch to begin a time interval (7,

15 , or 30 seconds) and then press it again to signal the end of the interval. The findings replicated the first study, with hyperactive children making significantly larger and longer errors of estimation than controls. Cappella et al. (1977) suggested that treatment programs with the objective of increasing hyperactive children's attention spans take the finding of impaired time perception into account.

Between this and a study by Barkley and coworkers in 1997 there does not appear to be any investigation in the literature of ADHD and time perception, although it has been discussed (Gerbing et al., 1987; White et al., 1994). As noted in Chapter 2, Barkley (1994) claimed that sense of time and working memory are deficient in ADHD as a result of poor behavioural inhibition. Barkley and colleagues initiated testing this contention in 1997. In this study, time reproduction was investigated using a time reproduction task, which had previously been used by Zakay (1992) to assess sense of time in normal children. This task involved the child lighting a flashlight on a box to reproduce the duration of time (12, 24, 36, 48 or 60 seconds) a display light had been lit by the experimenter.

Both ADHD and control children showed an increase in the inaccuracy of their reproduction of time intervals as the length increased, with ADHD children making significantly larger errors than controls. ADHD children significantly overestimated at 12 and 24 second intervals, but underestimated at 36, 48 and 60 second intervals relative to controls. This study also investigated the effect of distraction on time reproduction in ADHD, using the same task but with a jack-in-the-box figure causing distraction in half

of the trials at each duration (12, 24 36, 48, or 60 secs). This increased the likelihood of overestimating time reproductions at the 12- and 36- second intervals, but for the ADHD group only. This result differed to Zakays' (1992) findings with control children; where distraction shortened their reproductions. Finally, the effect of medication (methylphenidate) on time reproduction was examined, but no improvement in size of reproduction errors was found.

Kerns et al. (2001) attempted to explore Barkley's (1994) model of ADHD and his findings of deficient time perception in ADHD (Barkley et al., 1997) further, by examining time reproduction and its relationship to inhibition, attention and working memory. She used a computerized light bulb task to measure time reproduction of time intervals (2,5,6,9,12 or 17 seconds). There was a significant relationship between time reproduction and measures of inhibition (Go/No Go task and and CPT- β) but not the Stroop task (a measure of verbal inhibitory capacity). The former relationships indicated support for Barkley's Model (1994). There was also a significant relationship between time reproduction and CPT (a measure of attention). Kerns et al. (2001) found no difference between ADHD and control groups on the Working Memory Game or the Self-Ordered Pointing Test. In fact the ADHD group performed slightly better than controls on the latter, although not significantly. Furthermore, there was no relationship found between working memory and time reproduction in this study, a relationship which had been suggested by Barkley's (1994) model of ADHD but had not previously been formally tested.

If a subjective sense of time is causally linked to working memory, as Barkley (1994) states, it would be expected that performance on working memory tasks and time reproduction task would be correlated. Kerns et al. (2001) findings are perhaps further confusing, as a neural network comprising prefrontal and parietal regions in working memory (areas also found to be activated during time estimation tasks), is well documented (Goldman-Rakic, 1996; Mohl & Pfurtscheller, 1991). There has been much inconsistency in ADHD children's performance on working memory measures. Gorenstein et al. (1989) found differences on the sequential matching memory task. Shue & Douglas (1992) reported group differences between ADHD and control groups on the self-ordered pointing task, whereas Scheres et al. (2004) reported no group differences on this task. Siegle & Ryan (1989) reported no differences between ADHD with hyperactivity and controls on the sentence and counting span tasks, but did find young children (7-8 yr olds) diagnosed with ADHD without hyperactivity performed worse than controls on the sentence span task. An older group (9-13 yrs) failed to show significant differences. Kuntsi et al. (2001) found no significant differences between groups on the counting span task. They found a difference between a community sample of hyperactive children and controls on sentence span, but only when IQ was not controlled for, and suggested that poor performance on working memory tasks in children with hyperactivity is a consequence of low IQ.

Sonuga-Barke et al. (1998) investigated the relationship between time estimation and response inhibition in hyperactive and non-hyperactive children. The results supported the notion that hyperactive children tend to underestimate long time intervals compared

to control subjects, and it was suggested that this was due to an aversion to delay which appears to be a feature of ADHD (Sonuga-Barke et al., 1992), rather than an issue of a deficiency in response inhibition. In Sonuga-Barke et al. (1998) study, children performed a discrete trials intertemporal response task under two conditions. Under both conditions children had to respond within a 2 second window, which was delayed for a set period (either 5 or 15 seconds). In condition one (signalled condition), these response requirements were signalled by changes in the expression of a face drawn on a computer screen (i.e. inter-temporal response requirements were signalled and inhibition but not temporal estimation was required). In condition two (unsignalled condition), always presented on the trial following the signalled condition, these changes in expression were obscured by a hand drawn over the mouth of the face so that effective performance depended on the childs ability to estimate the point at which the facial expression changed on the preceding trial (i.e. inter-temporal response requirements were left unsignalled and good performance required both accurate time estimation and effective response inhibition). Hyperactive children significantly underestimated at both intervals compared to controls. Both groups of children had little difficulty inhibiting responses when the response requirements were signalled. All children made far more errors under the unsignalled condition.

Sonuga-Barke et al. (1998) argued that as a consequence of delay aversion, hyperactive children are especially sensitive to situations with marked temporal characteristics where time appears to drag. In turn, it is to be expected that when the subjective experience of time changes in this way, then hyperactive children will systematically underestimate the

actual interval required. Sonuga-Barke et al. (1998) argued that the underproductions using this task could also have been due to differences in visual structure between standard and reproduction intervals, whereby the less structured visual masking might have precipitated premature responses rather then true temporal underestimations.

Smith et al. (2002) explored time perception in ADHD children using a range of time perception tasks in different temporal domains. Time estimation was tested in a verbal estimation task of 10 seconds. No group differences were found for the verbal time estimation tasks. A temporal discrimination task was also conducted which aimed to determine the idiosyncratic threshold of minimum time interval (in milliseconds) necessary to distinguish two intervals differing by approximately 300 milliseconds. Children with ADHD were significantly impaired in their time discrimination threshold: on average, time intervals had to be 50 ms longer for the hyperactive children in order to be discriminated when compared with controls. Smith et al. (2002) suggested these children may have a perceptual deficit of time discrimination, which may only be detectable in brief durations which differ by several hundred milliseconds.

Time reproduction was also acquired for two time intervals of 5 and 12 seconds. For the 5 seconds time reproduction task a bomb appeared on the screen and exploded after 5 seconds. The child was asked to hold a key down as quickly as possible to activate sprinklers to put the fire out and was told that this would only work if the key was held down for exactly the same amount of time that the bomb had been on screen before it had exploded. No group differences were found for this task. The 12 seconds task was a

variant on the reproduction task used by Sonuga-Barke et al. (1998). Smith et al. (2002) aimed to minimise differences in visual stimulation, found in Sonuga-Barke et al's (1998) task by introducing visual targets in both parts of the task. In the standard part of the task, a succession of 'enemy' planets was presented to the child passing along a screen towards a window. After 12 seconds a clearly identifiable target 'planet earth' arrived in a window at the lower corner of the screen and the child was instructed to land on the planet by pressing a key when the planet entered the window. In the second part of the task, the child was instructed to try to land again on the target 'planet earth' but this time, all the enemy planets were disguised as 'planet earth'. The child had to remember how long it took to travel there in the first part of the task, in order to land on the right planet. Children with ADHD responded earlier on this task, which however only approached significance after controlling for IQ and short-term memory. However, when these reproductions were divided into either early correct or late responses, the ADHD group made significantly more early and fewer correct responses, while showing a trend for fewer late responses.

Smith et al. (2002) concluded that children with ADHD perform poorly on time reproduction tasks, not because of an intrinsic time perceptual problem, but because time reproduction tasks load heavily upon processes such as working memory, short-term memory, impulsiveness, attention deficits and especially motivational delay aversion (based on Sonuga-Barke et al's 1998 findings). They did not, however, test these assertions. Furthermore, Kuntsi et al. (2001) did not find a group difference on a delay aversion measure after controlling for conduct disorder and suggested that co-occuring

conduct disorder problems explain most, if not all, of the association between hyperactivity and delay aversion.

Toplak et al. (2003) investigated time perception and comorbid reading disability (RD) in children and adolescents diagnosed with ADHD. They evaluated duration discrimination (determine which if two intervals is the longest-a target duration of 400ms versus a comparison duration) and duration estimation (reproduction of 400ms, 2000 ms or 6000ms) using psychophysical tasks on computer. In the duration discrimination task children with ADHD and ADHD + RD were significantly less able to discriminate among durations in the 400ms range, compared to age-matched controls. In the duration estimation task all groups overestimated at the 400ms interval, and underestimated the 2000ms and 6000ms intervals. The ADHD+RD group made significantly longer reproductions at the 400ms interval, and significantly shorter reproductions at the 6000ms interval, than both of the other groups. The ADHD and control group did not differ in their reproductions. Both ADHD groups were more variable than the control group at the 2000ms and 6000ms intervals. The ADHD+RD group was more variable than both of the other groups at the 400ms interval. The adolescent group displayed slightly different results. In the duration estimation task, the adolescents with ADHD+RD were less able to discriminate among durations in the 400 ms range compared to the adolescents with ADHD and the age-matched controls. In the duration estimation task, all groups overestimated at the 400ms and the 2000 ms intervals and underestimated at the 6000 ms interval. The ADHD+RD group were significantly less precise than the other two groups at the 400ms interval, but not for the other intervals. The ADHD+RD group was more

variable than the other two groups at the 400ms interval. Both ADHD groups were more variable than the control group at the 2000ms and 6000ms intervals. The ADHD+RD adolescent groups displayed significantly lower scores than the other adolescent groups on working memory measures (Digit Span Forwards and Backwards), and these measures were found to be significant predictors of performance on the duration discrimination task. Estimated Full-Scale IQ and teacher reported hyperactive/ impulsive behaviours were found to be significant predictors of performance on the duration estimation task at the 400ms interval. The authors (Toplak et al., 2003) suggest that development with age influences time perception abilities, as overall, the adolescent groups displayed better performance on the measures than did the children.

Several studies have shown that ADHD children will apply themselves better to tasks to earn tokens, money or gifts (Abramowitz et al., 1987; Baer & Nietzel, 1991). Slusarek et al. (2001) found support for this using a Stop Signal paradigm; ADHD children performed worse than control children in a low incentive condition but comparably in a high incentive condition. Oosterlaan & Sergeant (1998) claim that ADHD childrens' performance relies more heavily on the presence of response contingencies and rewards than does the performance of normal children, and that a motivational deficit underlies poor response inhibition.

McInerney et al. (2003) examined whether motivation impacted on time reproduction, and furthermore whether it would differentiate between children with ADHD and matched controls. Two types of time reproduction task were used; 1) a regular light bulb

time reproduction task (a picture of a light bulb appeared on a computer screen for intervals between 3 and 17 seconds and had to be reproduced by the child), and 2) an enhanced time reproduction task, where firstly after each trial a cute animated rhinoceros walked across the screen and hurled a sham score onto the upper portion of the screen accompanied by words such as 'awesome') and secondly children were told they would receive a prize from a large attractively wrapped gift box located plainly in sight if they attained a high score. They were also told that if they did not a get a very high score they could still pick a prize, from a much smaller, more plainly decorated gift box. On the regular light bulb time reproduction task ADHD children performed less accurately than did control children, with a tendency towards overestimating at short intervals (3,5,6 and 9 second intervals) and underestimating at longer ones (12 and 17 second intervals). Control children also tended to underestimate at longer intervals, but their performance was comparatively consistent across trials. The ADHD children's performance did improve when doing the enhanced time reproduction task, but their performance was still significantly poorer than controls. It is not clear which factor of the enhanced task caused ADHD children to improve; the prize, the animated rhinoceros, the positive feedback, or a combination of all.

This study also found that time reproduction was dependent at least in part on working memory (tested using Children's Size-Ordering Task, Digit Span Backwards, Children's Paced Auditory Serial Addition Task, Sentence Span Measure) and response inhibition (tested using Stop Signal Task), in addition to motivation, but that something else other

than these factors might be in part responsible for the deficit in time reproduction in ADHD children.

2.8 Aims of the current thesis

Thorough examination of published research investigating the time deficit in ADHD reveals that there still remains an over-riding question that has not yet been answered, namely; why is there a perception of time deficit in ADHD? Before this can be answered, there are a number of smaller yet pressing micro-questions to be answered.

First, can a deficit in time reproduction actually be measured reliably? Investigators have not, to date, discussed piloting or securing the reliability of their measures. As this has not been done, these researchers cannot rightfully assert that their results definitely represent an actual deficit.

Second, none of the studies have selected their participants based on the separate ADHD subtypes, instead they have either examined only those who fit the criteria for ADHD-C children, or alternatively have used the blanket term of ADHD to refer to all of their participants. As discussed in the first chapter of this thesis, it is possible that including a mixture of ADHD subtypes, and not distinguishing the subtypes in comparison to controls, could possibly be hiding some core differences between the subtypes. Previous comparisons of the two subtypes demonstrate that impairments in executive function are

particularly present in ADHD-C (e.g. Houghton et al., 1999). Making this distinction may well teach us more about the disorder, the processes involved, and future treatment.

Third, the effect of MPH on the time deficit in ADHD has been examined and has not been found to ameliorate the deficit. Nevertheless, referring back to the first micro-query; if time reproduction tasks have not undergone strict assessment of reliability, the results cannot be interpreted as evidence of a real time deficit. Hence, the examinations of the effect of MPH on time reproduction must be completed again, using a reliable measure.

Fourth, the supposed time deficit in ADHD has been linked to a number of executive functions, including response inhibition and working memory. Barkley (1994) claimed sense of time is linked to working memory, and that both sense of time and working memory are deficient in ADHD as a result of poor behavioural inhibition. This contention is still unclear based on examination by Kerns et al. (2001). Further, investigators have not taken consideration of the obvious impact of a deficit in sustained attention, of which ADHD people are reported to have (Manly et al., 1999; Shallice et al., 2002), on time reproduction.

The current thesis attempts to probe all of the above micro-queries, having evolved from examination of research conducted on time perception in ADHD to date.

Chapter 3

Development of time reproduction measures and reliability study

3.1 INTRODUCTION

As stated in chapter 2, investigators have noted a trend in which children with ADHD tend to overestimate the target time duration at smaller intervals, and underestimate it at larger intervals (Barkley et al., 1997; McInerney et al., 2003). What constitutes a small or large duration fluctuates between studies, as a variety of intervals have been used across studies. For example, Barkley et al (1997) found that ADHD children significantly overestimated at 12 and 24 second intervals, but underestimated at 36, 48 and 60 second intervals. More recently McInerney et al. (2003) discovered that ADHD children tend to over-produce significantly more than controls between 2 and 9 second intervals but underproduce 12 and 17 seconds intervals. Nevertheless, all studies consistently find that ADHD groups display significantly more variability (over-and under-estimations) in their performance than controls.

None of the studies investigating time reproduction in ADHD have to date tested or discussed the reliability of their measures of time reproduction, despite time intervals varying between studies. The lack of reliability estimates for these measures could be a possible explanation for the inconsistency of results to date. The purpose of the current

study was therefore to conduct test-retest reliability with a set of control children on a time reproduction task.

3.1.1 Test-retest reliability

Test-retest reliability measures the results of two or more ratings of the instrument to the same subjects, under similar conditions, by the same rater after a certain interval. It is measured by looking at whether a respondent receives an equivalent score on the same (or a parallel) instrument at two different points in time, where you would not expect the time interval or what occurs during the interval to impact performance. Because tests for reliability are concerned with the degree of consistency between scores that are obtained at two or more independent times of testing, they are generally expressed in terms of correlation coefficients. Reliability coefficients (usually designated as *r*) range from a low of .00 to a high of 1.00. The closer to 1 the coefficient is, the more reliable the tool. It has been frequently suggested that the researcher needs to exercise caution regarding the length of the time interval (Standards for Educational and Psychological Testing, 1999). On the one hand, the subjects' recall of items can spuriously inflate the reliability coefficient. On the other the phenomenon being investigated may change over time. Test-retest is ultimately designed for measuring persisting traits, as opposed to measuring varying traits.

3.1.2 Methods used to study Time Perception

Three distinct kinds of tasks have generally been used in research to measure a person's sense of time. These are; time estimation, time production and time reproduction. In time estimation paradigms, subjects are presented with a temporal duration and must verbally report its perceived duration. In time production paradigms, subjects are told verbally a length of time, and must reproduce the duration in some way. Children identified as hyperactive have demonstrated impairments in both time production (Senior et al., 1979) and in time estimation (White et al., 1979).

Time reproduction or reproduction of durations is a method frequently used to study time estimation in humans. The reproduction method comprises two phases: (i) the presentation of the duration (of a visual stimulus, of an auditory stimulus, or of an interval between two flashes or two clicks): (ii) the reproduction of the duration proper. The subject has to evaluate and store the duration in order to reproduce it accurately.

3.1.3 Why use Time Reproduction ?

Although time production tasks appear to be easiest to perform, they are the least likely to assess one's subjective sense of time as one is given a verbal numerical standard to use in producing the time interval (Barkley et al., 1997). Time reproduction tasks are typically the most difficult, and are believed to measure one's subjective sense of time most accurately relative to the other methods (Zakay, 1990). In general, it has been observed that both children and adults make errors of progressively longer magnitudes when

estimating or reproducing time intervals as the target time interval increases (Brown, 1985; Michon & Jackson, 1984; Zakay, 1992).

3.1.4 Distraction

The effect of distraction on time reproduction has met with varying results. In one study it caused a shortening of the reproductions in control children (Zakay, 1992), yet in another it did not affect the accuracy of control children, and resulted in longer reproductions by ADHD children (Barkley et al., 1997). In the current study, a time reproduction task with a distraction element was also devised to assess this. Test-retest reliability was performed with a set of control children.

3.1.5 Reaction Time

As noted earlier (see chapter 2), many investigators of the topic of time perception in ADHD have found that ADHD participants overestimate the target time duration at smaller intervals. Working memory has been used as an explanation for this finding as it is assumed to be involved in storage and retrieval of time information (Nichelli et al., 1995). Adults with ADHD have showed lower performance and more variability on measures of reaction time compared to control groups (Leth-Steensen et al., 2000; Tinius, 2003) and ADHD children display significantly slower reaction times (Kerns et al., 2001). Therefore slower reaction time might be causing the overestimations at the small

intervals. A test was devised to explore this and test-re-test reliability was performed with the same group of control children.

3.1.6 Aim of current study

To explore test-retest reliability on a time reproduction task, a time reproduction task(with distraction), and a reaction time task using a group of 'normal' children.

3.2 METHOD

3.2.1 Participants

44 control children (8-13.5 years old; Mean = 10.47, SD = 1.27; Mean IQ = 104.8, SD = 10.9) were recruited from primary schools in the Dublin area. All children had been screened previously for dyslexia on The Dyslexia Screening Test (D.S.T.)(Fawcett & Nicolson, 1996). While the group of 44 control children were recruited for the purposes of establishing the reliability of the time reproduction paradigm employed in the present study, a subset of 25 of these control children (20% female) (8-13 years; Mean=10.1years, SD=1.2; Mean IQ=102.5, SD=10.5) were selected on the basis of being matched to the ADHD participants on age and gender. All were in good physical health, with no known cognitive or behaviour problems. Children who had an IQ score below 70 were excluded.

3.2.2 Materials and Procedures

Task 1: Time Reproduction Task

Design

It was proposed to develop an objective test of the perception of time. This computerized task was based upon that developed by Zakay (1992). The displayed icons comprised simple geometric primitives of varying colour. A graphics 3D API (provides a set of object-oriented interfaces that support a simple, high-level programming model to build, render, and control the behavior of 3D objects and visual environments) was chosen to do this. Programming was developed using Visual MS C++ so that the application could work on Microsoft windows 98, to allow presentation of stimuli and collection of data in different settings on the same machine (home or school). The icons varied in either colour (either red, green, blue, yellow, magenta, cyan, and white) or shape (sphere, cube, cylinder, diamond, dodecahedron, and cone) and were displayed against a black background.

The shapes were chosen based on their level of interest – it was important that no icon was any more interesting than another. To avoid confusion, it was also important that no unique icon was used twice throughout the trials. It was therefore necessary to have 30 unique icons, varying in either colour or shape. The icons were displayed against a black background. An example of the use of icons can be seen in figure 3.1.

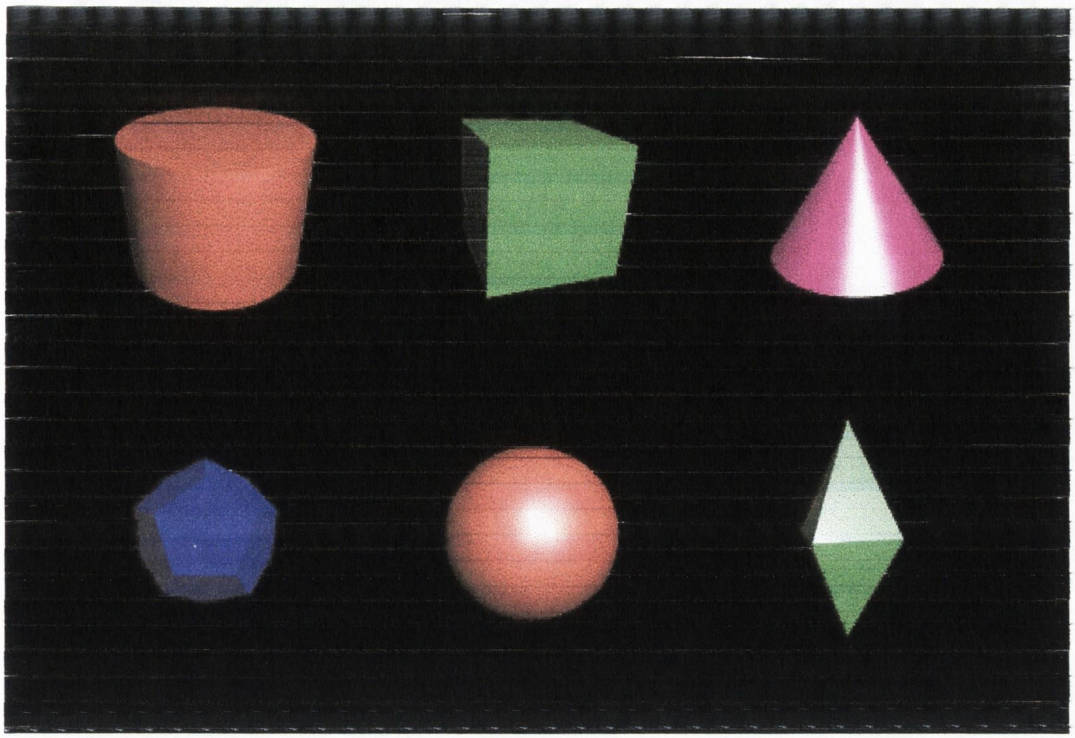


Figure 3.1: Icons used In Time Reproduction Task

Icons were displayed for periods of 2,4,6,8,10,12,24,36,48,60 seconds, with three trials per time period, presented in a randomised order. These time periods were chosen in order to cover a wide array of time intervals, and to inspect whether responses would differ based on the range of time used. Each presentation was preceded by a 2 second instruction: "*A new shape will appear... try to remember how long the shape stays on the screen*" (see figure 3.2).

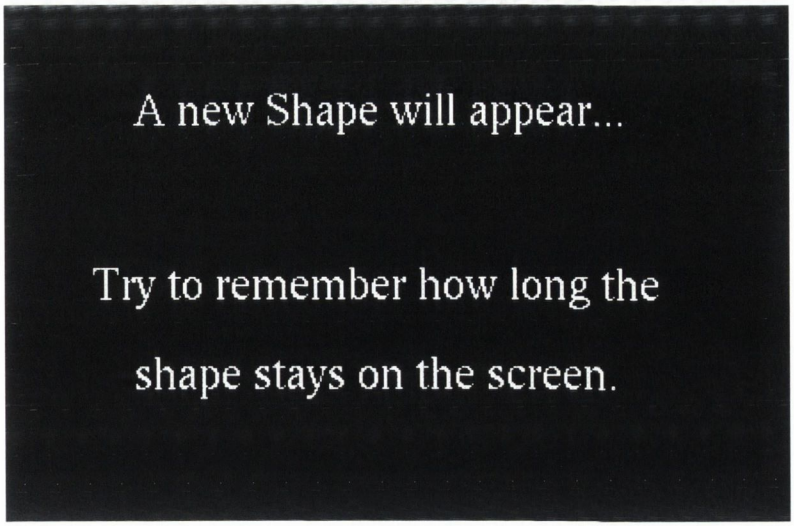


Figure 3.2: Example of Text used in Time Reproduction Task

Subsequently an icon appeared for the duration of the display period (as above). After a 2 second screen blank a new instruction was displayed: "*Click to see the shape again. Click again when it should disappear*". As instructed, the child clicked the mouse button once to make the icon reappear and then, after estimating the appropriate time interval, again to terminate its display. Encouraging feedback that was not contingent upon performance ('*well done*') was displayed before the next trial.

The Time Reproduction Task was preceded by 5 practice trials to make sure that the child understood the demands. Subsequently the child performed 30 trials (3 trials by 10 time periods). All participants completed the Time Reproduction Task twice, 7 days apart. The task was programmed to last for approximately twenty-two minutes (however, this would vary based on whether the child tended to underproduce/ overproduce intervals). They were tested individually in a quiet room either at home or in school.

Time Reproduction Task Dependent Measures

Absolute discrepancy score

The absolute discrepancy score was calculated as the absolute value of the magnitude of the discrepancy between the participant's time reproduction and the interval presented to the child. This provided a measure of the magnitude of the time-reproduction error made by the children, regardless of the direction of the error (under- vs. overestimate). It is possible, both within and between participants, for errors to vary on either side of the sample interval presented to the child. If absolute values were not employed, variations around the sample duration could average out across trials or individuals to create means that reflect a higher degree of accuracy of the time reproductions than may actually be the case. Absolute discrepancy scores provide a clearer picture of accuracy in time reproductions regardless of the direction in which subjects are making errors.

Accuracy coefficient score

The accuracy coefficient score is used to determine whether the participants tend to err in one direction more than the other (under-vs. over-estimates) in the time reproductions. This score is obtained by dividing each of the participant's time

reproductions by the time duration of the sample interval presented on that trial. Using such a coefficient, scores of 1.00 equal perfect reproduction of the sample interval, scores above 1.00 reflect overproductions, and scores below 1.00 reflect underproductions.

Intra-individual Variability

This is defined as the standard deviations for the absolute discrepancy scores and accuracy coefficient scores respectively.

Task 2: Time Reproduction with Distraction Task

This test used all the characteristics of the time reproduction task but with a flashing light (a distractor) occurring on half of trials in random order. The distractor was presented at the halfway point of a trial (i.e., after half the time period had elapsed) and appeared for one second. It did not occur at the point of reproduction of the interval. The Time Reproduction with Distraction Task was preceded by 5 practice trials to make sure that the child understood it, before proceeding. All participants completed the measure twice, 7 days apart. They were tested individually in a quiet room either at home or in school.

Time Reproduction with Distraction Task Dependent Measures

The raw time reproductions were converted into scores as for the Time Reproduction Task

Task 3: Onset-offset detection task

This test used all the characteristics of the time reproduction task, minus the time estimation element: children were simply told to respond when they saw a shape appear, and respond again when it disappeared. This task is therefore somewhat analogous to simple reaction time tasks, with the insertion of a variable delay period. All elements of the time reproduction task remained constant, other than the time estimation element, in an attempt to investigate the effect of reaction time on time reproduction i.e. whether over- or under-estimations are a result of a deficit in reaction time. An instruction, "Click when you see a shape..." was displayed for 2 seconds. Subsequently, an icon appeared, as in the reproduction task (i.e. time intervals were displayed in random order), along with the instruction: "Click when this disappears". The child had to press the mouse button for the program to record the reaction time (RT) for both onset and offset. If the child did not press the button the task continued regardless. A blank screen was displayed for 2 seconds and the next interval appeared. Participants were instructed to respond as quickly as possible when they saw the shape appear or disappear.

The Onset-Offset detection task was preceded by 5 practice trials to make sure that the child understood it, before proceeding. All participants completed the measure

twice, 7 days apart. They were tested individually in a quiet room either at home or in school.

Onset-offset detection task Dependent Measures

Individual RTs were recorded for onset and offset detection. From these scores average reaction times were calculated for the onset detection and for the offset detection. Intra-individual Variability, defined as the standard deviations for the reaction times was also examined.

3.3 RESULTS

3.3.1 Task 1: Time Reproduction Task

Establishing task reliability

Rather than using ten separate time periods, three main scores for low, medium and high time periods were used to make the analysis less cumbersome. Past research has found inconsistent over- and under-estimations on all the time periods used. In the current study the time periods between 2 and 10 seconds were grouped together as the direction of deviation was generally an overestimate at these time periods. The time periods of 12 as far up as 60 seconds were generally underestimated and thus could have been grouped as one time interval. However, it was felt that there was too much spread between these numbers and therefore they were split up into a medium (12-24 seconds) interval and a

high (36-60 seconds) interval. Each interval consisted of the mean score of the time periods in that interval. Absolute discrepancy scores, accuracy coefficient scores, and intra-individual variability for both of these scores were calculated for the three classes of intervals: - 2-10 s (low), 12-24 s (mid) and 36-60 s (high) respectively. 44 control children repeated the time reproduction task 7 days apart (SD = 2.2). Pearson correlations were calculated to look at test-retest reliability and also to investigate whether there was a relationship between each time interval and IQ.

Absolute Discrepancy Score (size of error)

Pearson correlations calculated for the *absolute discrepancy score* were as follows: low, $r = .636$, $p<.01$, 2-tailed; $r^2=.40$; mid, $r = .502$, $p<.01$, 2-tailed; $r^2=.25$; high $r = .686$, $p<.01$, 2-tailed; $r^2=.47$.

Pearsons correlations calculated between *absolute discrepancy score* and IQ revealed no significant correlations: low interval and IQ ($r = -.113$, $p= .499$, 2-tailed); mid interval and IQ ($r = -124$ $p= .468$, 2-tailed); high interval and IQ ($r = -.120$, $p=.473$, 2-tailed).

Intra-individual Variability for *absolute discrepancy scores* (variability in size of error)

Pearson correlations calculated for Intra-individual Variability for *absolute discrepancy scores* were low, $r = .785$, $p< .0005$, 2-tailed; $r^2=.62$; mid, $r = .013$, $p<.953$, 2-tailed; and high, $r = .421$, $p<.05$, 2-tailed; $r^2=.17$.

Accuracy Coefficient Score (direction of error)

The *accuracy coefficient score* correlations were: low, r = .538, p< .01, 2-tailed; r^2=.29; mid, r = .449, p<.01, 2-tailed; r^2=.20; and high, r = .420, p<.01, 2-tailed; r^2=.18.

Pearsons correlations calculated between *accuracy coefficient score* and IQ revealed no significant correlations: low interval and IQ (r = .043, p= .795, 2-tailed); mid interval and IQ (r = .203 p= .221, 2-tailed); high interval and IQ (r = .009, p= .958, 2-tailed).

Intra-individual Variability for *accuracy coefficient score*(variability in direction of error)

Pearson correlations calculated for Intra-individual Variability for *accuracy coefficient score* were low, r = .509, p< .015, 2-tailed; r^2=.25; mid, r = .160, p<.476, 2-tailed; and high, r = .629, p<.01, 2-tailed; r^2=.39.

Table 3.1: Test-Retest Reliability: performance across 2 testing session in size of error

		1st Test Session	2nd Test Session
2- 10	Mean	.5736	.6851
	St. Deviation	.438	.603
12-24	Mean	4.590	3.990
	St. Deviation	4.281	4.129
36-60	Mean	5.547	8.215
	St.Deviation	3.351	6.027

There was no evidence of practice effects across the testing sessions.

3.3.2 Task 2: Time Reproduction with Distraction

Establishing task reliability

To establish reliability, 44 control children were given this task on two occasions a mean of 7 (SD 2.2) days apart. It was planned to analyse the distraction data using the same time intervals (2-10secs, 12-24 secs and 36-60 secs) as in the previous analysis with the time reproduction task. However, due to technical difficulties with the program, it was not possible to extrapolate data in the necessary way. The program did not record all three trials at each time period. As there were only two trials being measured at each time period it was decided to create a composite score (2-60 seconds) across the distraction scores to examine test-retest reliability.

Mean scores were calculated across all intervals and Pearson correlations calculated for the reliability of these scores across the two occasions. There were significant correlations for the *absolute discrepancy score* ($r = .460$, $p < .05$, 2-tailed; $r^2 = .21$) and for the *accuracy coefficient score* ($r = .432$, $p < .05$, 2-tailed; $r^2 = .18$).

3.3.3 Task 3: Onset-Offset Detection Task

Establishing task reliability

To establish reliability, 44 control children were given this task on two occasions a mean of 7 (SD 2.2) days apart. Scores were calculated for onset and offset RT, and Pearson

correlations calculated for the reliability of these scores across the two occasions. The correlations were as follows: 'onset' detection, ($r = .492$, $p < .05$; 2-tailed; $r^2 = .24$) and 'offset' detection ($r = .702$, $p < .0005$; 2-tailed; $r^2 = .49$).

Table 3.2: Test-Retest Reliability: performance across 2 testing session on Onset-Offset detection

		1st Test Session	2nd Test Session
Onset	Mean	.8420	.7631
	St. Deviation	.2496	.2975
Offset	Mean	.6286	.6050
	St. Deviation	.1409	.1155

Intra-individual variability scores were also calculated for this task and test-retest reliability was established onset' detection, ($r = .438$, $p < .05$; 2-tailed; $r^2 = .19$) and 'offset' detection ($r = .780$, $p < .0005$; 2-tailed; $r^2 = .61$).

3.4 DISCUSSION

This study investigated test-retest reliability on a time reproduction task, a time reproduction with distraction task, and an Onset-Offset Detection (Reaction Time) task The findings of this study suggest that the three tasks have considerable reliability.

The time reproduction tasks' four main dependent measures of absolute discrepancy score, Intra-individual Variability for absolute discrepancy scores, accuracy coefficient score, and Intra-individual Variability for accuracy coefficient score had moderate to high reliability. The mid time interval (12-24 secs) failed to achieve reliability at the Intra-individual Variability for absolute discrepancy score or the Intra-individual Variability for accuracy coefficient score.

The time reproduction with distraction tasks' two main dependent measures of absolute discrepancy score and accuracy coefficient score had moderate reliability.

The onset-offset detection task showed moderate to high reliability at the mean reaction time scores and the intra-individual variability score of both the onset and offset phases.

These correlations are all in the positive moderate to high range and therefore it was deemed sufficient to proceed with further testing of ADHD children (ADHD-C and ADHD-I) in comparison with each other and in comparison with a control group. Further analysis in the next chapter (chapter 4) allowed a more valid investigation of the

hypothesized links between the domains of time reproduction, sustained attention, spatial attention and response inhibition.

Chapter 4

Time Reproduction (Group Comparison - ADHD groups vs. matched controls)

4.1 ***INTRODUCTION***

4.1.1 Time Perception in ADHD

Time perception is a complex cognitive process linked to basal ganglia, prefrontal cortex and cerebellar functioning (Casini & Ivry, 1999; Ivry & Keele, 1989; Rao et al., 2001). These areas of the brain have consistently been implicated in the pathophysiology of ADHD. Frontal and parietal lobes are also linked to time perception, perhaps due to their attention and working memory functions (Casini & Ivry, 1999; Meck & Church, 1987). Furthermore, timekeeping operations may be regulated through dopamine neurotransmission in the striatum (Artieda et al, 1992; Harrington et al, 1998) and dopamine dysfunction within this region may be key to the pathophysiology of ADHD (Dougherty, 1999) and the efficacy of stimulant medications, such as methylphenidate (Krause et al, 2003).

ADHD children manifest deficits in time reproduction, time production and motor timing, with a tendency to overestimate small time periods and underestimate long ones (Barkley et al., 1997; Kerns et al., 2001; Meaux & Chelonis, 2003; Smith et al., 2002). Overestimation at short intervals (milliseconds) also occurs following prefrontal cortical, basal ganglia and cerebellar lesions (Casini & Ivry, 1999). Underestimation at long

intervals has been associated with deficient inhibitory control mechanisms (Kerns et al., 2001), poor working memory (Rubia et al., 1999b), motivational deficits (McInerney et al., 2003) and delay aversion (Sonuga-Barke et al., 1998).

4.1.2 What causes Impaired time perception in ADHD ?

As Discussed in Chapter 1, a recent theoretical model of ADHD (Barkley, 1994, 1997) argues that the central deficiency in the disorder is one of impaired behavioural inhibition. This impairment is believed to result in secondary deficiencies in four executive functions that contribute to self-regulation. These are (1) working memory and sense of time, (2) self-regulation of emotional and motivational states, (3) the internalization of speech, and (4) reconstitution, or the formation of novel, complex behavioural sequences. Barkley (1997) suggests that individuals with ADHD, because of a deficit in working memory, should manifest a developmental delay in the psychological sense of time and should therefore perform like younger, non-ADHD individuals on tasks that assess sense of time. For example, young children without developmental disabilities appear to perceive time as progressing more slowly than do older children. Given the limited storage capacity of attentional and working memory systems, the more an individual must allocate attention to nontemporal information, the less they can allocate to temporal processing and so the less accurate (shorter) their sense of time will prove to be. Conversely, the more attention a person allocates to temporal processing, the longer a temporal duration appears to become. Should distractions occur during the processing of

the passage of time, thereby commanding nontemporal attentional resources, greater errors in time perception are to be expected (Zakay, 1992).

Some early investigations (Fraisse, 1963; Gerbing et al.,1987) showed that poor response inhibition is associated with deficits in sense of time, particularly on time reproduction paradigms. Less inhibited individuals make greater errors than more inhibited ones, frequently under-reproducing the duration (Gerbing et al., 1987; Levine et al, 1959). Nevertheless, Rubia et al (1999b) did not find a consistent tendency in ADHD boys to respond prematurely on a time discrimation task.

Most of the research suggests that impulsive individuals, such as those having ADHD, given their related difficulties with distractibility and attention, should manifest greater impairments in sense of time than nonimpulsive ones. This seems conceivable considering the overlap of brain structures and functions involved in both ADHD and in the perception of time, namely, prefrontal cortex, basal ganglia, and neocerebellum (Bush et al., 1999; Casey et al., 1997; Casini & Ivry, 1999; Castellanos et al., 2001; Ivry & Keele, 1989; Rao et al., 2001). It is also consistent with the opinions expressed by parents of children with ADHD, who often rate their child's use of time in daily life as significantly more impaired than do parents of children without ADHD (Barkley, 1990).

In comparison to the assertion made regarding a slow cognitive tempo (Barkley, 1997; Goddard, 2000), Wilson & Hernstein (1985) theorized that a 'present orientation' characterized by a rapid cognitive tempo and shortened "time horizon" underlies

impulsive, disinhibited behaviour. A number of studies have shown that subjects with a history of antisocial behaviour have difficulty on tasks designed to assess time estimation abilities (Barratt & Patton, 1983).

Cappella (1977) was the first to suggest that there is actually a deficiency in sense of time in ADHD compared to controls. She found that the differences between estimated and elapsed time were larger for hyperactive children than for normals, with the differences between the groups increasing with the length of the interval to be estimated. Barkley et al (1997) confirmed that the ADHD condition creates impairment in the capacity to accurately reproduce temporal durations relative to control children.

Barkley hypothesizes that deficits in working memory, and particularly in non-verbal or spatial working memory, should lead to deficits in one's subjective sense of time. This is based on the hypothesis that retaining a sequence of events in working memory, and making comparisons among the events in the sequence, leads to a sense of temporal continuity (Michon & Jackson, 1984). Working memory processes, however, are susceptible to disruptive or distracting events (Zakay, 1992) and must be protected from interference. Barkley (1997) hypothesized such protection to be provided by the behavioural inhibition system. In this model the expression of impulsivity may be linked to individual differences in the perception and understanding of time (White et al, 1994; Gerbing et al., 1987).

Evidence in support of Barkley's (1997) model has come from studies demonstrating that working memory appears deficient in children with ADHD. This has been inferred from poor performance on tasks such as mental arithmetic, digit span, Tower of Hanoi, and the imitation of hand movement sequences (Kemp & Kirk, 1993; Mariani & Barkley, 1997; Pennington & Ozonoff, 1996), all of which have been viewed as dependent on working memory.

Kerns et al. (2001) found that Children with ADHD made significantly larger errors in time reproduction than did controls. There were no significant correlations between performance on the time reproduction task and performance on the working memory tasks. This lack of correlation is noteworthy as it is inconsistent with the hierarchical organization inherent in Barkley's (1997) model of ADHD. It suggests that either this study lacked adequate power to observe such a relationship or that these abilities are not necessarily linked. It may be that some minimal level of working memory is required to maintain one's sense of time; in no way, however would this necessarily imply a linear relationship between these two constructs.

Interestingly, Kerns et al. (2001) found a significant relationship between time reproduction and measures of impulsivity and inhibitory control. These relationships, which were predicted by Barkley's model but had never been tested explicitly, have significant intuitive appeal as the 'waiting component' of a time reproduction task requires at least some level of behavioural inhibition. In addition, deficient inhibitory control provides a more parsimonious explanation for the consistent underestimations of

the target time duration than does a limitation of working memory. Kerns et al. (2001) suggest that although some capacity for working memory may be needed to engage in time reproduction tasks, performance on these measures may be influenced most by levels of inhibitory control. In other words, poor performance on time reproduction (and related) tasks may arise not from an inherently disturbed sense of time, but from a more fundamental deficit in inhibitory control, which is required to successfully complete time reproduction tasks.

Kerns et al. (2001) also reported fewer correct hits on Conners' (1995) Continuous Performance (Vigilance) Task (CPT) and a high correlation between this and time reproduction error. She did not however give precedence to them, focusing instead on the time reproduction-inhibition correlations. To date there has been little investigation of a connection between the vigilance and time perception.

Sustained attention is characterized by the subject's readiness to detect rare and unpredictable occurring signals over prolonged periods of time (Sarter et al., 2001). It has been shown that areas of the brain, thought to be connected to sustained attention, are active over periods as short as 40seconds (Pardo et al., 1991), and even 12 seconds (Whitehead, 1991). Areas of brain damage or degeneration have been identified which are correlated with impairments in sustained attention performance (Mesulam, 1990; Paus et al., 1997). In addition areas in the intact brain in which changes in metabolic activity correlate with sustained attention performance have been identified (Pardo et al., 1991). These neuropsychological and functional imaging studies suggest that a modality-

independent attentional network (Posner & Petersen, 1990) is involved in maintaining vigilance, involving the right frontal, locus coeruleus and parietal areas. Right parietal lesions usually have more profound attentional deficits than those with left parietal lesions, specifically in tasks requiring vigilance (Posner & Driver, 1992). Damage to the frontal cortex as well as lesions in the (inferior) parietal lobe, result in increased reaction time, and in the occurrence of a decrement in sustained attention performance over time-on-task. (Rueckert & Grafman, 1996). The judgement of time intervals lasting for several seconds appears to be right lateralized (Mohl & Pfurtscheller, 1991; Petrovici & Scheider, 1994). It is therefore feasible that the finding of underestimation of time intervals could be accounted for by difficulty in sustaining attention for the length of time required.

Event-Related Potential (ERP) studies (Novak et al., 1995; Robaey et al., 1992; Satterfield et al., 1990) suggest abnormalities in ADHD groups in the right frontal region, implicating the alerting (sustained) network. Hynd et al. (1991) and Filipek et al. (1997) also investigated the size of the frontal lobes in groups of ADHD and control children and reported smaller than average right frontal lobes, due to a lack of normal (larger right than left) asymmetry. These areas correspond to Posner and Petersens' (1990) alerting network. Children with ADHD consistently demonstrate deficits on tasks that measure sustained attention. They commit more errors on CPT tasks compared to control subjects (Seidel & Joshko, 1990) and get lower age-scaled scores on the sustained attention factor of the Test of Everyday Attention for Children (TEA-Ch) (Dobler, 2003; Heaton et al, 2001; Manly et al, 1998).

Although the importance of attentional factors in time perception is well established (e.g. Brown, 1985; Curton & Lordahl, 1974; Underwood & Swain, 1973; Zakay & Tsal, 1989) the methods used by investigators of time perception in ADHD (see above), have to date rarely taken account of sustained attention in their research. Practically all tasks used to measure frontal lobe function involve the ability to sustain attention to some extent, and it is very difficult to quantify, a priori, the degree to which a particular task will require, and can measure sustained attention (Rueckert & Grafman, 1996). Therefore it is conceivable that a test such as that of time reproduction, is similar to any other measure which examines the higher brain functions.

The neural substrates of the spatial orienting of attention in the human brain have been investigated by both brain imaging (e.g. Corbetta et al, 1993; Gitelman et al, 1999) and neuropsychological studies (see Mesulam, 1990 for review), the results of which suggest a large-scale frontoparietal network of brain regions that support spatial attention. Coull and Nobre (1998) used PET and fMRI to compare the neural systems involved in temporal and spatial orienting of attention, using cues to inform subjects when and/or where peripheral target stimuli would occur. There was considerable overlap between the activations seen in the two tasks in frontal and parietal regions.

Due to the purported link between the symptoms of ADHD, the frontal and parietal areas of the brain, and the effect of disruption to the dopaminergic system, one cannot restrict a theory of deficient time reproduction to dysfunctions in inhibition or working memory. It is necessary to investigate areas such as Posner & Raichle's (1994) alerting network and

the alleged relationship of temporal orienting, spatial attention and sustained attention to clarify further whether deficient time reproduction actually exists in the disorder. It is feasible that performing a time reproduction task requires sustained attention to keep on task as this domain has been found to be active during periods of 40 secs and less (Pardo et al., 1991). Alternatively, attention and timing appear to be interrelated functionally and therefore one cannot exist without the other. Koch et al. (2002) states that one cannot exclude a contribution of defective attentional control to a patient's poor time estimates. As stated earlier, when attention is diverted, a systematic shortening of subjective duration occurs (Rao et al., 2001).

In addition, because ADHD appears to be the result of neurological dysfunction and the behavioural nature of the subtypes is different, it make sense that neuropsychological differences may exist which might be echoed in a test of time perception, and have not to date been examined.

4.1.3 Variability

One of the themes running through the more recent studies appears to be that of variability in ADHD (Smith et al., 2002; Toplak et al., 2003). Unusually high response variability is a feature of ADHD (Castellanos & Tannock, 2002). Toplak et al. (2003) noted that intra-individual variability was most noticeable on a time estimation task in children who have ADHD with comorbid reading difficulties but also asserted that the variability seen in the duration estimation task is non-specific to timing, and is a reflection of variability in attentional focus. Smith et al. (2002) reported a trend for

greater variability in their ADHD sample in the responses for their 12 seconds reproduction task. These findings are in line with other studies where hyperactive children are found to be more variable in their speed and are generally slow and inaccurate in responding, for example, on the stop task (Kuntsi et al., 2001; Sergeant et al., 1999). Leth-Steensen et al., (2000) suggest that abnormal variability in reaction times (RT) across a variety of cognitive tasks may signify executive problems in top-down allocation of attention. Oosterlaan & Sergeant, 1996 assert that it indicates a lack of consistent effort. It may also explain poor control of motor timing (Rubia et al., 2003). Despite the relevance of performance variability to time reproduction few studies have directly examined this phenomenon, especially at the higher intervals.

Of particular interest to the current study, Hynd et al. (1989) discovered that ADD-H (with hyperactivity) children performed significantly more slowly and variably than controls on several speeded classification tasks whereas the ADD-WO (without hyperactivity) group did not (Hynd et al., 1989). It should be noted that all studies mentioned in this chapter have tested composite groups of ADHD children, with an emphasis on ADHD-C, without allowing for subtype comparisons. As there are inconsistent findings regarding neuropsychological, behavioural and cognitive differences between the ADHD subtypes, the present study examines, for the first time, whether there are subtype differences in time reproduction.

4.1.4 Aims of current study

The current study aimed to compare ADHD-C and ADHD-I subtypes, relative to matched controls, on three measures; 1) time reproduction task, 2) time reproduction with

distraction task and 3) onset-offset detection tasks. Comparisons on these tasks included analysis of intra-individual variability. The effect of reaction time on time reproduction was measured, as ADHD children often display slower reaction times than controls (Pennington & Ozonoff, 1996), and this could have an effect on their estimations at short time periods. Finally, it was hypothesized that the ADHD-C and ADHD-I subtypes would differ on at least some of these measures.

4.2 METHOD

4.2.1 Participants

Twenty children with Attention Deficit Hyperactivity Disorder Combined Type (ADHD-C) were recruited from Child Guidance Clinics and from ADHD Family Support Groups (Age 7.1 - 13.6 (Mean = 9.8, S.D. = 1.8;16% female). The mean estimated full scale IQ (Block Design and Vocabulary short form of the WISC-III) (Sattler, 1992) was 95.9 (SD = 14.13). Parents completed Conners' Parent Rating Scale-Revised Long Version (CPRS-R:L) (Conners, 1998), yielding a mean Conners DSM-IV score of 80.6 (SD 8.6) (see Table 4.1).

Nineteen children meeting DSM-IV (American Psychiatric Association, 1994) criteria for ADHD Inattentive Type (ADHD-I) were also recruited (age 7.7 -13.7 (mean = 10.4, S.D. = 1.95; 20% female); mean estimated full-scale IQ of 95.2 (SD = 11.9); mean Conners' DSM-IV score 71.3 (SD = 10.2) (see table 4.1).

While the two patient groups differed in the frequency of Conduct Disorder, with this being more frequent in the ADHD-C group (χ^2=4.265,df =1, p= .047), they did not differ significantly in the proportion having Comorbid Reading Disability (RD), ODD, Depression or anxiety disorder. They differed significantly on the Conners DSM-IV hyperactive/impulsive subscale (t= 4.53, df =37, p<.0005), thereby perhaps providing further confirmatory evidence for the subtype difference (see Table 4.1 below).

A subset of 25 of the original group of control children (N =44; see chapter 3) (20% female) (8-13 years; Mean=10.1years, SD=1.2; Mean IQ=102.5, SD=10.5) were selected on the basis of being matched to the ADHD participants by age and gender (see table 4.1). All were in good physical health, with no known cognitive or behaviour problems. Children who had an IQ score below 70 were excluded.

The three groups (ADHD-C vs. ADHD-I vs. Controls) did not differ in terms of age [F=1.608, p< .207], but did in terms of mean estimated full-scale IQ [[F=3.202, p< .048] , with the control group scoring higher.

Table 4.1. Demographic Characteristics and Clinical variables of ADHD and control groups

	ADHD-C (N=20)		ADHD-I (N=19)		Controls (N=25)	
	M	SD	M	SD	M	SD
Age (years,months)	9.8	1.83	10.4	1.95	10.1	1.2
Gender (% male)	84		80		80	
Estimated IQ	95.9	14.13	95.2	11.87	102.5	10.5
Conners hyp/imp	81.66	9.57	66.86	11.09		
Conners Inattentive	76.3	9.01	71.5	12.76		
Conners DSM-IV	80.6	8.6	71.3	10.2		
% Reading Disorder	16		11	0		
% Conduct Disorder	8		4			
% ODD	4		0			
% Depression	2		1			
% Anxiety	0		0			

Notes: **ADHD-C** = attention deficit hyperactivity disorder combined subtype; **ADHD-I** = attention deficit hyperactivity disorder inattentive subtype; **Conners hyp/imp**: Conners DSM-IV Hyperactive-Impulsive: High scores indicate above average correspondence with the DSM-IV diagnostic criteria for Hyperactive-Impulsive type ADHD; **Conners Inattentive**: DSM-IV diagnostic criteria for Inattentive type ADHD; **Conners DSM-IV**: DSM-IV diagnostic criteria for combined Inattention and Hyperactive-Impulsive type ADHD; **ODD** = Oppositional Defiant Disorder

4.2.2 Materials and Procedures

All ADHD children were diagnosed by a psychiatrist as either ADHD-C or ADHD-I using DSM-IV diagnostic criteria (Diagnostic and Statistical Manual, 1994). Confirmatory research diagnoses were made using the Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al., 1995).

The Child and Adolescent Psychiatric Assessment (CAPA) (Angold et al., 1995)

This is a semi-structured, investigator based interview designed to assess emotional and behavioural symptoms of clinical severity, and allows DSM-III, DSM-IV, and ICD-10 diagnoses for all child psychiatric disorders other than the pervasive developmental disorders. For the purposes of this study, the ADHD section and sections containing assessment for the most common comorbid disorders associated with ADHD (ODD, CD, Depressive Disorder, Anxiety Disorder) were used. The CAPA has been used in large epidemiological studies (e.g. the Virginia Twin Study of Adolescent Behavioural Development, Eaves et al. 1997). The CAPA is a rigourously operationalised interview and test-retest reliability for clinical cases shows it to be one of the most reliable of the child psychiatric assessment instrument.

Additionally, the Child Attention Deficit Hyperactivity Disorder Teacher telephone interview (CHATTI) (Holmes et al., 2004) was used to assess ADHD

symptoms and associated impairment in the classroom setting, thus fulfilling DSM-IV requirements for symptom pervasiveness.

Behavioural and IQ

Conners Parent Rating Scale (Long Version)(CPRS-R) (Conners,1998)

The Revised Conners Parent Rating Scale (CPRS-R; is a 57-item parent-rated measure of cognitive problems, oppositional behaviour, hyperactivity-impulsivity, anxious-shy behaviours, perfectionism, social problems and psychosomatic behaviours. Items are rated on a four-point scale from `not at all' to `very much' (see table 4.2). This was used to get a further assessment of differences in subtype symptoms.

Table 4.2: CPRS-R Subscales

A.	Oppositional	Are likely to break rules, have problems with authority, are easily annoyed.
B.	Cognitive Problems/ Inattention	Are likely to be inattentive, have organizational problems, have difficulty completing tasks, have concentration problems.
C	Hyperactivity	Have difficulty sitting still for very long, feel restless and impulsive
D.	Anxious/ Shy	Have atypical amount of worries and fears; prone to be emotional and sensitive to criticism, anxious in unfamiliar situations, are shy and withdrawn.
E	Perfectionism	Set high goals for themselves, are very fastidious about the way they do things, are obsessive about their work.
F	Social problems	Are likely to perceive that they have few friends, have low self-esteem and self-confidence, feel socially detached from their peers
G.	Psychosomatic	Report atypical amounts of aches and pains
H	Conners' ADHD Index	Identifies children/ adolescents "at risk" for ADHD
I	Conners' Global Index Restless-Impulsive	Indicates restlessness, impulsivity and inattentiveness.
J	Conners' Global Index Emotional Lability	Individuals with high scores are prone to more emotional responses/ behaviours (crying, anger,etc.) than is typical.
K	Conners' Global Index Total	Reflects general problematic behaviour. High scores tend to indicate hyperactivity, but often the problems are broader than this
L	DSM-IV Inattentive	High scores indicate an above average correspondence with the DSM-IV diagnostic criteria for Inattentive type ADHD
M	DSM-IV Hyperactive-Impulsive	High scores indicate and above average correspondence with the DSM-IV diagnostic criteria for Hyperactive-Impulsive type ADHD
N	DSM-IV: Total	High scores indicate and above average correspondence to DSM-IV diagnostic criteria for combined Inattention and Hyperactive-Impulsive type ADHD

Wechsler Intelligence Scale for Children – III (WISC-III)

A two sub-test short version from the revised Wechsler Intelligence Scale for Children (Wechsler, 1991) was used to estimate IQ (Block Design and Vocabulary). These combined sub-tests correlate .91 with the full administration of the WISC-R (Sattler, 1992) and are the most reliable subtests in predicting full-scale IQ (Groth-Marnat, 2003). Children who had an IQ score below 70 were excluded.

Time Reproduction Measures

1) Time Reproduction Task- See previous chapter for description

2) Time Reproduction with Distraction Task - See previous chapter for description

3) Onset-Offset Detection Task - See previous chapter for description

Medication was withdrawn at least 24 hours prior to testing. Participants were tested individually in a quiet room either at home or in school.

4.3 RESULTS

4.3.1 Behavioural Scale

The Conners Parent Rating Scale (Long Version) (Conners, 1998) was completed on all children (parents were asked to complete these by judging their responses based on when the child was not taking medication).

Independent t-tests were computed to examine difference in the responses of parents of ADHD-C children compared to parents of ADHD-I children (see table 4.3).

Table 4.3: Comparison of ADHD-C and ADHD-I on Conners subscales

Subscales	t	df	Sig. (2-tailed)
conners oppositional	-2.565	37	.016
conners cognitive problems/innattention	-1.823	37	.079
conners hyperactivity	-4.770	37	.000
conners anxious/shy	-.214	37	.832
conners perfectionisim	-1.874	37	.072
conners social problems	-2.631	37	.014
conners psychosomatic	.476	37	.638
Conners ADHD index	-1.753	37	.091
conners global index, restless-impulsive	-4.312	37	.000
conners global index emotional lability	-2.112	37	.044
conners global index:total	-3.784	37	.001
DSM IV inattentive	-1.330	37	.195
DSM IV hyperactive-impulsive	-4.533	37	.000
DSM IV	-3.098	37	.005

As was expected ADHD-C and ADHD-I children differed on the subscales measuring oppositional and hyperactive behaviour. The ADHD-C children scored significantly higher (more symptoms) than ADHD-I on all of these subscales. The two groups did not differ on the subscales measuring inattention, which makes sense in light of the fact that both subtypes must have at least six symptoms of inattention to meet the individual diagnostic criteria of ADHD-C and ADHD-I.

4.3.2 Time Reproduction Task

Data from the control groups first testing session was used in the following analyses. Eight of the ADHD-C children were tested initially on methylphenidate (see chapter 5) and therefore the data from their second testing session (off methylphenidate) was used for the current analysis. All analyses were initially conducted with the IQ as a co-variate. However when IQ was excluded as a co-variate, the results were not significantly different. It was decided therefore to report the second analysis (i.e. not using IQ as a co-variate) as it was more succinct. An example is provided below.

Absolute Discrepancy Scores

A two-way mixed ANOVA on *Absolute Discrepancy Scores*, with Group as the between subjects factor, Time Interval as the within-subjects factor [3 (Group) X 3 (Time Interval)] and IQ as covariate revealed significant main effects for Group, ($F_{(2,60)}$ = 12.353, $p < .0005$) for Time Interval ($F_{(2,60)}$ = 82.641, $p < .0005$), but not for IQ ($F_{(2,60)}$ =

.865, p= .357). The interaction of Group X Time Interval was significant ($F_{(2,60)} = 8.996$, p< .0005). There was no interaction between Time and IQ ($F_{(2,60)} = .515$, p= .476).

Without using IQ as a covariate, a two-way mixed ANOVA on *Absolute Discrepancy Scores*, with Group as the between subjects factor and Time Interval as the within-subjects factor [3 (Group) X 3 (Time Interval)] revealed significant main effects for Group, ($F_{(2,60)} = 13.629$, p< .0005) and for Time Interval ($F_{(2,60)} = 82.501$, p< .0005). The interaction of Group X Time Interval was significant ($F_{(2,60)} = 8.311$, p< .0005) (Figure 4.1), with controls scoring significantly better than the ADHD groups.

Analysis of simple main effects with Bonferroni corrections showed significant differences in *absolute discrepancy scores* between controls (M = .558) and ADHD-C (M = 1.286) at the low interval (p<.001); Controls (M = 1.870) and ADHD-C (5.578) at the mid interval (p<.005); and controls (M = 5.027) and ADHD-C (16.934) at the high interval (p<.0005) (Table 4.4). Significant differences were also found between controls and ADHD-I (Mean = 1.089) at the low interval (p <.05), and between controls and ADHD-I (M=14.203), at the high interval (p <.01). No significant differences emerged between the two ADHD groups at any time interval (see figure 4.1).

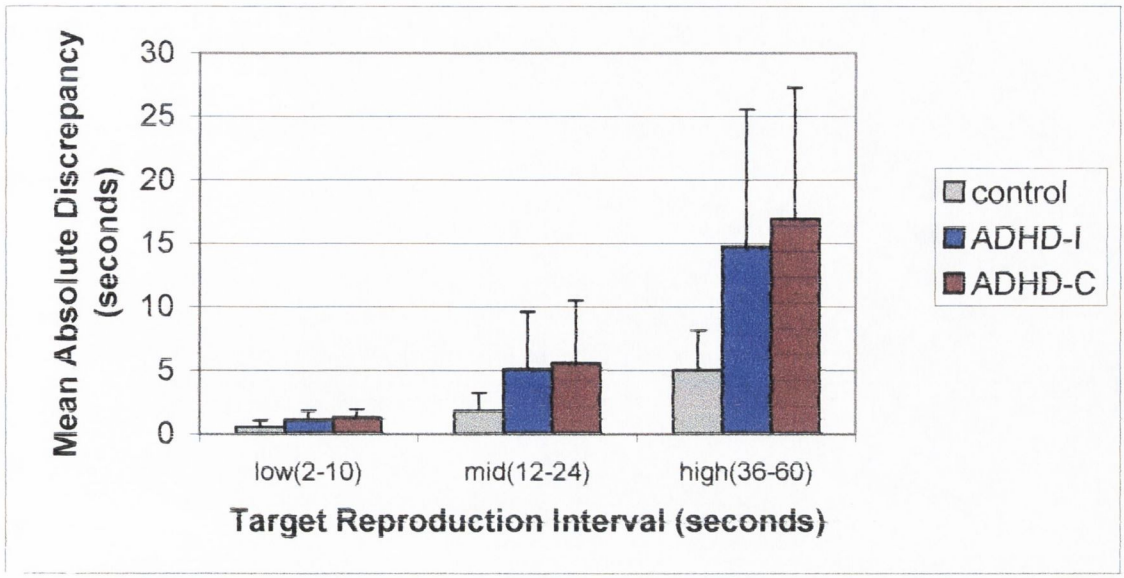


Fig. 4.1. The mean absolute discrepancy scores (size) on the time reproduction task.

Analysis of the *Variability of Absolute Discrepancy Scores* revealed significant main effects for Group ($F_{(2,60)} = 13.403$, $p < .0005$) and for Time Interval ($F_{(2,60)} = 47.413$, $p < .0005$). The interaction of Group X Time interval was significant ($F_{(2,60)} = 6.230$, $p = .0005$).

Analysis of simple main effects with Bonferroni corrections showed significant differences between controls (M = 1.435) and ADHD-C (4.305) in the standard deviations of their absolute discrepancy scores at the mid interval ($p < .05$) and between controls (M = 4.203) and ADHD-C (13.424) in the intra-individual variability of their absolute discrepancy scores at the high interval ($p < .0005$). The ADHD-I group did not differ from controls in their variability at any of the intervals. Importantly, there were significant differences between the ADHD-C (M = 13.424) and ADHD-I (M = 8.089) groups at the high interval ($p < .05$), such that the ADHD-C group were significantly

more variable in their time reproductions relative to the ADHD-I group (Table 4.4). Overall, variability was greater at the higher than the lower intervals for the two ADHD groups, but this was not the case for the control groups.

Accuracy Coefficient Scores

An analogous two-way mixed ANOVA on the *Accuracy Coefficient Scores* revealed significant main effects for Group ($F_{(2,60)} = 3.851$, $p < .05$) and for Time Interval ($F_{(2,60)} = 29.924$, $p < .0005$). The interaction of Group X Time Interval was also significant ($F_{(2,60)} = 5.721$, $p < .005$) (Figure 4.2).

Analysis of simple main effects with Bonferroni corrections showed significant differences between controls (M = .967) and ADHD-C (M = .783) in mean *accuracy coefficient scores* at the mid interval ($p < .05$) and between control (M = .936) and ADHD-C (M = .728) at the high interval ($p < .01$) intervals. Significant differences were also found between controls and ADHD-I (M = .756) at the high interval ($p <. 05$) (Table 4.4). No significant differences emerged between the two ADHD groups at any time interval. Across both ADHD groups, *accuracy coefficient scores* differed significantly between the low and mid intervals and between the low and high intervals; (p's<.0005). The control group did not significantly differ in their *accuracy coefficient scores* between any of the three intervals (see figure 4.2).

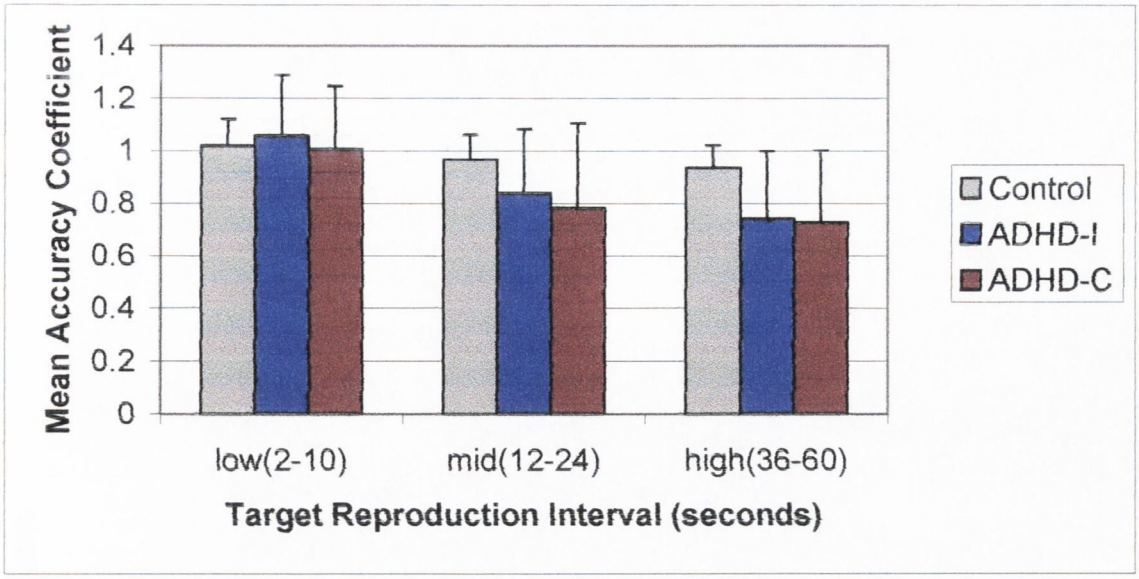


Fig. 4.2. The mean coefficient of accuracy scores (direction of error) on the time reproduction task.

An analysis of the *Variability in Accuracy Coefficient Scores* revealed significant main effects for Group, ($F_{(2,60)} = 7.113$, $p < .01$) and for Time Interval ($F_{(2,60)} = 21.254$, $p < .0005$). The interaction of Group X Time Interval was not significant ($F_{(2,60)} = 1.455$, $p = .220$).

Pair-wise comparisons revealed that the control ($M = .155$) and ADHD-C ($M = .349$) groups significantly differed ($p < .01$), while the control and ADHD-I groups did not ($p > .05$). The low interval produced significantly less variable scores than the mid interval ($P < .0005$) and the high interval ($P < .0005$) (Table 4.4).

Table 4.4. Means and Standard Deviations of scores on Time Reproduction Task for ADHD and control groups

		ADHD-C		ADHD-I		Control	
		M	SD	M	SD	M	SD
Absolute	Low	1.286	.143	1.089	.146	.558	.130
	Mid	5.578	.825	4.537	.846	1.870	.753
	High	16.934	1.939	14.203	1.989	5.027	1.770
Coefficient	Low	1.008	.042	1.095	.043	1.018	.038
	Mid	.783	.052	.854	.054	.967	.048
	High	.728	.049	.756	.050	.936	.045
Var (Ab)	Low	2.088	.474	2.228	.486	1.219	.442
	Mid	4.305	.823	3.435	.844	1.435	.767
	High	13.424	1.375	8.089	1.411	4.203	1.282
Var (Coef)	Low	.545	.095	.514	.097	.253	.089
	Mid	.204	.036	.182	.037	.111	.034
	High	.297	.027	.155	.028	.101	.026

Notes:

Absolute = Absolute Discrepancy Score; Coefficient = Coefficient Accuracy Score; Var (Ab) = Variability in Absolute Discrepancy Score; Var (Coef) = Variability in Coefficient Accuracy Score; Low = Low Time interval (2-10 seconds); Mid = Medium time interval (12-24 seconds); High = High time interval (36-60 seconds)

Pearson's correlations were run using the ADHD children's scores to examine whether those who displayed larger errors also displayed increased intra-individual variability (i.e. between *absolute discrepancy scores* and Intra-individual Variability for *absolute discrepancy scores)* (table 4.5).

Table 4.5: Correlations between *absolute discrepancy scores* and Intra-individual Variability in *absolute discrepancy scores*

	Variability at absolute low interval (2-10 secs)	Variability at absolute mid interval (12-24 secs)	Variability at absolute high interval (36-60 secs)
Absolute error low interval (2-10 secs)	.379*	.420*	.066
Absolute error mid interval (12-24 secs)	.522**	.835**	.052
Absolute error high interval (36-60 secs)	.350*	.313	.530**

* $p < .05$ (N= , two-tailed)

** $p < .01$ (N =, two-tailed)

Additionally, pearsons correlations between the Intra-individual variability scores across the *accuracy coefficient scores* and the *absolute discrepancy scores* were calculated (see Table 4.6).

Table 4.6: Correlations between the Intra-individual variability scores in the *accuracy coefficient scores* and the *absolute discrepancy scores*

	Variability in Coefficient low (2-10 secs)	Variability in Coefficient mid (12-24 secs)	Variability in Coefficient high (36-60 secs)
Variability in absolute low (2-10 secs)	.799**	.584**	-.170
Variability in absolute mid (12-24 secs)	.744**	.718**	-.288
Variability in absolute high (36-60 secs)	-.175	-.139	.766**

* $p < .05$ (N= , two-tailed)

** $p < .01$ (N =, two-tailed)

4.3.3 Time Reproduction with Distraction

As stated in chapter 3, it was originally planned to analyse the distraction data using the three time intervals (2-10secs, 12-24 secs and 36-60 secs). However, due to technical difficulties with the program, it was not possible to extrapolate data in the necessary way. The program did not record all three trials at each time period. As there were only two trials being measured at each time period it was decided to create a composite score (2-60 seconds) across the distraction scores to examine time reproduction with distraction.

Absolute discrepancy scores

Using the *absolute discrepancy scores* (mean across 2-60 seconds) a two-way mixed ANOVA with group as the between subjects variable and distraction phase (without Distraction, with Distraction) as the within subjects variable revealed a significant main effect for group ($F_{(2,60)}$ = 16.655, p<.0005) and for distraction ($F_{(2,60)}$ = 14.849, p<.0005). There was a significant interaction between Group and Distraction ($F_{(2,60)}$ = 4.642., p=.05) (see figure 4.3).

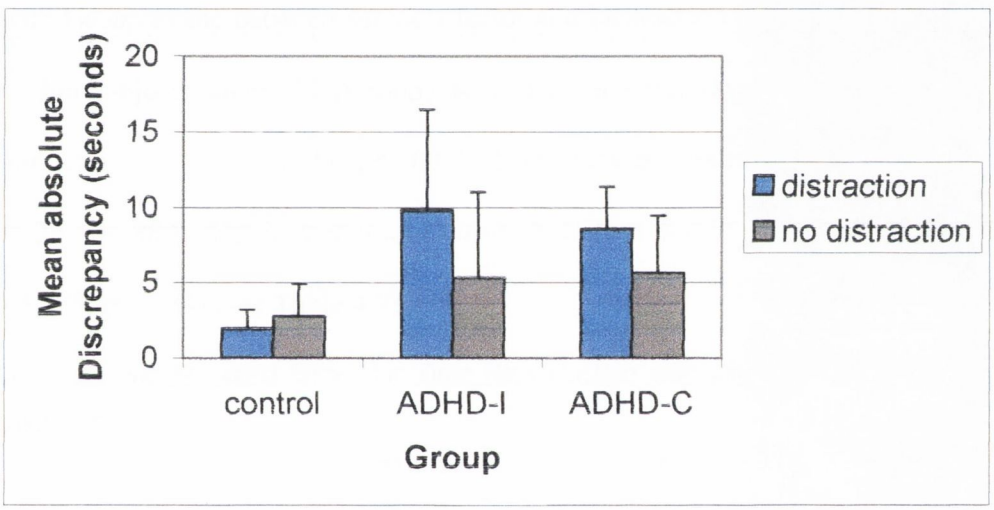


Fig. 4.3. The mean absolute discrepancy scores (size of error) on the time reproduction with distraction task.

Post-hoc t-tests showed significant differences between controls and ADHD-C in their mean absolute discrepancy scores with distraction (p< .0005). Significant differences were also found between controls and ADHD-I (p <.0005). No significant differences between the two ADHD groups emerged (p =.681). The mean responses of

the ADHD groups deteriorated (larger reproductions) with the presence of the distractor. The control group did not demonstrate any difference in the size of their errors ($t = -.800$, $p = .437$) on comparison of the distraction phases (with distraction vs. without distraction). Both ADHD-C ($t = 3.324$, $p < .01$) and ADHD-I ($t = 3.079$, $p < .01$) groups displayed significantly more errors in the distraction phase than the non-distraction phase

Variability in Absolute Discrepancy Scores

A two-way mixed ANOVA analysis of the variability of *Absolute Discrepancy Scores* with Group as the between subjects factor and Distraction (present or not present) as the within-subjects factor [3 (Group) X 2 (Distraction)] revealed significant main effects for Group ($F_{(2,60)} = 9.023$, $p < .001$). There was no main effect for Distraction ($F_{(2,60)} = .023$, $p = .880$). The interaction of Group X Distraction Phase was not significant ($F_{(2,60)} = 2.075$, $p = .137$) (see Table 4.7).

Table 4.7: Mean and Standard Errors for Time Reproduction with Distraction Task (with and without distraction)

		ADHD-Com (N =20)		ADHD-In (N = 19)		Control (N=25)	
Score Type	Distraction	M	SD	M	SD	M	SD
Absolute Discrepancy	On	8.58	2.80	9.82	6.67	1.97	1.24
	Off	5.671	3.81	5.31	5.69	2.76	2.15
Variability in Absolute	On	8.41	5.34	11.17	13	2.66	2.61
Discrepancy	Off	10.2	5.01	7.77	5.55	3.14	3.12
Accuracy Coefficient	On	1.61	.59	1.67	.36	1.08	.08
	Off	1.16	.71	1.34	.69	.93	.06
Variability in Accuracy	On	1.48	2.45	1.37	1.91	.17	.05
Coefficient	Off	1.25	.83	.98	.72	.56	.95

Coefficient of accuracy scores

Using the coefficient of accuracy scores (mean across 2-60 seconds) a two-way mixed ANOVA was performed with group as the between subjects variable and distraction (Without Distraction, With Distraction) as the within subjects variable. This revealed a significant main effect for group ($F_{(2,60)} = 7.701$, $p = .001$) and for distraction ($F_{(2,60)} = 20.579$, $p < .0005$). There was not a significant interaction between Group and Distraction phase ($F_{(2,56)} = 1.997$, $p = .146$) (see figure 4.4). All groups overestimated when a distraction was present.

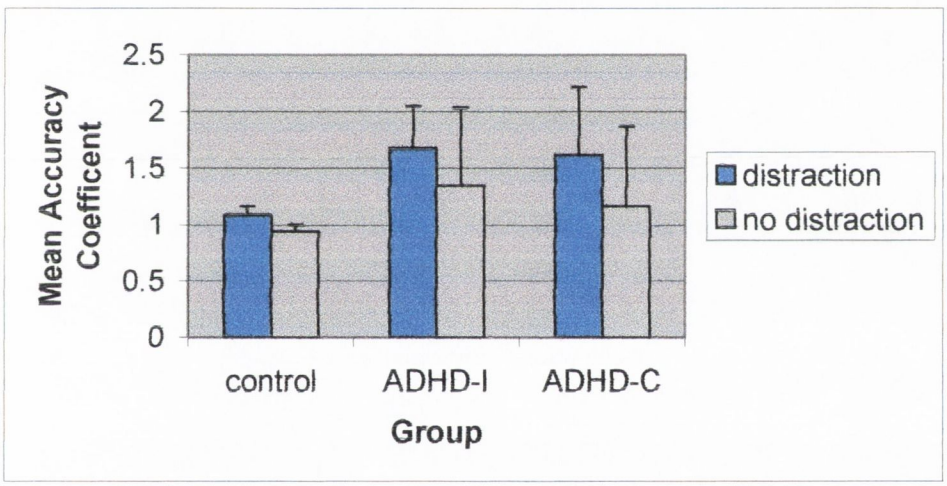


Fig. 4.4. The mean coefficient of accuracy scores (direction of error) on the time reproduction with distraction task.

Variability in Accuracy Coefficient Scores

A comparable analysis of the *Variability in Accuracy Coefficient Scores* revealed significant main effects for Group, ($F_{(2,60)} = 4.614$, $p < .05$) but not for Distraction ($F_{(2,60)}$

=.833, p= .366). The interaction of Group X Distraction phase was not significant ($F_{(2,60)}$ = .908, p= .411).

4.3.4 Onset-Offset Detection Task

A two-way mixed ANOVA, with group as the between subjects variable and 'detection phase' as the within-subjects variable, revealed a significant main effect for group ($F_{(2,63)}$ = 10.311, p<.0005), and for detection phase ($F_{(2,63)}$ = 56.012, p< .0005). The interaction of group X detection phase was not significant ($F_{(2,63)}$ = 2.160, p =.124). The ADHD groups had significantly higher RT's than the control group at each detection phase (p<.05). RT's were higher at the onset detection phase (.9573) than they are at the offset detection phase (.7377) (see table 4.5).

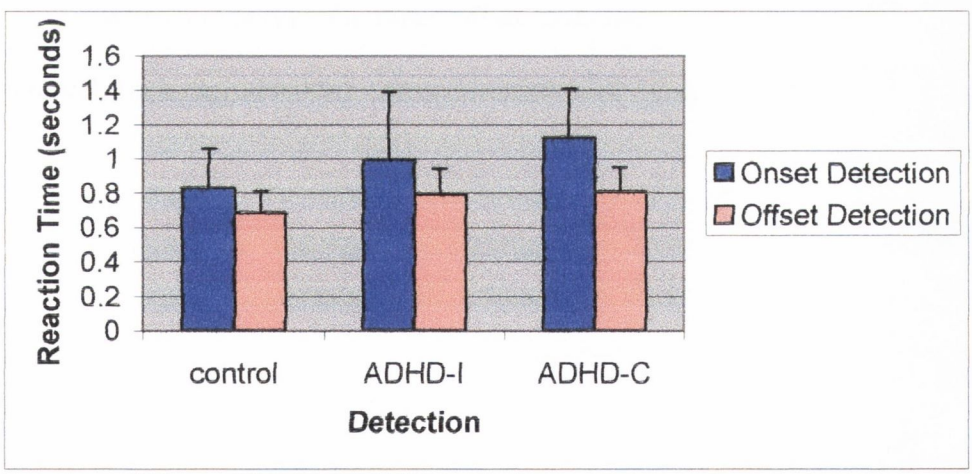


Fig. 4.5. Onset-Offset Detection task scores

Variability in reaction times

A two-way mixed ANOVA analysis of the variability of reaction times in the detection phases with Group as the between subjects factor and Detection phase (on/ off) as the within-subjects factor [3 (Group) X 2 (Detection phase)] revealed no significant main effects for Group, ($F_{(2,60)}$ =1.872, p= .163). There was a main effect for Detection phase ($F_{(2,60)}$ =4.085, p< .05). The interaction of Group X Detection phase was not significant ($F_{(2,60)}$ = 1.455, p= .242). The onset detection phase evinced more variable reaction times than the offset detection phase.

Time Reproduction and Onset-offset detection (Reaction Time)

When covarying for onset-offset detection (RT), the significant group by time interval (time reproduction) interaction remained ($F_{(2,63)}$= 10.949, p< .0005).

4.4 DISCUSSION

This study investigated the performance of three groups (ADHD-C, ADHD-I and matched controls) on a time reproduction task, a time reproduction task with distraction and an onset-offset detection (RT) task.

4.4.1 Group Comparison

Both ADHD subtypes demonstrated significantly less accurate time reproductions than did control children matched by age and gender. The ADHD subtypes differed significantly from each other on one of the dependent measures of the time reproduction task, namely in the variability of their Absolute Discrepancy Scores. ADHD participants differed from controls on the measure of reaction time. Time reproduction was not attributable to reaction time. However distraction did cause greater errors in the time reproductions of ADHD children compared to controls.

This finding of impaired time reproduction on ADHD-combined children is consistent with previous research (Barkley et al., 1997; Kerns et al., 2001; Meaux & Chelonis, 2003; McInerney et al., 2003), showing that this group tends to significantly underestimate at long time intervals. Although the ADHD groups did make significantly larger errors at the short intervals, the results did not reflect some of the previous research findings that ADHD groups make significantly larger overestimations at short time intervals (Barkley et al., 1997). In the current study all groups made overestimations between 2 and 10 seconds, but the ADHD groups did not overestimate significantly more

than controls. The target durations employed ranged from 2 to 60 seconds whereas Barkley et al. (1997) examined durations ranging from 12 to 60 seconds. The intervals at which Barkley found overestimations (12 and 24 seconds), in the current study revealed underestimations. Kerns et al. (2001) also found that ADHD and control groups underestimated at durations of 12 and 17 seconds. In that study, however, both groups underestimated at intervals as low as 3 seconds, with ADHD underestimating the target duration to a greater extent than controls (Kerns et al., 2001). The current results most closely resemble those of McInerney et al. (2003) where ADHD children performed less accurately than did control children, overestimating at short intervals (3,5,6 and 9 second intervals) and underestimating at longer ones (12 and 17 second intervals). In the current study, the ADHD groups did not significantly overestimate at the short intervals but they did make significantly larger errors than the control group. Among the most striking trends in the current and previous research is the constancy with which all groups make progressively greater time underestimations as the target time duration increases, with ADHD groups making significantly larger underestimations.

4.4.2 Variability in Time Reproduction

An analysis of the data revealed much more consistency across the errors in reproductions made by the control groups than is the case for the two ADHD groups, whose reproductions were observably more variable across the testing session. The ADHD-C group were significantly more variable than the control and ADHD-I group as the time intervals got larger. Children who made larger errors in their time reproductions were also more variable. Overall, variability was greater at the higher than the lower

intervals for the two ADHD groups, but this was not the case for the control groups. The more variable performance of the ADHD groups could be partly due to boredom or lack of motivation. McInerney et al. (2003) found that the deficit in time reproduction could be ameliorated to some extent, but not completely, by motivational levels. It seems the control group were less variable in their performance as they were generally more consistent and correct in their responses than the ADHD groups.

In the current study, the ADHD-I group demonstrated a similar pattern to the ADHD-C group on most of the tasks measured. There were, however, significant differences between the ADHD-C and ADHD-I groups in intra-individual variability in size of error at the high interval such that the participants in the ADHD-C group were significantly more variable in their time reproductions relative to the participants in the ADHD-I group. There were high correlations between variability in accuracy coefficient scores and variability in absolute discrepancy at the low, mid and high intervals. Nevertheless this ADHD group difference must be taken with caution as the current analysis involved multiple comparisons.

4.4.3 ADHD Subtypes

This finding reflects previous research that has distinguished neuropsychological deficits in the subtypes of ADHD (Houghton, 1999). It also lends support to Barkley's (1993) claim that ADHD-I should be recognized as a separate disorder and also to Clarke et al.'s (2001) suggestion that different neuroanatomical systems are involved in the subtypes of ADHD. It may be worthwhile examining some of the measures further with all three of

the ADHD subtype (ADHD-C, ADHD-H, ADHD-I) groups to investigate whether this intra-individual variability primarily co-occurs with symptoms of inattention or impulsivity. Response variability is the one ubiquitous finding in ADHD research across a variety of speeded-reaction-time tasks, laboratories and cultures (Kuntsi et al., 2001). Response variability reflects a high frequency of slow responses, as well as a high frequency of fast anticipatory responses. Research by Douglas (1983) has indicated that simply providing continuous positive verbal feedback can at least reduce the variability of reaction times of hyperactive children.

4.4.4 Onset-Offset Detection Task (RT)

Both ADHD subtypes had significantly longer reaction times than controls on the onset-offset detection task, reflecting Kerns (2001) findings of slower reaction times on a CPT. There were no group differences in intra-individual variability, surprising in light of previous findings (Douglas, 1972; Hynd et al., 1999; Silverstein et al., 1995). Reaction time did not emerge as a causal factor for larger overestimations. Many ADHD children did not respond at longer offset detections. This corresponds to Kerns et al. (2001) finding that ADHD children made significantly fewer hits on a CPT, and often looked away from the computer or stopped responding for short periods of time.

The confounding problems of motor persistence (Voeller & Heilman, 1988) and motor control in ADHD children (Barkley, 1997) were accounted for in the present study. Participants did not have to hold down the activation key in any of the reproduction tasks, and therefore the longer time intervals did not require motor persistence. There were still

errors in time reproduction and discrepancies between groups suggesting further support for a true time reproduction deficit in ADHD. Secondly, the onset-offset detection task tested reaction time, which was subsequently used as a covariate in analysis with time reproduction tasks with no effect on time reproduction. It has been suggested that an impairment in sense of time contributes to a problem in reaction time (Pastor et al., 1992). The current study found no support for this assertion.

4.4.5 Distraction

The control group were unaffected by the distraction whereas ADHD participants were affected. Both ADHD subtypes overestimated time intervals to a higher degree than controls when the distraction was present. All children overestimated the reproductions other than controls, who underestimated when there was no distraction present. The current findings must however be viewed with caution. As stated earlier, a composite score was produced with the distraction task and it therefore not possible to ascertain which time interval contributes to the difference. The finding is in support of Barkley et al's (1997) findings that controls were unaffected by the distraction whereas ADHD participants were. It does not support the earlier findings of Zakay (1992) who found that distraction caused normal children to underestimate intervals. Nevertheless, the intervals used by Zakay (1992) were below 10 secs. As a composite score had to be formed for the current time reproduction with distraction task, it is not possible in the present instance to investigate the separate time intervals further. Nevertheless, the finding of overestimation in ADHD make sense in view of Coull's (2004) assertion that increased attention to time allows more accurate processing of temporal pulses throughout the stimulus duration and

improves timing performance. It would be expected that ADHD children (who have a symptoms of inattention and are easily distracted) would be more easily exogenously distracted from the timing task by the distractor and therefore be less accurate in their estimations than controls. Rueckert & Grafman (1996) found that patients with right frontal lobe lesions are especially impaired on complex tasks of sustained attention, or when there were distractors present. In the light of the frontal lobe dysfunction theory of ADHD, this might explain why larger overestimations were made by the ADHD children when the distractor was present. Although distraction caused larger errors, it did not effect intra-individual variability.

The current finding is perplexing as both ADHD groups have symptoms of inattention (including being 'easily distracted' and 'fail to sustain attention in tasks or play activities'), and therefore are unable to attend to tasks as well as controls. Thus they make larger errors and a distraction would naturally be expected to take their attention away from the task to a greater extent than it would for controls, and hence affect ADHD children more in their time reproductions than controls. We now know that prefrontal and parietal brain areas are involved in estimation of intervals of several seconds (Mohl & Pfurtscheller, 1991) and that cortico-striatal circuits are thought to mediate time estimations based on lesion and brain imaging studies (Rubia et al., 1997). Moreover, Coull (2004) found that increasing attention to time selectively increased activity in a corticostriatal network, including the pre-supplementary motor area and right frontal operculum. It would be interesting to investigate through neuroimaging techniques the brain processes involved with time reproduction when distraction appears i.e. when

attention is purposefully drawn away from the time reproduction at hand, in comparison to when distraction does not occur, to explore whether further areas of the brain are involved when a distraction occurs, or if there is more activity in one of areas with timing when distraction occurs. This may tell us more about the brain areas involved in timing, attention and in ADHD.

4.4.6 Summary

In conclusion, results of the present study suggest that two subtypes of ADHD (combined and inattentive) manifest a true deficit in time reproduction. This finding remains after controlling for IQ, and did not appear to be a function of comorbid Reading Disorder, ODD, Conduct Disorder, depression, or anxiety. The impairment cannot be fully explained by reaction time discrepancies. This study provides support that a task which measures time reproduction is a valid test of time perception, as when covarying for onset-offset detection (RT) the significant group time reproduction difference remains. The fact that a time deficit is exacerbated by distraction, brings the area of attention into the forefront of further investigation. The finding that ADHD-I and ADHD-C may be distinguished on the basis of variability in time reproductions is a novel finding. These results support an emerging view that intra-individual differences in performance variability, rather than simply adding random noise, may provide important clues regarding the efficiency of cognitive processes within clinical populations (Stuss et al, 2003). This line of reasoning is particularly germane to ADHD research where it is the moment-to-moment fluctuations in performance and lapses of intention and attention that arguably characterize the disorder (Castellanos & Tannock, 2002). Clinically,

impairments in timekeeping may impact negatively on neuropsychological test performance where a speeded response is required or time restrictions are in place. A tendency to underestimate time may lead to a hurried and/or inconsistent response that does not accurately reflect ability of ADHD children. This scenario may impact most heavily on the performance of the ADHD-C group.

Chapter 5

Effect of medication on Behavioural and neuropsychological measures

5.1 INTRODUCTION

5.1.1Treatment of ADHD

Since the 1930's, stimulant medications have been used to effectively ameliorate ADHD symptoms (Bradley, 1937) and today are the first-line treatment of choice (Greenhill et al., 2002). Methylphenidate (MPH) is a central nervous system (CNS) stimulant. It has a notably calming effect on hyperactive children and a "focusing" effect on those with ADHD. It has consistently been shown to improve the core symptoms of ADHD (inattention, hyperactivity and impulsivity), and to improve oppositional behaviour, impulsive aggression and social interactions.

Very little is known clinically about the enduring effects of childhood stimulant exposure. Many suggested side effects include reduced weight gain, stunting growth, sleeplessness, moodiness, and depression. Research to date finds that MPH used during childhood produces temporary decreases in weight gain that are not apparent by adulthood (Rapoport, 1978; Spencer et al., 1998), although reports of growth retardation following exposure in preschoolers are emerging (Swanson & Volkow, 2003). It has been reported that some children on Ritalin have reported suicidal feelings. Additionally, some individuals abuse it for its stimulant effects: appetite suppression, wakefulness, increased focus/attentiveness, and euphoria.

MPH seems to act mainly by inhibiting the dopamine transporter protein and dopamine reuptake. In fact, its effect is probably related to an increase in extracellular levels of dopamine, especially in brain regions enriched in this protein (i.e. striatum). (Roman, et al., 2004). MPH has been shown to increase metabolism in the dorsolateral prefrontal cortex, the cerebellum, and the basal ganglia (Volkow et al., 1997). Dopamine transporter densities are particularly elevated in the brain of ADHD patients, decreasing after treatment with MPH. *In vivo* measurement of DAT in adults with ADHD show elevated densities (Dougherty et al., 1999) within the striatum that can be reduced to near-normal levels with MPH (Krause et al., 2000). Several molecular genetics studies have demonstrated an association between the 10-repeat (480bp) allele of a variable number of tandem repeats (VNTR) at the DAT1 locus and ADHD (Cook et al., 1995; Daly et al., 1999; Gill et al., 1997; Waldman et al., 1998). Vaidya et al. (1998) examined the effects of medication on functional activity with blood oxygen level dependent (BOLD) imaging and suggested that the mechanism of stimulant action differs between typical children and those with ADHD. These investigators propose that MPH selectively activates the prefrontal cortex and reduces activity in the striatum of children with ADHD, but not in typical children (also see Kim et al., 2001). Increased dopamine transporter (DAT) availability in ADHD could be decreased with 4 weeks of methylphenidate administration (Dougherty et al., 2000; Krause et al., 2000). Positron Emission Tomography (PET) imaging of MPH effects in resting healthy adults showed that changes in brain metabolism varied in individuals and brain regions as a function of dopamine receptor availability. These, findings support the possibility that an important feature of ADHD is atypical dopaminergic modulation of the striatum.

MPH has been shown to reduce predominantly externalising dysfunctions in ADHD such as hyperactivity (Butte et al., 1999) impulsive, oppositional (Schachar et al., 1997), and antisocial behaviors (Smith et al., 1998). In the cognitive domain, MPH has been shown to improve the executive functions of sustained attention (O'Toole et al., 1997; Pelham et al., 1997), self-regulation (Berman et al., 1999), working memory (Tannock et al., 1995b), cognitive flexibility (Solanto & Wender, 1989), and inhibitory control in hyperactive children (Tannock et al., 1995a). MPH has been shown to decrease within subject variability of response in cognitive domains such as response inhibition (Tannock et al., 1995 a, 1995b), selective attention (Thurston et al., 1991), sustained attention (Sonneville et al., 1991) and motor timing (Rubia, Noorloos et al., 2003)

Konrad (2004) examined the effects of MPH on different attentional functions and behavior in children with attention-deficit/hyperactivity disorder (ADHD). A comprehensive neuropsychological test battery was applied, including tests of alertness and sustained, focused, and divided attention as well as two executive tests, the stop-signal paradigm and a visual set-shifting task. A linear improvement was identified in the alertness and focused and sustained attention task, but no significant improvement was found for divided attention. Bedard et al. (2004) investigated the effect of MPH on visual-spatial memory in ADHD. MPH significantly improved performance on a self-ordered, updating visual-spatial working memory task and on maintenance of visual-spatial information but had no effects on measures of visual-spatial planning ability or recognition memory.

Recently (Bellgrove et al, under review) reported that left-sided inattention, which is sometimes found in ADHD (Dobler et al., 2003) is related to clinical ADHD symptomatology, the 10-repeat DAT1 allele and predicts therapeutic response to MPH.

5.1.2 Time Perception and methylphenidate

In both rats and pigeons, dopamine agonists, such as the amphetamines, cause the underproduction of time intervals, suggesting that these agents increase "clock speed" (Meck, 1983). Research in starlings, however, has shown that methamphetamine causes birds to underestimate the passage of time (produce time intervals that are too long), an effect opposite to that noted in both rats and pigeons (see Paule, Meck, et al., 1999). In monkeys, the dopamine antagonist chlorpromazine increased the percentage of correct duration lever holds and slightly shifted hold durations toward shorter values. These findings suggest that in primates, dopaminergic blockade may improve time estimation precision and increase internal clock speed (Paule, Meck et al., 1999).

The dorsolateral prefrontal cortex, the cerebellum, and the basal ganglia, areas compromised in ADHD, have been implicated in motor timing functions (Rubia et al., 1998, 2000; Rubia & Smith, 2001). It has been suggested that dopaminergic pathways may be involved in motor timing functions in healthy adults, based on the effect of dopamine agonists and antagonists on motor timing and time perception (Meck, 1986).

Nevertheless, the effect of methylphenidate on tasks measuring time perception in ADHD has had mixed results. Rubia, Noorloos et al. (2003) found that the persistent use of methylphenidate had a positive effect on the increased variability in externally paced

motor timing tasks. It decreased the variability of sensorimotor anticipation and of sensorimotor synchronization. Persistent administration of methylphenidate also increased the speed of synchronization and reduced the number of impulsive errors in an anticipation task. However, only the persistent use of methylphenidate improved variability of motor timing, while the single dose was not more effective than placebo. This is not in line with previous findings of a positive effect of acute administration of methylphenidate on cognitive functions such as inhibitory control, sustained attention, and working memory (O'Toole et al., 1997; Tannock et al., 1995a, 1995b). In Rubia et al.'s (2003) study, MPH had no effect on time perception. An acute dose of methylphenidate had no effect on either motor timing or time perception. It appears, therefore, that only persistent administration of methylphenidate has a positive effect on consistency of motor output timing but not on perceptual timing abilities. Various other studies of ADHD have found no change in time reproduction or production as a result of MPH. Barkley (1997) found no effect for medication on the time reproductions (12 –60 seconds) of ADHD children. Baldwin et al. (2004) found that MPH had no effect on the number of correct responses or on the mean duration of lever holds on a time-production task where the lever had to be held down for between 10 and 14 seconds. It did, however, significantly decrease timing response variability and increase holds of 10- to 11-s duration.

5.1.3Aims of current study

The effect of MPH on time reproduction with and without distraction, as well as on intra-individual time reproduction variability is examined in the current study. A comparison is

also made of parent rated Conners Parent Rating Scale (CPRS-R) to examine the effect of MPH on ADHD symptoms/ behaviour in the current sample. All participants are those who are taking MPH on a daily basis.

5.2 METHOD

5.2.1 Participants

Sixteen of the ADHD-C children from the previous group who take stimulant medication (MPH) for their ADHD symptoms were tested a second time whilst taking their medication to compare their results (Age 8 - 12 (Mean = 10.1, S.D. = 1.7). The mean estimated full scale IQ (Block Design and Vocabulary short form of the WISC-III) (Sattler, 1992) was 91.16 (SD = 13.36).

5.2.2 Materials and Procedures

Conners Parent Rating Scale (Long Version)(CPRS-R) (Conners,1998)

The Revised Conners Parent Rating Scale (CPRS-R; (Conners, 1998) is a 57-item parent-rated measure of cognitive problems, oppositional behaviour, hyperactivity-impulsivity, anxious-shy behaviours, perfectionism, social problems and psychosomatic behaviours. Items are rated on a four-point scale from `not at all' to `very much'. Parents had to

retrospectively rate their child's symptoms while 'on' and 'off' MPH for comparison of the children's behaviour on and off medication.

Time Reproduction Measures

1) Time Reproduction Task- See chapter 3 for description

2) Time Reproduction with Distraction Task - See chapter 3 for description

3) Onset-Offset Detection Task - See chapter 3 for description

Half of the group were tested off medication and the other half was tested on medication for the first testing session and then vice versa for the second testing session to counterbalance the procedure. These testing sessions were approximately 8 days (S.D.= 2.6) apart. The procedure was the same as previously for each occasion.

5.3 RESULTS

5.3.1 Effect of Medication on CPRS-R

Comparison of parent rated CPRS-R on and off MPH revealed highly significant differences on a number of the subscales (see table 5.1).

Table 5.1: Conners: on vs. off medication

SUBSCALE PAIRS	t(df=14)	Sig (2-tailed)
Conners oppositional,not on ritalin vs. Conners oppositional, on ritalin	7.296	.000
Conners cognitive problems/innattention, not on ritalin vs. Conners cognitive problems/innattention, on ritalin	9.139	.000
Conners hyperactivity, not on ritalin vs. Conners hyperactivity, on ritalin	6.863	.000
Conners anxious/shy, not on ritalin vs. Conners anxious/shy, on ritalin	1.167	.260
Conners perfectionism, not on ritalin vs. Conners perfectionism, on ritalin	.805	.432
Conners social problems, not on ritalin vs. Conners social problems, on ritalin	5.469	.000
Conners psychosomatic, not on ritalin vs. Conners psychosomatic, on ritalin	-.810	.430
Conners ADHD index, not on ritalin vs. Conners ADHD index, on ritalin	8.819	.000
Conners global index, restless-impulsive, not on ritalin vs. conners global index, restless-impulsive, on ritalin	8.213	.000
Conners global index, Emotional Lability, not on ritalin vs. conners global index, Emotional Lability, on ritalin	4.940	.000
Conners global index:total, not on Ritalin vs. Conners global index:total, on ritalin	9.251	.000
DSM IV inattentive, not on ritalin vs. DSM IV inattentive, on ritalin	9.140	.000
DSM IV hyperactive-impulsive, not on ritalin vs. DSM IV hyperactive-impulsive, on ritalin	6.759	.000
DSM IV, not on ritalin vs. DSM IV, on ritalin	8.606	.000

5.3.2 Task 1: Time Reproduction Task

Paired t-tests using the *absolute discrepancy scores* (size of error) showed no differences between medication trials at any of the intervals; 2-10 secs (t= -1.497, df = 15 , p=.231), 12-24 secs (t= -.595, df = 15 , p=.594), 36-60 secs (t= -.103, df = 15 , p=.924). There were no significant differences between medication trials in intra-individual variability of the *absolute discrepancy scores* at any of the intervals; 2-10 secs (t= -.792, df = 15 , p=.511), 12-24 secs (t= -.629, df = 15 , p=.574), 36-60 secs (t= .995, df = 15 , p=.393) (see Table 5.2).

There were no significant differences between medication trials on the *Accuracy Coefficient Score* at any of the intervals; 2-10 secs (t= -1.051, df = 15 , p=.370), 12-24 secs (t= .115, df = 15 , p=.916), 36-60 secs (t= .497, df = 15 , p=.653.). Comparison of Variability in *Accuracy Coefficient Score* showed no differences between medication trials at 2-10 secs (t= -.854, df = 15 , p=.456), 12-24 secs (t= -.319, df = 15 , p=.771) or 36-60 secs (t= 1.503, df = 15 , p=.230) (see Table 5.2 below).

Table 5.2. Time Reproduction Task: comparison of medication trials

		2-10 secs		12-24 secs		36-60secs	
Score	Trial	M	SD	M	SD	M	SD
Absolute Discrepancy	on MPH	1.84	1.64	5.53	6.8	14.27	14.55
	off MPH	.64	.31	3.02	3.57	13.07	10.36
Variability of Absolute	on MPH	1.18	.75	2.40	2.27	9.31	8.99
Discrepancy	off MPH	.718	.31	1.44	1.79	15.64	9.43
Accuracy Coefficient	on MPH	1.19	.44	.82	.48	.71	.28
	off MPH	.94	.02	.85	.21	.83	.24
Variability of Accuracy	on MPH	.49	.61	.08	.05	.15	.10
Coefficient	off MPH	.21	.09	.07	.09	.36	.26

5.3.3 Task 2: Time Reproduction Task with Distraction

Paired t-tests using the *absolute discrepancy scores* found a significant difference (t= 3.358, df = 15 , p<.01) between medication trials. Variability in *absolute discrepancy scores* (t= -.271, df = 15 , p=.812) found no differences on vs. off medication. There were no differences between medication trials in *Accuracy Coefficient Score* (t= -.714, df = 15, p=.549) or variability in *Accuracy Coefficient Score* (t= .815, df = 15 , p=.501) (see Table 5.3).

Table 5.3. Time Reproduction with Distraction Task: comparison of medication trials

Score	Trial	M	SD
Absolute Discrepancy	on MPH	5.94	2.28
	off MPH	9.76	3.57
Variability of Absolute Discrepancy	on MPH	9.6	7.25
	off MPH	7.0	9.32
Accuracy Coefficient	on MPH	1.67	.69
	off MPH	1.54	.42
Variability of Accuracy Coefficient	on MPH	.65	.51
	off MPH	.89	.52

5.4 DISCUSSION

5.4.1 Comparison 'on' and 'off' medication

This study explored the impact of methylphenidate on the Conners Rating Scale (CPRS-R), a time reproduction task and a time reproduction with distraction task in children diagnosed with ADHD-combined type. Significant differences were found between medicated and non-medicated rated CPRS-R. ADHD children's results on the time reproduction were unaffected by MPH. There was an improvement in mean size of error when a distraction was present on the time reproduction with distraction task, as a result of MPH.

Time reproduction of the ADHD subtypes did not improve as a result of the medication. While some of the ADHD children who were not taking stimulant medication only stopped taking their medication approximately 24 hours prior to testing, and dosage and type of medication among children varied, Barkley et al. (1997) controlled for most of these factors and also failed to find an effect of medication on the time reproductions.

That the participants in this study were responding to MPH was quite evident in the significant differences found between medicated and non-medicated parent rated CPRS-R. In particular there were significant differences in the subscales measuring oppositional behaviour, inattention, hyperactivity, social problems and emotional lability. Parents were not however blind to the medication status of their children and this may have influenced the ratings.

In chapter 4 ADHD participants made larger errors than controls in their time reproduction when the distraction was present. In the current study an improvement in the size of errors was found when ADHD children were medicated. It appears that MPH made the ADHD participants less prone to distraction (in the time reproduction with distraction task). Zakay (1992) asserted that the more an individual must allocate attention to nontemporal information, the less they can allocate to temporal processing and so the less accurate (shorter) their sense of time will prove to be. This, he argued is due to the limited storage capacity of attentional and working memory systems. Should distractions occur during the processing of the passage of time, thereby commanding

nontemporal attentional resources, greater errors in time perception are to be expected (Zakay, 1992). It makes sense therefore that time reproduction on the time reproduction with distraction task should improve, as a result of MPH, given that distraction takes attention away from the task and that MPH improves inhibitory control, sustained attention, and working memory in ADHD (O'Toole et al., 1997; Tannock et al., 1995a, 1995b, 1989).

5.4.2 Why is there no difference in time reproduction?

If perception of time is deficient in ADHD solely due to a deficit in working memory and behavioural inhibition as argued by Barkley (1997), an improvement in time reproductions would be expected, given that methylphenidate has been shown to improve working memory (Tannock et al., 1995b), and inhibitory control (Tannock et al., 1995a) in ADHD children.

Rubia (2003) asserts that it is possible that methylphenidate improves output related abilities rather than perceptual information processing; it reduces externalizing, rather than internalizing dysfunctions at a behavioral level (Butte et al., 1999; Schachar et al., 1997) and executive, rather than perceptive functions in the cognitive domain (Berman et al., 1999; O'Toole et al., 1997; Pelham et al., 1997; Tannock et al., 1995a, 1995b). A role of methylphenidate in improving output rather than input related functions would be in line with its attributed effect on the dopaminergic system (Volkow et al., 1998), which has been related primarily to motor and motivational control functions (Le Moal, 1995).

Bellgrove et al. (under review) have reported interesting findings regarding ADHD and MPH response, based on an associated gene, namely the DAT1 Genotype. ADHD probands in the high risk DAT1 group (those in possession of two copies of 10-repeat DAT 1 allele) evinced significantly more left-sided inattention on the Landmark task, than those in the low risk DAT1 group (in possession of one or no copies of the 10-repeat DAT 1 allele). The high risk group were reported (CPRS-R:L parents rating) to have a greater response to MPH than the other groups, showing greater symptom reduction than the Low-Risk DAT1 ADHD group in terms of both DSM-IV Hyperactive/Impulsive and DSM-IV Total symptoms with a tendency toward the same for DSM-IV Inattentive symptoms. Further, the High-Risk DAT1/Very Good Response group were the only group to display left-sided inattention, as compared to the High-Risk DAT1/Mediocre Response Group and the Low risk groups (Very good and mediocre response groups). Based on these findings, it is possible that the current sample belong to the Low-Risk DAT1 ADHD group i.e. a difference may not have been seen in time reproduction as a result of MPH, because this group do not generally improve on cognitive measures as a result of medication. However, Bellgrove et al. (under review) found in another study that low-risk ADHD children and adolescents do not display either sustained attention deficits or abnormal attentional asymmetries on the Greyscales Task (a task which has been shown to be sensitive to neglect). These findings are therefore inconclusive, as the Low risk group showed a leftward bias/ rightward inattention on the former study, yet no abnormal attentional asymmetry in the latter study. The assertion that the current sample might belong to this Low risk group and hence do not differ in their time reproductions as a result of non response to MPH is questionable based on the fact that the ADHD group

showed behavioural differences, in hyperactivity and inattention, according to parent rated CPRS-R, in addition to a smaller mean error in time reproduction when distraction was present, as a result of MPH.

5.4.3 Summary

In subsequent chapters I will investigate both sustained attention and spatial neglect in these ADHD children compared to matched controls. These findings will indicate whether the current sample show performance characteristic of the DAT1 low risk group, though in this study it was not possible to genotype them.

In conclusion, the impairment in time reproduction is not improved by medication. The finding of no effect of MPH on time perception supports previous findings (Baldwin et al., 2004; Barkley et al., 1997; Rubia et al., 2003). The implication here is that the pathways involved in time reproduction are at least to some extent different to those involved in working memory and inhibition. Perception of time may be a separate domain which is unaffected by methylphenidate.

Chapter 6

Time Reproduction and Attention

6.1.1 INTRODUCTION

Up to this point, the thesis has attempted to address a number of questions relating to the issue of whether a time perception deficit exists in ADHD. So far, it has clarified a number of issues. First it has shown that a time deficit can be measured reliably. Second, by means of a reliable measure, it has revealed that two subtypes of ADHD (combined and inattentive subtypes) manifest a deficit in time reproduction, hence supporting previous research (Barkley et al., 1997; Kerns et al., 2001; McInerney et al., 2003). Third, and of major significance, ADHD-I and ADHD-C may be distinguished on the basis of intra-individual variability in the size of their errors in time reproductions, with ADHD-C children performing significantly more variably than ADHD-I children. Fourth, replicating previous findings (Barkley et al., 1997; Rubia et al., 2003), but using a reliable measure, no evidence has been found that MPH improves time reproduction in children with ADHD. All findings have remained after controlling for IQ, as well as comorbid disorders such as Reading Disorder, ODD, Conduct Disorder, and Depression. Furthermore, the deficit in time reproduction is exacerbated by distraction.

However, it is not yet possible to extrapolate from these findings what it is that causes a deficit in the perception of time in ADHD. The following chapters will attempt to tackle this issue further using the evidence we have gathered so far.

That a subtype difference has been observed in intra-individual variability of time reproductions is most intriguing. Intra-individual variability is consistently seen in people who have impairments of executive functioning, such as children with ADHD (Castellanos & Tannock, 2002) and patients with frontal lesions (Stuss et al., 2003) Properties of top-down regulation of attention are instantiated in frontal structures. Stuss et al. (2003) assert that increased intra-individual variability seen in patients with frontal lesions is due to a general deficit in regulation of attention to any task, but that this could include a combination of or any one of the following; reduced sustained attention, poor working memory, perseveration, failure to inhibit a response, and poor action planning or strategy formulation. ADHD is a disorder associated with frontal dysfunction, impairments of executive functioning and increased intra-individual variability. That the current thesis has found that intra-individual variability is increased in ADHD on a task of time reproduction, may throw some light on what is causing this variability, in disorders associated with frontal dysfunction. Rubia et al. (1999b) suggest the possibility that variability of response reflects deficits in sustained attention as sustained attention to the passage of time underlies time estimation (Zakay, 1993); i.e. a deficit in sustained motor attention could lead to inconsistent anticipatory accuracy.

ADHD-C and ADHD-I subtypes clearly differ on behavioural measures, such as the Conners Parent Rating Scale (Conners, 1998), as evidenced in the current thesis. Yet to date, examination of neuropsychological differences between the subtypes have been rare and inconclusive. It is therefore necessary to examine these subtypes on measures of

executive functions, which have not yet been explored. A subtype examination may inform us as to the nature of the interaction between various attentional and executive functions and the basis of the time deficit.

6.1.2 Barkley's theory on time perception in ADHD

The role of response inhibition has long been of theoretical interest in understanding the deficits underlying ADHD (Still, 1902; cited in Barkley, 1990). While others have also argued that impaired response inhibition is central to ADHD (Quay, 1988), Barkley (1994) takes this argument one step further by suggesting that impaired delayed responding is the 'single deficiency' to which the various deficits observed in ADHD can be reduced. Barkley (1997) defines response inhibition in terms of 'three interrelated processes', which he describes as follows:

> 1) inhibiting the initial prepotent response to an event; 2) stopping an ongoing response or response pattern, thereby permitting a delay in the decision to respond or continue responding; and 3) protecting this period of delay and the self-directed responses that occur within it from disruption by competing events and responses (interference control).
>
> (p. 47-48).

On the basis of existing theories of language and frontal lobe function, Barkley (1997) has proposed that poor behavioural inhibition is the core deficit of ADHD and that

attention deficits are secondary rather than primary. In other words, deficient behavioural inhibition disrupts executive functions by not allowing sufficient opportunity for them to occur. Barkley (1994, 1997) asserts that impaired response inhibition accounts for the myriad behavioural, cognitive and social deficits seen in ADHD.

Barkley (1994, 1997) argues that the impairment of behavioural inhibition results in secondary deficiencies in four executive functions that contribute to self-regulation. These are (1) working memory and sense of time, (2) self-regulation of emotional and motivational states, (3) the internalization of speech, and (4) reconstitution, or the formation of novel, complex behavioural sequences. In this model the expression of impulsivity may be linked to individual differences in the perception and understanding of time (Gerbing et al., 1987; White et al., 1994).

6.1.3 ADHD and Response inhibition

Conflicting findings, nonetheless, exist with regard to the relationship between ADHD and response inhibition. Scheres et al. (2004) examined whether boys with ADHD demonstrate a deficit in response inhibition and deficits in other executive functions (EF), or alternatively, demonstrate a deficit in only response inhibition. They compared a group of ADHD boys with a control group on five domains of executive functioning: inhibition (inhibition of a prepotent response, inhibition of an ongoing response, and interference control), planning, set-shifting, working memory, and verbal fluency. The ADHD group demonstrated deficits in interference control, inhibition of an ongoing response, planning, and letter fluency. However, none of the EF deficits remained after

controlling for age, IQ, and non-EF measures (In some EF tasks, a non-EF control measure was built in to the calculation of the dependent variable - Stop Paradigm, Stroop Color-Word Test, Circle Tracing Task). Hence, these results did not provide supporting evidence for models proposing an EF deficit as the core problem in ADHD (e.g., Barkley, 1997). Half of the ADHD group tested by Scheres et al. (2004) also had comorbid Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD). This combination could in part account for these results. Recent studies, however, suggest that EF deficits in ADHD are independent of comorbid ODD (Klorman et al., 1999; Nigg et al., 1998). Furthermore, the group consisted of a mixture of ADHD-C and ADHD-I children, and an EF deficit is expected to be found only in ADHD-C (Barkley, 1997). Nevertheless, Murphy et al. (2001) did not find EF differences between different subtypes of ADHD and Chhabildas et al. (2001) showed that symptoms of inattention, and not symptoms of hyperactivity/impulsivity were responsible for the inhibition deficit in ADHD. As discussed in chapter 4, the response inhibition deficit displayed by ADHD children could be as a result of trying to finish the task as quickly (delay-aversion) as possible rather than a deficit in inhibition (Kuntsi et al., 2001; Sonuga-Barke et al., 1992). So it remains unclear whether response inhibition deficit is specifically related to the ADHD-C subtype, or to ADHD at all.

Regarding subtype comparisons, Houghton et al. (1999) examined ADHD-C and ADHD-I children on five measures of executive function (The Wisconsin Card Sorting Test, The Stroop Color-Word Test, The Matching Familiar Figures Test, The Trail Making Test, and The Tower of London). Both ADHD-I and ADHD-C children differed from controls,

but it was only the ADHD-C group which differed significantly in response inhibition. The authors asserted that this finding provided support for Barkley's (1997) proposed Unifying Theory of ADHD, as the absence of diagnosed comorbidity in the ADHD children at the time of testing demonstrated that the impairments in executive functions are clearly located in ADHD, particularly in the ADHD Combined subtype. However, the sample used (32 ADHD-I and 62 ADHD-C) was not a truly representative sample of ADHD. Nearly two thirds of children who are referred for clinical evaluation have at least one diagnosable comorbid disorder (Richters et al., 1995). It is therefore highly unlikely that one could find a sample of ADHD children of this size, who do not have some type of comorbid disorder. These results do not therefore make the picture any clearer.

6.1.4 Neuropsychological correlates of response inhibition

Casey et al. (1997) found support for a response inhibition deficit in ADHD. Children with ADHD had significantly slower reaction times and lower mean accuracy rates than controls during the inhibitory trials on three tests of response inhibition (a sensory selection task, a response selection task, and a response execution task), but had slower reaction times solely on control versions of these tasks (where no inhibition was required). Casey et al. (1997) examined the relationship between these tasks and both the prefrontal cortex and basal ganglia, based on the findings of neuroimaging studies that right frontal circuitry is involved in response inhibition (Corbetta et al., 1991; Pardo et al., 1990; Sieg et al., 1995). Consistent with other findings (Castellanos et al., 1994, 1996; Filipek et al., 1997), the right prefrontal cortex, right caudate nucleus and globus

pallidus volumetric measures correlated with task performance, whereas the putamen measures did not. By distinguishing between areas involved in the three tasks specifically, Casey et al. (1997) suggested that the right prefrontal cortex was involved in suppressing attentional and behavioural responses to salient, but otherwise irrelevant, events. They further indicated that the basal ganglia appeared to have a role in the execution of these behavioural responses. A larger left globus pallidus was associated with slower reaction times and higher accuracy. Most studies find longer stop-signal reaction times in ADHD patients (Nigg, 2000). ADHD boys who had better performance were more likely to have a similar caudate measure to that of the controls (with a significant negative correlation between age and right caudate volume).

Vaidya et al. (1998) found that ADHD children were impaired in inhibitory performance on go/no-go tasks compared to controls and examined the effects of methylphenidate on response inhibition. Response inhibition invoked widespread activation bilaterally in the frontal cortex. The authors asserted that this finding suggests that response inhibition involves multiple frontal-lobe processes, perhaps including selection, online maintenance of stimuli in working memory, and switching attentional set (go and no-go trials). MPH had different effects in ADHD and control groups; improving response inhibition in ADHD children only. MPH increased frontal activation in both groups to an equal extent, but increased striatal activation in ADHD children and reduced it in controls. MPH-related increases in striatal activation have been reported in ADHD in prior studies (Lou et al., 1989).

6.1.5 Response inhibition in ADHD and perception of time

Although a relationship between impaired behavioural inhibition and the psychological sense of time has been investigated previously (Kerns et al., 2001), this study left many unanswered questions. For instance, Kerns et al. (2001) used a Go/ NOGO task and the Stroop task to examine the relationship of inhibition and time reproduction, but this study had a number of problems. Firstly, Kerns et al. (2001) did not examine differences between ADHD-C and ADHD-I children on the various measures. That the current thesis has shown a subtype difference in the intra-individual variability of time reproduction illustrates the importance of examining ADHD-C and ADHD-I separately rather than as one combined group. Furthermore, Barkley (1994, 1997) has argued that ADHD-I children should not display a deficit in behavioural inhibition to the same extent as those diagnosed with ADHD-C, yet in the current thesis, the ADHD-I group make as many errors in time reproduction as the ADHD-C group. Hence, if a deficit in sense of time is linked to behavioural inhibition, one would expect both groups to perform significantly worse than controls on a task measuring this.

Secondly, Kerns et al. (2001) found that the ADHD group made significantly more errors of omission than the control group, but that there was not a significant difference between the groups in errors of commission. Yet she explored and found a correlation between both omission and commission errors with time reproduction. The correlation between commission errors and time reproduction does not indicate a relationship between poor response inhibition and time reproduction, as Barkley asserted deficient response inhibition causes deficient sense of time. If ADHD children were not worse on this part

of the test (there was not even a trend towards the ADHD group being any worse on the task), then the correlation found by Kerns et al. (2001) between commission errors and time reproduction tells us nothing. Furthermore, Kerns et al. (2001) found a relationship between the omission errors and time reproduction, with the ADHD group making a higher number of these errors than the control group. It may in fact be sustained attention that is the issue here:- omission errors are 'errors in not pressing when supposed to' rather than a problem with withholding a response (i.e. errors of commission)!

Finally, and of consequence, although Kerns et al. (2001) examined and found a significant relationship between time reproduction and a CPT (a measure of sustained attention), this was not expanded upon in that study. The investigators focused on the response inhibition deficit, without remarking on the CPT/ time relationship. Macar et al. (1994) have found that the less participant's attend to time, either implicitly or explicitly, the more they underestimate stimulus duration. This has been interpreted within the framework of the pacemaker-accumulator model of timing:-fewer attentional resources being allocated to timing result in a greater number of temporal pulses being lost from the temporal record, thus producing underestimates in duration. An attempt is now made to explore the time deficit and its link to sustained attention and response inhibition further.

6.1.6 Sustained Attention

Sustained attention is the capacity to maintain active attention to a task, a goal or one's own behaviour in spite of the fact that it is not necessarily an interesting task; 'the ability to self-sustain mindful, conscious processing of stimuli whose repetitive, non-arousing

qualities would otherwise lead to habituation and distraction to other stimuli' (Robertson et al., 1997, p.747).

6.1.7 Neuropsychological Correlates of Sustained Attention

The Vigilance (Sustained Attention) network in the brain is responsible for sustaining our attention over periods of time. Functional imaging studies (Coull & Nobre, 1998) and animals studies (Sarter & Bruno, 1997) have located areas in the intact brain in which changes in metabolic activity correlate with sustained attention performance. Neuropsychological investigations, both with normals and patients with lesions to the frontal cortex, have implied a role for the right frontal cortex in simple sustained attention (Whitehead, 1991; Wilkins et al, 1987). Frontal lesions impair performance on tasks that require sustained attention, such as the Wisconsin card sorting, maze learning, and planning (e.g. Shallice, 1982). Positron emission Tomography (PET) studies have localised areas associated with visual, somatosensory (Pardo et al., 1991) and auditory (Cohen et al, 1988) sustained attention in the right prefrontal and superior parietal cortices. Reported problems of attention and concentration occur in the majority of severely traumatically brain-injured patients. Sustained attention performance is always diminished in TBI (traumatic brain injury) patients where the injury has taken place in the frontal lobes (Robertson, Manly, Andrade et al., 1997).

Wilkins et al., (1987) used a simple test (a target counting task) to attempt to detect momentary lapses of attention in patients who had undergone unilateral neocortical

removals for relief of intractable epilepsy, and patients with unilateral cortical lesions who did not have longstanding epilepsy. They found that the groups of patients who had anterior lesions of the right hemisphere, made more frequent errors than those with posterior lesions in counting auditory and tactile stimuli at slow rates (1 second) of presentation. They asserted that attentional deficits found in epileptic patients were therefore not the result of epileptic abnormalities but could be attributed specifically to an effect of frontal lesions. Rueckert and Grafman (1996) argue that the fact that the difference between groups was larger when the rate of target presentation was relatively slow, suggests that the lack of external stimulation made it more difficult to maintain arousal in order to sustain attention

Rueckert and Grafman (1996) compared patients with right frontal lobe lesions, with left frontal lobe lesions and controls in change in performance over time on several tasks requiring sustained attention. These consisted of 1) a simple vigilance task, to assess changes in simple Reaction Time over time; 2) a CPT (the single 'X' version), to assess ability to respond to some stimuli and refrain from responding to others; and 3) a story test, to assess sustained attention under more 'natural' conditions (by presenting a short story and having participants respond to certain targets). Patients with right frontal lobe lesions had longer RTs and missed more targets than control subjects on all three tasks. There were not significant differences between the two patient groups, but the right lesion group performed consistently worse on all tasks. The left frontal lesion group did not differ significantly from, but did perform worse than the control group. The authors suggest that this result is due to these patients having also suffered some damage to the

right hemisphere. They also stated that it could be argued that the performance decrement shown by the frontal lesion patients could be due to an overall slowing in processing after right frontal lobe lesions, rather than to a specific problem with sustained attention. They argued that a better definition of sustained attention could be the change in performance over time which was in fact observed in a decrement in performance between the first and second half of the CPT in the right frontal patients compared to the left patients and controls i.e. the right frontal region becomes more important as the amount of time attention must be sustained for increases.

Some studies have shown that sustained attention constitutes both arousal and attentional elements. Paus et al. (1997) used PET and EEG to examine regional cerebral blood flow and electropshysiological responses during a 60-minute vigilance task Regression analysis identified two distinct networks that may underlie sustained attention (vigilance differs from sustained attention in that it spans a period from minutes to hours, as opposed to seconds to minutes (Coull & Nobre, 1998). These networks were a right-hemisphere dominant cortical network comprising dorsal and ventral frontal lobe, inferior cortex and mid-temporal cortex, which may constitute the attentional component; and a subcortical network comprising thalamus, striatum and anterior cingulate, which is linked to arousal.

6.1.8 Sustained Attention and ADHD

Inattention has been particularly problematic as a construct in ADHD. Douglas (1983) points out that an array of labels has been created to designate different features of attention. Among those implicated as impaired in ADHD are 1) the capacity to selectively focus, so that potential distractions do not result in impaired attentional performance, often referred to as 'selective attention', and 2) the capacity to maintain attentional performance over time, often called 'sustained attention' (Hooks et al., 1994). CPT studies have revealed that children, adolescents and adults (Epstein et al., 2001; Loo et al., 2003; Seidman et al., 1998) with ADHD are poorer and slower at detecting targets. Frontal lobe dysfunction has been reported in children with ADHD (Shue & Douglas, 1992).

Children with ADHD are consistently impaired on sustained attention, including continuous performance tasks (CPT) (Shallice et al., 2002), sustained attention subtests of the Test of Everyday Attention for Children (TEA-Ch) (Manly et al., 1999), and SART (Sustained Attention to Response Task; Robertson, Manly, Andrade, et al., 1997) (Shallice et al., 2002). Event-Related Potential (ERP) studies of children with ADHD (Novak et al., 1995) show right frontal abnormalities associated with sustained attention deficits.

There is considerable opposition to the existence of a sustained attention deficit in ADHD (Huang-Pollock & Nigg, 2003; Sergeant et al., 1999; van der Meere & Sergeant, 1988a, 1988b). Halperin et al. (1992) present data showing that inattention is not unique to ADHD. They warn against the ADHD diagnosis carrying the name of the symptom domain of attention. As there is a high proportion of non-ADHD children who are inattentive, other psychiatric diagnoses are at risk of being mislabelled ADHD. Additionally, there is much debate as to the periods of time over which sustained attention can be measured. Traditional views of vigilance emphasize decrements in the capacity to maintain an alert state over extended periods of monitoring (e.g., 10's of minutes), with target detection becoming poorer with increasing time-on-task (the so called vigilance decrement). However, sustained attention may operate over considerably shorter periods (Robertson, Manly, Andrade et al., 1997; Sturm et al., 1999), perhaps explaining inconsistency in time-on-task effects in ADHD. Research shows that right fronto-parietal systems are active over periods as short as 40sec (Pardo et al., 1991), and perhaps even over briefer periods as short as 12 seconds (Whitehead, 1991). Numerous imaging studies suggest that sustained attention is achieved through a predominantly right-focused network (Posner & Driver, 1992; Manly et al., 2003). Judgment of time intervals up to several seconds is also right lateralized (Petrovici & Scheider, 1994). Additionally, the preSMA and frontal operculum (ventral premotor cortex) are recruited when selectively attending to and estimating the passage of time (Coull, 2004).

There are clearly similarities between ADHD and patients with frontal lobe lesions, such as increased intra-individual variability found in both groups compared to controls (Hynd

et al., 1999; Stuss et al., 2003), as well as the sustained attention deficit reported in both groups (Robertson et al., 1997; Shallice et al., 2002). Distraction increases the size of errors made by the ADHD groups, but not by the controls in their time reproductions, as seen in Chapter 4. Therefore, sustained attention is examined to ascertain whether it may add to what is currently known and throw more light on the main question, namely; why is there a time deficit in ADHD?

6.1.9 Testing Sustained Attention

Observing attention or lack of it in people is obviously a difficult task as it is quite a subjective state. The simplest way to demonstrate it is by asking people to visually fixate on a computer screen over long periods of time and press a button every time they perceive a pre-determined target. This has generally been explored using variants of the Continuous Performance Task (CPT), a relatively unexciting task where attention must be maintained in order to monitor a stream (auditory or visual) in order to detect a rare target, with some forms requiring participants to detect a target and then to maintain attention in order to determine whether it is immediately followed by another, related target. For example, the original task of its kind asked participants to respond to the letter 'A' only if preceded by the letter 'X' (Rosvold et al., 1956). There is some debate regarding the interpretation of CPT performance deficits (Ballard, 1996). Stuss et al. (1995) argue that in a sustained attention task the schema mediating the appropriate response to a stimulus is deprived of externally driven activation for much of the time, as the events are repetitive, the discrimination required is relatively undemanding or targets

are separated by long intervals. At low levels of activation sustained attention and making the correct response becomes increasingly vulnerable to competition from other task-irrelevant schema which may be triggered by any distracting environmental or internal event. The more a sustained attention task manages to reduce the environmental support offered to the relevant schema, the better it will measure a person's ability to maintain subjectively willed supervisory control (their mind) on the task (Stuss et al., 1995).

Robertson, Manly, Andrade et al. (1997) distinguish between the capacity for endogenous modulation of alertness (self-sustained attention) with exogenously controlled alertness, which is governed by factors such as novelty, salience and stimulus change. They developed the Sustained Attention to Response Task (SART; Robertson, Manly, Andrade et al., 1997) which contrasts with previous perceptual detection paradigms used to test sustained attention requiring participants to respond to the infrequent target (e.g. Loken et al., 1995; Parasuraman et al., 1991). It has been argued that in these paradigms, where responses are required for rare target presentations, the automation of the simple target-response relationship rapidly minimize the need for active attention to task (Robertson et al., 1997; Manly et al., 1999). The SART requires a high level of continuous attention to response and is sensitive to transitory reduction in attention or 'lapses', while keeping to a minimum demands on other cognitive processes such as memory, planning and general intellectual effort (Robertson et al., 1997).

The SART is a computer based task designed to measure a person's ability to withhold responses to infrequent and unpredictable stimuli during a period of rapid and rhythmic

responding to frequent stimuli, in order to measure the person's capacity to endogenously sustain attention (Manly et al., 1999). Task performance is interpreted as reflecting the ability to sustain attention. In the standard version of the task, participants are presented with the digits 1 to 9 in random order as a rate of one every 1.15s. Each digit is presented for 250ms followed by a 900 ms mask and participants are required to respond to each digit as rapidly as possible by clicking the mouse, apart from when they see the number 3 when they must withhold the response. The task consists of a total of 225 trials (25 of each of the nine digits) and lasts approximately 4.3 minutes. Participants are instructed to respond as quickly as possible while making as few errors (i.e. incorrectly responding to a 3) as possible.

The central element of this test situation is that the continuous performance over 225 trials, together with the long and unpredictable intervals between targets, encourages the development of an automatic response to non-target 'go' trials and that vigilant monitoring is required to withhold this response on the infrequent 'no-go' target trials. *Withholding* to a rare target, as opposed to *responding* to a rare target in the case of CPT-like tasks, shifts the automatic response set to the non-targets and thus successful withholding places greater demands on the sustained attention system in order to overcome the pre-potent non-target response.

Manly et al. (2003) has shown that the endogenous maintenance of attention on the SART activates the alerting network (Posner & Peterson, 1990). Further, Robertson, Manly, Andrade et al. (1997) have demonstrated the sensitivity of the SART for indexing

self-reported absent-mindedness in adults, suggesting its utility as a task that indexes the transient lapses of attention that characterize ADHD. Shallice and colleagues have recently demonstrated the specificity of the SART for the sustained attention deficit of children with ADHD (Shallice et al., 2002). While evidence arising out of cognitive neuroscience suggests involvement of noradrenergic systems in sustained attention (Posner & Peterson, 1990; Smith & Nutt, 1996), two recent studies have found evidence for a DAT1 allele dosage effect on sustained attention capacity in children and adolescents with ADHD (Bellgrove et al., 2004; Loo et al., 2003). Loo et al. (2003) used a CPT in which subjects were required to respond each time any letter except the letter X was presented (and is therefore analogous to the SART). Those children in possession of two copies of the 10-repeat allele made more errors of commission (responses to the X) and were more variable (SD of RT) than those children who either did not possess this allele or possessed only one copy of it. Using the SART, Bellgrove et al. (2004) had similar findings.

The fixed-sequence Sustained Attention to Response Test ($SART_{Fixed}$) is a variant of the original SART test (henceforth referred to as $SART_{Random}$) (Robertson, Manly, Andrade et al., 1997). Successive digits (1-9) are presented in consecutive ascending order, rather than a randomly generated sequence of digits as in the original SART. Hence, the occurrence of the rare (no-go:3) target is entirely predictable. Manly et al. (2003) found activation differences between the two versions of the task using positron emission tomography (PET). The $SART_{Fixed}$ resulted in greater right dorsolateral prefrontal and parietal cortices activation than the original $SART_{Random}$. This was interpreted as

indicative of differing degrees of demand on a sustained attention system between the two tasks.

Fassbender et al. (2004) discovered two separate networks for the SART $_{Random}$ and Fixed SART, finding that response inhibition is more a component of the SART $_{Random}$ than the Fixed SART. During correct inhibitions on the SART $_{Random}$, activation was observed in the right ventral prefrontal cortex, right inferior parietal lobule, left dorsolateral prefrontal cortex and left putamen, consistent with previous findings in regard to response inhibition (Garavan et al., 1999; Konishi et al., 1998a, Rubia et al., 2001). Additionally, Moores and Andrade (2000) found a strong relationship between performance on the Random SART and the go-gap-stop test (GGST) of response inhibition.

The response-locked nature of the SART task allows RT to be equated across groups thereby satisfying an important internal control feature of the task. In a non-response locked / speeded task, errors of commission could reflect a response inhibition deficit, rather than a sustained attention deficit *per se*. Equating RTs across groups, makes this interpretation less likely. The fixed SART may require more controlled processing than the SART $_{Random}$, not because of the stimuli, but rather how difficult the task actually is. The SART $_{Random}$ might be perceived as being more difficult as a target can be presented at any time, unlike the Fixed SART where the presentation of the target is predictable. However, the fact that the Fixed SART is more boring makes it in fact more demanding on a person's endogenously maintained attention than the SART $_{Random}$. The SART $_{Random}$ is less taxing on a self-sustained attention system than the Fixed SART (Manly et al.,

2001). As participants must respond to all digits except for the occurrence of an unpredictable 3 digit, this task in addition to being a sustained attention task, requires response inhibition. Hence these two tasks were deemed suitable for exploring executive functioning in ADHD children.

In addition to using the Fixed and SART $_{\text{Random}}$ to explore the assertion that a deficit in time reproduction is as the result of an executive dysfunction, the ADHD children were tested and compared with matched controls on the The Test of Everyday Attention for Children (TEA-Ch; Manly, Robertson et al., 1998, 2001). This measures three domains of attention; sustained attention, selective attention and attentional control/switching. Multiple subtests assess each domain utilizing various sensory modalities during test administration, including visual, auditory, and motor modalities and hence the measure minimizes the potential confounding of attentional constructs with other factors such as motor speed, verbal comprehension (reading), expression (writing) and memory. The game-like format of the TEA-Ch increases the likelihood that a child will be engaged during test administration, and it closely simulates real world attentional demands, making it an ecologically valid measure of attention. ADHD children have consistently performed significantly worse on the sustained attention and attentional control factors, but not on the selective attention factor (Heaton et al., 2001; Manly et al., 2001).

6.1.10 Aims of current study

In summary, areas of the brain, thought to subserve sustained attention, such as the parietal cortex and dorsolateral prefrontal cortex are active over periods as short as 12 seconds (Whitehead, 1991), and as long as several minutes (Pardo et al., 1991). Sustained attention is achieved through a predominantly right-focused network (Manly et al., 2003; Posner & Driver, 1992) and judgment of time intervals up to several seconds is also right lateralized (Petrovici & Scheider, 1994). Frontal lobe dysfunction has been reported in children with ADHD (Shue & Douglas, 1992). This group are consistently impaired on sustained attention (Manly et al., 1999; Shallice et al., 2002). The current thesis finds a deficit in time reproduction in children diagnosed with ADHD. As yet, however, no connection between time reproduction, sustained attention and performance variability in ADHD has been investigated even though right frontal abnormalities have been associated with sustained attention deficits in ADHD (Novak et al., 1995).

Additionally, although sustained attention is asserted to be deficient in ADHD, there has been little investigation into the matter of whether ADHD-I are equally impaired in sustained attention. Many of the descriptors used to describe the inattention of the ADHD-I subtype such as 'daydreaming or getting lost in thought', 'sluggish cognitive tempo', 'slow processing', 'spacey', and 'lethargic' (Barkley, 1990; Carlson & Mann, 2002) would suggest such a deficit in ADHD-I as well as in ADHD-C.

The aim of this study was therefore to compare ADHD-C, ADHD-I subtypes and matched controls on various measures of attention for comparison with Time

Reproduction. Using the SART $_{Random}$, SART $_{Fixed}$ allowed an examination of sustained attention and response inhibition to explore the current authors assertions of the involvement of sustained attention in time reproduction, as well as the assertions of Barkley et al (1994, 1997) regarding response inhibition (see above). Comparing groups on the TEA-Ch allowed investigation of selective attention and atentional control/ switching, as further investigation of executive functions.

6.2 METHOD

6.2.1 Participants

Eighteen ADHD-C children from the previous sample were tested (Age 8.09 – 14.02; Mean = 11.5, S.D. = 2.1; 16% female). The mean estimated full scale IQ (Block Design and Vocabulary short form of the WISC-III) (Sattler, 1992) was 99.4 (SD = 12.7). Conners' Parent Rating Scale-Revised Long Version (CPRS-R:L) (Conners, 1998), yielded a mean Conners DSM-IV score of 83.1 (SD 5.4).

Eighteen children meeting DSM-IV (American Psychiatric Association, 1994) criteria for ADHD-I were also tested (age 9.02 –15.01 (mean = 12.0, S.D. = 2.02; 22% female); mean estimated full-scale IQ of 95 (SD = 11.8); mean Conners' DSM-IV score 70.9 (SD = 9.4)

While the two patient groups differed in the frequency of ODD (Oppositional Defiant Disorder), with this being more frequent in the ADHD-C group (χ^2=8.725,df =2, p= .013), they did not differ significantly in the proportion having Conduct Disorder,

Comorbid Reading Disorder (RD), Depression or anxiety disorder. They differed significantly on the Conners DSM-IV hyperactive/impulsive subscale ($t = -5.515$, $df = 34$, $p < .0005$), thereby perhaps providing further confirmatory evidence for the subtype difference.

A subset of sixteen of the original group of control children (18% female) (9.01-15.10 years; Mean =12.06years, SD=1.7; Mean IQ=103.3, SD=8.5) were selected on the basis of being matched to the ADHD participants on age and gender. All were in good physical health, with no known cognitive or behaviour problems.

6.2.2 Materials and Procedures

The Sustained Attention to Response Test (SART) - $SART_{Random}$ (Robertson, Manly, Andrade, Baddeley, Yiend, 1997).

The SART is a computerised test of sustained attention in which the digits 1-9 are presented on the screen and the participant must make a response to each digit, except a critical no-go '3' digit. In order to reduce the potential for speed-accuracy tradeoffs, participants are required to "lock" their response to a temporally predictable response cue that occurs after the presentation of the digit (Manly et al., 2000). In the random version of this task ($SART_{Random}$), the no-go digit occurs unpredictably within a pseudorandom order (Robertson et al., 1997). Performance on this task predicts everyday attentional failures (Robertson et al., 1997) and discriminates ADHD cases from controls (Shallice et al., 2002). Reaction times to the go-digits (Go-RT) are recorded and a measure of

response variability (SD $_{Go\text{-}RT}$/Mean $_{Go\ RT}$) is derived. Errors of commission on the no-go 3, as well as errors of omission on the go-digits, are recorded.

225 Digits from 1 to 9 (25 of each of the nine digits) were presented in random order over a 4.3 minute period. Each digit was presented for 313 ms, followed by a 125 ms mask (see figure). Participants were asked to respond with a key press to each digit, except on the 25 occasions when the digit 3 appeared, at which point the response was to be withheld. The target was presented in a pre-fixed quasi-random fashion where occurrence of the target trial was entirely unpredictable for the participant. The number 3 appears 9 % of the time and the sequence is ordered so that two or more 3's never appear consecutively. Participants were given a practice trial consisting of 18 presentations of digits, two of which were targets (see figure 6.1).

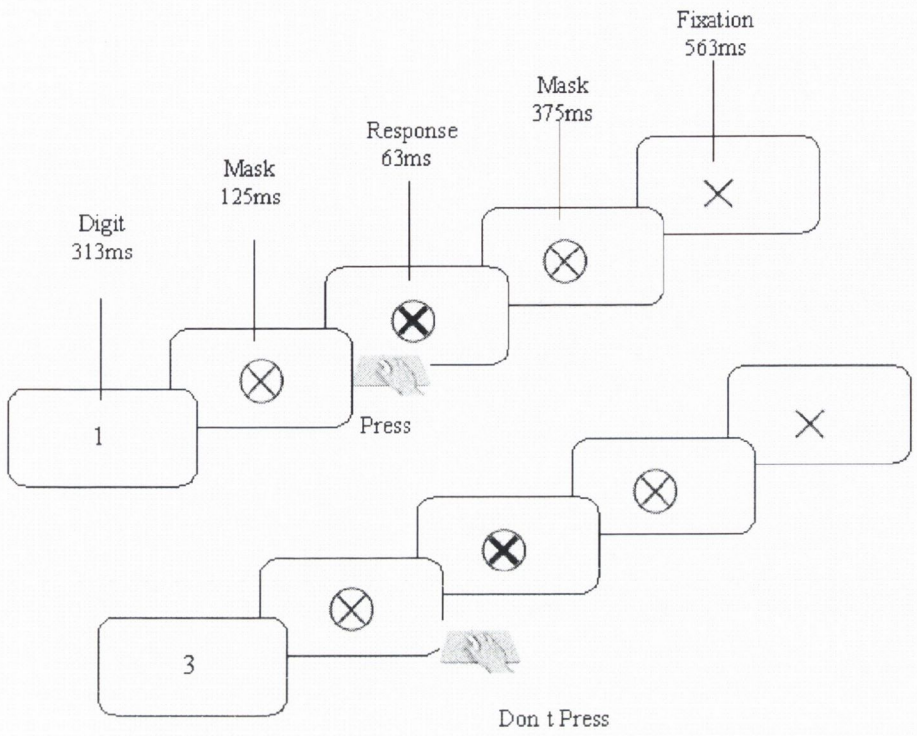


Figure 6.1: Sustained Attention to Response Task (SART) sequence. Adapted from Bellgrove et al. (under review). Participants were required to press to all digits (1-9), *except* the number 3.

The Sustained Attention to Response Task ($SART_{Fixed}$)

The fixed-sequence Sustained Attention to Response Test ($SART_{Fixed}$) is a variant of the original SART test (Robertson, Manly, Andrade et al., 1997) that activates right fronto-parietal sustained attention networks and is highly sensitive to sustained attention deficits (Manly et al., 2003). Participants respond to a fixed predictable sequence of 1,2,3 to 9 digits by a button press, and withhold to the number 3. 225 digits are presented of

which 25 are 3's. Inhibitory demands are very low as the onset of the no-go target can be predicted 9 trials in advance

Dependent measures for $SART_{Random}$ and $SART_{Fixed}$

The scores obtained included a) Total Errors (comprising errors of commission (i.e., failure to withhold to the no-go '3') plus errors of omission (i.e., failures to respond to the go digits); b) Mean RT (ms) to the go digits (GoRT); and c) the Coefficient of Variation in Reaction Time (defined as the SD_{GoRT}/Mean GoRT). This latter measure adjusts for differences in RT making it suitable for comparing intra-individual variability between patient and control groups (Manly et al., 2000; Stuss et al., 2003). Notably, the presentation of the Response Cue was designed to normalize reaction times (RTs) across participants in order not to disadvantage ADHD children with an impulsive response style.

Test of Everyday Attention for Children (TEA-Ch) (Manly, Robertson, Anderson, & Nimmo-Smith, 1998, 2001)

This 9-test battery is in a game format, with high reliability and confirmatory factor analysis/ structural equation modeling showing an exceptionally good fit with the underlying theoretical model of attention comprising the three factors of sustained, selective, and switching/control respectively (Manly et al., 2001). The TEA-Ch is normed for children ages 6-16 years. Five subtests assess the factor of sustained attention,

while two subtests each assess the factors of selective attention and attentional control/switching. It utilizes various sensory modalities (visual, auditory and motor) during test administration.

Dependent measures

The factor structure of the TEA-Ch has been established (Manly et al., 2001), showing three independent components of attention – sustained (subtests – Score!, Sky Search DT, Score DT, Walk, Don't Walk, and Code Transmission), selective (subtests – Sky Search Motor Control and Map Mission) and control (subtests – Creature Counting and Opposite Worlds). In most of the various subtests of the TEA-Ch a higher raw score represents better success. However, some of the subtests raw scores are the opposite, including Sky Search Time per Target, Sky Search Attention Score, Creature Counting Timing Score, Opposite Worlds, and Sky Search DT. Therefore it was necessary to transform some of the raw scores, so that all scores were in the same direction i.e. high score – good; low score = bad. Using the maximum score across the three groups (control, ADHD-I and ADHD-C), new scores were formed by subtracting each participant's score from the overall maximum score on that subtest. Mean and Standard Deviations were calculated for the control group for each subtest, thus standardizing according to the current independent sample rather than the normative sample (Manly, 1999). These were used to transform the raw scores into z scores for the individual groups. The z scores were utilized to derive the three factors of the TEA-Ch (sustained attention, selective attention and attentional control).

6.3 RESULTS

6.3.1 Test of executive functioning

SART $_{Random}$

The three groups did not differ in either age [F(2,48)=.293,p=.747] or IQ [F(2,48)=2.285,p=.113] .

A one-way ANOVA on commission errors revealed a main effect of Group [F(2,47)=9.832,p=0.0005] with ADHD-C (p =.0005) and ADHD-I (p=.003) significantly differing from controls, but not from each other. A one-way ANOVA on omission errors revealed a trend towards main effect of Group [F(2,47)=2.983,p=0.06] with ADHD-I (p=.056) appearing to influence the trend alone. A one-way ANOVA on the total number of SART $_{Random}$ errors (incorporating errors of commission and omission, as defined above) revealed a main effect of Group [F(2,47)=6.696,p=0.003], such that the ADHD-C group made significantly more errors (M=21.8,SD=9.9) on the SART $_{Random}$ than the control group (M=10.3,SD=7.2) (p =.02). The ADHD-I group also made significantly more errors (M=24.2,SD=15.7) than the control group (p = .004). The ADHD groups did not significantly differ (p= 1) from each other. There was no difference in the reaction times of the groups [F(2,47)=.783,p=.463]. There was however a significant effect on the Coefficient of Variation [F(2,47)=6.581,p=0.003], such that the ADHD-C group (M=.35,SD=.10) were significantly more variable than the control group (M=.26,SD=.06) [p = .02]. The ADHD-I group (M=.38, SD=.11) was also more variable than the control

group [p = .004]. The ADHD groups did not differ in their Coefficients of Variation [p=1] (see table 6.1).

Table 6.1. Group Comparison of SART Random Scores.

	ADHD-C (N=17)		ADHD-I (N=17)		Controls (N=16)	
	M	SD	M	SD	M	SD
Commission Errors	13.05	5.48	12.11	5.34	6.00	3.72
Omission Errors	8.76	7.24	12.11	12.84	4.31	5.73
Total Errors	21.82	9.92	24.23	15.78	10.31	7.23
Mean RT	546.151	96.11	571.08	137.24	596.13	106.02
Coefficient of Variation	.35	.10	.38	.11	.26	.066

A Pearson's Correlation was calculated to examine whether children who displayed larger errors also displayed increased intra-individual variability on the SART $_{Random}$ (i.e. between SART $_{Random}$ total errors and SART $_{Random}$ Coefficient of Variation). This resulted in a high positive correlation ($r = .583$, $p < .0005$, 1-tailed; $r^2 = .34$).

SART $_{Fixed}$

The three groups did not differ in either age [F(2,49)=.464,p=.632] or IQ [F(2,49)=2.294,p=.112] .

A one-way ANOVA on commission errors revealed a main effect of group (F(2,49)=11.105,p=0.0005). The ADHD-C (p<.0005) and the ADHD-I (p<.005) groups

made significantly more commission errors than the control group. A one-way ANOVA on omission errors revealed a main effect for group ($F(2,49)=4.415, p=.017$), with both ADHD groups differing from the control group ($p<.05$). ADHD groups did not differ from eachother (see table 6.2).

Table 6.2. Group Comparison of SART Fixed Scores.

	ADHD-C (N=18)		ADHD-I (N=18)		Controls (N=16)	
	M	SD	M	SD	M	SD
Commission Errors	7.16	3.71	5.94	2.36	2.62	2.27
Omission Errors	9.00	7.78	8.72	9.68	2.25	2.11
Total Errors	16.16	9.85	15.22	11.34	4.87	2.82
Mean RT	501.34	62.13	502.60	84.47	524.47	120.56
Coefficient of Variation	.44	.11	.36	.09	.29	.09

A one-way ANOVA on the total number of SART $_{Fixed}$ errors (incorporating errors of commission and omission, as defined above) revealed a main effect of Group [$F(2,49)=8.069, p=0.017$], such that the ADHD-C group made significantly more errors ($M=16.2, SD=9.8$) on the SART $_{Fixed}$ than the control group ($M=4.8, SD=2.8$) ($p=.002$). The ADHD-I group also made significantly more errors ($M=15.2, SD=11.3$) than the control group ($p=.002$). The ADHD groups did not significantly differ ($p=.1$) from each other.

There was no difference in the reaction times of the groups [F(2,49)=.340,p=.713]. There was however a significant effect on the Coefficient of Variation [F(2,49)=9.676,p=0.001], such that the ADHD-C group (M=.44,SD=.11) were significantly more variable than both the ADHD-I group (M=.36,SD=.09) [p = .049] and the control group (M=.29,SD=.09)) [p = .0005]. The ADHD-I and control groups did not differ in their Coefficients of Variation [p=.164].

A Pearson's Correlation was calculated to examine whether children who displayed larger errors also displayed increased intra-individual variability on the SART $_{Fixed}$ (i.e. between SART $_{Fixed}$ total errors and SART $_{Fixed}$ Coefficient of Variation). This resulted in a high positive correlation ($r = .651$, $p < .0005$, 1-tailed; $r^2 = .42$).

TEA-Ch

The three groups did not differ in either age [$F_{(2,67)} = 1.055, p = .354$] or IQ [$F_{(2,67)} = 2.918, p = .062$] .Three univariate ANOVA's revealed some significant group differences. On the sustained attention factor there was a significant group difference ($F_{(2,67)} = 12.03$, $p = .0005$), with ADHD-C ($p < .0005$) and ADHD-I ($p = .001$) making significantly larger errors than controls (see table 6.3). There was no subtype difference. As there was a trend towards a difference in group IQ's, a separate univariate analysis covaried for IQ, resulting in no significant difference to the original result.

On the attentional control factor there was a significant group difference ($F_{(2,67)}$ =3.307, p=.044), with the ADHD-C (p=.053) group making larger errors than controls. However, this effect disappeared when IQ was covaried for ($F_{(2,67)}$ =3.307, p=.044).

The selective attention factor revealed no significant group differences ($F_{(2,67)}$ =1.833, p=.168) (see Table 6.3 below).

.

Table 6.3. Comparison of TEA-Ch Subtest Scores (raw, age-scaled, z score)

			ADHD-C (N=27)		ADHD-I (N=18)		Controls (N=25)	
Factor	Subtest		M	SD	M	SD	M	SD
Sustained Attention	Score	Raw	6.88	2.30	7.77	1.92	8.64	1.11
		Age Scaled	7.51	3.53	7.77	3.49	9.48	2.51
		Z	-1.57	2.07	-.77	1.73	.00	1.00
	Sky Search DT	Raw	6.04	8.43	11.19	19.00	1.19	2.77
		Age Scaled	6.00	4.95	5.83	4.27	8.17	3.93
		Z	-1.81	3.19	-3.79	7.16	.00	1.00
	Score DT	Raw	12.76	3.26	14.55	3.05	17.40	1.68
		Age Scaled	6.28	2.83	7.94	2.79	10.88	1.92
		Z	-2.75	1.94	-1.68	1.81	.00	1.00
	Walk Don't Walk	Raw	12.30	2.67	13.05	3.45	16.56	2.80
		Age Scaled	5.96	2.63	6.72	3.30	10.64	3.60
		Z	-1.51	.95	-1.25	1.23	.00	1.00
	Code Transmission	Raw	29.08	6.63	32.50	7.35	38.04	2.05
		Age Scaled	5.65	3.92	7.66	4.24	10.92	2.36
		Z	-4.36	3.23	-2.70	3.58	.00	1.00
Selective	Sky Search	Raw	6.48	3.40	5.38	1.80	5.25	1.60
		Age Scaled	6.29	3.11	7.05	2.12	6.84	2.54
		Z	-.76	2.11	-.08	1.12	.00	1.00
	Map Mission	Raw	34.58	8.92	31.33	11.02	40.52	11.81
		Age Scaled	8.37	2.12	7.00	2.80	9.32	3.32
		Z	-.50	.75	-.77	.93	.00	1.00
Attentional Control	Creature Counting	Raw	5.62	2.21	5.44	1.96	4.37	1.20
		Age Scaled	6.59	3.36	6.62	3.46	8.80	3.02
		Z	-1.03	1.83	-.88	1.62	.00	1.00
	Opposite Worlds	Raw	38.49	10.17	37.23	10.21	31.89	6.12
		Age Scaled	6.24	3.28	6.33	3.23	8.16	2.19
		Z	-1.07	1.66	-.87	1.67	.00	1.00

As significant group differences were obtained in the sustained attention factor the subtests (Score, Sky Search DT, Score DT, Walk Don't Walk and Code Transmission) of this factor were investigated further with a serious of one-way ANOVA's and bonferroni corrected comparisons (see Figure 6.2 below).

The Score subtest revealed significant differences ($F_{(2,67)} = 5.763$, $p < .005$), between controls and ADHD-C ($p = .003$) with the ADHD-C group scoring significantly worse than controls (by at least 1.5 SD's) and ADHD-I. There was no difference between controls and ADHD-I ($p=.415$) or between the subtypes ($p=.362$).

Sky Search DT revealed significant differences ($F_{(2,67)} = 4.15$, $p < .02$), between controls and ADHD-I ($p=.016$), with the ADHD-I group scoring lower than the other groups (nearly 4 SD's below the control group and 2 SD's below the ADHD-C group) . There was no difference between controls and ADHD-C ($p=.426$) or the subtypes ($p=.416$).

Score DT revealed significant differences ($F_{(2,67)} = 18.353$, $p < .0005$) between controls and both ADHD-C ($p<.0005$) and ADHD-I ($p=.004$) with the ADHD-C group scoring the lowest of all groups (2.5 SD's below controls and 1 SD below ADHD-I). There was no subtype difference using a bonferroni post hoc comparison, but an LSD post hoc comparison revealed a significant subtype difference on this subtest ($p=.037$)

Walk-Don't Walk revealed significant differences ($F_{(2,67)} = 14.702$, $p < .0005$) between controls and both ADHD-C ($p=.0005$) and ADHD-I ($p=.001$), with ADHD-C having the

lowest scores of all groups (1.5 SD's below controls). There was not a significant subtype difference.

Code Transmission revealed significant differences (($F_{(2,67)}$ = 15.529, p< .0005) between controls and both ADHD-C (p<.0005) and ADHD-I (p=.007). The ADHD-C groups were the lowest scorers (nearly 4.5 SD's lower than controls, and over 1.5 SD's lower than ADHD-I). There was no subtype difference using a bonferroni post hoc comparison, but an LSD post hoc comparison revealed a trend towards a significant subtype difference on this subtest (p=.058).

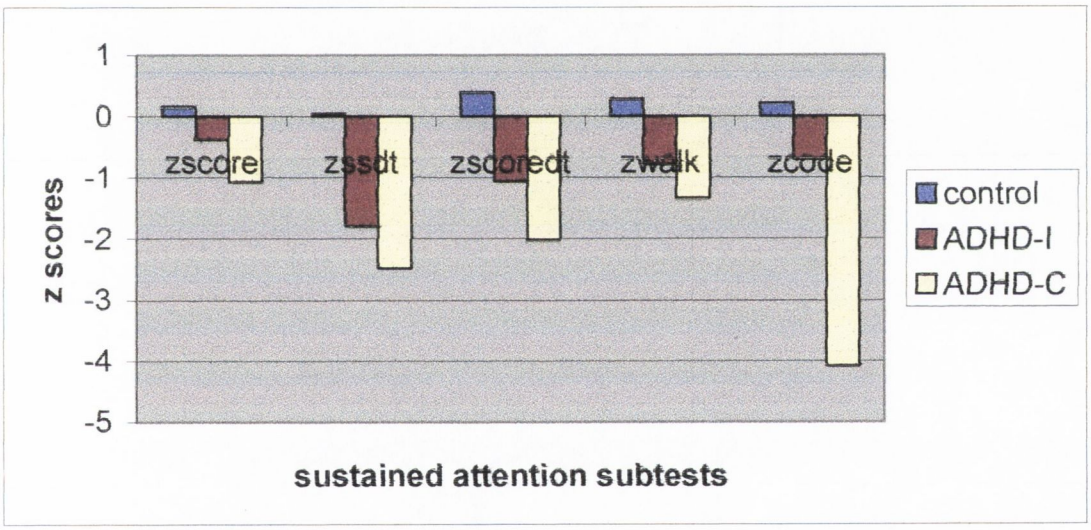


Figure 6.2: Comparison of sustained attention subtests of TEA-Ch using z scores

6.3.2 Time reproduction and executive functioning

The current analysis has revealed a subtype difference on the SART $_{Fixed}$, such that the ADHD-C group are significantly more variable than both the ADHD-I and control groups and the ADHD-I perform more similarly to the control group than to the ADHD-C group. Previously, in chapter 4, a subtype difference was found in time reproduction, with the ADHD-C group significantly more variable in the size of their errors than the ADHD-I group. A number of pearson's correlational analyses were run using the ADHD groups data to examine the links between variability at the time intervals and Fixed SART, Random SART Reaction Time variability (see Table 6.4 below).

Table 6.4: Comparison of Intra-individual variability on SART RT and Time reproduction

	$SART_{Fixed}$ RT variability	$SART_{Random}$ RT variability
Variability in coefficient at low interval (2-10 secs)	.054	-.078
Variability in coefficient at mid interval (12-24 secs)	-.127	-.020
Variability in coefficient at high interval (36-60 secs)	.399*	.193
Variability in absolute at low interval (2-10 secs)	-.013	-.128
Variability in absolute at mid interval (12-24 secs)	.171	.089
Variability in absolute at high interval (36-60 secs)	.237	.216

* $p < .05$ (N= 36, one-tailed)

** $p < .01$ (N = 36, two-tailed)

Note: *Absolute discrepancy score:* the absolute value of the magnitude of the discrepancy between the participant's time reproduction and the interval presented to the participant regardless of the direction. *Accuracy coefficient score:* determines whether the participants tend to err in one direction more than the other (under-vs. over-estimates) in the time reproductions. Scores of 1.00 equal perfect reproduction of the sample interval, scores above 1.00 reflect overproductions, and scores below 1.00 reflect underproductions.

As intra-individual variability at the *accuracy coefficient* of the high interval (36-60 seconds) and SART $_{Fixed}$ RT intra-individual variability were correlated when the two ADHD subtypes were combined for analysis, a similar investigation of this relationship was conducted for the subtypes separately. There were no significant correlations between the two variable for either of the subtype groups (ADHD-C: $r = .325$, $p = .110$; ADHD-I: $r = .180$, $p = .238$).

Intra-individual variability in SART $_{Fixed}$ RT and intra-individual variability in time reproduction were significantly correlated in the ADHD group. This provides some support for the connection between time and sustained attention. It could also reflect a common timing (cerebellar) problem. Pearsons Correlations between the ADHD groups time reproduction absolute discrepancy scores (size of error), accuracy coefficient score (direction of error) and the SART $_{Random}$ commission, omission and total errors were calculated to explore this relationship further. The ADHD groups were combined for these correlations as their scores did not differ on these measures (see Table 6.5 below).

Table 6.5: Comparison of SART $_{Random}$ and Time reproduction errors (size and direction)

	SART $_{Random}$ Commission errors	SART $_{Random}$ Omission errors	SART $_{Random}$ Total Errors
Absolute error at low (2-10 secs) interval	.377*	.219	.330
Absolute error at mid (12-24 secs) interval	.066	.015	.038
Absolute error at high (36-60 secs) interval	.185	.371*	.376
Coefficient at low (2-10 secs) interval	.320	.058	.176
Coefficient at mid (12-24 secs) interval	.092	.049	.077
Coefficient at high (36-60 secs) interval	-.046	-.380*	-.327

*$p < .05$ (N= 36, two-tailed)

** $p < .01$ (N = 36, two-tailed)

Comparison of SART $_{Random}$ commission, omission and total errors with absolute discrepancy scores (size of error), accuracy coefficient score (direction of error) in time reproduction found significant pearson's correlations between SART $_{Random}$ omission errors and both size and direction of error at the high interval. *Absolute Discrepancy* (size of error) at the low interval and SART $_{Random}$ commission errors were also significantly correlated (see Table 6.6 below).

Table 6.6: Comparison of SART $_{Fixed}$ and Time reproduction errors (size and direction)

	SART $_{Fixed}$ Commission errors	SART $_{Fixed}$ Omission errors	SART $_{Fixed}$ Total Errors
Absolute error at low (2-10 secs) interval	.311	.426*	.430*
Absolute error at mid (12-24 secs) interval	.024	.282	.221
Absolute error at high (36-60 secs) interval	.020	.338	.265
Coefficient at low (2-10 secs) interval	.218	.210	.241
Coefficient at mid (12-24 secs) interval	.006	-.155	-.121
Coefficient at high (36-60 secs) interval	.066	-.316	-.216

* $p < .05$ (N= 36, two-tailed)

** $p < .01$ (N = 36, two-tailed)

Comparison of SART $_{Fixed}$ commission, omission and total errors with absolute discrepancy scores (size of error), accuracy coefficient score (direction of error) in time reproduction found significant pearson's correlations between size of error at the low interval and both SART $_{Fixed}$ omission and total errors.

Significant differences were found between the ADHD groups and the control group on the sustained attention factor of the TEA-Ch. Therefore, using the combined ADHD

groups data, correlations between the TEA-Ch and time reproduction scores at each of the three time intervals (low:2-10 secs; mid:12-24 secs; and high: 36-60 secs) were calculated.

There were significant partial correlations (controlling for Group and IQ) between the sustained attention factor and the low interval (2-10 secs) *Absolute Discrepancy Scores* ($r = -.3193$, $p = .021$, 2-tailed; $r^2 = .10$). Significant correlations were also found between the sustained attention factor and the low interval *Accuracy Coefficient Scores* (direction of error) ($r = -.4873$, $p < .0005$, 2-tailed; $r^2 = .24$); and the low interval *Variability in Accuracy Coefficient Scores* ($r = -.2848$, $p = .043$, 2-tailed; $r^2 = .08$).

Had correction for multiple comparisons taken place, not all of the previous correlations would still stand, as the alpha level would be adjusted downward to consider chance capitalization. For example in the above analysis the alpha level would have been adjusted to .004 as the association between sustained attention and four calculations at three time intervals (.05/12) was being examined. Hence, the only correlation that would have remained intact in the previous paragraph would have been the sustained attention factor and the low interval *Accuracy Coefficient Scores* (direction of error) ($r = -.4873$, $p < .0005$, 2-tailed; $r^2 = .24$). The Bonferroni correction can cause a substantial loss in the precision of research findings, and therefore was not used in the current study.

Time Reproduction with Distraction Task

On the time reproduction with distraction task, the mean error in reproductions was significantly smaller when children were medicated (see chapter 5). As time reproduction alone was not effected by MPH, it is presumed that the effect of MPH on distraction is as a result of the improvement MPH has on the symptoms of attention in ADHD (see chapter 5). Hence a number of correlations were run to investigate time reproduction with distraction and executive functioning (see Table 6.7 below).

Table 6.7: Comparison of $SART_{Fixed}$ / $SART_{Random}$ and Time reproduction with distraction errors (size)

	Time Reproduction with Distraction errors (size)
$SART_{Fixed}$ Commission errors	.402*
$SART_{Fixed}$ omission errors	.703**
$SART_{Fixed}$ total errors	.665**
$SART_{Random}$ Commission errors	.349
$SART_{Random}$ omission errors	.738**
$SART_{Random}$ total errors	.740**

* $p < .05$ (N= 36, two-tailed)

** $p < .01$ (N = 36, two-tailed)

6.4.1 Summary of findings

Overall the results of this study are very interesting as they show that ADHD children in general have robust sustained attention deficits, confirming previous findings (Manly et al., 1999; Shallice et al., 2002). Both subtypes are clearly impaired relative to controls on tasks measuring sustained attention. The findings demonstrate that ADHD children regardless of specific diagnosis (ADHD-C or ADHD-I) have a very real problem in sustaining their attention to a variety of tasks relative to those without the disorder. This study has also found a relationship between time reproduction and both response inhibition and sustained attention. It provides further support for the notion that sustained attention may operate over relatively short time periods (Posner & Peterson, 1990; Robertson, Manly, Andrade et al., 1997).

6.4.2 SART $_{Fixed}$

The $SART_{Fixed}$ total errors (both commission and omission errors) succeeded in discriminating between the ADHD groups and matched controls, with ADHD groups making more errors than the controls. There was no difference in the reaction time of the groups indicating that the response cue had been successful in equating the RTs of the groups. This task revealed significantly more variability in the ADHD groups than in the control group. Of particular interest on this task was the difference in variability that emerged between the two ADHD subtype groups, with the ADHD-C group emerging as significantly more variable in their responses than the ADHD-I group.

6.4.3 SART $_{Random}$

In the SART$_{Random}$ participants perform a Go/No-go task in which they respond to all digits except for the occurrence of an unpredictable 3 digit. Thus in addition to sustained attention, this task requires response inhibition The SART $_{Random}$ revealed a significant difference between the ADHD groups compared to the control group in total errors. The groups differed significantly in their commission errors. There was also a trend towards a significant difference in Omission errors between the control group and the ADHD-I group but not between the control and the ADHD-C group. The groups did not differ in their reaction times on the SART $_{Random}$. The ADHD groups were significantly more variable than the control group.

6.4.4 TEA-Ch

The TEA-Ch results revealed large group differences on all tests of sustained attention. The groups did not significantly differ on measure of selective attention or attentional control. On four (Score, Score DT, Walk Don't Walk and Code Transmission) of the five subtests, the ADHD-C groups scores were consistently lower than both the ADHD-I and control groups.

6.4.5 Time Reproduction, sustained attention, response inhibition

It appears that although response inhibition does have a part to play, sustained attention is also involved. At the high time period, where underestimation is the norm for all groups (with ADHD groups underestimating significantly more than controls), response

inhibition contributes at least in part to the time reproduction deficit, consistent with Barkley's (1997) assertion that sense of time is related to response inhibition. Nevertheless, sustained attention must also be considered over all intervals of a time reproduction task. This is consistent with recent research claiming that sustained attention is involved over much shorter periods than originally thought (Robertson, Manly, Andrade et al., 1997; Sturm et al., 1999). Sustained attention might also be connected to variability.

There were also strong correlations between the time reproduction with distraction task and both SART $_{\text{Fixed}}$ and SART $_{\text{Random}}$. A relationship may exist between the effect of distraction on time reproduction errors and response inhibition due to the need for adequate inhibition in the form of interference control. This finding is logical, as ADHD is generally associated with a behavioural inhibition deficit, and ADHD children are described as being easily distracted. Additionally, a relationship would exist between the effect of distraction on time reproduction errors and sustained attention based on findings that that the less people attend to time, either implicitly or explicitly, the more they underestimate stimulus duration (Macar et al., 1994) and given that a distraction limits attention and working memory (Zakay, 1992). However, this finding must be treated with caution and cannot be interpreted further, as it was not possible to investigate the time intervals separately on this occasion.

6.4.6 Response inhibition

Scheres et al. (2004) examined the existence of deficit in response inhibition in ADHD, but found that when she covaried for age, IQ, and comorbidity the differences between her clinical and 'normal' groups disappeared. In the current study, when all of the above factors were covaried for the significant group difference remained. This further supports Houghton's (1999) findings, that response inhibition is impaired in ADHD, and also that this is the case for not only the hyperactive/ impulsive ADHD child but also for the inattentive children, who have either very few or no hyperactive/impulsive symptoms.

6.4.7 Subtypes and Response inhibition

Of major interest is the finding that both ADHD-C and ADHD-I subtypes of ADHD are impaired relative to controls on measures of sustained attention and response inhibition. On the SART $_{\text{Random}}$ the ADHD groups had significantly more commission errors (making a response when required to inhibit the response) than did the controls. The ADHD subtype groups did not significantly differ from each other in their commission errors. This questions Barkley's (1997) assertion that an EF deficit exists only in the hyperactive/impulsive subtypes of ADHD. He proposes that the attentional components of the two subtypes are different in cognitive function and neurological origin (Barkley, 1997). Although ADHD-C children are observably more impulsive/ less inhibited than ADHD-I children, there appears to be a problem in response inhibition in the ADHD-I group, almost comparable to the ADHD-C group. Though ADHD-C children exhibit

more impulsive behaviours, less self-control, as well as increased externalized problems compared to ADHD-I children, there appears to be an underlying neurocognitive impairment that exists in both subtypes of the disorder.

6.4.8 Subtypes and sustained attention

The significant subtype difference in Score DT (TEA-Ch) in the present study coupled with the trend towards a significant difference on Code Transmission (TEA-Ch) in post hoc LSD analysis is worthy of comment. The Score DT task required doing two things at once; keeping count of scoring sounds, where there are large silences between the sounds while simultaneously listening to short news stories and trying to pick out an animal which is mentioned during the course of the story. This task measures the child's ability to sustain their attention on the less appealing aspect of the task in the face of competition from the interesting news stories. The Code Transmission task requires the child to listen to a long series of spoken numbers, and identify certain patterns. It is an extremely monotonous and non-engaging task requiring actively maintaining attention in order to identify the important numbers. Although the post hoc analysis of these tasks finding a significant subtype difference are not the most stringent, it could be that what we are faced with is an issue of statistical power, as the groups are small. Both tasks are measures of sustained attention, and group comparison results on the tasks point towards evidence for a link between ADHD-C (who have the lowest scores) and a larger deficiency (than ADHD-I) in sustained attention.

However, although ADHD-C made more errors than ADHD-I on four of the five subtests of sustained attention, it is interesting that ADHD-I made more errors than ADHD-C on Sky Search DT. To obtain the dual task decrement in Sky Search DT, the 'time per target' score from Sky Search (a tests of selective attention), is subtracted from the weighted 'time per target' score in Sky Search DT. On Sky Search 'time per target' the ADHD-I group was lower (made more errors) (see table 6.3) than the ADHD-C group (two standard deviations below), meaning it took them longer to find the targets. This may actually represent either a more cautious approach to the task, or a slower level of processing than the ADHD-C group. The former is in line with Manly et al.'s (1999) assertions that as there is no restriction on time given to complete this task, a lower score on this task can represent a child who searches thorough the same spaceships repeatedly in an attempt to find more targets that are not there. The latter is in line with some of the previous descriptors used to describe the inattention of the ADHD-I subtype such as sluggish cognitive tempo, slow processing, spacey, and lethargic (Lahey et al., 1994; Milich et al., 2001). Either way, the lower ADHD-I scores on this task might represent something other than a sustained attention deficit, as the ADHD-C group were the lower scorers on all other sustained attention tasks.

6.4.9 Sustained Attention/ Response Inhibition and Intra-Individual Variability

One of the more pertinent findings to emerge in this study is that both ADHD groups are significantly more variable than the control group on the measures of sustained attention and response inhibition, taking reaction time into account. This supports previous research findings of more variability in the responses of ADHD compared to control

participants (Douglas, 1972; Kuntsi et al, 2001; Sergeant et al., 1999; Smith et al., 2002; Toplak et al., 2003), and research indicating a connection between intra-individual variability, sustained attention (Manly et al., 2000) and response inhibition (Bellgrove et al., 2004).

Importantly, on a task measuring sustained attention, a definite discrepancy between the two ADHD subtypes appears to lie in their intra-individual variability (Coefficient of Variation in Reaction Time). The ADHD-C group displayed significantly more intra-individual variability than the ADHD-I group. The ADHD-C group emerges as the most variable of the three groups. The ADHD-I and control group did not significantly differ in variability. In Chapter 4, it was demonstrated for the first time that ADHD-I and ADHD-C differ in time reproduction abilities, specifically in terms of variability at high time intervals. The current chapter has shown that variability in time reproduction correlates with measures of sustained attention and response inhibition subserved by brain networks also implicated in time perception. The ADHD groups could be distinguished in intra-individual variability in the size of their errors at high time periods (36-60secs). Variability in the direction of these errors was significantly correlated with SART $_{\text{Fixed}}$ variability, i.e. more variable under-estimations in time reproduction was related to more variable performance on a sustained attention task.

As the ADHD-C and ADHD-I groups differed in their performance variability at the high time interval, and variability at this interval was separately related to sustained attention performance across the ADHD groups, it is tempting to assert (as suggested earlier, in

relation to TEA-Ch scores) that in addition to a greater time reproduction deficit, the ADHD-C group may have a more pronounced sustained attention deficit than the ADHD-I group. Nevertheless, the relationship between sustained attention and time reproduction was observed for the variability in the direction (over- vs. under- estimation) of reproduction errors, whereas the ADHD subtype effect was observed for the variability in absolute reproductions (size of error). However, this discrepancy is not of concern as correlations occurred between variability at accuracy coefficient score and absolute discrepancy score (see chapter 4). Hence, the common feature in both sustained attention and time reproduction are whatever processes are causing the variability. Bellgrove et al. (2004) examined the relationship between SART total errors and the Coefficient of Variation. After controlling for the effect of Group, the Coefficient of Variation remained a significant predictor of error confirming it as an important index of sustained attention capacity. Although the time deficit seen in chapter 4 is very real, there appears to be some sort of underlying connection between it and sustained attention that is evident through subtype differences in variability (which appears to be the most sensitive measure of subtype difference). The variability issue appears to be a feature of the connection between time and sustained attention, rather than solely response inhibition, as the subtypes do not significantly differ from each other in response inhibition. Response variability may indeed be an important marker for impaired sustained attention (Bellgrove et al., 2004; Manly et al., 1999; Stuss et al., 2003) in ADHD.

Variability in the direction of the errors at the low time period was also related to a sustained attention task (sustained attention factor of the TEA-Ch). Though there was not

a significant group difference in the variability at this interval, (when the groups were explored using a repeated measures design with all time intervals on *Variability in Accuracy Coefficient Scores*), independent t-test revealed significant differences between the ADHD groups compared to controls, with the ADHD groups showing more intra-individual variability than controls in the direction of their error. Since time reproduction at shorter time intervals is thought to rely at least in part upon sub-cortical structures such as the basal ganglia and/or cerebellum (Ivry & Keele, 1989; Rao, 2001) these results support differential involvement of these regions, at least with respect to time reproduction, in the groups of ADHD children studied.

Variability in time reproduction might relate more closely to sustained attention than does either the absolute magnitude or direction (over- vs. under-estimation) of time reproduction errors, since a relationship was observed between time reproduction variability and sustained attention deficits. The relevance of performance variability as a marker of impaired top-down attentional control is demonstrated by studies of patients with focal frontal lesions (Stuss et al., 2003). These results provide empirical support for the relationship between sustained attention and time reproduction that has hitherto been inferred based upon common right-lateralised neural circuitry thought to subserve these processes (Pardo et al., 1991; Posner & Petersen, 1990; Rubia, Smith et al., 2003). The importance of attentional factors in adults' time perception is well established (e.g. Brown, 1985; Curton & Lordahl, 1974; Underwood & Swain, 1973; Zakay & Tsal, 1989). The attentional model views time estimation as a direct function of the amount of attention that is allocated for processing the passage of time. The less we attend to the

temporal properties of a stimulus, the more likely we are to misperceive its duration (Coull et al, 2004). When attention is diverted, a systematic shortening of subjective duration occurs, implying that pulses from the timekeeper may be lost (Rao et al., 2001). Attention may also mediate the flexible starting and stopping of pulses from the timekeeper, which enables anticipation of predictable events (Zakay & Block, 1996).

These results support an emerging view that intra-individual differences in performance variability, rather than simply adding random noise, may provide important clues regarding the efficiency of cognitive processes within clinical populations (Stuss et al., 2003). This line of reasoning is particularly germane to ADHD research where it is the moment-to-moment fluctuations in performance and lapses of intention and attention that arguably characterize the disorder (Castellanos & Tannock, 2002).

The present study provides some support that increased performance variability is at least in part due to problems in top-down allocation of attention. This is consistent with recent studies that have observed relationships between intra-individual variability and response inhibition (Bellgrove et al., 2004), and between intra-individual variability and sustained attention (Manly et al., 2000), with lower performance variability being related to more success on measures of the two domains. Conceivably, it is in this very topic of intra-individual variability that the discrepancy between the subtypes exists. Hynd et al. (1999) discovered that ADD-H (with hyperactivity) children performed significantly more variably than controls on several speeded classification tasks whereas the ADD-WO (without hyperactivity) group did not. The current findings point to the same incongruity,

with ADHD-C children performing in a more variable manner than both control and ADHD-I children. It could be argued that having more hyperactive/impulsive symptoms leads to more variability in responses, as the ADHD-I group (who have little or none of these symptoms) are more similar in their response to the control group than they are to the ADHD-C group. It appears that there is some connection between hyperactive/impulsive symptoms and variability that cannot clearly be explained by deficits in either response inhibition or sustained attention, as this variability is evident in tasks measuring both domains.

There have been many suggestions as to why more variability is evident in ADHD compared to controls, for example that it signifies a pervasive manifestation of regulatory problems involving the inconsistent allocation of effort (Oosterlaan & Sergeant, 1996; Douglas, 1999); that it suggests a problem with attentional focus (Toplak et al., 2003); and that it indicates executive problems in top-down allocation of attention (Leth-Steensen et al., 2000).

Stuss et al (2003) found that intra-individual variability is significantly increased in patients with focal frontal lesions compared to controls and patients with non-frontal lesions. It is increased particularly in those with left and right dorsolateral frontal lesions and those with superior medial frontal lesions. Patients with inferior medial lesions, however, have normal levels on Intra-individual variability, indicating that increased Intra-individual variability is not simply due to brain damage. Stuss et al. (2003) assert that variability is related to executive control of the deployment of attentional resources. He states that lesions in the right dorsolateral frontal lobe impair sensitivity –the ability to

differentiate the correct stimulus- and in this group the overall error rate is associated with intra-individual variability. These patients are insensitive to errors. In the current thesis, error rate correlated with intra-individual variability on all measures used. Further the results on all measures show that there is not necessarily a relationship between an individuals' lengthening of RT and individual variability. Although ADHD groups were significantly more variable than controls in their reaction times, they did not exhibit longer reaction times than controls. This is in accordance with Stuss et al.'s (2003) examination of various reaction time measures with frontal lesion patients.

Given the common underlying brain areas involved, the similarities between frontal patients and ADHD become clearer with the current findings. Perhaps it is, in part, an inability to differentiate between stimuli as a result of an inability to sustain attention consistently that causes the increased variability in ADHD compared to controls, and additionally what causes the ADHD-C group to be even more variable in their responses than the ADHD-I group.

Stuss et al. (2003) declared that sustained attention could not account for variability as there were no consistent changes in the slope of performance over time amongst patients with frontal lesions. However, with the current findings we can see that sustained attention is related to time reproduction. It is possible that the other areas of the brain, which are involved in ADHD outside of the frontal lobes, must be examined more specifically, for a connection with intra-individual variability. Stuss et al.'s (2003) non-frontal group comprised a combination of posterior hemispheric patients. It is possible

that this non-frontal group did not include patients who had lesions located in areas of the brain associated with ADHD, namely the cerebellum and the corpus callosum.

6.4.10 Response Inhibition and Sustained Attention: An Overlap

Finally, it must be noted that the patterns of correlations between the various tasks measuring response inhibition and sustained attention with the time reproduction were extremely similar, proving firstly that it is quite difficult to separate the domains of RI and SA and secondly that it is difficult to test them separately.

Barkley (1994) suggests that attention is a multidimensional construct and that the dimensions most impaired in ADHD have as their basis a response inhibition deficit. He further contends that 'where difficulties with attention have been noted, they have been most reliably found on measures of sustained attention or persistence of responding and are highly correlated with deficits in response inhibition'. He concludes that attentional difficulties observed in ADHD reflect 'difficulty inhibiting responses to parallel activities that compete with the performance of the assigned task' (Barkley, 1994, p.18). It does not seem possible to disentangle inhibition from attention on the basis of the current findings. What is most apparent is that the two subtypes of ADHD differ from controls on all tasks of response inhibition and sustained attention even when age, IQ and comorbid disorders are covaried.

6.4.11 Conclusion

In conclusion, results of the present study suggest that two subtypes of ADHD (combined and inattentive) do manifest a deficit in sustained attention and response inhibition. This finding remains after controlling for IQ, and does not appear to be a function of comorbid Reading Disorder, ODD, Conduct Disorder, Depression, or Anxiety. The impairment is not connected to reaction time, as this does not differ between any of the groups. This study further provides support for excessive intra-individual performance variability in ADHD children compared to controls. It also reveals a significant response inhibition deficit in the inattentive subtype of ADHD, as well as the combined subtype.

This and the previous chapter have demonstrated that tasks of sustained attention show consistent deficits in ADHD children relative to a control group. In some cases, the results showed extremely dramatic deficits in the ADHD groups, for example on some subtests of the sustained attention factor of the TEA-Ch, the ADHD groups scored over four standard deviations below the control group.

While children can be reliably diagnosed as ADHD-I or ADHD-C using behavioural measures, they cannot be distinguished by the amount of errors they make on neuropsychological tasks. However, it appears they can be distinguished on variability in reaction time on tasks measuring sustained attention, and also in the variability of the size of their time estimations on a time reproduction task.

It seems that even though the diagnostic labels imply that one can have a problem with attention only or, a problem with attention in addition to a separate problem with hyperactivity/ impulsivity, that an attempt made to examine these domains with neuropsychological tasks separately amongst the two subtypes results in quite similar results for the two groups (ADHD-C and ADHD-I), except in their variability, which most definitely should be considered for further investigation.

It is evident that both sustained attention and response inhibition are implicated in a task measuring time reproduction in ADHD children. There also appears to be a very real deficit of time perception in the ADHD groups, as when both sustained attention and response inhibition are accounted for, the discrepancy in time reproduction between ADHD and 'normals' remains.

Chapter 7

Spatial Attention, Temporal Order Judgement, Time Reproduction and Sustained Attention

7.1.1 INTRODUCTION

Overview

Although the ADHD children can be distinguished from matched controls in their time reproduction, and ADHD-C and ADHD-I subtypes can be distinguished on the amount of variability in size of their errors on a time reproduction task, these errors and variability are not improved by methylphenidate (MPH). It is puzzling that time reproduction is unaffected by MPH given its links with sustained attention and response inhibition, as shown by the current thesis. Both sustained attention and response inhibition have consistently been found to improve as a result of MPH (O'Toole et al., 1997; Pelham et al., 1997; Tannock et al., 1995a). Furthermore, methylphenidate has been shown to decrease within subject variability of response in response inhibition (Tannock et al., 1995a, 1995b), and sustained attention (Sonneville et al., 1991).

It was therefore deemed necessary to use a further task having a temporal aspect, to establish whether a time deficit is influenced by other domains apart from sustained attention and response inhibition but have not to date been tested, namely that of spatial attention.

7.1.2 Spatial Attention and time perception

'Attention is distributed in time as well as space' (Coull, 2004)

Walsh (2003) discusses links between space, number and time and attempts to marry them in A Theory of Magnitude (ATOM). He states that there is evidence linking space and time in the neurological literature and makes reference to Critchley (1953) who noted that following parietal cortex damage, spatial and temporal deficits often coincide; 'Pure temporal disorientation...occurring independently of spatial disorders, is a rarer phenomenon, for more often, the two are combined'. Specifically, the right inferior parietal cortex is activated by spatial and temporal stimuli (Rao et al., 2001). Studies using transcranial magnetic stimulation (TMS) have shown that parietal cortex stimulation in humans can cause deficits in spatial tasks (Bjoertomt et al., 2002) and time discrimination (Walsh & Pasual-Leone, 2003). The co-occurrence of space and time neurons has also been shown in a single-unit study with rhesus monkeys in which neurons with spatial response fields in the posterior parietal cortex show an association between spatial and temporal responses (Leon & Shadlen, 2003).

That stimuli appearing in predicted locations are detected more rapidly and accurately than those that are not is well established (Posner, 1980). Coull & Nobre (1998) were, however, the first to show that similar benefits could arise when attention was paid (cued) to moments of time. Attentional orienting in time concerns how and whether information about time intervals can be used to optimize behaviour in directing attention to a point in time when a relevant event is expected. Using cues to inform subjects when and/or where

peripheral target stimuli would occur, Coull & Nobre (1998) showed how healthy adults had significantly faster reaction time when cues were spatially and/or temporally informative, as compared with neutral cues. They used PET and fMRI to compare the neural systems involved in temporal and spatial orienting of attention. There was considerable overlap between the activations seen in the two tasks in frontal and parietal regions. Performance in the temporal orienting task engaged activity in frontoparietal networks, which overlapped extensively with brain areas engaged by spatial orienting tasks. Parietal cortex, particularly on the right, was activated to a greater extent when participants directed their attention across both space and time together, as compared with either dimension alone. This area has previously found to be involved in both spatial attention and sustained attention (Corbetta et al., 1993; Pardo et al., 1991). Coull and Nobre (1998) found, however, that temporal orienting was associated more with the left posterior parietal and inferior premotor cortex, and spatial orienting was associated more with the right posterior parietal cortex. This suggests that although there is some anatomical overlap between spatial and temporal orienting, they also have different regional specialisations, and may affect stimulus processing in different ways (Nobre, 2001).

Nevertheless, activation of the right temporal-parietal junction (TPJ) when both spatial and temporal orienting coincided may reveal a site where different information regarding selection can interact (Coull & Nobre, 1998). The TPJ is involved in crossmodal attention tasks (Macaluso et al., 2001) and has also been implicated in neglect (Rafal & Robertson, 1995).

Findings from patients with spatial attention deficits in the form of hemi-neglect support a relationship between spatial attention and cognitive functions linked to processing of temporal intervals (Basso et al, 1996). Basso et al. (1996) found a patient with left spatial neglect overestimated durations in an interval comparison task (300/700 ms) and in a time production (1 second) task when stimuli were presented in the neglected space and underestimated those presented in the good field.

7.1.3 **Spatial Attention and neglect**

Spatial selectivity refers to the selective enhancement of perception at certain spatial locations. The neural substrates of the spatial orienting of attention in the human brain have been investigated by way of both brain imaging (e.g. Corbetta et al., 1993) and neuropsychological studies (see Mesulam, 1990 for review). Working with brain-damaged patients (Mesulam, 1990) or brain imaging of normal volunteers (Corbetta et al., 1993; Nobre et al., 1997), these studies have revealed a frontoparietal network of brain regions that support spatial orienting of attention. The core elements are posterior parietal cortex around intraparietal sulcus, frontal eye fields in lateral and medial premotor cortex, anterior and posterior cingulate gyrus, and subcortical areas (Corbetta et al., 1993; Mesulam et al., 2001; Nobre et al., 1997). TMS (Transcranial Magnetic Stimulation) of the posterior parietal cortex has been shown to disrupt spatial attention between 100 and 370 ms after the onset of a visual target (Chambers et al., 2004). The right angular gyrus appears to be part of a lateralized ventral frontoparietal network that

links the inferior parietal lobule, temporal lobe and ventral frontal cortex. This network mediates automatic (involuntary) shifts of attention to salient stimuli and serves an attentional alerting function (Chambers et al., 2004).

Problems with focused visual and associated spatial attention have been studied in patients suffering from unilateral visual neglect. The hallmark of the neglect syndrome is a spatial attentional bias toward the ipsilesional side (i.e. contralesional neglect). The most common form of unilateral visual neglect is when patients with damage to the right hemisphere neglect or ignore visual stimuli in the left half of space. Left neglect patients typically bisect horizontal lines significantly to the right of veridical center, as though they either ignore the majority of the left-hand side of the stimulus or are, alternatively, hyperattentive to the right side (Jewell & McCourt, 2000). The problem is not simply one of being unable to see what is presented to the affected side because such patients also show neglect on tasks involving images rather than visual perception (Bisiach & Luzzati, 1978). It has been asserted that neglect may not be a unitary condition, but a cluster of inter-related deficits that must be teased apart (Riddoch & Humphreys, 1983).

7.1.4 Spatial attention and sustained attention

An attention framework developed by Posner et al., (1984) broke down the mechanisms of directing visual attention in space into the following three elementary mental operations that can be performed covertly, without overt movements of the eyes or head: (1) disengagement from a current focus of attention (spatial disengagement); (2) directing attention to a new spatial location (spatial orienting); and (3) engagement of the target.

In Posner and Petersen's (1990) model of attention, an attentional orienting system (located primarily in the parietal cortex) can be influenced by the activity of an alerting sustained attention system. Functional imaging studies have localised a system for sustained attention in right frontal and parietal lobes (Cohen et al., 1988; Pardo et al., 1991) and for spatial attentional shifts in right superior parietal cortex (Corbetta et al., 1993), suggesting that the parietal cortex provides a common neuroanatomical basis for both sustained and spatial attention, allowing for interaction between the two processes.

The coexistence of deficits of sustained and spatial attention in patients with right-hemisphere damage has led to the suggestion that these processes might have partially overlapping substrates, and that the sustained attention system might provide a modulatory influence on the spatial attentional system, whereby an attentional orienting system (located primarily in the right parietal cortex) can be influenced by the activity of an alerting/ sustained attention system (located primarily in the right frontal and parietal lobes) (Posner & Peterson, 1990; Robertson, Manly, Beschin et al., 1997; Robertson, et al., 1998). Robertson and Manly (1999) state that it may be 'plausible from a neuroanatomical point of view to suggest that a fundamental deficit in unilateral neglect is a deficit in the ability to sustain attention independently of spatial location'. Robertson et al. (1995) provided evidence for this link by showing that sustained attention training in patients suffering from unilateral spatial neglect, which is most often associated with lesions to the right parietal cortex, resulted in improvement in unilateral neglect. After training patients to improve their ability to sustain attention, performance improved

during tests of spatial neglect as well as tests of vigilance. These findings suggest the existence of a relationship between sustained and spatial attention and provide support for Posner & Petersons (1990) model of attention.

The prior entry hypothesis proposes that paying attention to a stimulus accelerates the sensory processing of that stimulus, and in doing so, reduces the time necessary for the stimulus to be perceived (Schneider & Bavelier, 2003). Researchers attempting to measure perceptual latency have usually employed a temporal order judgment (TOJ) task, in which the observers report which of two stimuli they perceive first. The TOJ may be quantified by the point of perceived simultaneity (PPS), which is defined as the stimulus onset asynchrony (SOA) between two stimuli at which an observer is maximally uncertain about their temporal order.

7.1.5 Spatial Attention, sustained attention and ADHD

A number of studies have investigated and supported the existence of a subtle left-sided spatial inattention in ADHD (Nigg et al., 1997; Sheppard et al., 1999; Voeller & Heilman, 1988). Klimkeit et al. (2003) recently used the greyscales task to demonstrate that children with ADHD had an attenuated leftward attentional bias, perhaps reflecting the reduced strength of the right-hemisphere spatial attentional system in ADHD. The existence of left spatial inattention is consistent with findings from structural and functional imaging studies that reveal predominantly right-focused frontostriatal abnormalities in ADHD (Casey et al., 1997; Castellanos et al., 1994; Castellanos et al., 1996). Neglect is also seen following lesions to a range of dopaminergically-modulated

frontostriatal structures such as the caudate and putamen (Karnath et al., 2002), areas connected with the symptomatology of ADHD. When a Stimulant such as methylphenidate is administered, it normalises a right bias asymmetry in line bisection (Sheppard, 1999). It is suggested that this is as a result of increasing an underlying (right hemispheric) hypoarousal in structures that are involved in moderating response inhibition and arousal (Sheppard et al., 1999).

Bellgrove et al. (under review) investigated the relationship between sustained attention, spatial attention and an established genetic risk factor for ADHD, the dopamine transporter gene DAT1. They compared ADHD children and adolescents in possession of two copies of the "high-risk" 10-repeat DAT1 allele, to those with the none or one 10-repeat DAT1 allele "low-risk" and a matched control group. They used a computerised version of the Greyscales Task to measure spatial attention and the SART to measure sustained attention. The High-Risk DAT1 ADHD group, relative to the Low-Risk DAT1 ADHD group, exhibited both sustained attention deficits and attenuated spatial asymmetries. The Low-Risk DAT1 ADHD group, however, performed comparably to controls and did not display either sustained attention deficits or abnormal attentional asymmetries. Bellgrove et al. (under review) also found that ADHD children who responded very well to MPH showed right spatial bias/left-sided inattention on the Landmark Task, and belonged to a high risk DAT 1 as compared to children who had the low risk Dat1, left spatial bias/right-sided inattention and either no response or a mediocre response only to MPH. Overall, these results suggest that sustained attention

and spatial attentional anomalies in ADHD may be at least partly linked to dopaminergic function.

Dobler et al. (2003, 2004 in press) investigated the possibility of neglect in ADHD children using the Prior Entry Task. In the first instance, one child (JK) only was examined. On left-first trials (i.e. trials in which the first stimuli occurred in the left visual field), the child made significantly more errors than controls, but performed as well as controls on right-first trials. This pattern is consistent with that seen in adult unilateral neglect. This child was also examined on two sustained attention subtests of the TEA-Ch ('Score' and 'Walk Don't Walk'). JK showed a deficit compared to controls and normative scores. Dobler (2004, in press) also went on to find the same trends in a group of 'normal' children, with children who scored low on the tests of sustained attention also making significantly more mistakes on left first stimuli of the prior entry task. She also investigated a group of children with ADHD, and found a sustained attention deficit in this group, compared to controls. This group did not however, exhibit impaired performance on prior entry and other tasks of spatial awareness. This reflects earlier findings of no evidence for hemineglect using a visual target cancellation task (Ben-Artsy et al., 1996). The findings of neglect with ADHD children are thus variable and inconclusive.

7.1.6 Aims of study

A possible association has been found between deficits in sustained attention, temporal order judgement and spatial attention in ADHD (Dobler e al., 2003). A relationship in the

current thesis has been discovered between time reproduction and sustained attention in ADHD. There is an overlap in the areas involved in attentional orienting to time and space (Coull & Nobre, 1998). Hence, an initial attempt to explore the relationship between time, space, and attention in Attention Deficit Hyperactivity Disorder is made in this, the final experimental chapter of the current thesis.

7.2 METHOD

7.2.1 Participants

Sixteen children with Attention Deficit Hyperactivity Disorder Combined Type (ADHD-C) were recruited from Child Guidance Clinics and from ADHD Family Support Groups (Age 8.09 –15.04(Mean = 11.8, S.D. = 2.03; 13% female). The mean estimated full scale IQ (Block Design and Vocabulary short form of the WISC-III) (Sattler, 1992) was 99.82(SD = 13.45). Parents completed Conners' Parent Rating Scale-Revised Long Version (CPRS-R:L) (Conners, 1998), yielding a mean Conners DSM-IV score of 81.9 (SD = 5.13).

Eighteen children meeting DSM-IV (American Psychiatric Association, 1994) criteria for ADHD Inattentive Type (ADHD-I) were also recruited (Age 9.02 – 15.01(mean = 12, S.D. = 2.03; 22% female); mean estimated full-scale IQ of 95(SD = 11.86); mean Conners' DSM-IV score 70.9 (SD = 9.49).

Sixteen control children (9.01-15.10 years old; Mean = 12.06, SD = 1.71; Mean IQ = 103.31, SD = 8.57; 19% female) were recruited from primary schools in the Dublin

area. All children had been screened previously for dyslexia on The Dyslexia Screening Test (D.S.T.) (Fawcett & Nicolson, 1996). All were in good physical health, with no known cognitive or behaviour problems. Children who had an IQ score below 70 were excluded.

7.2.2 Materials and Procedures

Prior Entry Task (Dobler et al, 2003)

The Prior Entry task required participants to make TOJ (temporal order judgments) of stimuli and judge SOA (stimulus onset asynchrony) by indicating a forced choice of either right or left. The task was presented using a Dell laptop computer with an active matrix 287 mm X 216 mm screen. At the beginning of each trial a fixation cross of 10mm X 12 mm appeared on the screen. After an interval of 350ms, one asterisk was presented 90 mm to the left or 90 mm to the right of the fixation cross. Following a variable stimulus onset asynchrony (SOA) of either 50 milliseconds (ms), 100ms or 200 ms a second asterisk appeared at the opposite location. SOAs were presented in a random sequence, each occurring with equal probability. Sixty left-first and 60 right-first trials were presented with equal probability within a random sequence. The stimuli remained on the screen until a response was given. Between trials a masking pattern consisting of a central row of asterisks appeared on the screen. The experiment was administered in four blocks, each block containing the same number of targets in each condition.

Before each trial, the children were instructed to maintain their gaze at the fixation cross in the centre of the screen with the trials being triggered by the examiner when stable

fixation was achieved. Fixation was not controlled. The child was asked to say which star had appeared first, the response being entered into the computer by the examiner. No movements were required from the children – an important factor given previous evidence showing significant effects of unilateral hand movements on children's spatial awareness in this task (Dobler et al., 2001).

Prior Entry Task Dependent Measures

Six scores are obtained for each participant; Left Temporal Order Judgment errors (TOJ) at stimulus onset asynchrony's (SOA) of 50 ms, 100ms, and 200 ms and Right Temporal Order Judgment errors (TOJ) at stimulus onset asynchrony's (SOA) 50ms, 100ms, and 200ms.

7.3 RESULTS

7.3.1 Spatial Inattention/ Temporal Order Judgement

Prior Entry (Dobler et al, 2003)

The three groups did not differ in either age [$F(2,49)=.464, p=.632$] or IQ [$F(2,49)=2.294, p=.112$] .A three-way mixed ANOVA on TOJ error scores, with Group (controls, ADHD-I and ADHD-C) as the between subjects factor and Side (3 TOJ's) as the within-subjects factor [3 (Group) X 2 (Side) X 3 (TOJ)], revealed significant main effects for Group, ($F_{(2,47)} = 7.335$, $p< .01$) and for TOJ ($F_{(2,47)} = 112.167$, $p< .0005$), and for side (($F_{(2,47)} = 6.312$, $p< .05$). The interaction of Group X TOJ was significant ($F_{(2,47)} =$

4.595, p< .01). There was no Group X Side interaction ($F_{(2,47)}$ = 1.970, p< .151), or Group X Side X TOJ interaction($F_{(2,47)}$= .780, p< .541).

Table 7.1. Group Comparison of Temporal Order Judgement Errors.

		ADHD-C (N=16)		ADHD-I (N=18)		Controls (N=16)	
		M	SD	M	SD	M	SD
Left	SOA 50	4.8235	3.28320	5.1667	3.79241	2.1250	1.82117
	SOA 100	1.9412	2.04544	2.7778	2.75586	.9375	1.34009
	SOA 200	1.5882	2.52633	1.3333	1.57181	.0625	.25000
Right	SOA 50	6.0000	3.64005	6.1111	4.08568	2.3750	1.70783
	SOA 100	2.9412	2.24918	4.2778	3.95274	.5625	1.03078
	SOA 200	1.6471	1.86886	1.5556	1.58011	.0000	.00000

Analysis of simple main effects with Bonferroni corrections showed significant differences at SOA 50 (p<.01), between controls (M = 2.504) and ADHD-C (M = 5.449) and between controls and ADHD-I (M=5.377) (p<.01). There were significant differences at SOA 100 (p<.01) between controls (M=.917)and ADHD-I (M=3.356), but not between ADHD-C and controls (p=.123). At SOA 200 there were significant differences (p <.01) between controls (M= .00837) and ADHD-C (M = 1.625); and between controls and ADHD-I (M=1.390) (p<.05) (see Figure 7.1).

The control groups responses differed between SOA 50 and both SOA 100 (p<.0005) and SOA 200(p<.0005), however their responses did not differ between the two higher

SOA's (p=.221). The ADHD-I groups responses differed between each SOA (p<.0005). The ADHD-C groups responses differed between SOA 50 and both SOA 100 (p<.0005) and SOA 200(p<.0005), however their responses did not differ between the two higher SOA's (p=.107).

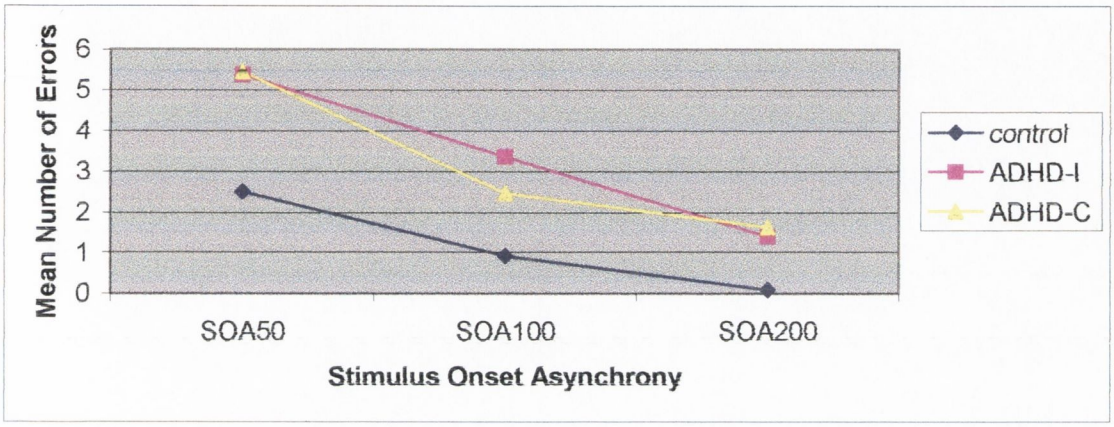


Figure 7.1: Temporal order judgement errors

ADHD-C and ADHD-I combined as one group vs. controls

Based on previous research (Dobler, 2003) a Group X Side interaction was expected – i.e. that ADHD participants would perform as well as controls on the right-first targets but significantly worse than controls on the left-first targets (ADHD people show inattention away from the left). As there was no significant Groups X Side interaction in the previous analysis, the ADHD-C and ADHD-I groups were combined as one group for further analysis to inspect whether an interaction might emerge due to an increase in power.

This analysis revealed a side X group trend ($F_{(1,47)} = 3.932$, $p = .053$) with the ADHD group making significantly less mistakes ($p<.01$) on the left hand side ($M= 8.82$) than they did on the right hand side ($M=11.3$), and making significantly more mistakes ($p <.0005$) overall than the controls. Control participants did not differ significantly in their left first ($M= 3.12$) or right first errors ($M=2.93$) ($p=.866$) (see Figure 7.2).

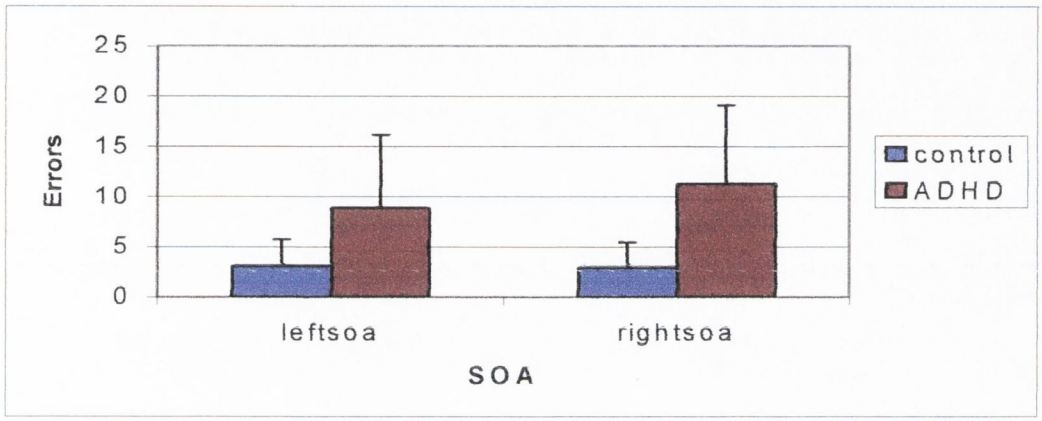


Figure 7.2: Comparison of ADHD vs. Controls on right first and left first Temporal Order Judgements

Perceived Point of Simultaneity (PPS)

If attention is biased to one side or the other, a stimulus on the relatively ignored side of space needs to appear earlier than one on the attended side in order for the two to be perceived as simultaneous. Logistic regression analysis (as used by Dobler, in press 2004) was implemented in the SPSS PROBIT command, to estimate the delay between left and right target onset at which children would have identified 50% of stimuli as right first (i.e. the estimated point of simultaneity). This analysis was conducted across SOA's. For the control group, this 50 % point was estimated at -2.31 ms (SD = 12.94), where left targets must precede right targets by 2.31 ms in order for both stimuli to be perceived as

appearing simultaneously. In contrast, for the ADHD group (ADHD-C + ADHD-I combined) the 50% point was estimated as +16.22ms (SD = 23.67), where right targets must precede left targets by 16.22ms in order for both stimuli to be perceived as appearing simultaneously. There was a trend towards a significant difference between the control and ADHD groups in their PPS ($F_{(2,47)} = 3.556$, $p < .066$).

7.3.2 Spatial attention, sustained Attention, response Inhibition

The ADHD group made significantly more errors than controls across all SOA's, suggesting a non-lateralised impairment in temporal order judgement. Using the ADHD group's data (two ADHD groups were combined for analyses as they did not significantly differ on these measures) correlations between these errors (irrespective of visual field), and both $SART_{Fixed}$ and $SART_{Random}$ performance were calculated (see Table 7.2 below).

Table 7.2 :Temporal Order Judgements (SOA 50, SOA 100 and SOA 200) with $SART_{Fixed}$ and $SART_{Random}$

	SOA 50	SOA 100	SOA 200
$SART_{Fixed}$ Commission	.397*	.352*	.503**
$SART_{Fixed}$ omission	.513**	.476**	.532**
$SART_{Fixed}$ Total	.573**	.541**	.609**
$SART_{Random}$ commission	.362*	.379*	.313
$SART_{Random}$ omission	.399*	.481**	.435*
$SART_{Random}$ Total	.463**	.536**	.473**

* $p < .05$ (N= 36, two-tailed)

** $p < .01$ (N = 36, two-tailed)

The relationship between Prior Entry and $SART_{Fixed}$, $SART_{Random}$ was further examined using multiple regression with all the groups data (controls, ADHD-C and ADHD-I). $SART_{Fixed}$ emerged as a predictor for SOA 50 (Beta = .608, p<.0005) ($F_{(2.46)} = 22.408$, p< 0.0005). Adjusted R square = .477), SOA 100 (Beta = .616, p<.0005) ($F_{(2.46)} =$,15.002, p< 0.0005). Adjusted R square = .373), and SOA 200 (Beta = .639, p<.0005) ($F_{(2.46)} = 25.648$, p< 0.0005). Adjusted R square = .512). $SART_{Random}$ did not emerge as a significant predictor in these models.

Prior Entry and TEA-Ch

To further examine this link between sustained attention and temporal order judgement, multiple regressions were performed with the Prior Entry and TEA-Ch. Group and the 3 factors of the TEA-Ch (sustained attention, selective attention and attentional control) were used as independent variables to assess their contribution to the temporal order judgements at each SOA (50, 100, and 200). The sustained attention factor emerged as the predictor variable for SOA 50 (Beta = -.357, p=.03) ($F_{(2.40)} = 6.798$, p= 0.003) (Adjusted R square = .216) and for SOA 200 (Beta = -.352, p=.031) ($F_{(2.40)} = 7.225$, p= 0.002) (Adjusted R square = .229).

7.3.3 Temporal order judgement and Time Reproduction

Using the ADHD groups data, correlations between the SOA's and both absolute discrepancy and accuracy coefficient scores at each of the three time intervals were calculated (see Table 7.3 below).

Table 7.3: Temporal Order Judgements (SOA 50, SOA 100 and SOA 200) and time reproductions (absolutes and coefficients)

	SOA 50	SOA 100	SOA 200
Absolute error at low (2-10 secs) interval	.460**	.350*	.415*
Absolute error at mid (12-24 secs) interval	.074	.133	.037
Absolute error at high (36-60 secs) interval	.075	.164	.098
Coefficient low (2-10 secs) interval	.455**	.388*	.459**
Coefficient mid (12-24 secs) interval	.036	-.079	.046
Coefficient high (36-60 secs) interval	-.003	-.121	-.044

* $p < .05$ (N= 36, two-tailed)

** $p < .01$ (N = 36, two-tailed)

A number of multiple regressions were run using all the groups data (controls, ADHD-C and ADHD-I) to examine the link between Temporal Order Judgements (SOA 50, SOA 100 and SOA 200) and time reproductions (absolute errors and accuracy coefficients).

Absolute Discrepancy Score

Using the enter method, a significant model emerged. Group (Beta = .295, p=.030) and SOA 50 (Beta = .422, p=.002) emerged as the predictor variables for *Absolute Discrepancy score* (2-10 secs, low). ($F_{(2.46)} = 14.381$, $p< 0.0005$). Adjusted R square = .358. SOA 100 and SOA 200 were not significant predictors in this model.

No significant model emerged for either Medium (12-24 secs) or high time (36-60 Secs) intervals using the SOA's (50, 100, 200).

Variability in Absolute Discrepancy Scores

Using the enter method, a significant model emerged. SOA 50 emerged as the predictor variable for *Variability in Absolute Discrepancy scores* (2-10 secs, low). (Beta = .317, p=.045) ($F_{(2.46)} = 4.498$, $p < 0.011$). Adjusted R square = .144. SOA 100 approached significance as a predictor (Beta = .526, p=.060). SOA 200 was not a significant predictor in this model.

No significant model emerged for either Medium (12-24 secs) or high time (36-60 Secs) intervals using the SOA's (50, 100, 200).

Accuracy Coefficient Score

Using the enter method, a significant model emerged. Group and SOA 50 emerged as the predictor variables for *Accuracy Coefficient* score (2-10 secs, low). (Beta = .522, p=.001) ($F_{(2.46)} = 6.421$, $p < 0.003$). Adjusted R square = .184. SOA 100 and SOA 200 were not significant predictors in this model.

No significant model emerged for either Medium (12-24 secs) or high time (36-60 Secs) intervals using the SOA's (50, 100, 200).

No significant models emerged for temporal order judgements and *Variability in Accuracy Coefficient score.*

7.4 DISCUSSION

7.4.1 Group Comparison

The results on the tasks of spatial attention are in ways the opposite to what one might have expected based on past research of ADHD, and its similarities with left hemispatial neglect patients. To be precise, there is no lateralised bias for controls, and a left lateralised bias in the ADHD group.

The prior entry results tell us that the control group are quite normal in their temporal order judgements; they make a comparatively very small amount of errors on both sides. They are better than the ADHD group on all intervals at detecting the correct target, regardless of SOA. The ADHD groups, however, make significantly more errors, perhaps indicating slower perceptual processing or inattention in these children. The results do not indicate neglect on the left side over the right side. In fact the ADHD group made less mistakes on the left than on the right! This is in line with findings by Ben-Artsy et al., (1996) using a Visual Target Cancellation Test, that 75% of ADHD children initiate scanning of a random array on the left side as opposed to 46% in controls, evidence against the notion of left-hemispace neglect. It was not possible to gain information as to where children were scanning in the current study (their fixation was not controlled), and therefore I cannot comment on this in the current sample. It is however something to consider in the future.

Of interest also, is an observation made by Ben-Artsy et al. (1996) that the major contributor of errors in all groups (ADHD, controls) were children who scanned chaotically irrespective of the side of its origin, with the ADHD group performing significantly more chaotically than the controls. Again this was not recorded in the current study, but it does make sense, in line with the increased intra-individual variability demonstrated on the time reproduction task, SART $_{\text{Random}}$ and SART $_{\text{Fixed}}$. Parents always report that the observable symptoms of ADHD vary from day to day, and hour to hour. Although there is no method for examining intra-individual variability with the Prior Entry, if ADHD children are performing more variably on all the other tasks, it is very possible that they are doing the same in their temporal order judgements. This is most probable given the links found between all tasks, and the findings of Ben-Artsy et al. (1996).

The ADHD groups performance on the prior entry reveal what appears to be pseudoneglect, which we would also have expected to see in the control group. There is no evidence of left side neglect, as would be expected due to similarities between the ADHD syndrome and unilateral neglect patients. The ADHD results do not reflect those of Dobler et al. (2003) with JK, but they do reflect her later findings of no relationship between the diagnosis of ADHD and leftward neglect (Dobler et al., 2004, in press).

It would have been expected, based on a left space advantage in 'normals' (Jewell & McCourt, 2000), that the control group would have needed right targets to precede left targets in order for the two targets to be perceived as simultaneous (PPS). Nevertheless,

this group required left targets to precede right targets, but only by a little more than two milliseconds. In fact the point of subjective simultaneity was at an SOA close to zero, as would be expected under conditions in which fixation is maintained centrally and attention is distributed equally between the two possible locations (Stelmach & Herdman, 1991). It was the ADHD groups who showed a left space advantage, needing right targets to precede left targets, by sixteen milliseconds, in order for the two targets to be perceived as simultaneous.

7.4.2 Prior Entry and attention

The problem with using the TOJ to measure prior entry is that inattention may act during multiple stages of the stimulus-response process and might influence the behaviourally measured PPS without affecting perception. The locus of attentional action has long been discussed in the literature, with some researchers believing that attention affects sensory processing (e.g. Bashinski & Bacharach, 1980; Downing, 1988) and others that attention only affects the decision process (e.g. Müller & Findlay, 1987).

It has been established that the ADHD groups did not show left neglect. They did however make significantly more errors than the control group, irrespective of side of first stimulus presentation. A non-spatially lateralised deficit was hence picked up in the current sample, and this is supported by the link to sustained attention. This was examined in relation to SART $_{\text{Fixed}}$ and SART $_{\text{Random}}$ performance to examine a connection between spatial attention and sustained attention (Dobler, 2003) and response

inhibition deficits (Sheppard et al., 1999). On this occasion the Prior Entry task did appear to overlap with a sustained attention deficit. It might be argued that Prior entry is another type of sustained attention task or at least has a sustained attention element to it. What is evident from these results is that a non-spatially lateralized deficit has been picked up in this sample. This is further supported by the link to sustained attention.

7.4.3 Prior Entry and Time

Mesulam (1981) showed that dysfunction of the right hemisphere network results in more severe and long-lasting spatial inattention than equivalent left hemisphere dysfunction because of the dominance of the right hemisphere for the control of spatial attention: while right hemisphere networks allocate attention to both left and right hemi-spaces, left hemisphere networks do so only for the right hemispace. Dysfunction of left hemisphere attentional networks can therefore be compensated readily by those on the right, but not vice versa. Left spatial inattention is therefore a more salient marker of right hemisphere dysfunction than the less commonly observed right inattention is of left hemisphere dysfunction. Coull & Nobre (1998) found that temporal orienting was associated with the left posterior parietal and inferior premotor cortex, and spatial orienting was associated more with the right posterior parietal cortex. There have been reports of parietal involvement in ADHD. Substantial increases in grey matter were recorded in large portions of the posterior temporal and inferior parietal cortices in children with ADHD (Sowell et al., 2003). That the current ADHD sample made significantly more errors in

their right first temporal judgements, is evidence that the prior entry may be picking up on a timing deficit rather than just a lateralized spatial deficit.

It also appears that temporal order judgments and time reproduction at low time periods have some common underlying mechanism. The temporal order judgments made at a stimulus onset asynchrony of 50 milliseconds, were the most difficult to judge for all groups, but particularly the ADHD groups. These were related to the size of error, variability in size of error and directions of error at the low time interval of the time reproduction task. In the previous chapter, time reproduction at the low time interval (where both ADHD groups made significantly larger errors than controls) was related to commission errors on the $SART_{Random}$ and to both omission and total errors on the $SART_{Fixed}$. Time reproduction at shorter time intervals is thought to rely at least in part upon sub-cortical structures such as the basal ganglia and/or cerebellum (Ivry & Keele, 1989; Rao et al., 2001). That time reproduction, temporal order judgement, sustained attention and response inhibition, are all linked, supports differential involvement of these regions, and a connection between all processes.

At the same time though, the current study also provides further support for a very real time deficit in ADHD. The shorter the SOA, the more difficult it was for all groups to judge the temporal order. At the shortest SOA (50 ms) the ADHD groups found it most difficult, with significantly more errors made than controls in detecting both right first and left first stimuli.

7.4.4 Prior Entry and Genes

Based on Bellgrove et al. (under review) findings using the Landmark Task it is possible that the majority of the ADHD sample used in the current study, if genotyped would belong to a low risk DAT1 group, who have left spatial bias/right-sided inattention. The current sample show left spatial bias/right-sided inattention similar to Bellgrove et al. (under review) Dat1 low risk sample. However, the current sample also show a very robust deficit in sustained attention compared to Bellgrove et al. 's low risk group who performed similar to matched controls on a test of sustained attention. Additionally, Bellgrove et al.'s (under review) DAT1 low risk sample had no or a mediocre response to MPH. In chapter 4 of this thesis, there was evidence of a good response to MPH based on CPRS-R. Specifically, and of most importance, there were significant differences found between medicated and non-medicated parent rated CPRS-R in the subscales measuring oppositional behaviour, inattention, hyperactivity. There was also evidence that these children respond to MPH in the time reproduction with distraction task.

7.4.5 Summary

There appears to be an association between sustained attention and spatial attention; between spatial attention and time reproduction and between sustained attention and time reproduction as extrapolated in the previous chapter. A connection has been found between all processes with temporal order judgements. The results provide evidence that ADHD may be characterized by a non-spatially lateralized deficit that is manifest across

SART, temporal order judgements and perhaps time reproduction, thus implying a right hemispheric dysfunction.

Chapter 8

General Discussion

8.1 ADHD

Attention Deficit Hyperactivity is a disorder that is full of uncertainties, both in its presentation and the contradictory performance of those diagnosed on neuropsychological tests. It is a disorder associated with a range of deficits, some of which are quite unsettling to the sufferer and others. Most of the deficits associated with the disorder are not outwardly obvious, yet still extremely disruptive to those who have it. Although there is a wealth of research examining this disorder, there is still a huge amount of debate as to what causes it and what can cure it. There are a range of theories which attempt to explain ADHD, currently the most popular ones being those that declare it as a disorder of executive functioning. There are however, multiple forms of the disorder (subtypes), making it very difficult to concur on one clear explanation. One aspect of the disorder that has only recently begun to receive much deliberation is that of a problem with the perception of time. The limited amount of attention it has received is however surprising, seeing as parents, teachers, and partners consistently remark on it.

8.2 Time Reproduction in ADHD

The current thesis has demonstrated that a time perception deficit is clearly an aspect of ADHD. It has also been shown that it is deficient in at least two subtypes of the disorder, and therefore is not linked solely to hyperactive/ impulsive symptoms. It has been

measured reliably on a time reproduction task (chapter 3) and it has been shown that both ADHD subtypes demonstrate significantly less accurate time reproductions than control children matched by age and gender (chapter 4). The time deficit is explored in relation to reaction time and distraction (chapter 4), medication (chapter 5), temporal order and spatial inattention (chapter 7), and various other aspects of attention (chapter 6). Although ADHD participants perform worse than controls on measures of sustained attention, response inhibition, temporal order judgement and reaction time, the time reproduction deficit remains when all of these factors are controlled. The finding of impaired time reproduction in ADHD-combined subtype children is consistent with previous research (Barkley et al., 1997; Kerns et al., 2001; Meaux & Chelonis, 2003). Among the most striking trends in the current and previous research is the constancy with which all groups make progressively greater time underestimations as the target time duration increases, with ADHD groups making significantly larger underestimations than controls.

8.3 Time Perception, Attention and stimulant medication

Difficulties in sustained attention impair initial encoding of material to be recalled and therefore, the retrieval of the material is often significantly impaired (Laatsch, 1998). Similar to TBI patients, people with ADHD often have difficulty sustaining their attention to what another person is saying, and therefore have a tendency to lose track of what is being said. Because there is a deficit in allocation of attention in ADHD, people frequently have difficulty processing more than one thing at a time. Both ADHD subtypes (ADHD-combined and ADHD-inattentive) made larger errors in their time

reproductions as a result of distraction (chapter 4). This concurs with Barkley et al.'s (1997) findings in that controls were unaffected by the distraction whereas ADHD participants were affected. The current sample overestimated time to a higher degree than controls when the distraction was present.

This auxiliary overestimation due to distraction was not found when ADHD children were medicated (chapter 5). The mean reproduction when tested on medication with distraction was more similar to the mean reproduction made when tested off medication without distraction. It appears that medication made the ADHD participants less prone to distraction (in the time reproduction with distraction task). The implication here is that the pathways involved in the two processes of time and attention are quite different. That there are strong correlations between time reproduction with distraction and both sustained attention and response inhibition, but smaller and rarer correlations between sustained attention and response inhibition and time reproduction without distraction is potentially interesting (chapter 6). All are deficient in ADHD, but appear to be as a result of separate processes. This provides evidence that sense of time may be a separate domain which is unaffected by methylphenidate (MPH). The reason such a relationship may exist between time reproduction with distraction and response inhibition could be due to the need for adequate inhibition in the form of interference control. This finding is logical, as ADHD is generally associated with a behavioural inhibition deficit, and ADHD children are described as being easily distracted. A relationship between sustained attention and time reproduction with distraction also fits as the more attention given to non-temporal processing, the more temporal pulses are lost (Zakay & Tsal, 1989) i.e. the

less we attend to the temporal properties of a stimulus, the more likely we are to misperceive its duration (Coull, 2004). People with ADHD have difficulties in maintaining their attention both endogenously and exogenously.

However, what would have been expected due to the effect of distraction on time reproduction and its attention and inhibitory facets, is supplementary underestimation of time due to reduction in subjective duration. What was observed instead was an increase in subjective duration and overestimations in time reproduction. It is difficult to comment on this as it is not known whether there was a tendency to overestimate at short time intervals only, at longer time intervals or across all intervals, due to the composite score across time intervals.

Regardless of the direction of errors, however, it is clear that children with ADHD are distracted more easily than those not diagnosed with ADHD. Furthermore, regardless of whether there is a distraction or not, attention mediates the flexible starting and stopping pulses from the timekeeper, which according to Zakay & Block (1996), enables anticipation of predictable events. Properties of top-down regulation of attention are instantiated in frontal and parietal structures, particularly in the right hemisphere (Stuss et al., 2003). The right dorsolateral prefrontal cortex is involved in the evaluation of time intervals Koch et al. (2002). The level of activation over dorsolateral prefrontal regions has been found to be predictive of performance on a time reproduction task, with activity level inversely related to the accuracy of the produced interval (Casini & Macar, 1996a). Children with ADHD are deficient in both reproducing time intervals and sustained

attention, demonstrating that although attention and timing are quite separate domains there is little doubt that they are functionally intertwined.

The current findings do not support Barkley's assertion that a time deficit in ADHD is solely as a result of impaired inhibition. Most of the correlations found between the SART tasks and time reproduction consisted of $SART_{Fixed}$ omission/ total errors and $SART_{Random}$ omission errors. Fassbender et al. (2004) found that during correct inhibitions (i.e. not making a commission error) on the $SART_{Random}$, activation was observed in the right ventral prefrontal cortex, right inferior parietal lobule, left dorsolateral prefrontal cortex and left putamen. These areas have all been linked to response inhibition (Garavan et al., 1999; Konishi et al., 1998a, Rubia et al., 2001). Hence, that most of the correlations found between time and $SART_{Random}$ were in the omission errors, provides support for the deficit in time reproduction being connected in some way to sustained attention above response inhibition, both of which have found to be deficient in ADHD in this study. Moreover, Intra-individual variability was a marker of some sort of difference between the subtypes on tasks measuring time reproduction and sustained attention ($SART_{Fixed}$). There was a correlation between Intra-individual variability on both of these tasks. There was no such relationship found between time and $SART_{Random}$.

That MPH has consistently been found to have no effect on time reproduction in ADHD is perplexing to say the least (see chapter 5). Dopamine (DA) depletion in Parkinsons disease patients leads to both time estimation and motor timing deficits. Depletion in

dopamine is thought to induce a slower clock, leading to underestimation of time (Pastor et al., 1992). Usually following administration of levodopa (L-Dopa) a significant improvement of temporal performance is improved. The dopaminergic system is an essential component of executive control and possibly of sustained attention (Castellanos, 1997; Malone et al., 1994). As ADHD has been associated with dysfunction within dopamine-rich areas such as the prefrontal cortex, basal ganglia and the neocerebellum (Bush et al., 1999; Casey et al., 1997; Castellanos et al., 2001) it is not surprising that, consistent with PD, those with ADHD have timing deficits. Nevertheless MPH blocks the reuptake of dopamine from the synaptic cleft (Swanson et al., 2000) and therefore regulates the amount of dopamine available. Hence, like the temporal performance improvement seen in PD patients on administration of levodopa (L-Dopa), a similar improvement would be expected in ADHD. It seems that speeding up the brain with stimulants does not necessarily slow down the perceived passage of time in ADHD children. It is not possible to answer this query in the current thesis.

8.4 Future Directions

The amount of Intra-individual variability observed in both ADHD subtypes but especially the ADHD-C group warrants much further investigation. It might be worthwhile investigating whether using some sort of consistent, but non-distracting prompt might improve this variability. Recent evidence shows that rehabilitation of brain function might be possible based on the experience-dependent plasticity of the brain (Robertson & Murre, 1999). Neuroimaging research has consistently found that ADHD is

a brain behaviour disorder involving prefrontal and basal ganglia regions, modulated by dopaminergic innervation from the midbrain (Laatsch, 1998). Since the prefrontal lobes are extensively involved in a large range of cognitive activities, a global and diverse effect on cognition is found in ADHD. Attention training or coaching cognitive strategies are believed to assist in the amelioration of executive dysfunction associated with symptoms of inattention (Castellanos, 1997). Laatsch (1998) has found that Cognitive Rehabilitation Therapy can reduce many of the deficits associated with ADHD. Robertson et al (1998) found that phasic alerting (occasional central warning sounds) can overcome perceptual left spatial neglect in patients with lesions of the right-hemisphere; a central sound drew their attention away from the right towards the left. Left neglect has been linked to sustained attention (Posner & Raichle, 1993), with an improvement in both sustained attention and left neglect as a result of training in verbal regulation of sustained attention (Robertson et al, 1995). Given the underlying similarities between neglect patients and ADHD in both symptoms and brain mechanisms (see chapter 7), and the links found in the current thesis between sustained attention and time reproduction (see chapter 6), it is possible that similar methods (phasic alerting or training in verbal regulation of sustained attention) might improve the deficit of sustained attention, time reproduction and the increased intra-individual variability seen across tasks in ADHD children.

Greenspan (1992) asserts that technologies aimed at strengthening motor planning, sequencing, timing, and rhythmicity may have a role in improving the capacity to attend and learn. Interactive Metronome Training (IMT) provides accurate real-time guide

sounds to indicate users' temporal accuracy as they perform a series of prescribed movements. Performance on IMT has correlated with severity of developmental, learning and attentional problems in school-aged children (Kuhlman & Schweinhart 1999). IMT has been used to test performance on motor and cognitive skills in boys with ADHD (Shaffer et al., 2001). The object of the IMT was to assist the boys improving their ability to selectively attend, without interruption by internal thoughts or external distractions, for extended periods, by way of simple limb movements (e.g. clapping both hands together, alternating toe taps on the floor). This was done in tune to a preset tempo of 54 repetitions per minute. It took place over 15, 1-hour sessions, during a three – five week timeframe. Comparison of pre-and post- testing sessions found that focusing perceptual activities in this way improved attention, motor control, language processing, reading and ability to regulate aggression. The interactive metronome may have facilitated more effective temporal processing, based on the overlap between brain areas involved in timing and motor control and which are implicated in ADHD i.e. reduced activation of fronto-striatal network (Rubia et al., 1999a). As this network is implicated in ADHD, it would be most interesting to see if such training would also improve performance on the current time reproduction, TEA-Ch and SART tasks and might decrease the intra-individual variability observed in time reproduction and SART $_{\text{Fixed}}$.

Recently a number of researchers have attempted to use continuously quantifiable phenotypes to investigate the basis of ADHD. A phenotype is the "outward, physical manifestation" of the organism. These are the physical parts, the sum of the atoms, molecules, macromolecules, cells, structures, metabolism, energy utilization, tissues,

organs, reflexes and behaviours; indeed anything that is part of the observable structure, function or behavior of a living organism. A Phenotype is determined to some extent by genotype, or by the identity of the alleles that an individual carries at one or more positions on the chromosomes. Many phenotypes are determined by multiple genes and influenced by environmental factors. Thus, the identity of one or a few known alleles does not always enable prediction of the phenotype. Nevertheless, phenotypes are much easier to observe than genotypes and might relate more closely to dysfunction within discrete neural systems, than do symptom-based categories. The use of such refined phenotypes may increase the power of genetic studies to detect associations with genes of small effect (Castellanos & Tannock, 2002).

Bellgrove et al. (under review) have shown that sustained attention deficits can be predicted by DBH genotype. The DBH gene may contribute to the susceptibility for ADHD, in part because of its varying effects on the development of brain mechanisms mediating sustained attention. Bellgrove et al. (under review) has also found that left-sided inattention in ADHD is related to both underlying DAT1 genotype and the therapeutic response conferred by MPH. Based on Bellgrove et al's findings it might be worthwhile dividing the current sample into phenotypes, rather than ADHD subtypes e.g. DAT1 low risk and DAT1 high risk groups for comparison with each other and controls. Only 12 of the current ADHD (ADHD-C) sample had been genotyped; a sample too small for a genetic association study.

Such a study in relation to time reproduction could help assess the role of various executive functions in both time perception and ADHD, and thus provide a more complete picture of relationships between cognitive functions and the different processes involved in time estimation.

8.5 Limitations

Given the flexibility of attention as an explanation for time reproduction deficits (Walsh, 2003) future studies will need to examine the relationship between time reproduction and discrete components of attention that are grounded in valid brain-behaviour relationships. While it is felt that the current analyses in relation to sustained attention/ response inhibition using a well-validated measure (the SART) satisfy this latter requirement, it is acknowledged that larger samples will be required to fully elucidate the relationship between ADHD subtypes, time reproduction, sustained attention and various other executive functions. For example, working memory is quite obviously involved in a task where reproduction of time intervals as long as 60 seconds is required. It is also a prominent aspect to the most popular psychological models of temporal cognition (see chapter 2). According to Gibbon et al. (1984), in the memory stage of the model of temporal information processing, the outcome from the accumulator corresponding to the current time is transiently stored in a working memory system for comparison with the content of reference memory. This contains a long-term memory representation of the approximate number of pulses accumulated on past trials. A mechanism then compares the current duration values with those in working or reference memory to decide on the adequate temporal response. Working memory was not measured in the current study,

and this could possibly be a major factor in significant underestimations observed in the ADHD groups based on the model of temporal information processing (Gibbon et al., 1984). There are many reports of deficient working memory in ADHD, although this is inconsistent across studies, with many studies finding no evidence of a working memory deficit. For example, Kuntsi et al. (2001) suggested that poor performance on working memory tasks in children with hyperactivity is a consequence of low IQ. Kerns et al. (2001) found no evidence of a working memory deficit in ADHD and further found no relationship between working memory and time reproduction. Therefore, it was not examined in the current thesis. As attentional factors have been shown to play an important role in time perception, i.e. when less attention is allocated to time, reduction in subjective duration occurs (Zakay & Tsal, 1989), it makes sense that a disorder such as ADHD which has as one of its main deficits in the area of attention, should have problems with time reproduction at least in part due to reduced attentional resources, with or without a working memory deficit.

8.6 Clinical Implications

The finding that ADHD-I and ADHD-C may be distinguished on the basis of variability in time reproduction and sustained attention is a novel finding. The results support an emerging view that intra-individual differences in performance variability, rather than simply adding random noise, may provide important clues regarding the efficiency of cognitive processes within clinical populations (Stuss et al., 2003). This line of reasoning is particularly germane to ADHD research where it is the moment-to-moment fluctuations in performance and lapses of intention and attention that arguably

characterize the disorder (Castellanos & Tannock, 2002). Secondly, the dissociation of the ADHD subtypes based upon a time reproduction measure and variability of reaction time on a sustained attention task provides further support for the assertion that ADHD-I should be recognized as a separate disorder (Barkley, 1993; Clarke et al., 2001). The finding that variability in under- vs. over-estimations significantly correlates with the SART is further evidence that neuropsychological research on ADHD should investigate the utility of variability effects for distinguishing both between ADHD, control participants, and ADHD subtypes. Delineating neuropsychological profiles as a function of ADHD subtypes will inform biological theory and guide treatment. Multifaceted intervention strategies that are aimed at improving consistency of behaviour over time are necessary. Treatment strategies might include more frequent external cues, prompts or physical reminders.

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