Oppositional Defiant and Conduct Disorder in Attention-Deficit/Hyperactivity Disorder: Child and Adolescent Profiles, Diagnostic Aids, Cognitive Markers and Implications for the Future DSM Nomenclature

A thesis submitted in total fulfilment of the requirements for the degree of Doctor of Philosophy by

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Declaration:

This thesis contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in text. To the best of the author’s knowledge, this thesis contains no material previously published or written by another person except where due reference is made in text. Where the work is based on joint research or publications, disclosure is made in text of the relative contributions of the respective workers/authors.

All experimental tasks and procedures incorporated in this thesis adhere to the Swinburne University of Technology Human Research Ethics principles and protocols. Ethics approval was successfully obtained prior to, and for the full duration, of this research.

Signed: _________________________________

Sharnel Miriam Perera

Dated: ________________________________
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<td>AD/HD+INT</td>
<td>AD/HD with internalising comorbidity (LD, Anxiety, Depression, etc)</td>
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<td>CPRS-RL</td>
<td>Conner’s Parent Rating Scale - Revised, Long Form</td>
</tr>
<tr>
<td>CPT</td>
<td>Continuous Performance Task</td>
</tr>
<tr>
<td>CRS-RL</td>
<td>Conner’s Rating Scale - Revised, Long Form</td>
</tr>
<tr>
<td>CSRS-RL</td>
<td>Conner’s Self Rating Scale - Revised, Long Form</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>--------------</td>
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<tr>
<td>CTRS-RL</td>
<td>Conner’s Teacher Rating Scale - Revised, Long Form</td>
</tr>
<tr>
<td>dB</td>
<td>decibel</td>
</tr>
<tr>
<td>DBD</td>
<td>Disruptive Behaviour Disorder</td>
</tr>
<tr>
<td>DEP</td>
<td>Depression</td>
</tr>
<tr>
<td>DEX</td>
<td>Dexamphetamine</td>
</tr>
<tr>
<td>DICA</td>
<td>Diagnostic Interview for Children and Adolescents</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and Statistical Manual of Mental Disorders</td>
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<tr>
<td>DSM-II</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (2nd edition)</td>
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<tr>
<td>DSM-III</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (3rd edition)</td>
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<tr>
<td>DSM-III-R</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (3rd edition, revised)</td>
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<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (4th edition)</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorders (4th edition, text revision)</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalography</td>
</tr>
<tr>
<td>EF</td>
<td>Executive Function</td>
</tr>
<tr>
<td>EOG</td>
<td>Electro-oculogram</td>
</tr>
<tr>
<td>ERP</td>
<td>Event-Related Potential</td>
</tr>
<tr>
<td>fMRI</td>
<td>functional magnetic resonance imaging</td>
</tr>
<tr>
<td>FN</td>
<td>False Negative</td>
</tr>
<tr>
<td>FP</td>
<td>False Positive</td>
</tr>
<tr>
<td>GNG</td>
<td>Go/No-Go task</td>
</tr>
<tr>
<td>HKD</td>
<td>Hyperkinetic Disorder</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>IQ</td>
<td>Intelligence Quotient</td>
</tr>
<tr>
<td>ISI</td>
<td>Inter-Stimulus Interval</td>
</tr>
<tr>
<td>KBIT-2</td>
<td>Kaufman Brief Intelligence Test (2nd edition)</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>LD</td>
<td>Learning Disorder</td>
</tr>
<tr>
<td>MPH</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>ms</td>
<td>milliseconds</td>
</tr>
<tr>
<td>µV</td>
<td>Microvolt(s)</td>
</tr>
<tr>
<td>ODD</td>
<td>Oppositional Defiant Disorder</td>
</tr>
<tr>
<td>Odd</td>
<td>Auditory Oddball Task</td>
</tr>
<tr>
<td>PCA</td>
<td>Principle Components Analysis</td>
</tr>
<tr>
<td>QEEG</td>
<td>Quantitative EEG</td>
</tr>
<tr>
<td>RT</td>
<td>Reaction Time</td>
</tr>
<tr>
<td>s</td>
<td>Second(s) (ref: time)</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SDRT</td>
<td>Standard Reaction Time/reaction time variability</td>
</tr>
<tr>
<td>SGWRT</td>
<td>Schonell Graded Word Reading Test</td>
</tr>
<tr>
<td>SOAT</td>
<td>Switching of Attention</td>
</tr>
<tr>
<td>SPHERE-12</td>
<td>Somatic and Psychological Health Report 12</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Sciences</td>
</tr>
<tr>
<td>TMT</td>
<td>Trail Making Test</td>
</tr>
<tr>
<td>UADD</td>
<td>Undifferentiated Attention Deficit Disorder</td>
</tr>
<tr>
<td>UK</td>
<td>The United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>The United States of America</td>
</tr>
<tr>
<td>VERP</td>
<td>Visual Event-Related Potential</td>
</tr>
<tr>
<td>VIT</td>
<td>Verbal Interference Task</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organisation</td>
</tr>
<tr>
<td>x</td>
<td>mean (average)</td>
</tr>
</tbody>
</table>
This thesis is dedicated to my Seeya, Walter Pathirana (4\textsuperscript{th} of May 1922 - 6\textsuperscript{th} of April 2010), for his love, resilience, generosity, stubbornness, and for being a “home-bird” just like his granddaughter.
Chapter 1:

General Abstract
Attention-Deficit/Hyperactivity Disorder (AD/HD) manifests as developmentally inappropriate levels of inattention, hyperactivity, and impulsivity. Despite the extensive research that has been conducted on AD/HD, the definition, classification, and treatment of the disorder remains highly controversial. There are numerous factors that complicate the diagnosis of AD/HD, but none greater than that arising from its inherent comorbidity and shared symptomatology with other psychiatric disorders. The two most frequently comorbid disorders with AD/HD are Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD); both of which typically co-exist since previous research has shown ODD to significantly increase susceptibility to CD.

There are as yet no definitive cognitive, genetic, neurological, or metabolic markers of AD/HD, and hence no conclusive medical test for the condition. Consequently, AD/HD is at present purely a ‘clinical diagnosis’, meaning that most clinicians are forced to rely upon their own expertise, and the observable behaviour information provided by the relevant respondents (for example, parents and teachers). The ambiguity surrounding AD/HD is, like most psychiatric diagnoses, partly due to its diagnosis relying on subjective symptoms rated via symptom checklist data (e.g. the DSM) and various self/parent/teacher-report rating scales. In order to refine the disorder’s definition to increase diagnostic specificity and homogeneity, the issue of comorbidity in AD/HD, particularly that of with ODD/CD, must first be addressed. From here, the impact of comorbidity can be fully appreciated.

The current thesis utilised a data-driven approach to investigate the impact of externalising disorders, such as ODD/CD, on AD/HD in both children (aged 6-12 years) and adolescents (aged 13-17 years). This was assessed using psychometric and psychophysiological data from six different tasks measuring executive function (EF), response inhibition (RI), and selective and sustained attention. These tasks were: the auditory Oddball task, Go/No-Go Task (GNG), Continuous Performance Task (CPT), Verbal Interference Task (VIT), Executive Maze (EM), and the Switching of Attention Task (SOAT). Variables from these tasks included Event-Related Potential data (ERPs) and behavioural performance data such as reaction time (RT) and number of errors. Data from a total of 152 AD/HD participants (64 children, and 88 adolescents), and 131
healthy Controls (52 children, and 79 adolescents) was analysed. AD/HD subgroups consisted of AD/HD-NK (with no known comorbidity), AD/HD+INT (with internalising comorbidity such as depression, anxiety, etc), and AD/HD+ODD/CD (with ODD/CD comorbidity).

The first experimental Chapter (7) of this thesis focused on compiling neurocognitive profiles of each AD/HD subgroup based upon the data from the six tasks named above. Results showed novelty-seeking behaviour and inattention to be prominent characteristics of AD/HD-NK and AD/HD+ODD/CD in childhood, while deficits in executive function, response inhibition, and attention were apparent in adolescence. AD/HD+INT displayed a symptomatically diffuse profile in childhood, though displayed significant impairment in adolescence. AD/HD+ODD/CD were the most impaired group irrespective of age. In childhood, AD/HD+INT were the least impaired group, while AD/HD-NK showed task-defined impairment somewhere in between AD/HD+INT and AD/HD+ODD/CD. This pattern was revered in adolescence, where AD/HD-NK was the least impaired group compared to AD/HD+INT and AD/HD+ODD/CD.

The second experimental Chapter (8) utilised the same psychometric and psychophysiological data from the six tasks, to investigation whether the ERP and psychometric performance profiles of AD/HD with and without ODD/CD comorbidity cluster into meaningful groups that show a divergence in nomenclature to that of the DSM-IV-TR. Two clusters were found in the analysis of the adolescent age group - a cluster dominated by Control and AD/HD-NK, while the second cluster was dominated by AD/HD+ODD/CD participants. A similar segregation within the child age group was not achieved. Significant impairments in the adolescent group were identified as task-related deficits in visuo-spatial learning, task performance, and visual response inhibition. Further analysis of these objectively determined clusters in terms of their clinical diagnoses indicated a significant effect of ODD/CD comorbidity on a concurrent AD/HD diagnosis. From this, it appeared that comorbid externalising behaviour in AD/HD constituted a distinct pathological entity in adolescence, whereas in childhood, it was argued that a dimensional approach to classification and diagnosis would provide a more meaningful depiction of AD/HD at this age.
The results of this thesis present the first investigation into the neurocognitive profiles of comorbid AD/HD in children and adolescents, specifically that of AD/HD+ODD/CD, in addition to new evidence supporting a re-visit of the current DSM nomenclature for AD/HD. The results showed that hyperactivity and impulsivity as indexed by novelty-seeking behaviour, and inattention, to be the primary indicators of task-defined impairment in childhood, which appeared to underlie global deficits in executive function, response inhibition, and attention in adolescence. The results also support previous claims that AD/HD+ODD/CD constitutes a separate pathological entity and should be classified as such in the DSM, similar to methodology adopted by the ICD-10, however this appears valid only in adolescence and not in childhood. In childhood, a diagnostic approach that considers a dimensional view of symptomatology and symptom severity would provide a more accurate depiction of the disorder, as well as help to identify ‘at-risk’ individuals.
Chapter 2: AD/HD - An Overview

Chapter Overview:
This chapter will introduce and define AD/HD, its common features, characteristics, and global prevalence. A comparison of both diagnostic guides currently in use (DSM-IV-TR and ICD-10) will be presented. However, since the DSM-IV-TR is the official diagnostic manual for psychiatric disorders in Australia, it is the DSM-IV-TR definition for AD/HD that will be adopted in this thesis. Issues relating to diagnosis of AD/HD such as gender and age with respect to DSM criteria will also be discussed, along with a brief summary of common treatment practices.
2.1 Definition and History

Attention-Deficit/Hyperactivity Disorder (AD/HD) manifests as developmentally inappropriate levels of inattention, hyperactivity, and impulsivity, and is categorised by three subtypes: Inattentive (AD/HD-I), Hyperactive/Impulsive (AD/HD-HI), and Combined (AD/HD-C; where both inattentive and hyperactive/impulsive symptoms are present). The condition, which typically presents around the ages of 3–7 years, affects around 8–12% of children worldwide (R.A. Barkley, 1997; S.V. Faraone et al., 2005; S.V. Faraone, Sergeant, Gillberg, & Biederman, 2003). Symptoms persist into adulthood in approximately half of the children diagnosed (Seidman, Valera, & Makris, 2005), with around 3–5% of adults (El-Sayed, Larsson, Persson, Santosh, & Rydelius, 2003; R.C. Kessler et al., 2006) diagnosed with AD/HD. AD/HD increases the risk of delinquency in adult life (J.H. Satterfield, Schell, Backs, & Hidaka, 1982).

Despite the extensive research that has been conducted on AD/HD, the definition, classification, and treatment of the disorder remains highly controversial. The International Consensus Statement on AD/HD published in 2002 (R.A. Barkley, 2002) delivered a stinging rebuttal over the long-running beliefs held by some that AD/HD comprised a trivial affliction which disqualified it as a valid disorder. The scepticism is not completely unfounded however since there are as yet no definitive cognitive, genetic, neurological, or metabolic markers of AD/HD, and hence no conclusive medical test for the condition.

Attentional dysfunction and overactivity were first coupled together and studied as being symptoms of a unique disorder by English paediatrician George Still early last century (Still, 2006). Several theories have been presented in an attempt to explain the symptomatology associated with AD/HD, such as developmental or maturational lag (El-Sayed et al., 2003), frontal lobe dysfunction (Giedd, Blumenthal, Molloy, & Castellanos, 2001), inhibitory system deficits (R.A. Barkley, 1997; Shallice et al., 2002), genetic factors (Bennett et al., 2006; Comings, 2001), and psychosocial influences (Loeber, Pardini, Stouthamer-Loeber, & Raine, 2007). However each theory has its
own faults and inconsistencies and hence, does not entirely explain the disorder. Even the nosology of AD/HD is quite complex; since 1980 AD/HD has undergone three different nomenclatures, effectively reconstructing its conceptualisation each time.

The first Diagnostic and Statistical Manual of Mental Disorders (DSM), which was published in 1957 by the American Psychiatric Association (APA), did not recognise AD/HD (American Psychiatric Association, 1957) and it was not until 1968 that DSM-II introduced Hyperkinetic Reaction of Childhood or Adolescence (American Psychiatric Association, 1968). In 1980 the condition was renamed to Attention Deficit Disorder (ADD) in DSM-III, and distinguished between two different subtypes; ADD with hyperactivity (ADD/H), and ADD without hyperactivity (ADD/WO) (American Psychiatric Association, 1980). This edition of the DSM was later revised in 1987 and re-named the condition AD/HD after concluding it was uni-dimensional in nature in order to avoid having to define each symptom under a discrete domain; children diagnosed with inattention symptoms were diagnosed as having Undifferentiated Attention Deficit Disorder (UADD) (American Psychiatric Association, 1987). Subsequent research highlighting the multidimensional nature of AD/HD triggered the re-conceptualisation of the condition in the current DSM published in 1994, where AD/HD symptomatology was divided into the three distinct diagnostic groups or subtypes known today (Inattentive, Hyperactive/Impulsive, and Combined) (American Psychiatric Association, 1994; A. E. Morgan, Hynd, Riccio, & Hall, 1996). A text revision of the DSM-IV was completed in 2000 (DSM-IV-TR) however the diagnostic criteria for AD/HD remain unchanged (American Psychiatric Association, 2000) until the release of the DSM-V which is currently being drafted. Possible changes to the nomenclature of AD/HD in the DSM-V include: the discontinuation of AD/HD-I and AD/HD-HI subtypes, the creation of AD/HD-I as a separate diagnostic entity where no hyperactive/impulsive symptoms are present, and changing the age of onset from ‘on or before age 7’ to ‘on or before age 12’ (American Psychiatric Association, 2010).

The seemingly constant changes in the definition of AD/HD along with the disorder’s characteristic heterogeneity and high rate of comorbidity – as high as 87% (Gillberg et al., 2004) – are undoubtedly the largest hurdles in the search for an accurate and comprehensive hypothesis which will ultimately aid our understanding and treatment
of the condition. The issue of comorbidity in AD/HD will be discussed in detail in Chapter 3.

2.2 Diagnosis

At present, there are two separate classification systems that exist to diagnose behavioural dysfunction in childhood; the DSM as mentioned earlier, and the World Health Organisation’s ICD (International Classification of Diseases). The following sections will discuss similarities and differences between the DSM and the ICD, DSM diagnostic criteria for AD/HD, and issues relating to diagnosis.

2.2.1 DSM vs. ICD

The 9th revision of the ICD released in 1968 classified AD/HD as “Hyperkinetic Syndrome of Childhood”, which was analogous to the classification listed in DSM-II of the same year. When both systems were revised and updated in 1994 (DSM-III-R, and ICD-10), the definition of AD/HD was almost identical in the two texts, though differing in classification criteria and terminology; AD/HD in DSM-III-R, and Hyperkinetic Disorder (HKD) in ICD-10 (World Health Organization, 1993).

The ICD is mainly utilised in Europe, while the DSM is an American standard which has been adopted by Australia. The most recent editions of both texts have made some progress in bridging the gap between the two schemata however there are still three substantive differences between them.

Firstly, the ICD-10 requires the full syndrome of HKD to be present in two independent situations (for example, at home and at school), whereas the DSM-IV-TR requires “clinically significant impairment in social, academic or occupational functioning” in two or more situations.

Secondly, the ICD-10 requires the presence of both attentional and behavioural (hyperactive/impulsive) dysfunction to confirm the HKD diagnosis, whereas AD/HD can
be diagnosed with either symptom profile according to the DSM-IV-TR. If both symptom profiles are present at levels that exceed the diagnostic threshold, then a diagnosis of AD/HD-C is made.

Thirdly, although the ICD-10 allows for the diagnosis of Hyperkinetic Conduct Disorder1, it generally disapproves of multiple diagnoses. If diagnostic criteria are met for another disorder, clinicians are encouraged to diagnose this rather than HKD. For example, a diagnosis of HKD is void if pre-existing internalising disorders such as anxiety or depression are present. This is in sharp contrast to the DSM-IV-TR, which almost expects multiple comorbid diagnoses (Lee et al., 2007). As a result, the ICD suffers when dealing with mixed cases; conversely, mutually exclusive diagnoses are problematic with the DSM.

From this, it seems that while the symptomatology of both HKD and AD/HD are strikingly similar, the ICD-10 diagnostic criteria are comparatively less liberal than that of the DSM-IV-TR. In support of this assertion, an early study found the incidence of HKD diagnoses in the UK tended to be lower than that of AD/HD in the USA (Prendergast et al., 1988). However Foreman, Foreman, Prendergast and Minty (2001) argue that the lower rate of diagnoses in the UK is likely due to assessment procedures rather than overly restrictive diagnostic criteria in the ICD. The DSM definition typically yields diagnosis rates of around 5-10%, whereas the ICD definition yields only around 1-2% (Swanson et al., 1998). A recent study by Döpfner, Breuer, Wille, Erhart and Ravens-Sieberer (2008) found 2.2% of their sample of 7-17 year old German participants met DSM-IV criteria for AD/HD, yet only 0.6% of this sample met ICD-10 criteria for HKD. It can be argued that the ICD rate reflects only those diagnosed as AD/HD-C as defined by the DSM since theoretically, a diagnosis of AD/HD-C should be equivalent to an ICD diagnosis of HKD due to the presence of both behavioural and attentional symptoms. However, a recent study conducted by Lee et al (2007) found that out of 246 cases which met criteria for AD/HD-C as defined by DSM-IV-TR, only 46 (19%) of those cases also met criteria for HKD as defined by ICD-10. Given this, it is undeniable that the DSM-IV-TR definition identifies a comparatively broader cohort

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1 Hyperkinetic Conduct Disorder is diagnosed when symptoms of both HKD and a conduct disorder (characterised by violation of social norms and repetitive aggression/violence) are present. This condition is analogous to AD/HD comorbid with Conduct Disorder as defined by the DSM-IV-TR (see Chapter 3).
than the ICD-10, particularly since the DSM-IV-TR includes a sub-classification of ‘Attention-Deficit/Hyperactivity Disorder Not Otherwise Specified’ which allows for the diagnosis to be made if the standard diagnostic threshold is not reached for AD/HD-I, AD/HD-HI, or AD/HD-C.

Clearly, while efforts have been made to close the nosological gap between AD/HD and HKD, the DSM-IV-TR’s definition is still substantially broader than that of the ICD-10. Whether this is an indication of over-diagnosis with the DSM-IV-TR or under-diagnosis with the ICD-10 is still under debate.

2.2.2 DSM-IV-TR Diagnostic Criteria for AD/HD

In the DSM-IV-TR, AD/HD is listed under the umbrella term of Disruptive Behaviour Disorders (DBDs) which also includes Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD); both ODD and CD will be discussed in greater detail in the next chapter. Since the official psychiatric diagnostic reference in Australia is the DSM, and all participants in the present thesis were diagnosed and assessed according to this text, only DSM-IV-TR diagnostic criteria will be presented here.

The following are the 9 symptoms of inattention as listed in the DSM-IV-TR:

a) Often fails to give close attention to details or makes careless mistakes in school work, work, or other activities.

b) Often has difficulty sustaining attention to tasks or play activities.

c) Often does not seem to listen when spoken to directly.

d) Often does not follow through on instructions and fails to finish school work, chores or duties in the workplace (not due to oppositional behaviour or failure to understand instructions).

e) Often has difficulty organising tasks and activities.

f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school work or homework).

g) Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books, or tools).
h) Is often easily distracted by extraneous stimuli.
i) Is often forgetful in daily activities.

The following are the 6 symptoms of hyperactivity as listed in the DSM-IV-TR:

a) Often fidgets with hands or feet or squirms in seat.
b) Often leaves seat in classroom or in other situations in which remaining seated is expected.
c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness).
d) Often has difficulty playing or engaging in leisure activities quietly.
e) Is often “on the go” or often acts as if “driven by a motor”.
f) Often talks excessively.

The following are the 3 symptoms of impulsivity as listed in the DSM-IV-TR:

g) Often blurts out answers before questions have been completed.
h) Often has difficulty awaiting their turn.
i) Often interrupts or intrudes on others (e.g. butts into conversations or games).

A diagnosis of AD/HD-I requires the presence of at least 6 symptoms from the Inattentive subset. Similarly, a diagnosis of AD/HD-HI requires the presence of at least 6 symptoms of the Hyperactive/Impulsive subset. If the symptom threshold is exceeded in both subsets, then a diagnosis of AD/HD-C is made. For a ‘symptom’ to be deemed valid, the DSM-IV-TR states that it must have “persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level” (American Psychiatric Association, 2000).

These symptoms must present before age 7, and cause some impairment in two or more settings (e.g. school, work, etc). Further, clinically significant impairment (which is not due to or better explained by any other mental disorder) must be evident in social, academic, or occupational functioning.
2.2.3 Issues Relating to DSM-IV-TR Diagnostic Criteria for AD/HD

While the diagnostic criteria seem quite specific, some questions still arise. Probably the most pertinent is: what is the DSM’s definition of ‘clinically significant impairment’? Since no answer is ever given, it is left to the diagnostician to decipher, which undoubtedly increases inter-rater variability. Also, the requirements that symptoms be present before age 7, and must persist for a minimum duration of 6 months seems rather arbitrary since no connection is made with any developmental milestone, behavioural standard or cognitive baseline.

Also, the DSM-IV-TR diagnostic criteria for AD/HD does not take into consideration gender or age/developmental course, which have repeatedly been shown to affect the syndrome’s presentation and outcome. Factors such as these can lead to errors in clinical diagnosis, which is why the development of a single diagnostic tool that is uniformly administered carries such potential in reliable AD/HD diagnosis; the pretext of the present thesis.

Gender and developmental course in AD/HD will be discussed further in the following two sections.

2.2.3.1 Gender

Although AD/HD is the by far the most researched childhood disorder, the majority of that research has been restricted to males due to their predominance in clinically referred samples. There is a significant discrepancy in the male-to-female ratio in both clinic-referred, and community samples of AD/HD children. In both instances, males are at least three times more prevalent that females; 10:1 in clinic-referred, and 3:1 in community based samples (Biederman et al., 2002). It has been argued that the gender ratio will never approach 1:1 if the same diagnostic criteria continue to be used for both males and females (Arnold, 1996).

In terms of overall impairment, Gaub & Carlson’s (1997) meta-analysis found that girls tended to be more impaired than boys, but only in clinic-referred AD/HD populations.
Non-referred AD/HD girls and boys showed comparable levels of impairment which lead the researchers to conclude that only the most severely affected girls are referred to clinics for treatment. Therefore, it is possible that clinic-referred girls with AD/HD do not provide an accurate representation of girls with AD/HD in general, and as such, research confined to either group could lead to misguided conclusions regarding the presentation and outcome of AD/HD in girls.

A more acute inspection of impairment reveals that compared to boys, girls are less likely to have a learning disability, less likely to suffer from social dysfunction, more likely to be AD/HD-I (Biederman et al., 2002; Newcorn et al., 2001; Spencer, Biederman, & Mick, 2007), and display less externalising pathology (such as Oppositional Defiant Disorder [ODD], Conduct Disorder [CD], delinquency, and aggression) (Arnold, 1996; Carlson, Tamm, & Gaub, 1997; Gaub & Carlson, 1997; R. Nass, D., 2006). The ratio of AD/HD-C does not seem to differ significantly between genders though at times it may appear this way; this seeming discrepancy is likely due to the overall scarcity of diagnosed AD/HD females in general rather than any subtype-related bias.

The lower rate of female AD/HD diagnosis is not necessarily indicative of a gender bias associated with the condition. Since most clinic referrals for AD/HD are based on overt/externalising problem behaviour and aggression, the comparative lack of female referrals is likely due to girls typically displaying more covert/internalising behaviour than boys. As such, it is likely that girls with AD/HD are simply being overlooked.

### 2.2.3.2 Age, Developmental Course, and Outcome

AD/HD is probably best described as a developmentally sensitive disorder. While ‘age’ in itself is an ambiguous variable in developmental research, one is compelled to question the appropriateness of using the same diagnostic criteria for both a 6 year old and a 60 year old, though this is the case with AD/HD diagnostic criteria in the DSM-IV-TR. Due to the heterogeneity and intra-subject variability associated with the disorder, there is no known developmental course for AD/HD that is applicable to all sufferers,
however previous research over the past few decades has revealed some key age-related characteristics.

Firstly, robust findings have shown a relative decline in AD/HD symptomatology with age. Overt symptoms of hyperactivity and impulsivity have been shown to rapidly decrease with age, however the covert symptoms of inattention tend to persist over time (Biederman, 2005; Spencer et al., 2007). A 4-year longitudinal study conducted by Hart, Lahey, Loeber, Applegate, and Frick (1995) showed that while hyperactivity and impulsivity in their sample of AD/HD boys declined with increasing age, the level of inattention remained stable from 8-15 years of age. This is supported by Hay and Levy (1996) who argued that hyperactivity is more common among younger AD/HD sufferers, while inattention is more common among older sufferers.

Secondly, longitudinal and follow-up studies have shown strong links between childhood AD/HD and social and academic dysfunction or failure, low self-esteem, poor peer relationships, antisocial behaviour, parental conflict, delinquency, smoking, substance abuse (as reviewed by Biederman, 2005; Biederman et al., 2006), criminal behaviour (Castellanos, 1997), poor work histories, non-psychiatric medical difficulties (Willoughby, 2003), and emotional difficulties (Spencer et al., 2007) in adolescence and young adult life.

Since academic underachievement is a frequently reported correlate of childhood AD/HD, it is hardly surprising that professional development in adulthood would be negatively affected. In a 25-year follow-up study conducted by Borland and Heckman (1976), adult men whom were diagnosed with AD/HD in childhood, were compared against their non-AD/HD adult siblings. Results showed the AD/HD adults to have lower socioeconomic status, more problems at work, and changed jobs more frequently than their non-AD/HD siblings. Compared to non-AD/HD Control adults, Murphy and Barkley (1996) found AD/HD adults to display more psychological maladjustment, have had multiple marriages, more traffic violations, and greater instability in their employment.

However, childhood AD/HD is not necessarily associated with impaired outcome in later life. Biederman, Mick, and Faraone (1998) found 20% of their adolescent AD/HD sample to be functioning well academically, emotionally, and socially. Sixty-percent of
their sample showed intermediate outcomes. Hence, their results were suggestive of a normalisation of functioning independent of syndromatic persistence. An important issue to note is that since it is quite common for AD/HD to progress into later age, the disorder’s occurrence among the elderly is not unheard of. The obvious problem here is how to distinguish AD/HD symptoms in this cohort who are undoubtedly also experiencing normal cognitive decline.

As described above, AD/HD varies significantly in both presentation and outcome between genders, and across the lifespan. Hence, the need to establish developmentally sensitive and gender specific diagnostic criteria for AD/HD is crucial in order to ensure accurate diagnosis and effective treatment.

### 2.3 Prevalence

The prevalence of AD/HD can be difficult to determine given the differing diagnostic methodologies adopted worldwide. Not only can there be incongruous opinions regarding symptom severity, but countries also differ in which diagnostic system employed (see previous section on Diagnosis). As such, there will always be some variance regarding the prevalence of AD/HD, which some researchers’ debate as being greater than currently estimated.

Presently, AD/HD is estimated to affect anywhere between 4-10% of children worldwide (R. T. Brown & Perrin, 2007; Castellanos, 1997; Spencer et al., 2007; Willoughby, 2003), with around 50-85% of children continuing to meet diagnostic criteria in adolescence (R. T. Brown & Perrin, 2007). It is thought that around 4% of adults are affected (Biederman, 2005), though it is probable that the lack of age appropriate symptom criteria in the DSM masks the true incidence of adult AD/HD. Childhood and adolescent prevalence estimates have been documented in previous research and are presented below in Table 2.1a, alongside a second comparative table.
2.1b showing prevalence rates of HKD (ICD-9). Additionally, Spencer et al (2007) have quoted prevalence rates of 4-7% for USA, Australia/New Zealand, Germany, and Brazil.

Unfortunately, there is a lack of sufficient AD/HD research in developing countries, and as such, no accurate estimate of the rate of the disorder’s occurrence. It is reasonable to assume though, that the presence of greater psychosocial risk factors associated with developing countries may be indicative of a relatively high prevalence of AD/HD, among other disorders.

<table>
<thead>
<tr>
<th>Subtype and DSM Diagnosis</th>
<th>Country</th>
<th>Age (yr)</th>
<th>Gender (M/F)</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-III ADD/H</td>
<td>USA</td>
<td>6-9</td>
<td>M</td>
<td>8%</td>
</tr>
<tr>
<td>DSM-III ADD</td>
<td>New Zealand</td>
<td>11</td>
<td>M/F</td>
<td>7%</td>
</tr>
<tr>
<td>DSM-III ADD/H</td>
<td>Canada</td>
<td>4-16</td>
<td>M/F</td>
<td>6%</td>
</tr>
<tr>
<td>DSM-III ADD/H</td>
<td>Puerto Rico</td>
<td>4-16</td>
<td>M/F</td>
<td>9%</td>
</tr>
<tr>
<td>DSM-III ADD/H</td>
<td>United Kingdom</td>
<td>6-8</td>
<td>M</td>
<td>5%</td>
</tr>
<tr>
<td>DSM-III-R AD/HD</td>
<td>Hong Kong</td>
<td>7</td>
<td>M</td>
<td>9%</td>
</tr>
</tbody>
</table>

In reference to subtype prevalence, it is suspected that AD/HD-HI is considerably rarer in school-age populations than either AD/HD-I or AD/HD-C (J.T. Nigg, 2005). Majority of research focusing on AD/HD has typically recruited AD/HD-C participants due to their comparative predominance in both childhood and adolescent populations.
2.4 Treatment

Since issues relating to treatment will not be assessed in this thesis, only a brief discussion will be presented here. For a detailed review, see Swanson et al (1993) or Purdie, Hattie and Carroll (2002).

At present, there are two prominent courses of treatment for AD/HD; (1) stimulant medications such as Methylphenidate or Dextroamphetamine, and (2) non-stimulant treatment primarily composed of psychosocial interventions such as behaviour modification and cognitive therapy, and in some cases medications such as Atomoxetine. These two methods are frequently combined in an attempt to more globally address the disorder.

2.4.1 Stimulants: Methylphenidate (MPH) and Dextroamphetamine (DEX)

Stimulants have become the major component of medication treatment regimes for AD/HD. They have been shown to positively affect hyperactivity, impulsivity, aggression, and attention (Swanson et al., 1993). However, there has been growing concern in recent years over the continuing administration of stimulants to children and adolescents since these drugs only temporarily suppress symptoms. The two stimulants most commonly prescribed to treat the behavioural symptoms of AD/HD are Methylphenidate (MPH), and Dextroamphetamine (DEX), both of which are dopamine and norepinephrine re-uptake inhibitors.

Much of the controversy surrounding the administration of stimulants to AD/HD children centres on the high incidence of side effects associated with these medications. The vast majority of AD/HD children who are treated with stimulants experience some adverse reactions such as insomnia, decreased appetite, headaches (Pliszka, 2007), stomach-aches, dizziness, irritability, tearfulness, and anxiety. These side effects are typically the main reason why stimulant medication is discontinued, however research as shown such reactions to be more commonly associated with DEX, rather than MPH (Efron, Jarman, & Barker, 1997).
Unfortunately, most studies investigating the efficacy of stimulants such as MPH and DEX have failed to use a placebo control, hence questioning the true extent to which stimulants benefit AD/HD patients. Some studies have reported placebo effects as large as 30% (DuPaul & Eckert, 1997; Spencer et al., 1996), and in an early review by Barkley (as cited in Kohn, 1989) placebo effects were reported to be as high as 40%. Also, the positive effects of stimulants are not isolated to AD/HD sufferers; the same effects have been shown in normal children and adults (Timimi et al., 2004; Whalen & Henker, 1991). This is hardly surprising since the core symptoms of AD/HD (hyperactivity and inattentiveness) are within the repertoire of normal human behavior (albeit to a significantly lesser extent). Rather than dampen activity levels, stimulants play their primary roles in redirecting behavior and sustaining attention. As a result, behavior and attention are more goal-directed rather than aimless. However, stimulants cannot correct cognitive deficits, nor can it create talent or ability. And although almost all parents expect their child to improve in both behavior and attention levels particularly at school, stimulants do nothing to directly benefit the child’s actual academic achievement. In the academic arena, psychosocial interventions have proven far superior to any stimulant.

2.4.2 Non-Stimulants: Atomoxetine (ATX) and Psychosocial Treatments

While stimulants like MPH and DEX are typically recommended in the first stage of medication treatment for AD/HD, there are significant limitations associated with these such as insomnia, decreased appetite, and irritability (see previous section). This coupled with the fact that stimulants can be ineffective or not well tolerated in around 30% - 50% of AD/HD children and adults (Wernicke & Kratochvil, 2002), has spurred the search for effective non-stimulant treatment alternatives. Thus far, there are two treatment regimes that steer well clear of the stimulant path; the non-stimulant medication Atomoxetine (ATX), and psychosocial interventions. Both of these will be discussed (respectively) in the following two sections. For a detailed review of stimulant and non-stimulant medications in the treatment of AD/HD, refer to Findling (2008) or Spencer, Biederman, Wilens and Faraone (2002).
2.4.2.1 Atomoxetine (ATX)

Atomoxetine (ATX), a norepinephrine re-uptake inhibitor, is a relatively new and promising non-stimulant medication for the treatment of AD/HD. Unlike stimulants, ATX is not a controlled substance (in the U.S.A.), and shows no abuse potential, however does produce a similarly concerning profile of side-effects. Despite this, several studies have shown ATX to significantly reduce the core symptoms of AD/HD; results from some of these studies will be discussed below. For a general discussion of ATX including the related pharmacology, see Simpson and Perry (2003).

A pilot study conducted by Kratochvil et al (2001) assessed the safety, tolerability, and efficacy of ATX in the treatment of paediatric AD/HD. Although their results showed ATX to significantly reduce AD/HD symptoms, their sample of 9-14 year old AD/HD patients also suffered a range of adverse side-effects including appetite suppression, gastro-intestinal symptoms, irritability, epistaxis, dry mouth, nightmares, headache, heart palpitations, fatigue, and dizziness. However, since these side-effects were transient, the authors concluded that ATX was safe and well tolerated among the administered sample. From this, the author’s argued that ATX represents a promising alternative medication for patients who fail to respond to such medications as MPH or DEX. These findings were complimented by a second pilot study incorporating a younger AD/HD population (5-6 years old); Kratochvil et al (2007) found significant improvement of AD/HD symptoms with ATX. However, majority of their sample also reported at least one side-effect, the most common being mood lability, decreased appetite, and weight loss.

Although both studies by Kratochvil et al (2001; 2007) show significant improvements in AD/HD symptoms, a considerable limitation of both are their open-label design. In order to ascertain the true efficacy of ATX in reducing AD/HD symptomatology, a placebo must be incorporated. Michelson et al (2001) found ATX doses at or greater than 1.2mg/kg/day to significantly decrease AD/HD symptoms better than that of a placebo. These results were supported in a recent meta-analysis by Kratochvil, Milton, Vaughan and Greenhill (2008) who also found ATX to be more effective than a placebo.
in reducing AD/HD symptoms in both young (6-7 years) and older (8-12 years) children. Again however, the reported side-effects included decreased appetite, vomiting, irritability, fatigue, and somnolence.

For ATX to be considered a viable avenue of medication for AD/HD, its ability to treat AD/HD symptoms must be either on par with, or superior to the current popular medication, MPH. In an open-label study comparing MPH and ATX, both medications were similarly effective in reducing AD/HD symptoms (Kratochvil et al., 2002). Recent research has also introduced the possibility of mixing both MPH and ATX in an attempt to maintain treatment effectiveness while reducing side-effects. In a case study by Agarwal and Sitholey (2008), titrated doses of MPH and ATX were administered to an 8-year old AD/HD patient. Results showed an overall decrease in side-effects (due to the smaller individual doses of MPH and ATX), while treatment efficacy was maintained. Therefore, in cases where drug effectiveness is compromised due to such issues as tolerance (or intolerance of high doses), a mixed MPH-ATX medication regime may prove superior to either MPH or ATX alone.

2.4.2.2 Psychosocial Treatments

Since the major benefit of stimulant medication is the temporary alleviation of behaviours such as hyperactivity, impulsivity and inattention, assuming that this will ultimately positively affect learning and academic achievement is, at first glance, not an unreasonable extrapolation. However, previous research has shown that while there is a slight improvement in general cognitive abilities, the major improvement seems to be isolated to social functioning rather than any school-based achievement (Purdie et al., 2002). Obviously, in order to enhance academic achievement in AD/HD patients, educational and/or behavioural solutions rather than medicinal are required.

Behavioural interventions such as ‘positive reinforcement’ and ‘punishment’ have been shown to generate behaviours that facilitate classroom learning. Similarly, Cognitive-Behavioural therapy (CBT) involving such methods as ‘self-instruction’ and ‘self-reinforcement’ have been shown to improve problem-solving abilities as well as
motivation and self-control, though some debate exists over whether or not the success of CBT is context specific (i.e. clinic-based vs. school-based therapy) (Purdie et al., 2002).

Educational programs, particularly those that are school-based can be beneficial not only for the AD/HD child, but for teachers as well. School-based programs which actively involve teaching staff are especially important as they enhance the teacher’s knowledge and understanding of how to effectively deal with and respond to the educational needs of the AD/HD student. Ultimately, the success of any school-based intervention depends on the expertise of the teacher, rather than the student. In a study conducted by Miranda, Presentación and Soriano (2002), teachers of 29 AD/HD students were trained in the use of behaviour modification techniques, cognitive behaviour, and instructional management strategies. Through both parent and teacher ratings, significant improvements in primary AD/HD symptoms (hyperactivity/impulsivity and inattention) along with behavioural difficulties such as antisocial behaviour, psychopathological disorders, and anxiety, were found. Additionally, academic performance, namely in mathematics and natural sciences, was also increased. Kohn (1989) contends that even simple teaching actions such as allowing students to work at their own pace, giving individual attention, and offering rewards for proactive behaviour can have positive effects. For a more detailed discussion and review of these and other psychosocial treatments in AD/HD, see Barkley (2002).

While stimulant medication is typically the first port of call in the treatment of AD/HD, it is important to note that not all children diagnosed with AD/HD will need medication, as this depends heavily on symptom severity, the child’s coping abilities, and the availability and cost of alternative treatments. As Doggett (2004) argues, “currently, parents, teachers, and doctors make decisions about drug therapy – being the same ones who appear to receive the greatest benefit from it” (p.79). Stimulants may provide effective short-term management of behaviour and inattention yet psychosocial interventions are more effective in the long-term as these target both social and academic issues. This is of particular importance since poor academic outcome and social functioning are two of the greatest risks for children with AD/HD.
2.5 Conclusions

AD/HD has gone through numerous changes in nomenclature over the past few decades, effectively changing its conceptualisation each time. While research has revealed many insights into the disorder, the answers to several key issues are still vague and open to interpretation. Diagnostic procedures that not only omit crucial factors such as gender and age, but also differ internationally, can hinder the diagnostic process, and the heterogeneity of the condition only adds to its ambiguity. Research has shown the presentation and outcome of AD/HD to vary significantly between genders and between age groups. These factors must be incorporated into the diagnostic process if treatment is to be successful.

From the above discussion, it is easy to see how effective treatment can become an exercise in trial and error rather than knowledge based on previously consistent treatment efficacy. While stimulants provide almost immediate relief from the core symptoms of AD/HD, the effects are only temporary and usually dissipate after around 4 hours. And while stimulants may help to focus attention and behaviour, they do not lend any promises towards greater cognitive ability or academic success. Psychosocial interventions have proven more successful in terms of academic achievement however these treatments are time consuming and less cost effective than stimulants. An optimal treatment regime may consist of a carefully tailored combination of the two therapies rather than one alone. In addition to this, education and counselling of parents and teachers are valuable and crucial adjuncts as it is important to keep the child’s best interests in mind rather than those of the parents, teachers, and clinicians.

Chapter 3 will discuss one of the biggest issues to complicate diagnosis and treatment in AD/HD - the high incidence of comorbidity. While there are several conditions that have been diagnosed as comorbid with AD/HD, two of the most prevalent are Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD), both of which manifest as behavioural dysfunction. Issues relating to the comorbidity of ODD and CD
with AD/HD including prevalence, diagnosis, and presentation will be discussed in the next chapter.
Chapter 3: Comorbidity in AD/HD

**Chapter Overview:**
This chapter will introduce and define the issue of comorbidity both as a phenomenon, and how it relates to AD/HD. Global prevalence rates of AD/HD comorbidity, along with the most common comorbid conditions (ODD/CD) with this disorder are presented. Symptom profiles along with DSM diagnostic criteria for both ODD and CD are also provided and discussed in terms of gender and age differences. The impact of ODD/CD comorbidity on AD/HD in reference to subtype clustering, psychosocial functioning, and executive function characteristics are also examined.
3.1 Comorbidity - An Overview

Comorbidity can be an ambiguous phenomenon, especially when there is some disagreement over its literal meaning. While some believe “comorbidity” to represent two (or more) disorders that share a common underlying aetiology, others believe it applies only when one disorder leads to another. The most widely accepted definition of “comorbidity” however, signifies the concurrent occurrence of two separate disorders; it is this definition that will be adopted here.

AD/HD is frequently comorbid with other psychiatric disorders, so much so that it has become a common characteristic of the AD/HD profile. Comorbidity can influence the presentation, diagnosis, and treatment of AD/HD. It seems that almost any psychiatric disorder can be comorbid with AD/HD such as mood disorders, anxiety disorders, oppositional and conduct disorders, cognitive performance and learning disabilities, developmental disorders, tic disorders, and substance abuse disorders; the first three are the most frequently diagnosed comorbid conditions with AD/HD (Spencer, 2006). Figure 3.1 below is a diagram adapted from Pliszka (2003) which roughly illustrates the complex interwoven nature of comorbidity in AD/HD.

Depending on the sample, AD/HD has been associated with at least one other DSM diagnosis with prevalence rates ranging from 60-100%; as many as two-thirds of AD/HD individuals also meet DSM criteria for at least two other diagnoses (Gillberg et al., 2004). Although AD/HD is not causal to comorbidity, it is typically the first disorder to present and hence increases susceptibility to comorbidity, especially if AD/HD symptomatology is severe. Furthermore, the existence of one comorbid disorder significantly increases the risk of developing additional comorbid disorders (Waxmonsky, 2003). The diagnosis of more than one comorbid disorder in AD/HD individuals is becoming more widespread.
3.2 A Global Perspective

The vast majority of the AD/HD research originates from western nations such as USA, therefore much of the reported prevalence rates are more reflective of these nations rather than others. As yet, a study dedicated to overall AD/HD comorbidity rates in Australia has not been done, however since cultural and societal norms in Australia are considered to be somewhat on par with other western nations such as USA, it is assumed that the overall AD/HD comorbidity rates will also be similar. In terms of specific comorbidity, Sanders, Arduca, Karamitsios, Boots and Vance (2005) found the most prevalent comorbid condition in their AD/HD cohort to be ODD (67%), followed by CD (33%), anxiety (27%), phobia (27% social; 27% specific), and Obsessive Compulsive Disorder (27%). These rates, particularly those of ODD and CD are comparable to those found in USA.
Unfortunately, research investigating the issue of comorbidity and AD/HD in culturally/ethnically different populations is scarce. A noticeable variance exists between the few studies that have explored this topic in different cultures.

An investigation into the genetically isolated community of Paisa, Colombia (South America) found comorbidity in their AD/HD sample to be only slightly lower than those reported in North America; 50% were comorbid with CD, 25% with ODD, 23% with depression, and 25% with a simple phobia (Palacio et al., 2004). It is likely that these rates would have been higher had learning disabilities also been examined.

In another region of South America, noticeably higher rates were found from an analysis of two geographically different areas in Brazil: Porto Alegre and Rio de Janeiro. Although results showed Rio de Janeiro to have higher overall comorbidity rates than Porto Alegre (82.1% vs. 67.3% respectively), these results did not reach significance, however comorbidity with ODD was found to be significantly higher in Rio de Janeiro than in Porto Alegre (51.3% vs. 39.1%) (Souza, Pinheiro, Denardin, Mattos, & Rohde, 2004).

A Korean study also found ODD to be the most common comorbid disorder with AD/HD (47.6%), with anxiety disorders (33.3%), and affective disorders (14.3%) being second and third most common respectively (Byun et al., 2006). Comparable to the above research, Byun et al.’s study found a 76.2% of their AD/HD sample had at least one comorbid disorder.

In a study exploring comorbidity trends in a Swedish community-based AD/HD population, Kadesjö and Gillberg (2001) found that 87% of those who met DSM criteria for AD/HD also met criteria for at least one additional diagnosis, 67% met criteria for two additional diagnoses, and 33% met criteria for three additional diagnoses. Their study found the most commonly diagnosed condition comorbid with AD/HD was ODD (60%).

From the select few studies that have investigated comorbid AD/HD in culturally and ethnically different populations, comorbidity rates are surprisingly consistent and correspond with those previously reported in USA.
3.3 Trends in Comorbidity

In the array of disorders that present comorbid with AD/HD, previous research has revealed certain trends and patterns with respect to both AD/HD subtype and gender. Since gender has been shown to be a significant moderator in the presentation and outcome of AD/HD (see Section 2.2.3.1 for a discussion), the subsequent influence on comorbidity is hardly surprising. Trends in comorbidity also appear according to AD/HD subtype; specifically in relation to symptom severity and expression which differs between subtypes. Before these trends can be understood however, an explanation of ‘internalising’ and ‘externalising’ pathology and their connection to AD/HD subtypes is needed. The following sections will discuss the relationship between AD/HD subtypes and internalising/externalising symptom pathology, gender, and the resulting effects on comorbidity.

3.3.1 Internalising and Externalising Symptoms - AD/HD Subtypes and Gender

As the names suggest, externalising and internalising behaviour are polar opposites. Externalising behaviour is typically described as rule-breaking, impulsive, aggressive, health-compromising (e.g. smoking, drug and alcohol abuse), anti-social, and narcissistic. On the other hand, individuals displaying internalising behaviour are described as anxious, depressive, lonely, inactive, underachieving, and unhappy (Laukkanen, Shemeikka, Notkola, Koivumaa-Honkanen, & Nissinen, 2002).

Upon inspection of the DSM-IV-TR diagnostic symptoms for AD/HD-C and AD/HD-HI, most if not all describe overt and disruptive behaviours which can be defined as externalising. For AD/HD-I, diagnostic symptoms are covert and almost esoteric; reflective of internalising behaviours (refer to Section 2.2.2 for DSM-IV-TR diagnostic criteria for AD/HD).

Since AD/HD-C possesses symptoms from both the inattentive and hyperactive/impulsive profiles, it is typically seen as the most symptomatic and hence most severe subtype of this disorder. Comorbidity in AD/HD typically occurs as a
function of symptom severity, and previous research has repeatedly found it to be most pervasive in AD/HD-C, accounting for the comorbid majority, particularly where multiple co-existing disorders are diagnosed (Levy, Hay, Bennett, & McStephen, 2005).

As discussed in Chapter 2, previous research has found that girls are more likely than boys to be diagnosed as AD/HD-I, and also less likely to display externalising behaviour (see Section 2.2.3.1 on Gender), hence further linking the AD/HD-I subtype with internalising pathology. This association tends to be vice versa for boys, that is, they are less likely than girls to be diagnosed as AD/HD-I, and more likely to display externalising behaviour (Carlson et al., 1997).

3.3.2 Tying It All Together - Behaviour, Subtype, and Gender in AD/HD Comorbidity

Both ODD and CD are predominantly defined by externalising behaviours, and tend to occur comorbid with AD/HD-C or AD/HD-HI more frequently than AD/HD-I (Decker, McIntosh, Kelly, Nicholls, & Dean, 2001). The typical presentation of ODD and CD can almost be seen as an extrapolation of the externalising pathology associated with AD/HD-C and AD/HD-HI.

Since girls are more likely to be diagnosed as AD/HD-I than either AD/HD-C or AD/HD-HI, both ODD and CD are more prevalent in AD/HD boys than girls (Carlson et al., 1997; Newcorn et al., 2001). However, girls and boys of the same AD/HD subtype show similar levels of ODD/CD comorbidity (Gabel, Schmitz, & Fulker, 1996; Levy et al., 2005), indicating that this type of comorbidity varies as a function of subtype rather than gender.

AD/HD girls typically display more internalising behaviours than boys, hence the risk of developing associated emotional disorders such as depression, anxiety, and mood disorders are seen as a greater risk for females rather than males (Gershon, 2002; Zahn-Waxler, Shirtcliff, & Marceau, 2008). In a review by Quinn (2008), AD/HD girls were found to be 5.4 times more likely than AD/HD boys to have a comorbid diagnosis of major depression. Other comorbid internalising conditions such as learning disorders (LDs) have also been found to be more characteristic of AD/HD in girls, than
boys. Gaub and Carlson (1997) argue that AD/HD girls tend to have greater intellectual impairment compared to boys, suggestive of a greater risk of comorbid LDs such as dyslexia and reading disability.

Comorbidity in AD/HD is highly dependent on the severity of core AD/HD symptoms. While gender is a significant discriminant in subtype diagnosis, it does not directly affect comorbidity; symptom severity is the only pivotal determinant in both comorbidity and AD/HD subtype.

### 3.4 Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD)

An exhaustive analysis of comorbid disorders in AD/HD is beyond the scope of this thesis due to (1) the large population size required for a representative analysis, and (2) the extensive overlap between comorbid disorders. For the sake of simplicity and clarity, only ODD and CD will be investigated since they are the most prevalent comorbid conditions in AD/HD and among the most reliably diagnosed. The following sections will therefore be restricted to both ODD and CD; characteristics of their comorbid presentation with AD/HD, and their DSM-IV-TR diagnosis.

#### 3.4.1 ODD and CD - An Overview

ODD is characterised by a persistent pattern of negativistic, hostile, and defiant behaviour towards authority figures which results in significant impairment. CD is characterised by a repetitive and persistent pattern of behaviour where the basic rights of others are violated, along with major age-appropriate societal norms (American Psychiatric Association, 2000).

In the long-term, ODD has been found to significantly affect psychiatric, family, and social functioning status, along with an increased risk of major depression. CD by comparison, over the long-term has been found to significantly increase the risk of
psychoactive substance use disorders, smoking, and bipolar disorder. It has also been associated with school expulsion, criminal behaviour, sex before the age of 16 years, and being fired from a job (Biederman et al., 2008). Hence, in terms of symptom severity and impairment, ODD is significantly milder than CD. However, ODD is commonly seen as a major risk factor for the later development of CD, particularly when comorbid with AD/HD (van Lier, van der Ende, Koot, & Verhulst, 2007); it is important to note that not all children with AD/HD and comorbid ODD will progress to CD (Biederman et al., 2008). An early study by Loeber, Lahey and Thomas (1991) argued that while nearly all youths diagnosed with CD also met criteria for ODD, the opposite was not true. This contention was supported in a subsequent study by Biederman et al (1996), who hypothesised the existence of two distinct subtypes of ODD; one that is prodromal to CD, and another that is subsyndromal in nature but unlikely to lead to CD. The authors found that while similar correlates were found for both ODD and CD, ODD rarely progressed to CD, however almost all children with CD were comorbid with ODD. This suggests that while both ODD and CD may be part of the same disease process (with CD being the more severe between the two), the likelihood of ODD being prodromal to CD increases with the severity of ODD.

CD likewise and particularly when comorbid with AD/HD, is commonly seen as a major risk factor for the later development of Antisocial Personality Disorder (APD) and subsequent criminal behaviour (Loeber, Burke, Lahey, Winters, & Zera, 2000), however the latter seems more apparent in males than females (Lahey et al., 1998). Figure 3.2 below illustrates the relationship between AD/HD, ODD, CD, and APD. In a study conducted by Gelhorn, Sakai, Price and Crowley (2007), 75% of their CD cohort progressed to APD. Their study found that CD symptoms such as those relating to weapons use, cruelty to people, and lies, were strong predictors of CD persistence and adult antisocial outcome. Similarly, Copeland, Miller-Johnson, Keeler, Angold and Costello (2008) argue that both conduct and substance abuse problems are important predictors of criminality and violence.

The aggressive behaviours that define both ODD and CD are moderated by gender in a similar fashion as with AD/HD; both disorders are less prevalent in females compared
to males. However despite this lower prevalence in females, once the diagnosis has been made the disorder is as stable as in males. Diagnosis of either CD or ODD is noticeably more difficult in females likely due to gender-associated methods of expressing aggression that are not considered in the DSM-IV-TR. Unlike males who tend to act out anger in displays of physical aggression, females tend to engage in indirect, verbal, and relational aggression such as alienation, ostracism, and character defamation aimed at breaking the relational bonds between “friends” (Loeber et al., 2000; Loeber & Hay, 1997). These behaviours may be considered more manipulative and calculating rather than overtly aggressive.

The following sections will list the DSM-IV-TR diagnostic criteria for both ODD and CD.
AD/HD diagnosis

ODD

If DSM criteria for ODD is met
AD/HD+ODD

If DSM criteria for ODD is not met
AD/HD

CD

If DSM criteria for CD is met
AD/HD+ODD/CD

If DSM criteria for CD is not met
AD/HD+ODD

APD

If DSM criteria for APD is met
APD

If DSM criteria for APD is not met
AD/HD+ODD/CD

Early childhood

Adolescence

Young adulthood

Figure 3.2 Relationship between AD/HD, ODD (Oppositional Defiant Disorder), CD (Conduct Disorder), and APD (Antisocial Personality Disorder). Red arrows represent “increased risk”, e.g. AD/HD increases the risk of ODD, AD/HD+ODD increases the risk of CD, etc.
3.4.2 DSM-IV-TR Diagnostic Criteria for ODD

ODD typically presents before 8 years of age and usually no later than early adolescence. The onset of symptoms is generally quite gradual and can occur over several months or even years.

For a valid diagnosis of ODD, firstly, a pattern of negativistic, hostile, and defiant behaviours including at least 4 those listed below must be present for at least 6 months. The behaviour or symptom must occur more frequently than is naturally observed in children or adolescents of comparable age and developmental level.

(1) Often loses temper.
(2) Often argues with adults.
(3) Often actively defies or refuses to comply with adults’ requests or rules.
(4) Often deliberately annoys people.
(5) Often blames others for his or her mistakes or misbehaviour.
(6) Is often touchy or easily annoyed by others.
(7) Is often angry and resentful.
(8) Is often spiteful or vindictive.

Secondly and similar to AD/HD, the disturbance of behaviour must cause clinically significant impairment in either social, academic, or occupational functioning, however if they occur exclusively during the course of a Psychotic or Mood Disorder then a diagnosis of ODD is invalidated.

Thirdly, if diagnostic criteria for CD are met as well as that for ODD, the more severe diagnosis of CD is always adopted over ODD. Similarly, if the individual is aged 18 years or over and meets diagnostic criteria for APD, then this diagnosis is also adopted over ODD.
3.4.3 DSM-IV-TR Diagnostic Criteria for CD

ODD is seen as an antecedent to CD; both are classified as DBDs and hence display familial symptoms however CD symptomatology is significantly more severe.

Diagnostic criteria for CD are separated into 4 groups as shown below. A valid diagnosis requires the presence of at least 3 symptoms in the past 12 months, with at least one symptom present in the last 6 months.

*Aggression to people and animals*

1. Often bullies, threatens, or intimidates others.
2. Often initiates physical fights.
3. Has used a weapon that can cause serious physical harm to others (e.g., a bat, brick, broken bottle, knife, gun).
4. Has been physically cruel to people.
5. Has been physically cruel to animals.
6. Has stolen while confronting a victim (e.g., mugging, purse snatching, extortion, armed robbery).
7. Has forced someone into sexual activity.

*Destruction of property*

8. Has deliberately engaged in fire setting with the intention of causing serious damage.
9. Has deliberately destroyed others’ property (other than by fire setting).

*Deceitfulness or theft*

10. Has broken into someone else’s house, building, or car.
11. Often to obtain goods or favours or to avoid obligations (i.e., “cons” others).
12. Has stolen items of nontrivial value without confronting a victim (e.g., shoplifting, but without breaking and entering; forgery).
Serious violations of rules
(13) Often stays out at night despite parental prohibitions, beginning before age 13 years.
(14) Has run away from home overnight at least twice while living in parental or parental surrogate home (or once without returning for a lengthy period).
(15) Is often truant from school, beginning before age 13 years.

As with ODD and AD/HD, CD symptoms must cause clinically significant impairment in social, academic, or occupational functioning. If the individual is aged 18 years or over and criteria are met for APD, then this diagnosis is adopted over that of CD.

Diagnostic criteria for CD also specifies 3 subtypes based on the age of onset:

I. **Conduct Disorder, Childhood-Onset Type**: Where first onset of at least one CD symptom occurs prior to age 10 years.

II. **Conduct Disorder, Adolescent-Onset Type**: Where first onset of at least one CD symptom occurs after age 10 years (that is, there is an absence of any CD symptoms prior to 10 years of age).

III. **Conduct Disorder, Unspecified Onset**: Where age of onset is unknown.

The severity of the CD symptoms is also categorised:

i. **Mild**: Few if any conduct problems in excess of those required to make the diagnosis, and conduct problems cause only minor harm to others (e.g., lying, truancy, staying out after dark without permission).

ii. **Moderate**: Number of conduct problems and effect on others intermediate between “mild” and “severe” (e.g., stealing without confronting a victim, vandalism).

iii. **Severe**: Many conduct problems in excess of those required to make the diagnosis, or conduct problems cause considerable harm to others (e.g., forced sex, physical cruelty, use of a weapon, stealing while confronting a victim, breaking and entering).
Like AD/HD, both gender and age can have a significant effect on the presentation and outcome of ODD and CD. Neither ODD or CD diagnostic criteria take into consideration gender differences, and while age is highlighted in CD, it is overlooked in ODD. Since girls typically display less overtly aggressive behaviour, it is likely that considerable gender differences exist particularly in CD. The next section will discuss both gender and age issues in the diagnosis of ODD and CD.

### 3.4.4 Diagnostic Issues in ODD and CD

The validity and reliability of ODD and CD diagnostic criteria depends entirely only on its ability to accurately describe behaviour pathology in all sufferers. However as with AD/HD, factors such as gender and age carry a significant influence on behaviour pathology. This is particularly pertinent to CD which specifies a subtype according to age of onset, with research showing age-related differences in the manifestation of aggression (Maughan, Rowe, Messer, Goodman, & Meltzer, 2004), and associated comorbidity (Connor, Ford, Albert, & Doerfler, 2007).

Attempting to understand the development of behavioural problems in children and adolescents without any knowledge of age and gender differences can only result in misinformed conclusions, which in turn will misrepresent the phenomenon of behavioural dysfunction. The following sections will discuss diagnostic issues relating to both gender and age in ODD and CD.

#### 3.4.4.1 Gender Differences in ODD and CD

Gender differences in the prevalence of CD are far more consistent than for ODD, likely due to the comparatively greater severity of behavioural dysfunction associated with CD than ODD. As a rule, DBDs tend to be less prevalent in females than in males. However in ODD, most previous research into male/female prevalence rates have been inconclusive (Loeber et al., 2000). In a nationwide study of behaviour pathology among non-institutionalised youths in the USA, McDermott (1996) found ODD to be
more prevalent in males rather than females, however this was only in their group of 5 – 8 year olds, and not in any other age group analysed. This is in sharp contrast to results by Maughan, Rowe, Messer, Goodman and Meltzer (2004) which revealed a clear male predominance in ODD, similar in strength to that for CD. On the other hand, Lahey et al (2000) found no gender difference in the prevalence of ODD in their sample of 9 – 17 year old youths based on parent reports. Their study did however find a significant difference between genders in the prevalence of CD; boys were more likely than girls to be diagnosed as CD according to both youth reports, and combined youth plus parent reports. The robust findings of male predominance in CD prevalence is highlighted in Loeber et al.’s (2000) review which argues that boys are around 3-4 times more likely than girls to be diagnosed as CD, across different ages.

These gender differences (or lack thereof) may be linked to the type of behavioural dysfunction displayed by males and females, rather than the amount. In terms of CD, females are often arrested for non-aggressive and covert forms of delinquency such as fraud and shop-lifting (Ogle, Maier-Katkin, & Bernard, 1996). If the conduct problems typically displayed by females are more covert and manipulative rather than overtly aggressive and violent, it may help to explain the lower prevalence of females since CD diagnostic criteria is largely focused on overtly aggressive behaviour.

There has been considerable support to append CD subtypes to include a distinction between overt or impulsive and covert or controlled aggressive behaviour. Overt/impulsive aggressive behaviour is defined as physically confrontational, impulsive, unprofitable and maladaptive, usually following little provocation, with a poorly controlled affective response. Covert/controlled aggressive behaviour is typically defined as non-physical, concealed, planned, goal-directed, and usually profitable in some respect (Loeber et al., 2000; Masi et al., 2008). According to this distinction, female aggressive behaviour is more covert and controlled, while male aggressive behaviour is more overt and impulsive. A wealth of research exists which describes males as more physically violent and aggressive than females (Loeber & Hay, 1997; Maughan, Pickles, Rowe, Costello, & Angold, 2000; Yang & Coid, 2007; Zahn-
Waxler et al., 2008), with subsequent prevalence rates of APD also being significantly higher in males than in females (Hicks et al., 2007).

Aggressive behaviour associated with ODD appears to be comparatively more inwardly focused than that of CD, indicative of different aetiologies. ODD symptomatology in girls may stem from more internalising pathology than boys, such as negative emotions/temperament, anxiety, depression, or withdrawal. ODD has previously been linked to withdrawn, anxious, and depressed behaviour (Boylan, Vaillancourt, Boyle, & Szatmari, 2007; Carlson et al., 1997), therefore, even though ODD is classified as an externalising disorder, internalising conditions such as depression and anxiety may play as antecedents to ODD in females. Since internalising pathology tends to be more common in females than males, it may partly explain their lower ODD prevalence, or the lack of significant gender differences in some studies. While there is some possibility that reporter and/or situational differences may play key roles in determining prevalences, research has found more than half the variance in ODD (and AD/HD) in males and females to be accounted for by genetic influences, of which some were gender-specific (Derks, Dolan, Hudziak, Neale, & Boomsma, 2007). This finding attests to the significance of gender in disruptive behaviour disorders, perhaps above any methodological bias, though further research supporting this contention is needed.

3.4.4.2 Age Differences in ODD and CD

The manifestation of aggression is multifaceted and developmentally variable. While aggression can develop at a young age, its manifestation changes quite markedly with age. In a detailed review by Loeber and Hay (1997), how aggressive and violent behaviour in boys changes with age was described. Using prospective and retrospective information from parents and sons (where possible), the authors were able to create age-of-onset graphs of different forms of aggression. Three levels of aggressive behaviour were defined: ‘minor aggression’ was deemed as annoying others and bullying; ‘physical fighting’ was defined as physical or gang fighting; and
‘violence’ was regarded as strongarming, attacking someone, or forced sex. The authors described a developmental ordering of the seriousness of aggression with age; minor aggression first appeared around age 3, with an almost linear increase in aggression till age 16; the emergence of physical fighting accelerated from age 10 onwards, followed by violent behaviour accelerating from age 11 onwards. Therefore the onset of aggression in boys is almost confined to the preschool period, and that the number of boys who experience the onset of aggression increases throughout childhood and into early adolescence. However, aggression (particularly physical fighting) was shown to decrease from early adolescence onward, though more serious violence increased with age, reaching its peak in late adolescence/early adulthood, before beginning to decrease. This increase in serious violence may pertain specifically to children who experienced an early onset of delinquency, since this has been linked to involvement in more serious offences over a longer period of time, compared to those who experienced a late onset (Lahey et al., 1999; Tolan & Thomas, 1995).

There seems to be no significant early-age trends in ODD however, with prevalence rates remaining relatively constant from age 5 till around age 10, with a linear decrease in late childhood and through adolescence; and while there were significantly more ODD boys than girls, this age trend was seen in both genders (Maughan et al., 2004). Results for CD in Maughan et al’s (2004) study painted a noticeably different picture though, with rates of CD being low in both genders in the early years of life (till age 5). A steady increase in rates with age was found for boys however rates did not increase until the early teens for girls. Hence, while the rates of CD were dominated by males in childhood and early adolescence, this difference tended to dissipate by the mid-teen years. This finding supports the conjecture that females tend to display a comparatively later onset in aggressive behaviour than males, suggesting that the early teen years presents a critical risk period for girls. This is likely linked to the increase in status violations and other non-aggressive behaviour, which parallels the decrease in physical aggression between childhood and adolescence (Maughan et al., 2004). Since non-aggressive behaviour (such as status violations) are more common in females than males, and physical aggression is more common in males than in females, it is likely
that the noted increase in female CD in adolescence may be somewhat illusory; a seeming increase attributable to the parallel decrease in male CD (physical/violent behaviour) during that age period. While many authors have argued that girls experience a comparatively later onset of conduct problems than boys, this issue is still under debate (Keenan, Loeber, & Green, 1999) since some studies have been unable to find any significant relationship between gender and age of onset (Lahey et al., 1999; Lahey et al., 1998).

While research into the age of onset of delinquent and aggressive behaviour is far from comprehensive, findings thus far have highlighted important developmental trends which will inevitably effect how treatment regimes are structured. At present, CD but not ODD makes a diagnostic distinction between early and late onset of symptoms; since no fundamental differences were found between genders for ODD, and prevalence rates remained relatively constant during a key susceptibility period, distinguishing between genders and age of onset at this stage seems unnecessary. Due to conflicting results for gender differences in the age of onset of CD, it is premature to suggest that this also be taken into consideration in the diagnostic process, but warrants further research. Unfortunately, CD subtypes are rarely reported in the literature due to the unreliable nature of symptom recall, particularly if CD symptoms have been present for numerous years.

Due to the comparatively greater level of impairment associated with CD, the majority of research attention has focused on this rather than ODD. This is also because individuals with CD typically meet diagnostic criteria for ODD as well, but in accordance with DSM-IV-TR guidelines, if both ODD and CD criteria are met, the more severe diagnosis of CD is adopted over ODD (refer to Section 3.4.2 for ODD diagnostic criteria and guidelines). For this reason, when CD is investigated, it is typically combined with ODD to form a disorder amalgamation known simply as ‘conduct problems’. The following section will discuss AD/HD comorbid with ODD and CD.
3.5 AD/HD Comorbid With Conduct Problems (AD/HD+ODD/CD)

Pure AD/HD, pure ODD/CD, and AD/HD+ODD/CD have long been considered to be different manifestations of the same underlying pathophysiology. Both ODD and CD have an approximate 50% overlap with AD/HD in terms of aetiology, presentation, and outcome, and have frequently been considered to represent a rather robust ‘severity hierarchy’. The severity of DBDs can be viewed as:

\[
\text{AD/HD} \Rightarrow \text{AD/HD+ODD} \Rightarrow \text{AD/HD+ODD/CD}
\]

(Arrows represent direction of increasing symptom severity)

This pattern of severity has been supported by previous research (Connor & Doerfler, 2007; Spencer, 2006).

The development of ODD/CD comorbidity is greatly dependant on the persistence and severity of AD/HD symptomatology; the longer the duration and greater the symptom severity in AD/HD (particularly symptoms of hyperactivity/impulsivity), the greater the risk of ODD and/or CD development in later life. The disabling effects of ODD/CD in addition to those of AD/HD have been found to produce a ‘hybrid’ condition incorporating symptomatology from both disorders resulting in an increased susceptibility for later psychiatric impairment (Schachar & Tannock, 1995; Waschbusch, 2002). This has led some researchers to argue that AD/HD+ODD/CD represents a separate pathological entity, rather than a ‘hybrid’ per se (Banaschewski et al., 2003). Indeed, this is the view adopted in the ICD-10 (see Chapter 2), but not in the DSM-IV-TR. For a detailed review on this issue, see (Waschbusch, 2002).

The following sections will present the characteristics of AD/HD+ODD/CD in terms of (1) psychosocial functioning, and (2) executive functions.
3.5.1 Psychosocial Characteristics of AD/HD+ODD/CD

In comparison to pure AD/HD, children and adolescents with AD/HD+ODD/CD have been found to be more impulsive (Newcorn et al., 2001), have elevated rates of dyslexia, school dysfunction, impaired verbal skills, visuo-spatial deficits, (Waxmonsky, 2003), and other comorbid disorders such as substance use disorders, anxiety, depression, and bipolar disorder (Biederman et al., 2008; Thompson, Riggs, Mikulich, & Crowley, 1996), have higher rates of academic failure, and delinquent behaviour (Kuhne, Schachar, & Tannock, 1997; Moffitt, 1990), engage in more rule-breaking behaviour, display more aggression, are more easily provoked (Abikoff et al., 2002; Waschbusch et al., 2002), are more hyperactive, inattentive, and short-tempered (C. Kadesjö, Hägglöf, Kadesjö, & Gillberg, 2003), have lower IQ, reading difficulty, higher rates of antisocial behaviour (Moffitt, 1990), and deficits in social problem solving ability (Matthys, Cuperus, & Van Engeland, 1999).

Even AD/HD children and adolescents without a formal comorbid diagnosis of ODD or CD but were classified as “highly aggressive”, showed a greater level of impairment including emotional disregulation, compared to “non-aggressive” AD/HD subjects (Melnick & Hinshaw, 2000).

When examining an older cohort, similar results are still found; in Gadow, Sprafkin, Schneider, Nolan, Schwartz and Weiss’s (2007) study of AD/HD comorbidity in a clinic and community sample of adults, they found adults with AD/HD+ODD to present with significantly higher severity of behavioural and emotional difficulties than adults with either AD/HD or ODD alone.

3.5.2 Executive Function (EF) Characteristics of AD/HD+ODD/CD

The spectrum of cognitive deficits that define AD/HD have been collectively labelled “Executive Function” (EF) deficits, which involve either (or both) cognitive and behavioural control processes such as self-monitoring, adaptive strategy generation, goal-directed planning, and inhibition. As such, AD/HD and ODD/CD can be partly
distinguished by the nature of their deficits; AD/HD being more related to the
cognitive abilities that govern self-control (known collectively as ‘EF deficits’), while
ODD/CD to psychosocial deficits however, these constructs are not mutually exclusive.
Before a discussion of EF deficits in AD/HD and comorbidity is undertaken, a brief
definition of EF is warranted.

3.5.2.1 Executive Function (EF) - A Definition

In simple terms, EF can be defined as the set of cognitive processes that govern self-
regulation. Lezak (1995) defines EF as “those capacities that enable a person to
engage successfully in independent, purposive, self-serving behaviour” (p.42), and has
been described as incorporating the following facets of behaviour and cognition (R. A.
Barkley, 2000):

- Volition, planning, and purposive, goal-directed, or intentional action,
- Inhibition and resistance to distraction,
- Problem-solving and strategy development, selection, and monitoring,
- Flexible shifting of actions to meet task demands,
- Maintenance of persistence toward attaining a goal, and
- Self-awareness across time.

The above facets can be collapsed into 5 distinguishable EFs, presented below in Table
3.1 along with their psychosocial correlates.

These major EFs are the foundation of social intelligence. Deficits in either of these EFs
would be easily detectable via their ensuing psychosocial correlates. The diagnosable
characteristics of AD/HD have been widely accepted to be a product of underlying EF
deficits; one of the most renown theories of AD/HD centres on deficits in response
inhibition (R.A. Barkley, 1997), however this theory is inapplicable to the inattentive
subtype (inhibition in AD/HD will be discussed in greater detail in the following chapter).

It is important to note that no theory based on a singular EF can completely define AD/HD, since no EF operates in complete isolation. Theories of inhibition for example, are dependent on modulatory systems such as arousal, activation, and attention which in turn interact with motivational and affective inputs. Even if a central deficit existed in only one EF, it will inevitably result in the subsequent failure of others.

**Table 3.1**

*Executive functions and their psychosocial correlates (taken from Barkley, 2000).*

<table>
<thead>
<tr>
<th>Executive Function</th>
<th>Psychosocial Correlates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response inhibition</td>
<td>Impulse control/self-regulation; delay of gratification; regulation of activity level to setting/task demands.</td>
</tr>
<tr>
<td>Nonverbal working memory</td>
<td>Holding events in mind; imitation/vicarious learning; sense of past; sense of future; delayed reciprocal altruism; autonoetic awareness; sense of time; cross-temporal organisation of behaviour.</td>
</tr>
<tr>
<td>Verbal working memory</td>
<td>Self-description; reflection; instruction; questioning; rule-governed behaviour; reading comprehension; moral control of conduct.</td>
</tr>
<tr>
<td>Self-regulation of emotion and motivation</td>
<td>Emotional self-control; intrinsic motivation/persistence; activation to task demands.</td>
</tr>
<tr>
<td>Reconstitution</td>
<td>Verbal/nonverbal fluency; goal-directed inventiveness; flexibility and ideational syntax.</td>
</tr>
</tbody>
</table>

There are several different measures of EF, but those that require automatic behaviour to be resisted, and a new behaviour to be planned and formed (e.g. inhibition) are where deficits in AD/HD are most frequently seen (Pennington & Ozonoff, 1996). Such tasks traditionally comprise of short-duration trials of a single specific problem with a set goal that is provided by the examiner. Other tasks which typically require decision-making and self-monitoring also highlight EF deficits in AD/HD.
Whether alone or comorbid with ODD/CD, one of the most robust and replicable findings in AD/HD are EF deficits. Compared to children and adolescents with ODD/CD only, those with AD/HD or AD/HD+ODD/CD have been found to display greater EF-related cognitive deficits in verbal and verbal memory functions (Moffitt & Silva, 1988), self-regulation, planning, generating management strategies for problem-solving (C. Clark, Prior, & Kinsella, 2000), adaptive communication skills, and reading (C. Clark, Prior, & Kinsella, 2002). The existence of significant EF deficits in ODD/CD at present is still unclear. In an extensive review by Pennington and Ozonoff (1996), the authors presented strong evidence of EF deficits in AD/HD cohorts, but not in CD unless it occurred comorbid with AD/HD; pure CD did not display any EF deficits. Unfortunately, the author’s assessment of EF relied on tasks that were not well-validated, and hence did not have clear theoretical or empirical connections with EF. In contrast, a meta-analytic review by Morgan and Lilienfeld (2000), found antisocial behaviour (including CD) to be significantly related to greater deficits in EFs, however there was no specificity of antisocial behaviour to EF deficits per se rather than a general deficit of neuropsychological functioning.

The conjecture that unlike AD/HD, the core deficit in ODD/CD appears to lie outside the domain of EFs was supported by Nigg, Hinshaw, Carte and Treuting (1998) who argued that the deficits seen in AD/HD on effortful neuropsychological tasks could not be adequately accounted for by ODD/CD comorbidity. This contention was supported by both van Goozen et al’s (2004), and Oosterlaan, Scheres and Sergeant’s (2005) studies which only found EF deficits in AD/HD but not ODD/CD, hence concluding that such deficits are unique to AD/HD. However as highlighted above, this argument is debatable due to some inconsistencies in the previous literature; some studies have shown small EF deficits in ODD/CD on certain EF tasks, whereas others have not (see Sergeant, Geurts, & Oosterlaan, 2002 for a review). If EF deficits are a trait of ODD/CD, there is some speculation that these deficits may only exist in early-onset CD (J. T. Nigg, 2003).
3.6 Conclusions

AD/HD is so frequently comorbid with other disorders that the diagnosis of multiple other conditions has now become the norm rather than the exception to the diagnostic rule. Comorbid conditions not only add to the symptom profile of AD/HD, but also negatively alter its inherent manifestation. The two most prevalent comorbid conditions in AD/HD are ODD/CD, the presence of which effectively alters both the clinical presentation and the course of AD/HD; symptomatology is markedly more severe, and the longitudinal risk of APD is amplified. The robust link between APD and criminal behaviour presents considerable pressure for effective treatment at an early stage when aggression is first apparent.

Compound conditions like AD/HD+ODD/CD create an added complexity to a diagnostic process that is already wanting of greater specificity in regards to age and gender. Considering the striking change in behaviour/misbehaviour (whether AD/HD or ODD/CD) with age, it is as yet unclear why an age distinction is made in CD, but not in ODD or AD/HD. One possible explanation may be that ODD and CD are both severity- and age-related manifestations of the same underlying condition. It is well documented that CD is more severe than ODD, but it may also be that ODD is only applicable to younger individuals, while CD to older. Upon examination of the diagnostic criteria for both disorders, ODD symptoms are all well within the mental and behavioural repertoire of the average 4-year old. In comparison, the diagnostic behaviour for CD such as using a weapon and forced sexual activity are indicative of a significantly older cohort. Understandably, there may have been some apprehension with diagnosing a disorder like CD in young children. Consequently, the taxonomy of DBDs may have in part been expanded to include ODD so that severe misbehaviour can be diagnosed in the early years of life, and a subsequent distinction can be made between delinquent behaviour in childhood and that in adolescence/young adulthood. While CD does allow for diagnoses in children less than 10 years of age, the process is hindered by its reliance on the subjective recall of the onset of symptoms.
Subjective diagnoses such as those for AD/HD and ODD/CD will always be problematic as it relies entirely on the perspective of either health care professionals, parents, teachers, and where applicable, on the patient themselves. The problem of multiple informants lies in their low agreement between reports; ultimately, these reports are based on opinion (whether educated or otherwise) and vary according to such factors as diagnostic biases, social background, observational skills, attitudes towards questionnaires, etc (R. D. Nass, 2006). The divergence of perspectives has led many researchers to seek more objective assessments of AD/HD and ODD/CD in order to partially alleviate the current diagnostic dependence on subjective measures. One such method is electrophysiology. Identifying psychophysiological markers of AD/HD and ODD/CD has made a major contribution to our understanding of these disorders to date. Techniques providing an objective assessment of brain activity, such as Event-Related Potentials (ERPs) and associated psychometric performance measures, allow some insight into how neurophysiological correlates of perception and cognition may differ in the AD/HD and AD/HD+ODD/CD patient. Such insight could subsequently aid in a re-definition to enhance diagnostic homogeneity among these disorders. Chapter 4 will discuss the neuropsychology of AD/HD and AD/HD+ODD/CD.
Chapter 4:

Neuropsychophysiology of AD/HD and AD/HD+ODD/CD

Chapter Overview:
This chapter will introduce and define the common neuropsychophysiology of AD/HD, and AD/HD comorbid with ODD/CD. Characteristics of selective attention, sustained attention, and inhibition will be discussed along with a brief introduction to the typical testing materials used to measure these facets of cognitive functioning. The issue of objective testing methods and materials to aid in the diagnosis of AD/HD will be presented, alongside an introduction to both EEG and ERPs. A discussion of previous literature assessing EEG and ERPs in both AD/HD, and AD/HD+ODD/CD is provided.
4.1 Developmental Neuropsychophysiology

Neuropsychology as a discipline arose from the general consensus that in order to understand human behaviour, one must first understand human brain function. Developmental neuropsychology focuses on how cognitive dysfunction may manifest as behavioural abnormalities in the developing child.

The plethora of neuropsychological research in children and adolescents with AD/HD has focused largely on two areas: executive function (which was discussed earlier in Section 3.5.2.1) particularly inhibitory control, and inattention. Since both inhibition and inattention are considered core deficits in AD/HD, the intensity with which they have been investigated is hardly surprising; majority of this research has focused on identifying specific deficits on fixed concepts of inhibition such as behavioural or response inhibition, and attention such as selective attention (orienting to a stimulus) and sustained attention (vigilance). Inattention (in terms of selective and sustained attention), and inhibition characteristics in AD/HD and AD/HD+ODD/CD will be discussed in the following sections.

4.1.1 Selective and Sustained Attention Deficits in AD/HD and AD/HD+ODD/CD

Probably the best recognised measure of selective attention is the oddball paradigm (whether visual or auditory), and that of sustained attention is the Continuous Performance Task (CPT) which is usually a visual task. Basic versions of both tasks involve selective attention and a behavioural response to an infrequently occurring target stimulus however CPT tasks are significantly longer in duration than oddball tasks in order to sufficiently measure sustained attention. Usually, a preliminary investigation of the performance results from these tasks offer telltale indicators of attentional functioning; AD/HD children and adolescents have repeatedly shown longer reaction times to target stimuli and a greater number of errors, suggestive of attentional and inhibitory deficiencies.
A variety of attentional deficits seem to be apparent in AD/HD since no component of the attentional system operates in isolation; selective attention and sustained attention for example, perform different but interrelated functions. Therefore, the attentional disturbance in AD/HD is likely a result of varying abnormalities in several different attention networks, rather than simply a dysfunction in one. If there was a singular attentional dysfunction in AD/HD, attempting to isolate this would prove near impossible since typical attentional tasks require several different aspects of attention for successful completion that cannot easily be teased apart. A pivotal study by Posner and Peterson (1990) detail three separate yet interconnected neural networks in the human brain, each relating to a specific attentional process; orienting, detecting, and alerting. Both orienting and detecting are elements of selective attention, while alerting is related to vigilance and hence, sustained attention.

A deficit in selective attention is typically seen as an inability to focus attention on pertinent information, while ignoring irrelevant information. A deficit in sustained attention refers to the gradual decline in the amount of attention devoted to a pertinent stimulus or task; this is classically characterised by a time-on-task related decline in performance. Both sustained attention and selective attention are represented on the inattentiveness scale when diagnosing AD/HD; selective attention: “is often easily distracted by extraneous stimuli”, and sustained attention: “often has difficulty sustaining attention in tasks or play activities” (refer to Section 2.2.2 for DSM-IV-TR diagnostic criteria for AD/HD).

A plethora of research has identified deficits in either or both selective and sustained attention in AD/HD children and adolescents compared to normal Controls (Banaschewski et al., 2003; Borger et al., 1999; Brodeur & Pond, 2001; Greimel, Herpertz-Dahlmann, Gunther, Vitt, & Konrad, 2008; Heaton et al., 2001; Hooks, Milich, & Lorch, 1994; Kilic, Sener, Kockar, & Karakas, 2007; Konrad, Neufang, Hanisch, Fink, & Herpertz-Dahlmann, 2006; Mason, Humphreys, & Kent, 2005; Shallice et al., 2002; Stins et al., 2005; Tsal, Shaley, & Mevorach, 2005; O. Tucha et al., 2006). In light of
such research, these attentional deficits are a widely accepted characteristic of AD/HD despite some studies failing to find similar results (Berwid et al., 2005; Huang-Pollock, Nigg, & Carr, 2005; Mason, Humphreys, & Kent, 2003; Stins et al., 2005; L. Tucha et al., 2008; van der Meere & Sergeant, 1988). Such negative findings can be attributable to two things: (1) the sensitivity, complexity, or appropriateness of the attentional task used, or (2) that the inattentive subtype of AD/HD constitutes an aetiologically distinct group characterised by an attentional dysfunction not present in either AD/HD-HI or AD/HD-C; since the vast majority of studies have assessed AD/HD-C rather than AD/HD-I, the lack of significant results in terms of attentional deficits are not surprising.

Although there is a paucity of research on attentional deficits in AD/HD+ODD/CD, abnormal attentional systems in this cohort are also suspected. If deficits in attention are an accepted core dysfunction in AD/HD, the assessment of comorbid groups such as AD/HD+ODD/CD should also yield results that show a comparable deficit, particularly since such comorbidity has been shown to exacerbate AD/HD symptomatology (refer to Chapter 3), and disorders such as ODD have shown attentional deficits independent of AD/HD comorbidity (Baving, Rellum, Laucht, & Schmidt, 2006). There are few behavioural studies that have focused on attention dysfunction in AD/HD+ODD/CD, but those that have are supportive of such a deficit (R. A. Barkley, Edwards, Laneri, Fletcher, & Metevia, 2001; Pritchard, Neumann, & Rucklidge, 2008). Hence, while inattention is a fundamental deficit in AD/HD, the same cannot be said for ODD/CD; though it is highly likely that inattention is present in ODD/CD, it is doubtful that this deficit plays any pivotal role in the expression of the disorder.

4.1.2 Inhibitory Control in AD/HD and AD/HD+ODD/CD

Attempts to refine the diagnostic picture of AD/HD including its causal determinants have led some researchers to move away from an inattention perspective to focus on one of inhibitory control. Although sustained attention and inhibition are closely related constructs, they are at least partly independent. Inhibition refers to the
withholding or interruption of a preponent response; that is, the stopping or modification of an ongoing action or thought in order to facilitate controlled, goal-directed behaviour. The most prominent AD/HD theory of the 20th century argued that deficits in inhibitory control comprised the core deficit of the disorder; Barkley’s (1997) model posits that a normal response inhibition process is a vital catalyst to the efficacy of such EFs as working memory, self-regulation, and reconstitution. Hence, response inhibition was hypothesised to be dysfunctional in AD/HD, producing secondary impairments in dependent EFs and supposedly leading to the disorder’s known manifestation. This theory is not applicable to the inattentive subtype however, since inhibition deficits supposedly characterise symptoms of hyperactivity and impulsivity, not inattention. This however is questionable since research has found comparable inhibitory deficits between AD/HD-I and AD/HD-C (J. T. Nigg, Blaskey, Huang-Pollock, & Rappley, 2002).

The most common assessments of inhibitory control include such tasks as the Go/No-Go (GNG), and Stop-Task, which both require the inhibition of a preponent response. Typical findings show AD/HD children and adolescents to respond more impulsively on such tasks and hence make more errors (i.e. errors of commission), suggestive of an inhibitory deficit. Although such a deficit is repeatedly found in the previous literature (Booth et al., 2005; Houghton et al., 1999; Pasini, Paloscia, Alessandrelli, Porfirio, & Curatolo, 2007; Pliszka, Liotti, & Woldorff, 2000; Quay, 1997; Schachar, Mota, Logan, Tannock, & Klim, 2000; Shallice et al., 2002; Stins et al., 2005), it is still under debate (Banaschewski et al., 2004; Berwid et al., 2005; Geurts, Verte, Oosterlaan, Roeyers, & Sergeant, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). For a detailed discussion and review on this issue, see Nigg (2001) or Willcutt et al (2005).

While it is generally accepted that the core deficit in AD/HD lies within the domain of EF, the opposite has been argued for ODD/CD. As mentioned in the previous chapter, some studies such as Oosterlan et al (2005), and Nigg et al (1998) were unable to find any EF deficits in ODD/CD and hence concluded that the central deficit lay outside the realm of EF. However, few of these studies examined inhibition. Unfortunately,
numerous studies have produced conflicting findings regarding whether or not comorbid AD/HD possesses an inhibitory deficit. Though some have found a comparable inhibition deficit between AD/HD, AD/HD+ODD/CD, and ODD/CD against Controls (Hobson, Scott, & Rubia, 2011; Oosterlaan, Logan, & Sergeant, 1998), others have found no inhibition deficit at all between these groups (Scheres, Oosterlaan, & Sergeant, 2001). Some researchers have argued that inhibition deficits are more related to AD/HD than ODD/CD. A study by Schachar et al. (2000) for example, found greater inhibitory impairment in AD/HD compared to either Controls, AD/HD+ODD/CD, or ODD/CD. This was later supported by Berlin and Bohlin (2002) who found inhibition deficits to be related to hyperactivity and not to conduct problems, and by van Goozen et al. (2004) who also argued that deficits in inhibitory control were not present in ODD. However, later work by Wiersema, van der Meere, Roeyers, Van Coster and Baeyens (2006) found the exact opposite result, where any inhibitory deficit found in AD/HD was no longer present after controlling for ODD/CD comorbidity. Similarly, recent work by Hobsen et al. (2011) found inhibition deficits in their sample of ODD/CD group, independent of an AD/HD diagnosis. Undoubtedly, varying methodology (such as the type of task used) and participant inclusion criteria between these studies have contributed to the inconsistent results. For example, Wiersema et al’s (2006) comorbid sample of nine AD/HD+ODD/CD participants included an undisclosed number of females, however gender was not considered in the analyses; a critical flaw since female CD participants do not typically display inhibition deficits (Hartung, Milich, Lynam, & Martin, 2002).

Due to such divergence in results, researchers have turned their attention to obtaining more objective assessments of constructs such as inhibition, in an effort to support or challenge behavioural anomalies. The most prominent objective assessments typically utilise electroencephalography (EEG) to acquire what is thought to be the indices of attention and cognition, in the form of event-related potentials (ERPs). The following section will briefly define both EEG and ERPs and how the latter are linked to attention and cognition.
4.2 Electroencephalography (EEG) and Event-Related Potentials (ERPs)

An electroencephalogram (EEG) is a recording of the electrical potentials generated from large dendritic trees of pyramidal neurons in the cerebral cortex. Though pyramidal neurons comprise around 70-80% of the neuronal population in the cortex, the EEG signal is primarily reflective of those dendritic trees that lie perpendicular to the plane of the scalp surface. The major benefit of EEG is its high temporal resolution which allows neural activity to be measured in milliseconds.

The electrical activity of EEG patterns are characterised by two variables: frequency [measured in hertz (Hz)] and amplitude [measured in microvolts (µV)]. In the normal human EEG, activity is shown between 1-100Hz, with amplitudes between 2-20µV (Altenmuller & Gerloff, 1999; Speckmann & Elger, 1999).

Brief changes in the EEG signal occur in response to an external stimulus that is selectively attended to, and readily distinguishable from the surrounding environment. These endogenous changes in the EEG signal are called event-related potentials (ERPs) and have been repeatedly correlated to attention and cognitive processes associated with distinguishing relevant from irrelevant information. Consequently, previous research has attempted to tie different components of the ERP to varying stages of information processing. ERP components are only clearly visible when multiple epochs (time segments) co-registered around the event times are averaged together; the ERP wave pattern is typically most distinguishable at 100ms post-stimulus. ERP components produced between 100-300ms post-stimulus onset are thought to be associated with automatic and/or controlled attentional and cognitive processes in relation to a salient stimulus, and are classified by their latency and polarity. ERP component terminology is an amalgamation of their polarity (either positive ‘P’, or negative ‘N’) and their predominant post-stimulus latency, for example, ‘N100’ or simply ‘N1’ denotes a negative deflection occurring around 100ms after a stimulus is presented. Figure 4.1 below shows a typical averaged EEG signal with principle ERP components. A description of each ERP component and their respective
attentional/cognitive correlates are presented below. For the sake of simplicity, ERPs will hereafter be referred to as N1, N2, etc, rather than N100, N200, etc.

![EEG signal waveform with the five major ERP components: P100 or 'P1' occurring approximately 100ms post stimulus, N100 or 'N1' occurring approximately 100ms post stimulus, P200 or 'P2' occurring approximately 200ms post stimulus, N200 or 'N2' occurring approximately 200ms post stimulus, and P300 or 'P3' occurring approximately 300ms post stimulus.](image)

*Figure 4.1* An averaged EEG signal waveform with the five major ERP components: P100 or 'P1' occurring approximately 100ms post stimulus, N100 or 'N1' occurring approximately 100ms post stimulus, P200 or 'P2' occurring approximately 200ms post stimulus, N200 or 'N2' occurring approximately 200ms post stimulus, and P300 or 'P3' occurring approximately 300ms post stimulus.

- **P1**

The P1 ERP component is a positive deflection in the ERP waveform that occurs around 100ms after stimulus presentation. Unfortunately, there is a scarcity of research on the P1 ERP component and as such, its role in attention and/or cognition is only speculative at best; it is thought to reflect mandatory visual feature processing (Banaschewski et al., 2003).
• **N1**

The N1 ERP component is the largest negative deflection in the ERP waveform that occurs around 100ms after stimulus presentation. Though 100ms is the classical norm, it is not uncommon for the peak to occur anytime between 90-200ms post-stimulus.

N1 is thought to represent the initial extraction of information, that is, the ‘orienting’ or ‘orienting of attention’ response (selective attention), and always occurs after the presentation of novel stimuli (Altenmuller & Gerloff, 1999; Barry, Johnstone, & Clarke, 2003; Loiselle, Stamm, Maitinsky, & Whippe, 1980; Smith, Johnstone, & Barry, 2004).

• **P2**

Similar to P1, there is comparatively insufficient research on the association of the P2 ERP component with attentional/cognitive indices. The little information available suggests that P2, which typically occurs around 200ms post-stimulus, may reflect the automatic inhibition of sensory input from further processing (Barry, Johnstone et al., 2003; Smith et al., 2004), such as extraneous or irrelevant sensory input.

• **N2**

The N2 ERP component is the largest negative deflection of the ERP waveform that occurs around 200ms post-stimulus. It is thought to represent a stimulus discrimination or ‘mismatch detection’ process (Barry, Johnstone et al., 2003; Smith et al., 2004). It is also a reliable marker of the inhibitory process (Banaschewski et al., 2004; Dimoska, Johnstone, Barry, & Clarke, 2003; Kok, 1986; Pliszka et al., 2000).

• **P3**

The P3 ERP component is the largest positive deflection of the ERP waveform that occurs around 300ms from stimulus onset, but has been known to occur anytime between 280-700ms post-stimulus. Of all the ERP components, P3 has drawn the
greatest interest from researchers due to its robust correlation with context updating, event categorisation, and/or context closure (Altenmuller & Gerloff, 1999; Barry, Johnstone et al., 2003; Pallant, 2004; Smith et al., 2004). In simple terms, it represents the “process of updating an internal model of the outer world” (Altenmuller & Gerloff, 1999 p. 642). Similar to N2, oddball tasks also typically elicit clear P3 responses.

An inverse relationship is suspected between P3 amplitude and stimulus probability, while task-relevance and difficulty are thought to be directly related to amplitude (Croft, Gonsalvez, Gabriel, & Barry, 2003). P3 latency on the other hand, has to some extent been correlated with categorisation/evaluation of the stimulus, and is therefore thought to represent task difficulty (Altenmuller & Gerloff, 1999). Also, unlike the earlier components N1 and P1 which are both automatic in nature, the endogenous P3 is related to controlled, purposive information processing, and memory processes (Hegerl, 1999; Polich, 1999) involved in such tasks as decision-making and planning.

The inspection of ERPs allows the researcher to envision the hierarchical route taken by sensory information as it is processed; the progression from the automatic orienting of attention, to controlled information processing. Several attempts have been made to link the behavioural symptoms of AD/HD to abnormalities in attention and/or information processing (e.g. inhibition) as indexed by these ERPs. This research will be discussed in the following section.

4.2.1 ERPs in AD/HD, AD/HD+ODD/CD, and ODD/CD

ERPs allow the researcher to overcome the constraints associated with purely behavioural analysis by allowing the assessment of stimulus-elicited brain activity before a behavioural response occurs. Therefore, ERPs show considerable promise in objectively measuring attentional and information processing dysfunction in AD/HD. Even in children and adolescents simply labelled as “distractible” or “attention deficit” without any formal AD/HD diagnosis have been found to display information
processing deficits marked by attenuated P3 amplitudes compared to Controls (Aleksandrov, Polyakova, & Stankevich, 2005; Maatta et al., 2005). The ERP findings from AD/HD studies will be discussed in terms of the task modality utilised: auditory or visual. For a more extensive review, see Barry et al (2003).

4.2.1.1 Auditory ERPs (AERP)

The most common auditory ERPs (AERPs) utilised in AD/HD research are obtained via an Oddball task; while some studies have incorporated a visual component, the ERPs are always assessed according to an auditory stimulus or trigger. Unlike previous inconsistencies in other areas of AD/HD research, AERP findings have been surprisingly consistent, with the vast majority of studies reporting deficits in early (e.g. N1) and/or late (P3) ERP components. AERP amplitude results from some of these studies are shown below in Table 4.1.

As mentioned earlier, there is a noticeable scarcity of the assessment of the P1 ERP component in the AD/HD literature, though this may be due to the relative lack of significant correlations with cognitive function or attention. As a result, the role of P1 in the information processing hierarchy is perceived to be comparatively minor. Trends in subsequent early components such as N1, P2, and N2 provide enough detail to suggest deficits in attentional orienting, selective attention, and inhibition. While some studies have found no difference in these early components between AD/HD and Controls, the majority have found results that lend objective support to findings from behavioural studies.

The almost unanimous finding of smaller P3 amplitudes in AD/HD provides compelling support for the contention that controlled, purposive information processing and associated memory functions are hindered.
Table 4.1
AERP amplitude results from previous AD/HD research compared to normal Controls.

<table>
<thead>
<tr>
<th>Author(s) (year)</th>
<th>Task</th>
<th>Cohort</th>
<th>Auditory ERP Component*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown et al (2005)</td>
<td>inter-modal Oddball task (targets = auditory; non-targets = visual)</td>
<td>AD/HD-I, Controls</td>
<td>– ↓ ↓ ns ↓</td>
</tr>
<tr>
<td>Smith et al (2004)</td>
<td>auditory Go/No-Go task</td>
<td>AD/HD-C, Controls</td>
<td>↑ ↓ ↓ ↑ ns</td>
</tr>
<tr>
<td>Dimoska et al (2003)</td>
<td>Stop Signal Task (targets = auditory; non-targets = visual)</td>
<td>AD/HD-C (n = 11), AD/HD-I (n = 2), Controls</td>
<td>– ↓ ↑ ↓ ns</td>
</tr>
<tr>
<td>Kuperman, Johnson, Arndt, Lindgren &amp; Wolraich (1996)</td>
<td>auditory Oddball task</td>
<td>AD/HD-C (n = 12), AD/HD-I (n = 1), Controls</td>
<td>– – – – – ↓</td>
</tr>
<tr>
<td>Johnstone &amp; Barry (1996)</td>
<td>auditory Oddball task</td>
<td>AD/HD-C, Controls</td>
<td>– – – – – ↓</td>
</tr>
<tr>
<td>Kemner et al (1996)</td>
<td>auditory Oddball task</td>
<td>AD/HD-C, Controls</td>
<td>↓ ↓ ns ns ↓</td>
</tr>
<tr>
<td>Loiselle et al (1980)</td>
<td>auditory selective attention task</td>
<td>AD/HD-C, Controls</td>
<td>– ↓ – – ↓</td>
</tr>
<tr>
<td>Satterfield &amp; Braley (1977)</td>
<td>passive auditory attention task</td>
<td>AD/HD-HI, Controls</td>
<td>– – ↓ ↓ –</td>
</tr>
</tbody>
</table>

* (For this and subsequent ERP tables): Arrows represent an increase (↑) or decrease (↓) in amplitude in AD/HD compared to Controls, e.g. research by Brown et al (2005) showed smaller N1 amplitude in AD/HD compared to Controls, etc. Unless otherwise stated, results are significant at the .05 level; ns = results were not significantly different between groups; “—” = authors either did not assess or did not report results for this component; all Controls were matched for age and gender. Some of the studies listed differed in their method of how each ERP component was derived for statistical comparison (i.e. from a single electrode, or from specific electrode group).

ª .05 < p < .10
4.2.1.2 Visual ERPs (VERP)

Visual ERPs (VERPs) are typically elicited from tasks such as the CPT, Stop-Task, and GNG task. In contrast to AERP research in AD/HD, the literature on VERPs is somewhat inconsistent and distinctly lacking in early component analysis. Table 4.2 below lists VERP amplitude results from some of these studies.

With such conflicting results, it is difficult to draw conclusions in relation to the cognitive functioning in AD/HD. Similar to AERP results, there is an almost unanimous finding of a visual P3 deficit in AD/HD compared to Controls, indicating impaired controlled information processing. While it is tempting to claim an N2 deficit also, the variance in the results prohibits such a claim. Drawing meaningful conclusions for P1, N1, and P2 is problematic due to the paucity of research incorporating these components; an enhanced P2 in AD/HD compared to Controls is a tentative yet interesting observation as it contrasts with the auditory P2 deficit. An increased P2 compared to Controls is suggestive of an over-activation of the automatic sensory inhibitory process. If AD/HD patients are unable to stay focused or are “hyper-attentive”, then an enhanced P2 as an automatic filter of extraneous stimuli is expected, particularly if visual material facilitates a comparatively broader sensory stimulation than auditory.

It is as yet unclear why the VERP findings show considerably more variability than those of AERPs. As mentioned above, visual stimuli may provide a greater array of sensory stimulation than auditory, producing a larger variability in VERP responses, or it may be that AD/HD suffers process auditory information better than visual, resulting in more consistent AERP responses. These explanations are purely exploratory however, and require empirical support.
Table 4.2
VERP amplitude results from previous AD/HD research compared to normal Controls.

<table>
<thead>
<tr>
<th>Author(s) (year)</th>
<th>Task</th>
<th>Cohort</th>
<th>P1</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodriguez &amp; Baylis (2007)</td>
<td>visual Go/No-Go task</td>
<td>AD/HD-I, AD/HD-C, AD/HD-HI, Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Wiersema, van der Meere, Roeyers, Van Coster &amp; Baeyens (2006)</td>
<td>visual Go/No-Go task</td>
<td>AD/HD-C, Controls</td>
<td></td>
<td></td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Albrecht, Banaschewski, Brandeis, Heinrich &amp; Rothenberger (2005)</td>
<td>visual Stop-Signal Task</td>
<td>AD/HD-C, Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Jonkman et al (1997)</td>
<td>visual selective attention task</td>
<td>AD/HD-C, Controls</td>
<td>↑</td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
</tr>
<tr>
<td>Kemner et al (1996)</td>
<td>visual Oddball task</td>
<td>AD/HD-C, Controls</td>
<td>↓</td>
<td></td>
<td></td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Robaey, Breton, Dugas &amp; Renault (1992)</td>
<td>visual selective attention task</td>
<td>AD/HD-C, Controls</td>
<td></td>
<td></td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Holcomb, Ackerman &amp; Dykman (1985)</td>
<td>visual selective attention task</td>
<td>AD/HD-C, AD/HD-I, Controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ns</td>
</tr>
</tbody>
</table>

* See notes for Table 4.1
ª .05 < p < .10
4.2.1.3 **ERPs in AD/HD+ODD/CD and ODD/CD**

Both VERPs and AERPs in AD/HD+ODD/CD and ODD/CD are acquired using the same tasks as those for AD/HD. Results for this cohort mirror those of pure-AD/HD, however early component analysis is almost completely lacking. Table 4.3 below lists both AERP and VERP amplitude results from studies assessing comorbid AD/HD.

<table>
<thead>
<tr>
<th>Author(s) (year)</th>
<th>Task</th>
<th>P1</th>
<th>N1</th>
<th>P2</th>
<th>N2</th>
<th>P3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Du et al (2006)</td>
<td>passive auditory Oddball task</td>
<td>—</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>↓</td>
</tr>
<tr>
<td>Wiersema et al (2006)</td>
<td>visual Go/No-Go task</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Albrecht et al (2005)</td>
<td>visual Stop Task</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↓&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Rothenberger et al (2000)</td>
<td>auditory selective attention task</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>↓&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

* See notes for Table 4.1
<sup>a</sup> .05 < p < .10

While there are comparatively few studies assessing ERPs in AD/HD+ODD/CD, the available results suggest similar deficits as those existing in AD/HD; namely a deficit in N2 and P3, indicative of poor inhibition and controlled information processing. Despite the lack of ERP data, some assumptions can be extrapolated from pure AD/HD research; AD/HD+ODD/CD would be expected to possess some or most of the ERP deficits seen in pure AD/HD since this is the underlying disorder. However, since the symptom severity of AD/HD+ODD/CD is known to be greater than that of AD/HD (refer to Chapter 3 on Comorbidity), it is reasonable to assume that the ERP deficits associated with AD/HD+ODD/CD may be comparatively greater than that in AD/HD.
A referral to the pattern of ERP deficits in AD/HD would also be warranted when assessing ODD/CD, again due to the scarcity of ERP research in this cohort (particularly in regards to the early components). Table 4.4 below lists both AERP and VERP amplitude results from studies assessing ODD/CD. Similar to findings from AD/HD+ODD/CD research, there is an apparent deficit in both N2 and P3 in ODD/CD suggesting dysfunctions in inhibition and controlled information processing, however considering the scarceness of research dedicated to this cohort, these ‘deficits’ are preliminary and require further empirical support.

Table 4.4

<table>
<thead>
<tr>
<th>Author(s) (year)</th>
<th>Task</th>
<th>ERP Component*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albrecht et al (2005)</td>
<td>visual Stop-Signal Task</td>
<td>P1 N1 P2 N2 P3</td>
</tr>
<tr>
<td>Banaschewski et al (2003)</td>
<td>visual Continuous Performance Task - AX</td>
<td>P1 N1 P2 N2 P3</td>
</tr>
<tr>
<td>Kim, Kim &amp; Kwon (2001)</td>
<td>auditory Oddball task</td>
<td>P1 N1 P2 N2 P3</td>
</tr>
</tbody>
</table>

* See notes for Table 4.1

Despite the comparative lack of research with ODD/CD and to some extent AD/HD+ODD/CD, the corresponding deficits between AD/HD, and ODD/CD (and therefore AD/HD+ODD/CD) are not surprising considering there is an approximate 50% overlap between the two disorders. This however, complicates the proposal of using ERPs in the diagnostic process; though objective, the extensive similarities between disruptive behaviour disorders such as ODD/CD and AD/HD would likely impede successful discrimination. The following section will discuss the use of ERPs and psychometric performance as possible discriminants to aid in the diagnostic process.
4.3 ERPs and Psychometric Performance in AD/HD Diagnosis

DSM-IV-TR criteria for AD/HD requires the exclusion of other psychiatric diagnoses that may better encapsulate a patient’s symptomatology, and it is not uncommon for patients who present with symptoms suspect of AD/HD to in fact have an alternative diagnosis such as learning disorders, movement disorders, epilepsy, Fragile X Syndrome, some genetic disorders, affective disorders, and in some cases neurometabolic disorders (Pearl, Weiss, & Stein, 2001). The increased risk of misdiagnosis has spurred researchers to search for markers (both biological and behavioural) unique to AD/HD which could increase the sensitivity and specificity of the diagnostic process.

The discriminant value of electrical brain function has previously been investigated in AD/HD using ERPs, and quantitative EEG (QEEG: cerebrally generated electrical activity typically recorded while resting). Early attempts at distinguishing between hyperactive and normal children using ERPs were made by Satterfield and Braley (1977), who were able to correctly classify 81% of 7-8 year-olds, and 77% of 10-11 year-old male subjects using P1-N1 and P2-N2 ERP amplitudes. While the overall rate of accuracy appears quite high, the authors do not individually specify the number or percentage of hyperactive and Control cases correctly classified, or how many were misclassified. A similar rate of accuracy incorporating comparable ERP amplitudes (P250, N250, P350, and P500) was found in a later study by Robaey et al (1992); overall, 79.2% of 6-8 year-old male AD/HD and Control children were correctly identified with only 3 Control and 2 AD/HD children misclassified. Using QEEG, Chabot and Serfontein (1996) were able to successfully classify 93.7% of Controls, and 88% of AD/HD children, however a corresponding ERP analysis was not completed. Similarly, Mann, Lubar, Zimmerman, Miller and Muenchen (1992) were able to correctly classify 80% of AD/HD and 74% of Controls in their sample of 9-12 year olds, using topographic brain mapping.

2 The “Sensitivity” of a diagnostic test is indicative of its ability to positively identify patients with a given disorder (e.g. the ability to recognise AD/HD patients). The “Specificity” of a diagnostic test is indicative of its ability to negatively identify people without that disorder (i.e. the ability to recognise Controls).
In terms of methodological differences, there is as yet no consensus regarding which technique is superior in a discriminatory role: QEEG or ERPs, particularly since their discriminant value with AD/HD populations is still a relatively new avenue of investigation. There is a wealth of previous research that has consistently identified both QEEG (for a review see: Barry, Clarke, & Johnstone, 2003) and ERP (for a review see: Barry, Johnstone et al., 2003) differences between AD/HD, Controls and other clinical groups. From this, it appears that both techniques carry appreciable potential as diagnostic aids.

The discriminant validity of performance data from neuropsychological tasks has also been examined in the literature. A study by Pineda, Ardila and Rosselli (1999) which assessed EF-related performance and abilities (such as language, memory, and spatial aptitude), were able to correctly classify 85.5% of children with and without AD/HD. A similar result was obtained in a subtype analysis by Lockwood, Marcotte and Stern (2001) who were able to successfully distinguish between AD/HD-I and AD/HD-C with 80% accuracy based on variables relating to attention and language/verbal abilities.

Johnstone, Barry and Anderson (2001) conducted one of the first studies to investigate both auditory ERPs and psychometric performance data (for example reaction time, number of errors, etc) between AD/HD subtypes (AD/HD-I and AD/HD-C) and Controls. Several significant differences were revealed including some that were unique to clinical subgroups; P2 amplitude and latency were found to be similar between the two subtypes however differed from that of Controls. Subtype specific results showed that target N1, N2, P3 amplitude, standard N2 amplitude and target P2 latency were all significantly different in AD/HD-I compared to Controls, while target N1, P2, N2, and P3 amplitude, target N2 and N2 latency were all significantly different in AD/HD-C compared to Controls. While no discriminant analysis was done, the results suggest that P2 carries potential as a diagnostic marker, since both AD/HD subtypes showed similar topographic differences in this component against Controls.
These results lend considerable support to the concept of using such data in the diagnostic realm. As such, the discriminant value of electrical brain activity and psychometric performance in AD/HD has continued to receive research interest. Results from these studies are hardly surprising given the significant differences in such domains as electrical brain activity, behaviour/performance, attention, etc, previously found between AD/HD and Control children, and between AD/HD subtypes. However as mentioned earlier, the presence of abnormal brain activity or abnormal behaviour are not specific to AD/HD, and is present in any number of disorders which share a similar symptomatology. Such abnormalities in concert with other clinical information could considerably increase the likelihood of a correct classification; the more clinically relevant information attained, the more detailed the picture of the patient or patient group is (AD/HD or otherwise), and the more accurate the diagnosis and treatment can be. Given the breadth of the previous research on this topic, the inclusion of both ERPs and psychometric performance data in the discriminatory process seems a logical next step; one which may deliver substantial gains in isolating markers that are specific to AD/HD and perhaps even AD/HD subtypes. Thus far, only one study has utilised both ERPs and psychometric performance to differentiate between AD/HD and Controls, and between AD/HD subtypes (AD/HD-I and AD/HD-C). Using an active auditory Oddball task, Smith, Johnstone and Barry (2003) assessed the diagnostic utility of ERPs and psychometric performance measures in AD/HD. Their study breaks new ground by not only assessing both ERPs and behavioural domains in the discriminant analysis of AD/HD subtypes, but also by making an age distinction between child (8-12 years) and adolescent (13-18 years) patients (see Section 2.2.3.2 in Chapter 2 on the effects of age in AD/HD symptomatology and diagnosis). A summary of their results from each discriminant function analysis is presented below in Table 4.5.
Table 4.5  
Summary of discriminant function analyses results from Smith et al's (2003) study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>8 - 12 yr</th>
<th>13 - 18 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD vs. Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Accuracy (%)</td>
<td>73.3</td>
<td>71.4</td>
</tr>
<tr>
<td>Chance Accuracy (%)</td>
<td>54.7</td>
<td>56.9</td>
</tr>
<tr>
<td>Individual Accuracy (%)</td>
<td>73.3</td>
<td>56.9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AD/HD-I vs. AD/HD-C</th>
<th>8 - 12 yr</th>
<th>13 - 18 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Accuracy (%)</td>
<td>69.4</td>
<td>77.8</td>
</tr>
<tr>
<td>Chance Accuracy (%)</td>
<td>50.2</td>
<td>73.9</td>
</tr>
<tr>
<td>Individual Accuracy (%)</td>
<td>74.4</td>
<td>77.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AD/HD-C</th>
<th>8 - 12 yr</th>
<th>13 - 18 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Accuracy (%)</td>
<td>64.7</td>
<td>45.8</td>
</tr>
<tr>
<td>Chance Accuracy (%)</td>
<td>69.4</td>
<td>50.2</td>
</tr>
<tr>
<td>Individual Accuracy (%)</td>
<td>74.4</td>
<td>50.2</td>
</tr>
</tbody>
</table>

‡ Each variable is presented with three sections representing (1) topography (F = frontal, FC = frontocentral, PO = parieto-occipital), (2) ERP component (N1, P2, N2, P3), and (3) indicators of amplitude (A), or latency (L), combined with target (T), or standard (S); for example, PO P3 LS represents parieto-occipital P3 latency to standard stimuli. Mean RT = mean reaction time; FPs = false positives (i.e., errors of commission).
The results from Smith et al.’s study clearly show greater classification accuracy in younger subjects than older, which would be expected given the attenuation of overt AD/HD symptoms with age. This contention is particularly evident in the AD/HD vs. Controls comparison, where 73.3% of subjects were correctly classified in childhood, compared to just 58.7% in adolescence, which was only marginally above chance level (56.5%).

In the subtype comparison, the discrimination of AD/HD-I was distinctly greater than that of AD/HD-C. While this finding occurred irrespective of age, it was considerably more prominent in adolescence than in childhood, where only 45.8% of AD/HD-C were correctly classified, which was lower than chance (50.2%). Again, this is likely due to the attenuation of overt (i.e. hyperactive/impulsive) symptoms with age, while the inattentive symptoms persist. Therefore, the low classification accuracy in the adolescent subtype comparison can be explained by the supposed convergence of symptom profiles between AD/HD-C and AD/HD-I with age. However given this contention, the finding that AD/HD-I were consistently better classified than AD/HD-C even in adolescence, suggests that there was considerably less operationally defined variability in the AD/HD-I profile than that of AD/HD-C. It is also of some interest that FPs, typically interpreted as a marker of hyperactivity and impulsivity, was a predictor of subtype group membership in adolescence and not in childhood. Ergo, while most overt symptoms may diminish with age in AD/HD-C, some are presumed to linger beyond the adolescent phase. The selectivity of these symptoms (beyond them being within the hyperactive/impulsive realm) is as yet unknown.

Overall, the most prominent predictors in the analyses were P2 and P3, as these were the most frequently reported variables which substantially contributed to classification. This supports Johnstone et al.’s (2001) suggestion that P2 carries potential as a diagnostic marker for AD/HD. The finding that P3 also carries diagnostic potential is hardly surprising given the wealth of previous research that has identified P3 deficits in AD/HD compared to Controls.

When assessing the discriminant value of electrical brain function and/or psychometric performance in AD/HD comorbid groups, the literature is painfully lacking.
Unfortunately, only one study has examined the discriminant value of motivational and EF-related behaviour in AD/HD+ODD, ODD, and Controls; van Goozen et al (2004) found task-specific perseveration to be the primary predictor between the three groups. Based on this variable alone, 77% of AD/HD+ODD and Controls were correctly classified, 90% of ODD and Controls were correctly classified, and 65% of AD/HD+ODD, ODD and Controls were correctly classified. From this, the authors concluded that rather than a dysfunction in EF, children with ODD/CD suffered more from a motivational deficit.

While the concept of using objective measures such as electrical brain activity to aid in the diagnostic process for AD/HD is not a new one, early progress in this area was hindered by the difficulty in finding unique markers between AD/HD and Controls. Presently however, several potential markers in the form of ERPs and operationalised behaviour have been uncovered that show some promise in the diagnostic field. The utility of such data continues to show significant potential in enhancing the accuracy of the AD/HD diagnostic process. The extrapolation of this methodology to include comorbid groups such as ODD/CD would aid in the development of the clinical picture of disruptive behaviour disorders.

### 4.4 Conclusions

While there exists a general acceptance among the research community that inhibition is a core deficit in AD/HD, the *exclusivity* of an inhibitory deficit in AD/HD has not been validated. As mentioned in the previous chapter, the failure to take into consideration parallel processes such as attention, imply that current theories of AD/HD are incomplete. Deciphering the core deficit(s) in ODD/CD is just as problematic due to the significant amount of symptom overlap with AD/HD coupled with their high rate of comorbidity. And although the symptomatology between AD/HD and ODD/CD possess many commonalities, attempts at identifying the underlying pathology has consistently produced a divergence of results. For example, though inattention is a fundamental
deficit in AD/HD, the same cannot be said for ODD/CD, and while it is generally accepted that the core deficit in AD/HD lies within the domain of EF, the opposite has been argued for ODD/CD. While such findings support a dichotomy of AD/HD and ODD/CD, the task of obtaining a clear picture of DBDs, particularly with AD/HD, is still in its early stages.

Gaining a better understanding of AD/HD pathology in order to enhance diagnostic accuracy and treatment efforts has been the driving force behind research attempting to isolate neuropsychological markers of this disorder. Research incorporating ERPs have shown great promise in procuring features of electrical brain function that may be unique to sufferers of AD/HD. In support of previous ERP research with AD/HD, discriminant analyses have shown most ERP components to possess discriminant potential in varying degrees; those proposed to carry the most weight are the late positive components P2 and P3, as these were consistently found to be primary predictors in each analysis. Discriminant AD/HD research with psychometric performance data (though scarce) revealed a clear tendency for EF-related variables, such as attention and language, to contribute the greatest weight in the analyses. Since EF does not play a major role in ODD/CD, whether these results can be extrapolated to include AD/HD+ODD/CD is still debatable.

Using ERPs as part of the diagnostic process is still relatively new; using such data in concert with known behavioural dysfunction is newer still. Using ERPs alone, classification accuracies in AD/HD tend to fluctuate around 75 – 80% with a clear advantage in younger children. The addition of psychometric performance data produces classification accuracies ranging from 55 – 75%, again with an advantage in children rather than adolescents. Although the inclusion of psychometric performance data seems disputable due to the perceivably lower rate of accurate discrimination, these results were only from a single study and require replication. To discount the potential of such methodology based merely on a single study would oppose fundamental research practice. Since using psychometric performance data alone can produce classification accuracies around 80%, its inclusion in the discriminatory process is more than justified.
Utilising ERPs and psychometric performance data to gain a better understanding of AD/HD with and without ODD/CD comorbidity forms the foundation of this thesis. This will be discussed in greater detail in the following chapter.
Chapter 5: Rationale

Chapter Overview:
This chapter will outline in detail the rationale for this thesis: the on-going issues relating to the current method of assessment and diagnosis of AD/HD, and the concern regarding the heterogeneity of AD/HD symptoms in addition to the high rate of comorbidity, in particular that of ODD/CD. The need for neurocognitive profiles of AD/HD with and without ODD/CD comorbidity are stressed, in order to gain a more comprehensive understanding of AD/HD in the presence of comorbid externalising pathology, and whether such comorbid diagnoses warrants a change to existing AD/HD nomenclature in the DSM-IV-TR.
AD/HD children and adolescents are by definition inattentive, impulsive and careless in situations which call for self-control, however this behavioural pattern does not provide any insights into the core dysfunction(s) of the disorder. In fact, in addition to inhibition, competing theories of inattention, motivation, hypoarousal, etc, all contribute in some form to the diagnostic profile of AD/HD, yet neither are able to fully account for its aetiology or presentation. There are numerous factors that complicate the diagnosis of AD/HD, but none greater than that arising from its shared symptomatology with other psychiatric disorders. With the rising rate of children and adolescents presenting with AD/HD-like symptoms, the differential diagnosis of this disorder has become a vital issue. A ‘differential diagnosis’ reflects all of the diagnostic possibilities given the patient’s symptomatology, and hence is a crucial cornerstone in medicine. There is an array of medical conditions that can simulate the diagnosable symptoms of AD/HD, and hence potentially compromise diagnostic sensitivity and specificity. Some of these medical conditions are: anaemia, congenital brain anomalies, *Enterobius Vermicularis* (pinworms), epilepsy, foetal alcohol effects/syndrome, fragile X syndrome, hearing loss, lead poisoning, learning disabilities, medication effects, mental retardation, metabolic disorders (e.g. adrenoleucodystrophy), narcolepsy, Neurofibromatosis I, pervasive developmental disorders (such as ODD/CD), sex chromosome abnormalities, sleep apnoea, sleep deprivation, static encephalopathy, Sydenham’s Chorea, thyroid disorder, Tourette Syndrome, and vision loss (Pearl et al., 2001). While there are a range of effective medical tests and procedures to rule out most of these diagnostic possibilities (e.g. DNA testing for Fragile X Syndrome), most are never implemented in the clinical setting due to time constraints and the unavailability of resources. Consequently, AD/HD is at present purely a ‘clinical diagnosis’, meaning that most clinicians are forced to rely upon their own subjective judgements, and the observable behaviour information provided by the relevant respondents, which are typically the parents and teachers of the ‘problematic’ child, however it is not uncommon for such respondents to disagree (R. D. Nass, 2006).

At least 80% of those diagnosed with AD/HD also meet criteria for at least one other comorbid disorder (B. Kadesjö & Gillberg, 2001), which can complicate the objective
diagnosis of AD/HD. In a recent study by Brown, Hertzer and Findling (2011), a survey of over 2000 health care providers (psychologists, psychiatrists, paediatricians, etc) revealed significant practise gaps related to effective communication with the family (59%), knowledge of AD/HD epidemiology, comorbidities and diagnostic criteria in childhood and adolescence (35%), and a review of the AD/HD diagnosis upon treatment failure (45%). The latter is of particular concern as it reflects a refusal or aversion of the health care provider to revisit the diagnosis of AD/HD when treatment was ineffective. Instead, health care providers chose to modify the treatment medication rather than consider the differential diagnosis. The authors argued that this indicates a construct bias towards AD/HD over other potential (and possibly equally valid) diagnoses in clinical practise, particularly when symptoms of hyperactivity are present. Health care providers also admitted to an over-reliance on AD/HD rating scales and an under-use of the family interview to establish and confirm the AD/HD diagnosis. This shows a somewhat solidification of treatment practise in AD/HD despite the inherent heterogeneity commonly seen in AD/HD populations that is further complicated by the high rate of comorbidity with other disruptive behaviour disorders such as Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD).

At present, there is no objective test for AD/HD. Rating scales, at best, identify at-risk factors typical of the disorder being measured however the diagnosis itself is at the discretion of the treating clinician. Comorbidity of AD/HD with ODD/CD has become so commonplace that it is essential to gain a comprehensive understanding of the impact of such externalising pathology on the presentation and outcome of AD/HD. This can only be achieved via an inspection of the neurocognitive profiles of AD/HD with and without ODD/CD comorbidity. There has been considerable debate over whether or not AD/HD+ODD/CD encompasses enough unique symptomatology to warrant a separate diagnosis in the DSM, as has been adopted in the ICD-10 (Hyperkinetic Conduct Disorder). While some authors argue the affirmative (Albrecht et al., 2005; Banaschewski et al., 2003), others argue that AD/HD+ODD/CD does not constitute a symptom profile distinct from AD/HD or ODD/CD alone (Schachar & Tannock, 1995; Waschbusch, 2002).
The aim of the current thesis is therefore to investigate and compile the neurocognitive profiles of AD/HD without comorbidity, AD/HD with ODD/CD comorbidity, and AD/HD with internalising comorbidity (such as depression, anxiety, etc), and to assess the relative impact of ODD/CD comorbidity on AD/HD and the subsequent proposed change in AD/HD nomenclature to recognise AD/HD+ODD/CD as phenotypically distinct. To accomplish this endeavour, this thesis will utilise event-related potential (ERP) components and psychometric performance data gained from six neurocognitive tasks assessing executive function (EF), response inhibition (RI), selective and sustained attention. In order to reduce methodological variability and experimenter error, a standardised testing environment was employed for data collection (this will be discussed in detail in the following Methodology and Sample Population Statistics Chapter 6). In terms of EEG technique, ERPs were preferred over QEEG as the former allows an objective assessment of the neurophysiological correlates of perception and cognition during an active task, which cannot be attained with QEEG.

Since the present thesis aims to investigate the behavioural and/or neurophysiological characteristics or patterns of AD/HD with and without ODD/CD that may also aid its identification and diagnosis, both hypothesis-driven and “data-driven” approaches were adopted in this thesis. Data driven analyses have gained considerable support over the past decade for their holistic approach to theory and modelling of biological systems which stems from the idea that such systems are best determined and understood by assessing them in their entirety, rather than studying each individual component separately (Ruegg, Tissot, Farmer, & Mariotti, 2008). While a hypothesis-driven approach has previously been the hallmark of scientific research, it is undeniable that a data-driven approach may allow the researcher to learn more about the dataset by assessing large amounts of unbiased information in one analysis, thereby revealing previously unknown important or interesting variables, relationships and interactions. In short, data-driven research can often generate unexpected findings that would not have been anticipated by hypothesis-driven research alone. Probably the greatest example of success from data-driven research methods is that of the Human Genome Project (Lander et al., 2001; Venter et al., 2001), a multi-site
initiative to sequence and catalogue the entire human genome. While this research was initially and predominantly hypothesis-driven, it failed to uncover approximately 40% of the genes sequenced which was ultimately achieved via data-driven analyses (Kell & Oliver, 2004). Hence, a hypothesis can only take you as far as the current knowledge in any given field permits. It is worth remembering that hypotheses can be the result of epidemiological research, rather than the starting point, and this is the primary goal of the data-driven approach; it is an induction and synthesis of ideas from data by analysing the complexities and interactions unique to the intact system rather than its individual parts.

Although some researchers label data-driven analysis as “data mining” and hence not reflective of true scientific study, it is important to note that ‘data-mining’ is synonymous with ‘knowledge discovery’, since a major part of such scientific discovery revolves around the identification of generalisable rules and/or theories that are inferred from patterns in the data. Scientific discovery itself, particularly that pertaining to behaviour, is often associated with pattern recognition rather than critical experiments and hypothesis testing per se. Even if such pattern recognition does precipitate critical experiments and hypothesis testing, the findings from these tests are usually integrated into the body of knowledge for that field after they have been replicated to show a generalisable pattern (Weinstein, 2002).

Data-driven approaches have been used in the behavioural and neurosciences. Probably the most well-known data-driven research of AD/HD was the NIMH Collaborative Multisite Multimodal Treatment Study of Children with AD/HD (The MTA Cooperative Group, 1999). This was a randomised clinical trial of treatment strategies for AD/HD where 579 children aged 7-9.9 years were assigned to a specific treatment group (for example medication management, behavioural treatment, etc) for a duration of 14 months. This study was purely investigative rather than hypothesis-driven, and while some researchers criticised this approach (Breggin, 2001; Klein, 2001), it nevertheless set a new benchmark for future clinical trial studies (Jensen, 1999).

In the field of neuroscience, recent research conducted by Ecker et al. (2010) utilised a multi-parameter classification approach to identify the structural pattern of gray
matter anatomy characteristic of adults with Autism. Their research uncovered patterns of spatially distributed brain regions that were able to discriminate individuals with Autism from Controls with a sensitivity and specificity of up to 90% and 80% respectively. The discriminating anatomical patterns could not be attributed to any one hypothesis or group of hypotheses. Similar to AD/HD, Autism Spectrum Disorder is a heterogeneous condition that can have numerous causes and comorbid conditions in addition to varied type and symptom severity. Hence, deciphering the aetiology for either of these disorders is inherently difficult. It is here that data-driven analyses can prove most beneficial as a method of uncovering new patterns and associations in AD/HD behaviour and cognition, and hence propose new hypotheses for the research field.

In an attempt to encapsulate as many core features of AD/HD as possible and allow greater distinction from ODD/CD, selective attention, sustained attention, impulsivity and hyperactivity, and EF (for example, RI) will be measured using such tasks as the CPT (sustained attention), auditory oddball (selective attention), and GNG (inhibition) tasks, among others. A detailed description of each task utilised in this thesis will be given in the following Methodology chapter.

This thesis consists of three experimental chapters that aim to disambiguate the impact of ODD/CD comorbidity on AD/HD in childhood and adolescence. The first chapter, Chapter 7, constitutes a hypothesis-driven investigation of symptom behaviour profiles (as defined by the Conners Parent Rating Scale – Revised, Long form: CPRS-RL) and cognitive-behavioural profiles (as defined by ERP component data and psychometric performance from a battery of six neuro-cognitive tasks) of AD/HD-alone, AD/HD+ODD/CD, and AD/HD+internalising symptomatology. The second experimental Chapter (8), is an extension of previous work by Smith, Johnstone and Barry (2003); it is a data-driven investigation into the diagnostic utility of an active auditory Oddball task in predicting group membership in comorbid AD/HD. Such a study has not been conducted in the previous research to date. Finally, Chapter 9 constitutes a data-driven assessment of whether AD/HD+ODD/CD encapsulates enough symptom uniqueness to warrant a change in DSM AD/HD nomenclature, allowing the delineation of a new diagnosis. The findings from each of the three
experimental Chapters will be collated and discussed in Chapter 10, with reference to the previous literature and implications for the current and future conceptualisation of AD/HD with and without ODD/CD comorbidity. It is hoped that this thesis will not only form a valuable adjunct to the existing research, but will also aid our understanding of AD/HD, in particular when comorbid with externalising pathology, and alleviate some of the ambiguity associated with its presentation and diagnosis.
Chapter 6:

Methodology and Sample Population

Statistics

**Chapter Overview:**
This chapter will present a detailed account of the methodology behind the experimental chapters in this thesis. Participants and recruitment methods are described including demographic information, diagnostic methods, and exclusion and inclusion criteria. Each aspect of the data collection process is discussed with a detailed description of the tasks used and the corresponding testing protocols. Finally, the proposed data analysis methods for the experimental chapters are given.
6.1 Participants

Although both male and female participants were tested, only the data for male AD/HD and Control participants will be assessed in this thesis. This is due to an insufficient number of female AD/HD participants in the dataset to allow a reliable analysis by gender. Therefore, data from a total of 342 male participants (170 AD/HD; 172 Controls) was originally included for analysis in this thesis. After data screening procedures (see Section 6.4), several participants were excluded due to missing data. Although the maximum 5% of missing data were replaced with the variable mean³, this still resulted in 46 children aged 6-12 years (30 Controls, and 16 AD/HD), and 13 adolescents aged 13-17 years (11 Controls, and 2 AD/HD) excluded from the analysis. Therefore, data from a total of 152 AD/HD participants and 131 healthy Controls were incorporated into the analyses of this thesis.

Of the 152 AD/HD participants included in the analyses of this thesis, 48 AD/HD (and a further 17 Control) participants were recruited and tested by the author of this thesis in Melbourne and Adelaide (see Section 6.1.2 for further details regarding recruitment methods across sites). The data from the additional 104 AD/HD participants was provided in accordance with the funding agreement between the academic research collaborators in Melbourne, Adelaide, and Sydney, and our industry partner The Brain Resource Company. Although data from a selection of tasks relevant to the aims of this thesis were utilised, the full assessment battery of 12 electrophysiological tasks, 10 psychometric tasks, and 3 additional cognitive tasks (total duration of the full assessment battery was 3.5 hours; see Sections 6.3.2-4 for a complete list of measures) was administered to each AD/HD and Control participant.

All participants were grouped according to age; those aged 6 - 12 years were categorised as “children”, whereas those aged 13 - 17 years were categorised as

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³ Imputation is a common and recommended practise in statistics (Wayman, 2003 #724), with 5% of imputation considered an acceptable standard (IBM, 2011 #725)
“adolescents”. Mean age and years of education for both AD/HD and Controls are shown in Table 6.1 below.

Table 6.1
Average age and level of education for AD/HD and Control groups.

<table>
<thead>
<tr>
<th></th>
<th>AD/HD Subtype*</th>
<th>Subtype</th>
<th>Total N</th>
<th>Mean Age (yr) (SD)</th>
<th>Years of Education Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>AD/HD</td>
<td>I</td>
<td>18</td>
<td>9.08 (1.52)</td>
<td>3.71 (1.60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HI</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td>52</td>
<td>9.08 (1.52)</td>
<td>3.77 (1.59)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>AD/HD</td>
<td>I</td>
<td>38</td>
<td>14.12 (1.43)</td>
<td>8.66 (1.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HI</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td>79</td>
<td>14.13 (1.43)</td>
<td>8.86 (1.58)</td>
</tr>
</tbody>
</table>

* AD/HD subtypes: I = Inattentive, C = Combined, HI = Hyperactive/Impulsive.

A one-way ANOVA was conducted to test whether there was a significant age difference between AD/HD and Controls. There was no significant different between AD/HD and Controls for either children \[F(1,160) < 0.01, \ p = .998\], or adolescents \[F(1,178) < 0.01, \ p = .983\]. When educational level was inspected between AD/HD and Controls, there was no significant difference for children \[F(1,160) = .050, \ p = .824\] or for adolescents \[F(1,178) = .746, \ p = .389\]. Table 6.2 below shows average age for each AD/HD subtype and Controls.

6.1.1 AD/HD Comorbidity Profile

Details regarding primary diagnosis and comorbidity for each AD/HD participant was provided by their respective clinician and further corroborated by the Diagnostic Interview for Children and Adolescents [DICA; Reich, Shayla and Taibelson (1992)], completed by the parent or guardian at the time of testing. Comorbidities among the AD/HD population were categorised as either ‘externalising’ or ‘internalising’ disorders. Externalising disorders comprised wholly of ODD/CD, since
AD/HD+ODD/CD is the primary focus of the present thesis. Internalising disorders consisted of Learning Disorder, Anxiety, and Depression; however three AD/HD participants were also included in this group with the following comorbidities (1) social problems and high IQ, (2) fine motor delay, and (3) retardation. Learning Disorder was included under the ‘internalising’ umbrella since it has previously been associated with internalising pathology (Becker & Langberg, 2012) and typically does not incorporate any overt/externalising behaviour. Table 6.2 below shows the number of AD/HD children and adolescents with externalising, internalising, or no known comorbidity.

Table 6.2
Prevalence of externalising, internalising, and no known comorbidity in the AD/HD children and adolescent population.

<table>
<thead>
<tr>
<th></th>
<th>Externalising (ODD/CD)</th>
<th>Internalising* (LD/ANX/DEP)</th>
<th>None/Not known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>32 (50%)</td>
<td>11 (17%)</td>
<td>21 (33%)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>35 (40%)</td>
<td>17 (19%)</td>
<td>36 (41%)</td>
</tr>
</tbody>
</table>

* Includes three AD/HD participants with (1) social problems and high IQ, (2) fine motor delay, and (3) retardation; ‘LD’ = Learning Disorder, ‘ANX’ = Anxiety, ‘DEP’ = Depression.

A one-way ANOVA with Bonferroni post-hoc comparisons confirmed that there were no significant differences in age between comorbid child \[F(3, 158) = .123, p = .947\], or adolescent groups \[F(3, 176) = .746, p = .526\].

Of the AD/HD participants who had comorbidity, twelve (12.63%) had more than one comorbid disorder. No AD/HD participant had more than three comorbid conditions (only two participants had three comorbid conditions). Where more than one comorbid disorder was present, grouping was based according to the presence or absence of ODD/CD. If ODD/CD was present as well as Depression for example, the participant was grouped into the externalising category. This grouping method has been shown to be valid in previous research, where AD/HD groups with both

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4 The term “retardation” here refers to developmental/maturational retardation, rather than mental retardation. This participant’s IQ was above the threshold of 80, and therefore was included in this research.
externalising and internalising comorbidities were shown to be more similar to AD/HD with externalising pathology, than internalising (Takeda, Ambrosini, deBerardinis, & Elia, 2012).

The ‘None/Not Known’ comorbidity group is labelled as such since preliminary assessments for comorbidity (in particular that of ODD/CD) by each AD/HD participant’s paediatrician/clinician were negative at the time of interview. This assessment was later supported at the time of testing via the DICA. Therefore, the possibility of significant comorbidity that was undetected in this group is thought to be highly unlikely. Most importantly, this group did not meet DSM-IV-TR diagnostic criteria for ODD/CD comorbidity in AD/HD, which is the focus of this thesis.

For the remainder of this thesis, AD/HD with ODD/CD comorbidity will be labelled as AD/HD+ODD/CD. AD/HD with internalising comorbidity (Learning Disorder, Anxiety, Depression) will be labelled as AD/HD+INT. AD/HD with no known comorbidity will be labelled as AD/HD-NK.

Severity of behavioural pathology in the AD/HD cohort was measured via the Conners’ Parent Rating Scale – Revised, Long form (CPRS-RL) (Conners, Sitarenios, Parker, & Epstein, 1998a), with all subscales included: oppositional, cognitive problems/inattention, hyperactivity, anxious-shy, perfectionism, social problems, psychosomatic, AD/HD index, restless-impulsive, emotional lability, global index total, DSM-IV inattentive, DSM-IV hyperactive-impulsive, and DSM-IV symptoms total. Scores on each of these subscales were converted to T-scores prior to analysis via a one-way ANOVA with Bonferroni post-hoc comparisons. In children, AD/HD+INT scored higher on the anxious-shy and emotional lability subscales than AD/HD-NK ($p = .003$, $p = .013$ respectively). AD/HD+ODD/CD children scored higher on the social problems subscale than either AD/HD+INT ($p = .01$) or AD/HD-NK ($p = .005$). AD/HD+INT children scored higher than either AD/HD+ODD/CD or AD/HD-NK on the inattentive subscale ($p < .001$ for both comparisons). In adolescents, AD/HD+ODD/CD scored higher on the oppositional subscale than either AD/HD-NK ($p = .048$) or AD/HD+INT ($p = .005$). AD/HD+ODD/CD adolescents also scored higher on the hyperactivity subscale than either AD/HD+INT ($p = .042$) or AD/HD-NK ($p = .036$).
AD/HD+ODD/CD adolescents scored higher than AD/HD+INT on the restless-impulsive \((p = .011)\), emotional lability \((p = .009)\), and the global index total subscales \((p = .003)\). On the latter subscale, AD/HD+ODD/CD adolescents also scored higher than AD/HD-NK \((p = .019)\).

### 6.1.2 Recruitment Methods

All data utilised in the current thesis formed part of the Brain Resource International Database (BRID); a large standardised international database of psychometric and psychophysiological information acquired across the lifespan from tasks designed to tap into the brain’s major networks (E. Gordon, 2003a, 2003b). The BRID holds data gathered from laboratories located within their five major collection sites: The United States of America (USA), The United Kingdom (UK), The Netherlands, South Africa, and Australia.

Each site obtained ethics approval for this research from their relevant authority, and informed consent was obtained from each participant. Informed consent was two-fold; University/Hospital informed consent was sought for initial participation in the study, and subsequent informed consent was sought for the addition of the de-linked data to the BRID for scientific research purposes.

Testing and practise protocols were identical between laboratories to ensure comparability of the data collected. Consistency between sites has been demonstrated (E. Gordon, Cooper, Rennie, Hermens, & Williams, 2005; Paul et al., 2007; Williams et al., 2005), along with the reliability and validity of each psychophysiological and psychometric task contained within the BRID standard testing battery (C. R. Clark et al., 2006; Paul et al., 2007; Williams et al., 2005).

All AD/HD children were referred from paediatricians and psychologists located within Australia (Melbourne, Adelaide, and Sydney). All AD/HD participants were either new or existing patients of their respective clinician for the duration of the study, however their participation in this research did not affect their prescribed treatment regime since participation was voluntary.
All participants (both Clinical and Controls) included in this thesis were reimbursed $100 for their time and any travel costs associated with their participation in this research. Importantly, all participants whether Clinical or Control, were treated equally at the time of testing (that is, neither group was given any preferential treatment).

In order to be included in the study, a primary diagnosis of AD/HD was required, as per the DSM-IV-TR (see section 2.2.2 for DSM-IV-TR diagnostic criteria for AD/HD). The Conner’s Parent Rating Scale – Revised, Long form (CPRS-RL) was also employed as a measure of dimensional severity. In addition to a primary diagnosis of AD/HD, AD/HD+ODD/CD children were required to have a secondary diagnosis of ODD and/or CD as per the DSM-IV-TR (see section 3.4.2 for DSM-IV-TR diagnostic criteria for ODD, and section 3.4.3 for DSM-IV-TR diagnostic criteria for CD).

A Control group matched for age, gender, and IQ, were recruited via advertisements in schools and community groups. Although this was primarily in Australia, some data were also collected in the USA, the Netherlands, and South Africa.

6.1.3 Exclusion/Inclusion Criteria

Both Clinical and Control children were excluded if they met any of the following exclusion criteria:

- English not being a primary language.
- A personal history of physical brain injury.
- Unconsciousness resulting from a blow to the head (within the last 5 years only).
- A personal history of stroke or neurological disorder (e.g. Parkinson’s disease, Epilepsy, Alzheimer’s disease, or Multiple Sclerosis).
- A personal history of a serious medical condition related to the thyroid or heart, or a history of cancer.
- A blood borne illness (e.g. HIV, Hepatitis B, or Hepatitis C).
A severe impediment in vision (or colour vision) that could not be corrected, for example with glasses.

A severe impediment in hearing, or hand movement.

A personal history of addiction to drugs (e.g. Heroin, Cocaine, or amphetamines).

A personal history of heavy consumption of Marijuana or alcohol.

A personal or family history of a genetic disorder (e.g. Fragile X Syndrome).

Participants (both AD/HD and Control) were also excluded if their IQ was below 80, as measured by the full-scale (WISC III) IQ, or the Kaufman Brief Intelligence Test (K-BIT2) (Kaufman & Kaufman, 2004). All participants (AD/HD and Controls) completed the Spot-the-Word test (Baddeley, Emslie, & Nimmo-Smith, 1993) to provide an ‘IQ estimate’ where WISC III or K-BIT2 information was not available. This measure has shown a high correlation ($r = 0.76$) with the full-scale WAIS III IQ (Paul et al., 2005).

The Spot the Real Word test is described in detail in Section 6.2.2.5 of this Chapter. A one-way ANOVA revealed Control children to be significantly higher in their IQ estimate than AD/HD+ODD/CD children ($p < .001$). No significant differences in IQ estimates were found between any of the other child groups. No significant differences were found in IQ estimates between any of the adolescent groups [$F(3, 177) = .137, p = .938$].

Exclusion criteria specific to Controls consisted of any personal or family history of AD/HD, or any other psychiatric disorder. To screen for any undiagnosed common psychiatric disorders within this cohort, the Somatic and Psychological Health Report 12 (SPHERE-12: Hickie, Davenport, Hadzi-Pavlovic et al., 2001; Hickie, Davenport, Naismith, & Scott, 2001) was administered. The SPHERE-12 consists of 12 questions, six of which refer to somatic symptoms (for example “muscle pain after activity?”), and six of which refer to psychiatric symptoms (for example “feeling nervous or tense?”). The questionnaire is shown in full in Appendix A. These 12 questions were found by the authors to be efficient identifiers of both somatic and psychiatric symptoms hence, any individuals with the possibility of a common psychiatric disorder can be identified. Each question is scored on a 3-level likert-type scale ranging from 0 “never or some of
the time” to 2 “most of the time”. If individuals scored a minimum of 3 on the Somatic set in addition to a minimum of 2 on the Psychiatric set, they were identified as a “SPHERE-12” case, indicative of the possible presence of a depressive, somatic, or anxiety disorder. In the present thesis, all Controls identified as SPHERE-12 cases were excluded.

Exclusion criteria specific to Clinical participants consisted of a current diagnosis of any psychiatric disorder other than AD/HD (for example Tic Disorder, Autism Spectrum Disorder, etc). With regard to the AD/HD comorbid groups, AD/HD was required to be the primary diagnosis for inclusion in the study.

All Clinical participants were required to be medication-free at the time of testing. For participants who were not medication-naïve at this time, a minimum washout period of 48 hours was required. Stimulant medication regimes for the Clinical group consisted of Methylphenidate (MPH), or Dextroamphetamine (DEX), however the majority of AD/HD participants were medication naïve at the time of testing. The plasma half-life of both MPH and DEX in children is approximately five hours (Solanto, 2000). The pre-test medication status and the duration of washout for each AD/HD participant are shown below in Table 6.3. Recruitment was not restricted to medication-naïve participants as this would reduce the study’s external validity by possibly limiting analyses to less severe cases.

<table>
<thead>
<tr>
<th>Washout</th>
<th>MPH</th>
<th>DEX</th>
<th>Naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 - 10 days</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>11 - 30 days</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>31 - 60 days</td>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>61 days - 1 year</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>8</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>34</strong></td>
<td><strong>14</strong></td>
<td><strong>122</strong></td>
</tr>
</tbody>
</table>

**Relative %**

<table>
<thead>
<tr>
<th>MPH</th>
<th>DEX</th>
<th>Naïve</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>8.24%</td>
<td>71.76%</td>
</tr>
</tbody>
</table>

MPH = Methylphenidate; DEX = Dextroamphetamine
6.2 Tasks and Apparatus

The tasks comprising the BRID test battery are categorised as either psychophysiological or psychometric. The psychophysiological tasks aim to measure brain-body processes, and involve the collection of electrocortical (EEG, ERP), electrodermal (skin conductance level, skin conductance response), and autonomic (heart rate, respiratory rate) information. Reaction time and accuracy provide the psychometric performance elements to these tasks. The psychophysiological tasks utilised in this thesis are: the auditory Oddball, and the GNG. From these tasks, only electrocortical data in the form of ERPs, and related psychometric performance data will be assessed in this thesis. Although the CPT comprises both ERP and psychometric performance components, only the latter will be assessed here. This is primarily due to most previous research isolating only the psychometric variables as indicators of sustained attention rather than ERPs. As stated previously, a sustained attention deficit is typically characterised by a time-on-task related decline in performance. Therefore, only the psychometric performance data will be explored. This will also limit the number of variables incorporated into each analysis, and hence limit the possibility of Type 1 error. Since no ERPs from the CPT will be assessed in the present thesis, this task will be treated as psychometric rather than psychophysiological.

The psychometric tasks by contrast, are focused purely on psychometric performance and do not contain a measured physiological component. The psychometric tasks utilised in this thesis are: the Executive Maze, Switching of Attention (SOAT), and

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5 “Type 1 Errors” are also called “false positives”. It is the failure to reject the null hypothesis when the null hypothesis is valid. Multiple comparisons can increase Type 1 error.
Verbal Interference. As stated above, the CPT will be considered a psychometric task also. All performance data gleaned from these tasks will be assessed in this thesis. Each psychophysiological and psychometric task employed in this thesis will be described in the following sections.

6.2.1 Psychophysiological Tasks and EEG Acquisition

All participants were seated 60cm directly in front of a computer screen, in a sound and light attenuated room. Standardised pre-recorded task instructions are delivered both binaurally via headphones, and visually via the computer screen. An iterative human-computer protocol was employed to ensure task comprehension and compliance. Responses were measured and recorded via a button-box placed in front of the participant. Responses can be categorised as one of two types: (1) a false positive (FP) – responding to a non-target stimulus or (2) a false negative (FN) – failing to respond to a target stimulus.

EEG data from 26 scalp sites: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, and O2 (32 channels; Nuamps; 10-20 International system), were acquired via an electrode cap (Neuroscan ‘QuikCap’) and recorded relative to the offline average of A1 and A2 (mastoid) electrode sites. Figure 6.1 below shows the location of each scalp electrode site. Since the inclusion of both amplitude and latency variants of each ERP at each scalp site would create superfluous data that could not possibly be meaningfully analysed together, ERPs were instead averaged across scalp sites of maximal activation. This is detailed below in Section 6.4.2.

Horizontal eye movements were recorded with electrodes placed 1.5cm lateral to the outer canthus of each eye. Vertical eye movements were recorded with electrodes placed 3mm above the middle of the left eyebrow, and 1.5cm below the middle of the left bottom eye-lid. Impedances were below 5kΩ at the beginning of testing.
EEG and electrooculogram (EOG) potentials were continuously amplified and digitised using SCAN 4.3 (NuAmps), with a sampling rate of 500Hz. EEG data were also screened visually for artefacts, normal variants, and changes in alertness by technicians blinded to group status. EOG correction was carried out as per Gratton, Coles, and Donchin (1983).

Prior to averaging, each single-trial epoch was filtered using a 25Hz low-pass filter (with a Tukey or cosine taper to 35Hz); no signal was passed above this frequency. Conventional ERP averages were formed at each scalp recording site in relation to target stimuli within a window of –300ms to 600ms. Only target stimuli that corresponded with a correct button response were included in the target average. Peak amplitudes and latencies of the N1, P2, N2, and P3 ERP components were derived from the averaged single-trial epochs (relative to a pre-stimulus baseline window of –300 – 0ms) at each scalp site using an automated algorithm. This algorithm was

Figure 6.1 EEG montage showing the 26 scalp electrode sites. Ground (GND), A1, and A2 are reference electrodes.
validated (minimum 98% accuracy rate) by trained technicians who were blinded to group status. Component peaks were extracted using pre-determined latency windows, which varied only in the GNG task. Therefore, aside from the GNG task, the following component windows were used: N1 (70 – 120ms), P2 (120 – 220ms), N2 (120 – 300ms), and P3 (220 – 550ms). Component windows utilised in the GNG task are listed in section 6.2.1.3 below. Indicators of psychometric performance were also extracted in the form of reaction time (RT: the average time taken to respond to a target stimulus), standard RT (SDRT: a measure of RT variability), and accuracy (FPs: responding to a non-target stimulus; FNs: failure to respond to a target stimulus).

The following sections will describe each psychophysiological task utilised in this thesis.

### 6.2.1.1 Auditory Oddball Task

The Oddball task (which can be administered in either the auditory or visual modality) is designed to assess the ability to detect rare salient stimuli (‘targets’) embedded within frequent irrelevant stimuli (‘standards’). The process of detecting the target stimuli is believed to require (aside from vigilance to maintain task performance) orienting and allocation of attention, both of which are primary components of selective attention.

An auditory Oddball task was utilised in this thesis. Participants were presented with high ‘target’ tones (1000Hz) and low ‘standard’ tones (500Hz) binaurally via headphones at 75dB. The duration of each tone was 50ms, with an ISI of 1s. Rise and fall times of each tone was 5ms. All participants were instructed to press two buttons on a button box simultaneously with the index finger of both hands to target tones only; instructions were given to ignore standard tones. Speed and accuracy in responding were equally stressed in the instructions prior to commencing the task, and a short practise session was allowed to ensure task instructions had been understood. For the duration of the task, participants were instructed to focus on a red dot at the centre of an otherwise blank screen, shown below in Figure 6.2.
A total of 340 tones were presented, of which 280 were standard tones, and 60 were target tones. Tones were presented in a quasi-random order with the only constraint being that two target tones could not appear consecutively. The duration of the entire task was six minutes.

Indicators of psychometric performance on this task consisted of RT, SDRT, FPs, and FNs.

6.2.1.2 Go/No-Go (GNG) Task

Similar to the Oddball task, the GNG encompasses both salient and irrelevant stimuli. The GNG however, is designed to measure response inhibition (also known as behavioural disinhibition), rather than selective attention. In contrast to the Oddball task, salient stimuli are more frequent than irrelevant stimuli, hence creating a prepotency to respond. The rare irrelevant stimuli therefore require a response inhibition.

The stimuli for the GNG task employed in this thesis consisted of the word “PRESS” which was written in either green or red. A green PRESS was identified as the ‘Go’ stimulus, while the red PRESS was identified as the ‘No-Go’ stimulus. Each stimulus was presented on a computer screen for 500ms, with an ISI of 1s. All participants were
instructed to press two buttons on a button box simultaneously with the index finger of both hands to the green Go stimuli only; participants were instructed to ignore the red No-Go stimuli (that is, the inhibition of a response). This is illustrated below in Figure 6.3. Speed and accuracy in responding were equally stressed in the instructions prior to commencing the task, and a short practise session was allowed to ensure task instructions had been understood.

![Figure 6.3 Go/No-Go Task. Correct responses were denoted by button presses only to a green “PRESS” (left), incorrect responses were button presses to a red “PRESS” (right).](image)

The word PRESS was presented on the computer screen in a pseudo-random order, a total of 28 times. A green (Go) PRESS was shown 21 of those times, while a red (No-Go) PRESS was shown 7 times. The green (Go) PRESS stimulus appeared 6 times consecutively at the beginning of the task so as to increase the perceived stimulus probability. This was followed immediately by a red (No-Go) PRESS stimulus. The remainder of the tasks consisted of random presentations of the Go and No-Go stimuli. The duration of the entire task was five minutes.

As mentioned above, the ERP component windows varied slightly in this task, and are defined as follows: N1 (95 – 170ms), P2 (200 – 280ms), N2 (220 – 350ms), and P3 (300 – 450ms). Indicators of psychometric performance consisted of RT, SDRT, FPs, and FNs.

**6.2.2 Psychometric Tasks**
All participants were seated in front of a touch-screen in a sound and light attenuated room. Standardised pre-recorded task instructions (using an iterative human-computer protocol) were delivered prior to the commencement of each task both visually on the touch-screen, and binaurally via headphones. These instructions also incorporated a computerised visual demonstration followed by a ‘test trial’ prior to acquiring the data; if the participant failed the test trial, then the task instructions were automatically reiterated and elaborated upon. This procedure was repeated until the test trial was successfully completed, however after 3 unsuccessful trials, the task was discontinued and the next task commenced.

With the exception of the Executive Maze task and the CPT, all other psychometric tasks were presented on this touch-screen with which all responses were measured and recorded. The Executive Maze task and the CPT formed part of the psychophysiological test battery, and hence was administered according to the protocol described above in section 6.2.1. However, since no ERPs will be examined from this task, the Executive Maze and the CPT will be treated as psychometric tasks instead.

The following sections will describe each psychometric task utilised in this thesis.

6.2.2.1 Continuous Performance Task (CPT)

Originally developed in 1963 by Mackworth and Taylor (Mackworth & Taylor, 1963), the CPT is designed to measure attentional control, or more specifically, sustained attention or ‘vigilance’. Although there are many variants of this task, the primary goal and principal arena of investigation remains within sustained attention.

The CPT utilised in this thesis consisted of a series of letters (B, C, D and G) which were written in white Arial font on a black background, and were presented one at a time on an otherwise blank computer screen. The duration of each letter was 200ms, with an inter-stimulus interval (ISI) of 2.5s. All participants were instructed to press two buttons on a button box simultaneously with the index finger of both hands when the
same letter appeared twice in a row; an example is illustrated below in Figure 6.4. In CPTs where targets are identified as the consecutive representation of the same stimulus, the task is generally labelled an “XX-CPT”, however in the present thesis this will simply be referred to as ‘CPT’ since no other variant of this task is used. Speed and accuracy in responding were equally stressed in the instructions prior to commencing the task, and a short practise session was allowed to ensure task instructions had been understood.

![Figure 6.4 Continuous Performance Task. Responses to two consecutive representations of different letters were incorrect (left); responses that included a checkerboard pattern were incorrect (middle); responses to consecutive representations of the same letter were correct (right).](image)

A total of 125 stimuli were presented, of which 85 were background letters (non-target letters), 20 were pseudo-randomly presented target letters (that is, repetitions of the previous letter), and 20 were distracter stimuli. The distracter stimulus consisted of a black and white checkerboard (with each black/white square being approximately 1x1cm), which was randomly interleaved with the letter stimuli. All participants were
instructed to ignore the checkerboards. The duration of the entire task was eight minutes.

Indicators of psychometric performance on this task consisted of RT, SDRT, FPs, and FNs.

6.2.2.2 Executive Maze Task

The Executive Maze task is a variant of the Austin Maze which primarily assesses visuo-spatial ability, memory, and learning, and also provides secondary insight into planning, error utilization, and working memory abilities (Crowe et al., 1999).

The Executive Maze task was presented on a computer screen as a grid (8 x 8 matrix) of circles. The objective of this task is to find and remember the hidden path through the grid from a start point (yellow dot at the bottom of the grid) to an end point (blue dot at the top of the grid). Participants were required to use a directional button box in order to navigate their way through the grid and find the hidden path through trial and error. Correct moves were denoted by a green tick at the bottom of the screen and accompanied by a tone, whereas incorrect moves were denoted by a red cross at the bottom of the screen and accompanied by a different, lower-pitched tone. The grid is illustrated below in Figure 6.5.

A short practise grid (where the end point was located close to the bottom of the grid) was allowed to ensure task instructions had been understood. The maze did not change between test trials. When the participant was able to complete the maze twice (consecutive trials) without any errors, the task concluded. Each participant was given no longer than seven minutes to reach this goal, after which this task was discontinued.
Indicators of psychometric performance consisted of the total number of errors made, and the total time taken to complete the task.

6.2.2.3  Switching of Attention (SOAT) Task

The Switching of Attention (SOAT) task is a variant of the Trail Making Test (Reitan, 1971) and assesses general attentional functioning and executive function (planning, and switching of attention), visuomotor tracking, and motor speed. The SOAT task comprises two components or ‘trails’ of differing difficulty levels; the first trail measures the basic ability to maintain attentional focus on a simple task, while the more challenging second trail measures the ability to alternate attention between two simple mental sets.

In the first trail, participants are presented with 25 numbered circles in ascending order (that is, 1 – 2 – 3, etc). These circles are scattered in a fixed pseudo-random order on the touch-screen and the participant is required to identify each circle in ascending numerical sequence. The second trail involves the identification of both numbers and letters in ascending but alternating order (that is, 1 – A – 2 – B – 3 – C, etc). The numbers 1 – 13 and the letters A – L are presented in circles, again in a fixed pseudo-random order on the touch-screen. This is illustrated below in Figure 6.6.
Figure 6.6 Switching of Attention Task. This animated visual demonstration was given before the commencement of the task for (a) the first trail showing only numbers, and (b) the second trail showing alternating numbers and letters. Illustrations shown above are for the practise trials.

A short practise session was allowed to ensure task instructions had been understood; the numbers 1 – 8 were presented in the practise session for the first component, and the numbers 1 – 4 and the letters A – D were presented in the practise session for the second component. The duration of the entire task was four minutes.

Indicators of psychometric performance consisted of the time taken to complete each trail.

6.2.2.4 Verbal Interference Task (VIT)

The Verbal Interference Task (VIT) is a variant of the Stroop Colour-Word Test (Stroop, 1935) which assesses the asymmetric pattern of interference control between colour-naming and word-reading (Sugg & McDonald, 1994). The VIT differs qualitatively from the Stroop test only in the method of response; while the Stroop test requires a verbal response, the VIT employed a computerised (touch-screen) response system. Despite this minor difference, both tasks are a measure of interference control. The VIT utilised here comprises two components of progressive difficulty.

Both components involved the presentation of the words: “red”, “yellow”, “green”, and “blue” on a touch-screen. Each of these colour words was printed in an incongruent colour of either: red, yellow, green, or blue (for example, the word “red”
Colour words were presented on the touch-screen one at a time. In the first component, the participant was only required to identify the colour word by pressing the matching response word at the bottom of the touch-screen. In the second component, rather than identifying the colour word, the participant was required to identify the colour that the word was printed in, by pressing the matching response word. Both speed and accuracy were equally stressed in the task instructions and a short practise session was allowed to ensure these instructions had been understood. In both components, colour words would remain on the screen until the participant responded. The duration of each component was one minute.

Indicators of psychometric performance consisted of the number of correctly identified colour words from component one, and typeface colour from component two.
6.2.2.5  **Spot-the-Word Test**

The Spot-the-Word test is a computerised adaptation of the Spot-the-Real-Word Test by Baddeley et al. (1993), and was utilised to provide an estimate of intelligence, or ‘IQ estimate’. Presented on a touch-screen, participants (both AD/HD and Control) were shown two words: a nonsense word and a ‘true’ word in the English language. The participant is required to touch the ‘true’ word in each trial. This measure has shown a high correlation ($r = .76$) with WAIS III full scale IQ (Paul et al., 2005).

Indicators of psychometric performance were word score (how many ‘true’ words correctly identified) and RT. In order to establish an ‘IQ estimate’ from this measure, the RT was divided by the word score. This is because RT naturally tends to increase as task difficulty increases, hence word score or RT *singularly* do not provide the best indicator of performance, let alone provide a reliable IQ estimate. This approach has previously been adopted (Mevorach, Humphreys, & Shalev, 2006).

6.3  **Procedure**

As mentioned earlier in section 6.1.1, all data from Control participants were acquired in laboratories located in the USA, UK, Netherlands, South Africa, and Australia, while data from Clinical participants were acquired in Australia only. For Clinical participants, two testing sessions were involved; the first was conducted while the participant was medication naïve (or after a 48-hour washout), while the second was after a minimum of four weeks on medication. However, since the effects of medication are not a central focus of the present thesis, data from the second (medicated) session will not be presented.

All participants underwent two test batteries in each of the two sessions: (1) psychophysiological, and (2) psychometric. An initial computer-based questionnaire was also administered (in the first session only). Additionally, AD/HD participants
underwent a brief IQ test and reading test, along with a subjective assessment of problem behaviour including both parent and teacher perspectives. These will be presented below in the order that they were administered.

### 6.3.1 Computer-Based Questionnaire

The computer-based questionnaire provided a means for assessing a wide range of psychological and demographic domains (refer to Appendix B for the full list). Since this questionnaire is administered prior to either the psychophysiological or psychometric testing, it also served as an effective screening tool. This questionnaire was completed by the participant if they were aged 12 years or above, otherwise it was completed by a parent or guardian.

Other than the SPHERE-12 (see section 6.1.2) which was used as a screening tool for inclusion, data acquired from the computer-based questionnaire was not utilised in the present thesis. Therefore, a detailed description of this questionnaire would be extraneous.

### 6.3.2 Psychophysiological Test Battery

Measurements of brain and body function (electrocortical, electrodermal, and autonomic) were recorded simultaneously during each psychophysiology session which is designed to tap a profile of the brain’s primary neural networks. The tasks comprised within this test battery begin with the fundamental or baseline tasks, and become progressively more difficult by increasing in cognitive demand. The order in which these tasks are administered (shown below) is therefore important. The duration of each task is given adjacent to the task name.

- Resting (eyes open) – 3 minutes
- Resting (eyes closed) – 3 minutes
- Auditory Habituation – 2 minutes
- Auditory Oddball – 6 minutes
- Visual GNG – 7 minutes
- Eye Tracking – 3 minutes
- Letters Passive Primer – 3 minutes
- Visual CPT (including an embedded novelty task) – 8 minutes
- Executive Maze – up to 7 minutes
- Prepulse Inhibition – 5 minutes
- Conscious processing of Facial Emotions – 6 minutes
- Subconscious processing of Facial Emotions – 6 minutes

Where applicable, RI was recorded via button presses on a button box. Since the only tasks utilised in the present thesis were the Auditory Oddball, the GNG and the CPT, the other tasks will not be discussed here. Although the Executive Maze is listed as part of the psychophysiological test battery, it is employed as a psychometric measure in the present thesis. The duration of the entire psychophysiological test battery (including instructions and practice time) was approximately 50-60 minutes.

6.3.3 Psychometric Test Battery

The tasks comprising the psychometric test battery are based on standard neuropsychological tests of cognitive function, which also allow for covariance with the brain measures assessed in the psychophysiological test battery. Areas of assessment are sensori-motor, language, attention, memory, and EF. These tasks are shown below in the order that they were administered.

- Motor Tapping
- Choice Reaction Time
- Timing
- Span of Visual Memory
- Digit Span
- Memory Recall and Recognition
- Verbal Interference
- Switching of Attention
- Spot-the-Word
• Word Generation (FAS task)

All responses were registered via the touch-screen, and where applicable via a microphone (for verbal responses) which were recorded as audio (.wav) files. Since the only psychometric tasks utilised from this test battery in the present thesis were the SOAT and the VIT, the other tasks will not be discussed here. The duration of the entire psychometric test battery was approximately 50 minutes.

6.3.4 Additional Tasks

After the completion of both the psychophysiological and psychometric test batteries, three additional measures were incorporated into the testing procedure for each Clinical participant. The data from these measures however, will not be assessed in the present thesis. These three measures are listed below.

1) The second edition of the Kaufman Brief Intelligence Test (KBIT-2; Kaufman & Kaufman, 2004) was completed only in the pre-treatment session. The KBIT-2 is an individually administered, brief (approximately 20 minutes) assessment of nonverbal and verbal cognitive ability that acted as an adjunct to intelligence testing carried out by the respective clinicians and paediatricians.

2) The Schonell Graded Word Reading Test (SGWRT; Schonell & Schonell, 1960) was employed as an indication of verbal reading ability and general word knowledge. The duration of this task was dependent on the participant, but typically did not exceed five minutes. This task was also only completed in the pre-treatment session.

3) The revised Conners Rating Scales (CRS-R; Conners, 2001) were utilised to measure AD/HD symptomatology and evaluate problem behaviour in children and adolescents via observer and self-report ratings. The long forms of both the parent (CPRS-RL; Conners et al., 1998a), and teacher (CTRS-RL; Conners, Sitarenios, Parker, & Epstein, 1998b) were administered both pre- and post-treatment, along with the self-report
(CSRS-RL) version if the participant was aged 12 years or over. The CRS were employed as a confirmatory measure of clinician diagnosis.

6.4 Statistical Analysis

Each analysis in the present thesis was conducted using the Statistical Package for the Social Sciences (SPSS) version 20. ERPs and psychometric performance data were screened according to Tabachnick and Fidell (2001) prior to analysis. This included normality tests to identify outliers (extreme values) which were defined as values greater than or less than three standard deviations from the variable mean. These outliers were replaced with values according to the above formula (either three standard deviations above or below the variable mean). Missing values in the dataset were replaced with the variable mean, however not more than 5% of the data on any variable was replaced. Where more than 5% of data were missing on a variable, the maximum (5%) was replaced while the remainder were left blank.

A description of each statistical analysis conducted is provided within the relevant experimental chapters. Also (as mentioned earlier), ERP components were spatially averaged across scalp sites of maximal activation so as to reduce superfluous data analysis. This is discussed below in Section 6.4.1.

6.4.1 ERPs – Spatial Averaging

As outlined earlier in this Chapter, the inclusion of each amplitude and latency variant of each ERP at every scalp site would result in an excessive amount of data incapable of being analysed collectively. However to reduce the data to consist of amplitude and latency ERPs from only one scalp site (for example using only the midline sites) could potentially neglect meaningful information. Discriminant analyses in particular, require that the number of variables do not exceed the number of participants (or
participant groups) (Tabachnick & Fidell, 2001). Therefore, in order to maximise the amount of meaningful data included in the analysis, ERPs (amplitude and latency) to target stimuli were averaged across multiple scalp sites according to topographic location and areas of maximal activation (see Table 6.4 below). Since the underlying neuronal electrical activity that is recorded by any one electrode site exceeds the area covered by that site, “diffuse” electrical activity can, as a result, be recorded by neighbouring electrode sites also (Bertrand, Perrin, & Pernier, 1985). Given this, spatial averaging of neighbouring electrode sites can reduce noise and improve the clarity of the EEG signal; a method that is typical of studies that incorporate a large amount of ERP data (see: Hermens et al., 2005; Kuperman et al., 1996; Smith et al., 2003; Spronk, Jonkman, & Kemner, 2008).

Table 6.4
Spatial averaging of ERPs

<table>
<thead>
<tr>
<th>Topographic Location*</th>
<th>Scalp Sites Averaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fronto-Central N1</td>
<td>Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4</td>
</tr>
<tr>
<td>Fronto-Central N2</td>
<td>Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4</td>
</tr>
<tr>
<td>Central P2</td>
<td>T3, C3, Cz, C4, T4, CP3, CPz, CP4</td>
</tr>
<tr>
<td>Centro-Parietal P3</td>
<td>CP3, CPz, CP4, T5, P3, Pz, P4, T6</td>
</tr>
</tbody>
</table>

* The letter ‘A’ or ‘L’ is added later to the end of each ERP to denote amplitude or latency respectively, for example ‘N1A’ denotes Frontal N1 amplitude.

In order to obtain an averaged ERP that was representative of its topographic location, at least half of the individual ERPs from the respective scalp sites were required. If less than half of these were present (due to missing data), no value was recorded for that topographic location.
Chapter 7:

Group Profiling – Comparing Controls, AD/HD, and AD/HD Comorbid Groups

Chapter Overview:
The aim of this experimental chapter was two-fold: (i) to investigate the CPRS-defined symptom profiles of AD/HD-alone (AD/HD-NK) and AD/HD comorbid with internalising (for example depression, anxiety; AD/HD+INT), and externalising (Oppositional Defiant/Conduct Disorder; AD/HD+ODD/CD) disorders, and (ii) to measure psychometric performance and psychophysiological data in an attempt to compare the cognitive-behavioural profiles of these same three AD/HD groups. Data from the total sample of 152 AD/HD and 131 neurotypical Control participants was collected and subdivided by age group (children = 6-12 years; adolescents = 13-17 years). Results from study (i) showed an increase in Oppositional behaviour scores with age for AD/HD-NK and AD/HD+ODD/CD, in addition to an increase in Hyperactive-Impulsive behaviour scores in later adolescence for AD/HD-NK. AD/HD+INT showed an increase in Social Problem scores with age, while Anxious-Shy scores decreased. The age band of 9-11 years is thought to represent a particularly reactive phase in development. Results from study (ii) showed novelty-seeking behaviour and inattention to be prominent characteristics of AD/HD-NK and AD/HD+ODD/CD in childhood, while deficits in executive function, response inhibition, and attention were apparent in adolescence. AD/HD+INT displayed a symptomatically diffuse profile in childhood, though displayed significant impairment in adolescence. AD/HD+ODD/CD was the most impaired group irrespective of age.
7.1 Preamble

Comorbidity in AD/HD is so ubiquitous that it has become a common characteristic in the disorder’s profile. In previous research, about 60-100% of AD/HD populations have met diagnostic criteria for at least one other DSM diagnosis, and around 66% for at least two other diagnoses (Gillberg et al., 2004). AD/HD can be comorbid with a myriad of disorders, yet the most common is ODD/CD with a prevalence as high as 67% (Sanders et al., 2005, refer to Chapter 3 for a discussion). ODD/CD, like AD/HD, also falls under the Disruptive Behaviour Disorders umbrella. Such comorbidity increases symptom severity, and hinders diagnosis and treatment of AD/HD.

In a typical clinical setting, AD/HD is almost always assessed within the context of comorbidity, which is complicated even further by the inherent heterogeneity of AD/HD itself. The aim of the present Chapter is two-fold: (i) to investigate the CPRS-defined (Conners Parent Rating Scale – Revised, Long form) symptom profiles of AD/HD-alone, and AD/HD with and without externalising (Oppositional Defiant Disorder/Conduct Disorder: ODD/CD) comorbidity, and (ii) to identify differences between Controls, AD/HD-alone and AD/HD with and without externalising comorbidity, using a large test battery (six measures in total), to decipher objective cognitive-behavioural profiles for each comorbid group based on task-defined characteristics. While previous studies have repeatedly shown ODD/CD comorbidity to be associated with more extreme AD/HD symptoms, the question of how the cognitive-behavioural profiles of AD/HD and AD/HD+ODD/CD differ has still not been addressed adequately in the previous literature. For example, researchers have debated whether or not the central deficit in AD/HD+ODD/CD lies within the realm of executive function, namely response inhibition, as has been argued for AD/HD-alone (see Section 4.1.2 of Chapter 4 for a detailed discussion), however results from these studies have produced conflicting findings, with no resolution evident. Importantly, no study to date has investigated how the CPRS-defined symptom profiles and cognitive-behavioural profiles of AD/HD and AD/HD+ODD/CD change with age. While considerable work has been done on the age-related changes in the core symptoms of
AD/HD (inattentive and hyperactive/impulsive), the impact of externalising comorbidity such as ODD/CD on these age-related changes have not been addressed. Given this, the studies of this Chapter will investigate the age-related changes in CPRS-defined symptoms, in addition to an investigation into the cognitive-behavioural profiles of AD/HD-alone, AD/HD+ODD/CD and AD/HD+INT (with internalising comorbidity such as Depression, Anxiety, and Learning Disorder). With regard to study (i), AD/HD-NK are expected to show a gradual decline in overt symptoms such as that measured by the Hyperactivity-Impulsivity CPRS subscale with age, in addition to a retention of covert symptoms such as that measured by the Cognitive Problems-Inattention subscale with age. A similar decline in overt subscale scores are not expected for AD/HD+ODD/CD however, rather, it is thought that scores on such subscales including the Oppositional subscale will increase with age. It is believed that AD/HD+INT will show an overall increase or retention of covert symptoms with age, particularly those relating to social interaction such as the Social Problems and the Anxious-Shy subscale. With regard to study (ii), AD/HD+OD/CD are expected to display greater task-defined impairment than either AD/HD-NK or AD/HD+INT in both children and adolescents, as measured by the six neuro-cognitive tasks.

Since AD/HD-alone constitute the ‘baseline profile’, that is, the profile that AD/HD+ODD/CD and AD/HD+INT are compared to, the tasks employed in this investigation aim to assess what is widely believed to be the core set of deficits in AD/HD. These include selective attention, sustained attention, hyperactivity and impulsivity, and executive function (EF: such as response inhibition and visuo-spatial planning abilities). The auditory Oddball Task was employed as a measure of selective attention, the Continuous Performance Task (CPT) as a measure of sustained attention and working memory, the Go/No-Go (GNG) as a measure of response inhibition, the Executive Maze (EM) Task as a measure of visuo-spatial learning and context updating, the Switching of Attention Task (SOAT) as a measure of task-switching abilities and working memory, and the Verbal Interference Task (VIT) as a measure of response inhibition (refer to Chapter 6 for a detailed description of each task). The EM, SOAT, and VIT are all reported to assess facets of executive function. All of the tasks named above have uncovered cognitive or performance deficits in AD/HD compared to normal Controls. The following sections discuss each domain being assessed and the
relevant task being used in this Chapter, in addition to related findings from the previous AD/HD literature.

7.1.1 Changes in AD/HD Pathology with Age

The changes in AD/HD symptomatology with age have been well documented in the previous literature; however the DSM-IV-TR nomenclature for this disorder does not yet take into account these age-related changes. Previous studies on this topic have shown an overall decline in AD/HD symptomatology with age.

An early meta-analysis conducted by Hill and Schoener (1996) found the rate of AD/HD to decline exponentially with age. More specifically, the authors observed that the rate of AD/HD declined by 50% with every 5 years of age, and hence hypothesised that around 0.84% of the population would meet diagnostic criteria for AD/HD at age 20, and 0.21% at age 30. However, a more recent meta-analysis by Faraone, Biederman and Mick (2006) argued that the findings by Hill and Schoener may represent an overly optimistic view. Here, Faraone et al. assessed both syndromatic (full diagnosis) and symptomatic (sub-threshold/partial diagnosis) persistence of AD/HD. They found that if only considering syndromatic persistence, then the prevalence of AD/HD is low at older ages, however symptomatic persistence is considerably higher. Given this, the authors argued that when considering the full diagnosis of AD/HD, the prevalence at 25 years of age is around 1.2%, while the prevalence of sub-threshold or individuals in partial remission of AD/HD is around 3.2%.

Despite these discrepancies, there is a general consensus that the overall symptom profile of AD/HD (whether considering the full disorder or sub-threshold) appears to dissipate with age. This decline in symptoms however, is not uniform across externalising (hyperactive/impulsive) and internalising (inattentive) symptoms, but appears to differ between the two types. Symptoms of hyperactivity and impulsivity have been found to dissipate at a faster rate than symptoms of inattention which tended to persist with age (Biederman, 2005; Biederman, Mick, & Faraone, 2000; Clarke, Barry, McCarthy, & Selikowitz, 2001a; Muller et al., 2011; Spencer et al., 2007).
In a 4-year longitudinal study conducted by Hart et al. (1995), the authors found hyperactivity and impulsivity declined with increasing age in their AD/HD sample, while inattentive symptoms remained stable from 8-15 years of age. This was supported by Hay and Levy (1996) who argued that hyperactivity is more common among younger AD/HD sufferers, while inattention is more common among older sufferers.

In AD/HD+ODD/CD, there appears to be a similar decline in overt symptomatology and a comparatively lesser decline in covert symptomatology with age (Biederman, Mick, Faraone, & Burback, 2001). A study by Lahey et al. (1999) similarly found that the number of youths who engaged in aggressive and non-aggressive conduct problems was lower when the age of onset of conduct problems was higher. With an older age of onset, non-aggressive conduct problems were more frequent than aggressive conduct problems, hence it appears that severity is at its most severe, at younger ages.

7.1.2 Measuring Selective Attention in AD/HD – the auditory Oddball Task

A well-documented psychophysiological method of investigating attentional functioning is the Oddball paradigm (either visual or auditory), which requires the detection and response only to infrequent ‘target’ stimuli, while ignoring frequent ‘standard’ stimuli. The ability to detect and respond to the targets is thought to involve both orienting and allocation of attention, in addition to vigilance in order to maintain task performance (Stevens, Calhoun, & Kiehl, 2005). The ERP data gleaned from this task allows the inspection of psychometric and psychophysiological responses to both targets and standards. As such, the Oddball task has become one of the most frequently employed assessments of attention and related cognitive function in studies of AD/HD populations.

A moderate body of literature has been published focusing on the psychometric performance and ERP differences that exist between children with AD/HD and normal Controls using auditory Oddball tasks, with the vast majority of findings pointing to a comparative deficit in AD/HD. This literature has produced replicable and robust
findings of (1) impairment in psychometric components such as reaction time (RT) and number of errors (Holcomb et al., 1985; Loiselle et al., 1980; Overtoom et al., 1998; J. H. Satterfield, Schell, & Nicholas, 1994; J. H. Satterfield, Schnell, Nicholas, & Backs, 1988; Winsberg, Javitt, & Shanahan/Silipo, 1997), and (2) impairment in both automatic and controlled processing, as indexed by deficits in most, if not all, ERPs; see Table 7.1 below for a brief summary of such results from research using the Oddball paradigm (see also Table 4.1 in Chapter 4 for other studies assessing auditory ERPs in AD/HD). Typically this research has focussed on the three recognised subtypes of ADHD: HI = hyperactive/impulsive subtype, I = Inattentive subtype, C = combined subtype.
Table 7.1

ERP results from previous Oddball studies.

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Age (yr)</th>
<th>AD/HD Subtype*</th>
<th>Results Compared to Matched Controls#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loiselle et al. (1980)</td>
<td>12-13</td>
<td>HI</td>
<td>↓P3 lat and amp.</td>
</tr>
<tr>
<td>Satterfield et al. (1984)</td>
<td>6-8</td>
<td>HI</td>
<td>↑P1 lat, ↓P2 amp, ↓N2 amp, ↑N2 lat.</td>
</tr>
<tr>
<td>Satterfield et al. (1984)</td>
<td>7-9</td>
<td>HI</td>
<td>↓N1 amp.</td>
</tr>
<tr>
<td>Holcomb et al. (1985)</td>
<td>8-12</td>
<td>HI &amp; I</td>
<td>↓P3 amp, ↓P3 lat.</td>
</tr>
<tr>
<td>Satterfield et al. (1988)</td>
<td>6-7</td>
<td>HI</td>
<td>↓N2 amp.</td>
</tr>
<tr>
<td>Satterfield et al. (1990)</td>
<td>8</td>
<td>HI</td>
<td>↓P3b amp.</td>
</tr>
<tr>
<td>Satterfield et al. (1990)</td>
<td>6</td>
<td>HI</td>
<td>↓N1 amp, ↓P2 amp, ↓P3b amp.</td>
</tr>
<tr>
<td>Robaey et al. (1992)</td>
<td>6-12</td>
<td>HI</td>
<td>↑P2 amp, ↓P3b amp.</td>
</tr>
<tr>
<td>Satterfield et al. (1994)</td>
<td>6</td>
<td>HI</td>
<td>↓N1 amp, ↓N2 amp, ↓P3b amp, ↓N1 lat, ↑P2 amp.</td>
</tr>
<tr>
<td>Kemner et al. (1996)</td>
<td>6-13</td>
<td>HI</td>
<td>↓P1 amp, ↓P3b amp.</td>
</tr>
<tr>
<td>Jonkman et al. (1997)</td>
<td>7-13</td>
<td>HI</td>
<td>↓P3b amp.</td>
</tr>
<tr>
<td>Overtoom et al. (1998)</td>
<td>6-14</td>
<td>C</td>
<td>↓P3 amp.</td>
</tr>
<tr>
<td>Johnstone et al. (2001)</td>
<td>8-18</td>
<td>C &amp; I</td>
<td>↑P2 amp (AD/HD-I: 8-16yr), ↓P2 amp (AD/HD-I: 16-18yr), ↓N1 amp (AD/HD-C)</td>
</tr>
<tr>
<td>Hermens et al. (2005A)</td>
<td>11-17</td>
<td>C &amp; I</td>
<td>↓N2 lat, ↓P2 amp.</td>
</tr>
<tr>
<td>Hermens et al. (2005B)</td>
<td>9-17</td>
<td>C &amp; I</td>
<td>↑N1 lat, ↓P2 amp.</td>
</tr>
<tr>
<td>Senderecka, Grabowska, Gerc, Szewczyk &amp; Chmylak (2011)</td>
<td>6-12</td>
<td>C</td>
<td>↑P2 amp, ↓N2 amp, ↓P3 amp.</td>
</tr>
</tbody>
</table>

* HI = hyperactive/impulsive subtype of AD/HD, I = inattentive subtype of AD/HD, C = combined subtype of AD/HD.

* amp = amplitude, lat = latency. Arrows represent an increase (↑) or decrease (↓) in amplitude or latency in AD/HD compared to normal matched Controls.
Unfortunately there is a scarcity of research incorporating the auditory Oddball task with AD/HD comorbid with ODD/CD. One study by Rothenberger et al. (2000) compared AD/HD+CD with normal Controls and found significantly greater commission errors, and lower mismatch negativity (mean amplitude) in the clinical group. No significant differences were found between AD/HD+CD and AD/HD for either mismatch negativity or task performance (e.g. commission errors).

8.1.1 Measuring Sustained Attention in AD/HD – the Continuous Performance Task (CPT)

The CPT is perhaps the most frequently used measure of sustained attention and vigilance in clinical research (the CPT utilised in this thesis was presented earlier in Section 6.2.2.1 of Chapter 6, and illustrated in Figure 6.3). The typical CPT involves the presentation of an infrequently occurring single target stimulus (or a pattern of target stimuli) among regularly presented standard stimuli. The greater level of difficulty involved with targets defined as stimulus patterns have shown superior sensitivity in clinical populations (Riccio, Reynolds, Lowe, & Moore, 2002). The CPT paradigm employed in the present thesis defines targets as a stimulus pattern, specifically, the consecutive appearance of congruent letters (e.g. the letter ‘D’ followed by another letter ‘D’), on a computer screen.

Despite the differences in the type of CPT employed, previous research has repeatedly shown a deficit in sustained attention and vigilance in AD/HD compared to normal Controls as indexed by their comparatively poor psychometric performance on these tasks. This was shown in an early study by Chee, Logan, Schachar, Lindsay and Wachsmuth (1989) who found their AD/HD population to display slower RT, more FNs and FPs, and lower accuracy than a group of age- and IQ-matched normal Controls. Deficits in RT, SDRT, and error rate in AD/HD have been replicated numerous times in the previous literature which utilised a CPT paradigm to measure attentional dysfunction (Banaschewski et al., 2003; Banaschewski et al., 2004; Epstein et al., 2003; Halperin, Matier, Bedi, Sharma, & Newcorn, 1992; O'Brien et al., 1992; Overtoom et al., 1998; Stins et al., 2005; Strandburg et al., 1996). These robust findings have been
supported by literature investigating the discriminant value of CPT defined performance indicators of sustained attention. Such an investigation was conducted by Levy and Hobbes (1997) who were able to successfully discriminate between AD/HD and normal Controls using CPT-related RT and FPs to achieve an overall accuracy rate of 96.4%. Similarly, Inoue et al. (1998) were also able to successfully distinguish 85% of AD/HD and Controls using FPs and FNs from a CPT.

Previous research assessing CPT-defined sustained attention deficits in comorbid AD/HD+ODD/CD is relatively scarce. Unsurprisingly, the limited research that has been conducted on this topic has also shown a sustained attention deficit compared to normal Controls. In a study conducted by O’Brien et al. (1992), AD/HD+ODD/CD were found to make more FNs than either normal Controls or pure ODD/CD. This was later supported by Barkley et al.’s (2001) investigation which also found a CPT-related attention deficit in AD/HD+ODD compared to a group of community Controls. While CPT measured sustained attention abnormalities have been found in a pure ODD group, this deficit was only apparent in ERP components; performance deficits were not significantly different between ODD and Controls (Baving et al., 2006). While pure ODD/CD groups do display a sustained attention deficit as measured by CPTs, it does not seem to be greater than that of AD/HD or AD/HD+ODD/CD, but rather seem to fall somewhere in between these groups and Controls. Chee et al. (1989) found ODD/CD to display slower RT, lower accuracy, and more errors than Controls, but their performance was not worse than that AD/HD or AD/HD+ODD/CD. This finding was supported by a recent study by Hobson et al. (2011). Therefore, although deficits in sustained attention as defined by performance on the CPT have been demonstrated in AD/HD, AD/HD+ODD/CD and ODD/CD-only samples, there does not appear to be a pattern of severity between groups.

7.1.4 Measuring Executive Function in AD/HD

Executive function (EF) is defined as a set of cognitive processes including: inhibition, memory, planning, and attention that work in concert with each other to govern self-regulation. The myriad of dysfunctions that characterise AD/HD have been argued to
exist almost wholly within the realm of EF. Indeed, there has been a plethora of previous research that has identified EF deficits in both AD/HD and comorbid AD/HD groups (though the latter is to a lesser degree); this research was discussed earlier in Chapter 3, Section 3.5.2.

The EF tasks utilised in this Chapter are discussed in relation to AD/HD in the following sections.

### 7.1.4.1 Response Inhibition - the Go/No-Go (GNG) Task

The pattern of target stimulus presentation in the GNG task is the exact opposite to that of the CPT, in that the target “go” stimuli appear frequently compared to the rare non-target “no-go” stimuli. Therefore, a pattern of responding develops that must be inhibited when the rare no-go stimuli appear (the GNG task utilised in this thesis was presented earlier in Section 6.2.1.2 of Chapter 6, and illustrated in Figure 6.4). The ability to inhibit a pre-potent response [i.e. ‘response inhibition’ (RI)] is believed to be an integral component of behavioural regulation, and one that is thought to be a central (R.A. Barkley, 1997; Quay, 1997), but not the causal (J. T. Nigg, 2001) deficit in AD/HD.

Since RI is only required during the no-go trials of this task, it is these trials that are the focus of research looking for a RI deficit in AD/HD. Failure to inhibit a response during these trials results in a FP, which has repeatedly been shown to be greater in AD/HD than Controls (Berlin & Bohlin, 2002; Booth et al., 2005; Rubia, Smith, & Taylor, 2007; Schulz et al., 2004; Wodka et al., 2007; Yong-Liang et al., 2000). From these studies, those that have incorporated an ERP analysis have also found poor RI to be associated with diminished N2 amplitude, a result that has been supported by additional AD/HD research with the GNG task and other robust measures of RI\(^6\) (Dimoska et al., 2003; Johnstone, Barry, Markovska, Dimoska, & Clarke, 2009; Pliszka et al., 2000; Smith et al., 2004). The association between N2 amplitude and RI has also been shown in Control populations (Eimer, 1993).

\(^6\) For example the Stop Task (Kenemans et al., 2005).
Since a deficit in RI has been a consistently strong finding in the previous research, it is assumed that AD/HD+ODD/CD also possess a comparable deficit given that AD/HD is the underlying disorder. Recent research found RI deficits in groups with ODD/CD independent of whether they were also diagnosed with AD/HD (Hobson et al., 2011). The finding by Hobson et al. is in sharp contrast to an earlier study by Berlin and Bohlin (2002) that found deficits in RI to be more associated with AD/HD than ODD/CD. Hence, the impact of ODD/CD on RI in AD/HD is still unclear and under debate; this issue was introduced previously in Chapter 4 (see Section 4.1.2).

8.1.2.1 Interference Control - the Verbal Interference Task (VIT)

The VIT is a variant of the well-known Stroop task, where responses to incongruent colour words are used as a measure of interference control (the VIT task utilised in this thesis was presented earlier in Section 6.2.2.4 of Chapter 6, and illustrated in Figure 6.7). The “Stroop interference effect” is characterised by the difficulty encountered when attempting to name the colour of a word which spells an incongruent colour. That is, the interference generated by the automatic response of word reading must be controlled in order to name the colour the word is printed in. Significantly increased RT in colour naming and number of errors on incongruent vs. congruent trials compared to normal Controls, are typically interpreted as representative of an EF (Executive Function) deficit, or a greater interference effect.

Whether an EF deficit as indexed by the Stroop task exists in AD/HD is as yet unclear due to the conflicting findings of previous research. While some studies have identified such a deficit in AD/HD (Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995a; Homack & Riccio, 2004; Lansbergen, Kenemans, & van Engeland, 2007), others have not (Gaultney, Kipp, Weinstein, & McNeill, 1999; Schwartz & Verhaeghen, 2008; van Mourik et al., 2009). This may be due to conflicting methodology regarding how the interference score is calculated, that is whether the difference between the congruent and incongruent trials is more indicative of the interference effect than a ratio of correct/incorrect responses (see Lansbergen et al., 2007 for a discussion). Provided that the number of trials completed between groups is the same, the
difference approach should suffice, whereas if the number of trials differed between groups, then the ratio would provide a more accurate depiction of accuracy and hence, the interference effect.

Surprisingly, previous research investigating Stroop interference effects in comorbid AD/HD is scarce. A recent study by Quian, Shuai, Cao, Chan and Wang (2010) found their cohort of AD/HD+ODD children to perform significantly worse than their Control counterparts on a Stroop task. Similar results in an adolescent sample were found more recently by Hummer et al. (2011) with their cohort of AD/HD+ODD/CD who showed significant task-related impairment compared to normal Controls.

There appear to be conflicting results when assessing the Stroop performance of ODD/CD without the presence of AD/HD. While earlier work with Conduct Disordered adolescents revealed significantly worse Stroop performance compared to matched Controls (M. S. Kim, Kim, & Kwon, 2001), these findings were not replicated in recent research with ODD/CD adolescents (Hummer et al., 2011).

7.1.4.3 The Executive Maze (EM) Task

The Executive Maze task is a variant of the Austin Maze which requires participants to find a hidden path through trial and error (the Executive Maze task utilised in this thesis was presented earlier in Section 6.2.2.2 of Chapter 6, and illustrated in Figure 6.5). Since this task requires problem solving, visuo-spatial planning and working memory, and the evaluation of self-produced errors, it is an ideal measure of EF.

Although several studies have utilised maze tasks in animal models of hyperactivity, such research with AD/HD populations is lacking. One investigation by Tirosh, Perets-Dubrovsky, Davidovitch, and Hockerman (2006) which assessed the performance of AD/HD children and matched Controls on the Porteus Maze7, found a significantly longer maze completion time and a greater number of errors in the AD/HD group.

7 The Porteus Maze (Porteus, 1933) is a test of non-verbal intelligence that consists of a set of mazes of graded complexity. The subject is required to find their way from a start point to an end point in one continuous line, while avoiding blind alleys, dead ends, and back-tracking.
compared to the Controls. To date, a study assessing AD/HD groups using the Austin Maze has not been done, however, EF deficits in spatial working memory and planning have consistently been found to characterise AD/HD (Willcutt et al., 2005). In addition to this, error monitoring has repeatedly been shown to be deficient in AD/HD, as reflected by their considerably greater error rate in almost all EF tasks (for example the CPT, GNG, etc).

Therefore, in extrapolating these findings to the Austin Maze, the performance of AD/HD groups would be predicted to be poorer than their Control counterparts. In terms of comorbid AD/HD+ODD/CD, Pennington and Ozonoff (1996) reviewed previous literature which showed maze-related EF deficits in this group, but not in ODD/CD-only groups.

### 7.1.4.4 The Switching of Attention Task (SOAT)

The SOAT is based on the well-known Trail Making Test (TMT) and consists of two levels or “trails” (trails A and B) of progressive difficulty aimed at measuring EF (the SOAT task utilised in this thesis was presented earlier in Section 6.2.2.3 of Chapter 6, and illustrated in Figure 6.6). In an investigation of which cognitive mechanisms are behind the TMT, Sánchez-Cubillo et al. (2009) found that trail A requires primarily visuo-perceptual abilities, while trail B requires working memory and task-switching abilities. Their research also found that the difference in completion times between trail A and B provides a relatively pure indicator of executive control abilities (and hence EF), since visuo-spatial and working memory demands are minimised.

Previous research has consistently found ADHD to display a significantly longer trail completion time of either trail B alone (Hale et al., 2009; Martel, Nikolas, & Nigg, 2007; Pasini et al., 2007; Pennington & Ozonoff, 1996; Willcutt et al., 2005), or in both trails A and B (Oades & Christiansen, 2008). In addition to this, a greater number of trail-making errors committed by AD/HD groups have been argued to be representative of an inhibitory deficit (Hale et al., 2009).
Again, since diminished EF has been found to be typical of AD/HD rather than ODD/CD, studies investigating deficits as indexed by the TMT in comorbid AD/HD populations are likely to uncover results consistent with this contention. In a review by Pennington and Ozonoff (1996), AD/HD+ODD/CD were found to display greater impairment on Trail B than ODD/CD-only groups. A similar result was also reported by Aronowitz et al. (1994) who found a greater TMT-defined deficit in AD/HD+ODD/CD than the ODD/CD-only group. In both of these studies, trail A was either not included, or the results were not reported. Whether there is any impact of ODD/CD on AD/HD as defined by the TMT however, requires further investigation.

7.2 Method

Details pertaining to participant demographics, task descriptions, and procedures were outlined in detail in Chapter 6 and therefore are not reiterated here. A brief overview is provided in the following sections.

7.2.1 Participants

Data from the total sample of 152 AD/HD participants (64 children, and 88 adolescents), and 131 healthy Controls (52 children, and 79 adolescents) is presented in this Chapter\(^8\). All AD/HD participants were either medication naïve at the time of testing, or had undergone a washout period of at least 48-hours prior to testing (refer to Table 6.3 in Chapter 6).

For information regarding recruitment methods and inclusion/exclusion criteria, refer to Sections 6.1.1 and 6.1.2 (respectively) of Chapter 6.

\(^8\) The total sample of 152 AD/HD and 131 Controls is the same sample as that described in detail in Chapter 6 (Methodology).
7.2.1.1 AD/HD comorbidity profile

Comorbidities among the AD/HD population were varied, but have been grouped into Externalising, Internalising, and None or Not Known. Thus the Externalising group comprised those comorbid with ODD/CD; while the Internalising Group comprised those with Learning Disorder (LD), Anxiety (ANX), and Depression (DEP). AD/HD participants were grouped according to the presence or absence of ODD/CD comorbidity. Children and adolescents with ODD/CD comorbidity (regardless of the presence of other comorbid disorders) were grouped as ‘AD/HD+ODD/CD’. Those with internalising pathology such as DEP or ANX were grouped as ‘AD/HD+INT’, and those without any known comorbidity were grouped as ‘AD/HD-NK’. Refer to Section 6.1.1 of Chapter 6 for a more detailed discussion.

7.2.2 Tasks and Procedure

The measures employed in this Chapter are categorised by the two investigations: (i) the CPRS-defined symptom profiles, and (ii) the cognitive-behavioural profiles. The CPRS is described below, followed by the tasks utilised in study (ii).

7.2.2.1 Study (i) - The CPRS-Defined Symptom Profiles

The symptoms of AD/HD were assessed via the Conners Parent Rating Scale – Revised, Long form (CPRS-RL) (Conners, 2001), which is a widely used assessment of dimensional symptomatology in AD/HD. The CPRS-RL has shown reliability and criterion validity (Conners et al., 1998a). All of the seven symptom subscales of the CPRS are utilised in this study to compile symptom profiles of AD/HD-NK, AD/HD+ODD/CD and AD/HD+INT: (1) Cognitive Problems, (2) Oppositional, (3) Hyperactivity-Impulsivity, (4) Anxious-Shy, (5) Perfectionism, (6) Social Problems, and (7) Psychosomatic. Some examples (taken from: Conners et al., 1998a) of the behavioural symptoms/characteristics that underlie each subscale are provided below in Table 7.2.
Table 7.2
Subscales of the Conners Parent Rating Scale: Revised – Long form (CRPS:R-L), with examples of behavioural symptoms that define each subscale.

<table>
<thead>
<tr>
<th>Subscale name</th>
<th>Behavioural examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive problems</td>
<td>“needs supervision”, “avoids mental effort”, “trouble concentrating”</td>
</tr>
<tr>
<td>Oppositional</td>
<td>“angry”, “loses temper”, “blames others”</td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td>“restless”, “difficulty waiting”, “excitable”</td>
</tr>
<tr>
<td>Anxious-Shy</td>
<td>“afraid of people”, “afraid of being alone”, “clings to parents”</td>
</tr>
<tr>
<td>Perfectionism</td>
<td>“keeps checking”, “has rituals”, “sets high goals”</td>
</tr>
<tr>
<td>Social Problems</td>
<td>“no friends”, “loses friends”, “feels inferior”</td>
</tr>
<tr>
<td>Psychosomatic</td>
<td>“aches and pains”, “complains”, “seems tired”</td>
</tr>
</tbody>
</table>

7.2.2.2 Study (ii) – The Cognitive-Behavioural Profiles

The six tasks employed in this investigation (and their abbreviations) are listed below. The primary construct measured by is shown alongside each task.

i. Auditory Oddball Task - selective attention
ii. Continuous Performance “one-back” Task (CPT) - sustained attention
iii. Go/No-Go Task (GNG) - response inhibition (RI)
iv. Verbal Interference Task (VIT) - (RI)
v. Executive Maze Task - executive function (EF)
vi. Switching Of Attention Task (SOAT) - (EF)

A detailed description of each task is provided in Chapter 6 (see Section 6.2). Both speed and accuracy were equally stressed during the task instructions for each measure. A practise trial was performed beforehand for each task to ensure these
instructions had been understood. Both Clinical and Control groups underwent the same test battery with the same practise trials.

All of the tasks except for the auditory Oddball and GNG were psychometric only. The Oddball and GNG tasks contain ERP components in addition to performance indicators. ERP components were averaged across scalp sites of maximal activation and topographic location. This was presented earlier in Chapter 6 (see Section 6.4.2). EEG acquisition was discussed in Section 6.2.1 of Chapter 6.

7.2.3 Statistical Analysis

The statistical approach employed for studies (i) and (ii) are detailed below.

7.2.3.1 Study (i) – Statistical procedure

One-way ANOVAs were conducted to assess any linear age-related changes (between children and adolescents) in each of the seven CPRS subscales. Where normality assumptions were violated due to skewed distributions, Mann-Whitney U tests were done in place of Independent-Samples T-Tests. To investigate whether there exists a non-linear relationship between age and CPRS subscale, Regression analyses with Curve Estimation were conducted.

7.2.3.2 Study (ii) – Statistical procedure

Due to the skewed distributions of the variables, non-parametric analyses were conducted. Attempts to counteract skewness were made via transformations of the data however normality was not able to be attained. Therefore, Mann-Whitney U Tests and Kruskal Wallis Tests were performed to uncover significant psychophysiological (ERP components) and psychometric (task performance) differences between groups. Bonferroni corrections were applied to the Mann-Whitney U Tests. Since analyses were non-parametric, median values are reported rather than means and standard deviations.
Statistical comparisons consisted of: (1) a ‘diagnostic’ analysis with AD/HD versus Controls, and (2) a ‘comorbidity’ analysis where each comorbid group was compared to Controls in addition to between-comorbid group comparisons. For both of these statistical comparisons, analyses were conducted for both children and adolescents.

7.3 Results

The results of this Chapter are categorised according to the study conducted. The results for study (i): CPRS-defined symptom profiles are presented first, followed by the results for study (ii): cognitive-behavioural profiles.

Study (i): The CPRS-Defined Symptom Profiles of AD/HD-NK, AD/HD+ODD/CD and AD/HD+INT

Each group was assessed separately to investigate any age-related changes in each of the seven CPRS subscales. The results from the one-way ANOVA for AD/HD-NK are presented first in Table 7.3, those for AD/HD+ODD/CD are shown in Table 7.4, and those for AD/HD+INT are shown in Table 7.5 below.

7.3.1 AD/HD-NK

Of the seven CPRS subscales, a significant linear relationship with age was only found for the Oppositional subscale. Here, AD/HD-NK adolescents scored significantly higher in oppositional behaviour, than AD/HD-NK children ($p = .02$). Non-linear relationships were found between age and the Hyperactivity-Impulsivity, Anxious-Shy, and
Perfectionism subscales, shown below in Figure 7.1. For each of these three subscales, a significant cubic relationship with age was found.

For the Hyperactivity-Impulsivity subscale, an overall significant cubic model was found: $F(3,62) = 8.49, p < .001$, which accounted for 30.1% of the variance. With this cubic model, age was found to be a significant predictor of scores on the Hyperactivity-Impulsivity subscale ($p < .001$).

For the Anxious-Shy subscale, an overall significant cubic model was found: $F(3,54) = 2.94, p = .042$, which explained 14.7% of the subscale variance. Age was again found to be a significant predictor of scores on this subscale ($p = .006$).

For the Perfectionism subscale, an overall significant cubic model was found: $F(3,54) = 2.78, p = .05$ that explained 14.1% of the subscale variance. Age was a significant predictor of scores on this subscale ($p = .018$).

Table 7.3
*One-way ANOVA results for AD/HD-NK: CPRS subscales vs. age group as a linear relationship*

<table>
<thead>
<tr>
<th>CPRS Subscale</th>
<th>Age group</th>
<th>Mean (x)</th>
<th>SD</th>
<th>Sig (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppositional</td>
<td>6-12 years</td>
<td>62.00</td>
<td>16.25</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>70.91</td>
<td>13.64</td>
<td></td>
</tr>
<tr>
<td>Cognitive Problems-Inattention</td>
<td>6-12 years</td>
<td>70.29</td>
<td>10.07</td>
<td>.67</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>71.26</td>
<td>7.94</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td>6-12 years</td>
<td>66.71</td>
<td>15.37</td>
<td>.37</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>70.31</td>
<td>16.24</td>
<td></td>
</tr>
<tr>
<td>Anxious-Shy</td>
<td>6-12 years</td>
<td>54.38</td>
<td>13.64</td>
<td>.23</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>59.14</td>
<td>15.34</td>
<td></td>
</tr>
<tr>
<td>Perfectionism</td>
<td>6-12 years</td>
<td>51.88</td>
<td>9.47</td>
<td>.31</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>54.86</td>
<td>11.60</td>
<td></td>
</tr>
<tr>
<td>Social Problems</td>
<td>6-12 years</td>
<td>55.19</td>
<td>12.65</td>
<td>.38</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>58.17</td>
<td>12.31</td>
<td></td>
</tr>
<tr>
<td>Psychosomatic</td>
<td>6-12 years</td>
<td>58.69</td>
<td>14.33</td>
<td>.49</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>61.69</td>
<td>17.30</td>
<td></td>
</tr>
</tbody>
</table>
Figure 7.1 Significant cubic relationships between age and the CPRS subscales: (a) Hyperactivity-Impulsivity, (b) Anxious-Shy, and (c) Perfectionism in AD/HD-NK. Mean CPR S subscale scores for are shown in the bar charts alongside each cubic graph, with 2-year age-bands (6-8 years, 9-11 years, 12-14 years, 15-17 years) shown on the x-axis and CPRS subscale scores are shown on the y-axis. Green horizontal brackets above the bars represent significant differences in subscale scores between those two age-bands.

No other significant relationships were found between age and CPRS subscales for AD/HD-NK.

To assess whether the age-related changes in subscale scores seen in the cubic regression models were significant, the two age groups were further subdivided into two-year age-bands: 6-8 years, 9-11 years, 12-14 years, and 15-17 years (shown above in Figure 7.1). A one-way ANOVA revealed a significant difference between these age bands only for the Hyperactivity-Impulsivity subscale. There was a significant increase in Hyperactivity-Impulsivity scores from 9-11 years to 15-17 years ($p = .002$), and also from 12-14 years to 15-17 years ($p = .024$). No other significant differences were found. The two-year age-band mean scores for the remaining three CPRS subscales (Cognitive Problems-Inattention, Social Problems, Psychosomatic) are shown below in Figure 7.2.
7.3.2 AD/HD+ODD/CD

Similar to results for AD/HD-NK, a significant linear relationship with age between was only found for the Oppositional subscale in AD/HD+ODD/CD. Again, AD/HD+ODD/CD adolescents scored significant higher on the Oppositional subscale than their child counterparts. However, significant non-linear relationships were found for the Cognitive Problems-Inattention and Social Problems subscales, shown below in Figure 7.3.

For the Cognitive Problems-Inattention subscale, an overall significant quadratic model was found: \( F(2,46) = 3.36, p = .044 \), which explained 13.3% of the subscale variance. Age was again found to be a significant predictor of scores on this subscale \( (p = .039) \).

For the Social Problems subscale, an overall significant inverse model was found: \( F(1,44) = 4.33, p = .043 \), which explained 9.1% of the subscale variance. Age was again found to be a significant predictor of scores on this subscale \( (p = .043) \).
Table 7.4
One-way ANOVA results for AD/HD+ODD/CD: CPRS subscales vs. age group as a linear relationship

<table>
<thead>
<tr>
<th>CPRS Subscale</th>
<th>Age group</th>
<th>Mean (x)</th>
<th>SD</th>
<th>Sig (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppositional</td>
<td>6-12 years</td>
<td>72.12</td>
<td>10.46</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>77.93</td>
<td>9.00</td>
<td></td>
</tr>
<tr>
<td>Cognitive Problems-Inattention</td>
<td>6-12 years</td>
<td>70.06</td>
<td>8.21</td>
<td>.28</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>72.61</td>
<td>7.55</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td>6-12 years</td>
<td>75.39</td>
<td>8.75</td>
<td>.22</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>79.11</td>
<td>10.70</td>
<td></td>
</tr>
<tr>
<td>Anxious-Shy</td>
<td>6-12 years</td>
<td>60.59</td>
<td>9.88</td>
<td>.73</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>59.19</td>
<td>14.52</td>
<td></td>
</tr>
<tr>
<td>Perfectionism</td>
<td>6-12 years</td>
<td>55.53</td>
<td>11.77</td>
<td>.23</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>51.85</td>
<td>8.44</td>
<td></td>
</tr>
<tr>
<td>Social Problems</td>
<td>6-12 years</td>
<td>69.53</td>
<td>16.97</td>
<td>.20</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>63.70</td>
<td>13.01</td>
<td></td>
</tr>
<tr>
<td>Psychosomatic</td>
<td>6-12 years</td>
<td>63.41</td>
<td>13.72</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>56.67</td>
<td>11.56</td>
<td></td>
</tr>
</tbody>
</table>

No other significant relationships (whether linear or non-linear) were found between age and CPRS subscales for AD/HD+ODD/CD. No significant differences in the two-year age-bands were found for Cognitive Problems-Inattention or Social Problems. The two-year age-band mean scores for the remaining four CPRS subscales (Psychosomatic, Hyperactivity-Impulsivity, Anxious-Shy, and Perfectionism) are shown below in Figure 7.4. No significant differences were found between the two-year age bands for any of these four subscales.
Figure 7.3 Significant non-linear (a) quadratic and (b) inverse relationships between age and the CPRS subscales: (a) Cognitive Problems-Inattention and (b) Social Problems in AD/HD+ODD/CD. Mean CPRS subscale scores are shown in the bar charts alongside each cubic graph, with 2-year age-bands (6-8 years, 9-11 years, 12-14 years, 15-17 years) shown on the x-axis and CPRS subscale scores are shown on the y-axis.
### 7.3.3 AD/HD+INT

A one-way ANOVA revealed two CPRS subscales to have a significant linear relationship with age, however since normality assumptions were violated, Mann-Whitney U tests were conducted *post hoc* to confirm these significant linear relationships.

For the Anxious-Shy subscale, AD/HD+INT adolescents showed a significant decrease in scores compared to AD/HD+INT children ($U = 23.00$, $z = -2.21$, $p = .03$). For the Social Problems subscale, AD/HD+INT adolescents showed a significant increase in scores compared to AD/HD+INT children ($U = 22.50$, $z = -2.25$, $p = .02$).

No other significant relationships (whether linear or non-linear) were found between age and CPRS subscales for AD/HD+INT. No significant differences in the two-year age-bands were found for the remaining five CPRS subscales (Perfectionism, Oppositional, Cognitive Problems-Inattention, Psychosomatic, and Hyperactivity-Impulsivity). Mean scores on these five subscales are shown below in Figure 7.5.
Table 7.5

One-way ANOVA results for AD/HD+INT: CPRS subscales vs. age group as a linear relationship

<table>
<thead>
<tr>
<th>CPRS Subscale</th>
<th>Age group</th>
<th>Mean (x)</th>
<th>SD</th>
<th>Sig (p)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppositional</td>
<td>6-12 years</td>
<td>66.33</td>
<td>14.42</td>
<td>.93</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>65.93</td>
<td>8.87</td>
<td></td>
</tr>
<tr>
<td>Cognitive Problems-Inattention</td>
<td>6-12 years</td>
<td>66.78</td>
<td>13.76</td>
<td>.53</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>69.64</td>
<td>7.55</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity-Impulsivity</td>
<td>6-12 years</td>
<td>74.22</td>
<td>13.82</td>
<td>.25</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>68.00</td>
<td>11.30</td>
<td></td>
</tr>
<tr>
<td>Anxious-Shy*</td>
<td>6-12 years</td>
<td>73.44</td>
<td>16.06</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>57.25</td>
<td>8.80</td>
<td></td>
</tr>
<tr>
<td>Perfectionism</td>
<td>6-12 years</td>
<td>53.33</td>
<td>8.53</td>
<td>.22</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>49.25</td>
<td>6.11</td>
<td></td>
</tr>
<tr>
<td>Social Problems*</td>
<td>6-12 years</td>
<td>47.33</td>
<td>5.92</td>
<td>.04</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>59.67</td>
<td>15.48</td>
<td></td>
</tr>
<tr>
<td>Psychosomatic</td>
<td>6-12 years</td>
<td>69.78</td>
<td>16.68</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>13-17 years</td>
<td>63.25</td>
<td>16.96</td>
<td></td>
</tr>
</tbody>
</table>

* Normality assumptions violated

Figure 7.5 Mean CPRS subscale scores for Perfectionism, Oppositional, Cognitive-problems-inattention, Psychosomatic, and Hyperactivity-Impulsivity for AD/HD+INT. The 2-year age-bands (6-8 years, 9-11 years, 12-14 years, 15-17 years) are shown on the x-axis for each of the two subscales, while CPRS subscale scores are shown on the y-axis.
Study (ii): The Cognitive-Behavioural Profiles of ADHD-NK, ADHD+ODD/CD and ADHD+INT

The following sections display the results according to the type of analysis conducted. Section 7.3.4 below presents the diagnostic analysis results between Controls and AD/HD, while Section 7.3.5 below presents the results from the comorbidity analyses. The results from both analyses form the basis for creating the first comorbid profiles for AD/HD+ODD/CD, AD/HD+INT and AD/HD-NK. Results are subsequently collated and discussed in Section 7.4.

7.3.4 Diagnostic Analysis: AD/HD vs. Controls

Preliminary statistics from the child and adolescent diagnostic analyses are shown below in Table 7.6 and Table 7.7 respectively. The grand average waveforms for ERP components N1, P2, N2 and P3 from the Oddball and GNG tasks are shown below in Figures 7.6a and 7.6b for children and Figures 7.7a and 7.7b for adolescents respectively. The six tasks yielded a total of 41 variables, with results presented below according to age group; the results for children are presented first, followed by those for the adolescents.

7.3.4.1 AD/HD vs. Controls - Children

Table 7.6 below displays the mean rank and 2-tailed asymptotic significance from the Mann-Whitney U Tests results between AD/HD and Control children (only variables that showed a significant difference between groups are shown in this table).
Table 7.6
Significant differences between AD/HD and Control children: mean rank, median values and effect sizes.

<table>
<thead>
<tr>
<th>Task</th>
<th>Variable*</th>
<th>Group</th>
<th>Mean Rank</th>
<th>Median</th>
<th>Effect size (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Auditory Oddball</td>
<td>SDRT (ms)</td>
<td>Controls</td>
<td>72.23</td>
<td>98.36</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>91</td>
<td>108.5</td>
<td></td>
</tr>
<tr>
<td>FPs</td>
<td></td>
<td>Controls</td>
<td>62.4</td>
<td>2.00</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>101.08</td>
<td>6.00</td>
<td></td>
</tr>
<tr>
<td>FNs</td>
<td></td>
<td>Controls</td>
<td>69.15</td>
<td>1.00</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>94.16</td>
<td>3.00</td>
<td></td>
</tr>
<tr>
<td>P2A</td>
<td></td>
<td>Controls</td>
<td>84.01</td>
<td>1.54</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>65.86</td>
<td>0.55</td>
<td></td>
</tr>
<tr>
<td>Go/No-Go (GNG)</td>
<td>SDRT (ms)</td>
<td>Controls</td>
<td>69.71</td>
<td>139</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>93.58</td>
<td>170.62</td>
<td></td>
</tr>
<tr>
<td>FNs</td>
<td></td>
<td>Controls</td>
<td>68.46</td>
<td>2.00</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>94.87</td>
<td>3.17</td>
<td></td>
</tr>
<tr>
<td>N1A</td>
<td></td>
<td>Controls</td>
<td>72.76</td>
<td>-9.39</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>88.24</td>
<td>-7.93</td>
<td></td>
</tr>
<tr>
<td>Continuous Performance Task (CPT)</td>
<td>FPs</td>
<td>Controls</td>
<td>53.75</td>
<td>3.00</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>86.01</td>
<td>7.85</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FNs</td>
<td>Controls</td>
<td>61.52</td>
<td>3.00</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>78.36</td>
<td>3.04</td>
<td></td>
</tr>
<tr>
<td>Executive Maze Task (EM)</td>
<td>Path Learning Time (seconds)</td>
<td>Controls</td>
<td>58.31</td>
<td>224.02</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>74.3</td>
<td>291.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Perseverative Errors</td>
<td>Controls</td>
<td>53.65</td>
<td>22.50</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>79.33</td>
<td>33.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total Errors</td>
<td>Controls</td>
<td>53.13</td>
<td>54.00</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>79.89</td>
<td>78.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trials to Complete Task</td>
<td>Controls</td>
<td>57.63</td>
<td>10.50</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>75.03</td>
<td>12.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Maze Completion Time (seconds)</td>
<td>Controls</td>
<td>58.03</td>
<td>262.20</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>74.6</td>
<td>327.22</td>
<td></td>
</tr>
<tr>
<td>Verbal Interference Task (VIT)</td>
<td>Colour-Word Errors</td>
<td>Controls</td>
<td>70.28</td>
<td>1.00</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>93</td>
<td>2.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Word-only Errors</td>
<td>Controls</td>
<td>73.31</td>
<td>0.00</td>
<td>0.19</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AD/HD</td>
<td>89.89</td>
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<td>Controls</td>
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</table>

* RT = reaction time, SDRT = reaction time variability, FPs = false positive errors, FNs = false negative errors, ms = milliseconds.
Figure 7.6a Oddball grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD vs. Control children.
Figure 7.6b GNG grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD vs. Control children.
Several significant differences were found between the AD/HD and Control children. Compared to AD/HD children, Control children displayed greater amplitudes for both the Oddball P2A and GNG N1A, in addition to less reaction time variability for both of these tasks. Control children also made fewer FPs and FNs in the Oddball task, along with fewer FNs in the GNG task. In the EM task, Control children were quicker to learn the correct path, required fewer trials to successfully complete the task, made fewer perseverative errors and fewer errors overall, and were able to complete the task in a shorter duration of time than their AD/HD counterparts. In the VIT, Control children committed task fewer word and colour-word errors than the AD/HD children. In the CPT, Control children displayed less FPs and less FNs than the AD/HD children. In the SOAT, Control children made fewer errors in both trail A (numbers only) and trail B (numbers and letters), compared to AD/HD children.

7.3.4.2  AD/HD vs. Controls - Adolescents

Table 7.7 below displays the mean rank and 2-tailed asymptotic significance from the Mann-Whitney U Tests results between AD/HD and Control adolescents (only variables that showed a significant difference between groups are shown in this table).
Table 7.7
Significant differences between AD/HD and Control adolescents: mean rank, median values and effect sizes

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<tr>
<th>Task</th>
<th>Variable*</th>
<th>Group</th>
<th>Mean Rank</th>
<th>Median</th>
<th>Effect size (r)</th>
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<td>Controls</td>
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<td>326.50</td>
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<td>Controls</td>
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<td>Controls</td>
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<td>Controls</td>
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</tr>
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<td>Controls</td>
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<td>105.67</td>
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<td>0.30</td>
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* Refer to notes for Table 7.6
Figure 7.7a Oddball grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD vs. Control adolescents
Figure 7.7b GNG grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD vs. Control adolescents.
There is a noticeable increase in the number of significant differences between AD/HD and Controls in this age group, compared to results from the child comparison. Out of the 41 variables, scores on 26 of these variables were found to significantly differ between the two adolescent groups. For each of these 26 variables that showed a significant difference between AD/HD and Control adolescents, Controls consistently outperformed their AD/HD counterparts with larger ERP component amplitudes, fewer errors, shorter reaction times, and greater accuracy scores on all 6 tasks.

7.3.5 Comorbidity Analysis: AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, Controls

Kruskal-Wallis tests were conducted to search for significant group effects between AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Controls on the same 41 variables, in both children and adolescents. Mann-Whitney U tests were utilised to isolate the source of any significant group effects, with Bonferroni corrections applied ($\alpha = .008$). Preliminary statistics from the child and adolescent comorbid analyses are shown below in Table 7.8 and Table 7.9 respectively. The grand average waveforms for ERP components N1, P2, N2 and P3 from the Oddball and GNG tasks are shown below in Figures 7.8a and 7.8b for children and Figures 7.9a and 7.9b for adolescents respectively. The results for children are presented first, followed by those for the adolescents.

7.3.5.1 Comorbidity Analysis – children

Table 7.8 below displays the mean rank and 2-tailed asymptotic significance from the Kruskal Wallis Test results between AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control children (only the variables with a significant group effect are shown in this table).
Table 7.8
AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control children: mean rank, median values and significant group effects.

<table>
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<tr>
<th>Task</th>
<th>Variable*</th>
<th>Group</th>
<th>Mean Rank</th>
<th>median</th>
<th>Asymp. Sig (2-tailed)</th>
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* See notes for Table 7.6.
Figure 7.8a Oddball grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control children.
Figure 7.8b GNG grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control children.
Between AD/HD-NK and Controls, greater task performance and accuracy were observed in the latter cohort. In the Oddball task, Controls displayed greater P2 amplitude ($U = 757, z = -3.39, p = .001$), and less FPs ($U = 859.5, z = -3.82, p < .001$) compared to AD/HD-NK children. In the EM task, Controls made less perseverative errors ($U = 497.5, z = -3.06, p = .002$), and less errors overall ($U = 485, z = -3.16, p = .002$) than AD/HD-NK. In the GNG task, Controls made fewer FNs ($U = 1010, z = -2.95, p = .003$) than AD/HD-NK. Finally, in the SOAT, Controls committed less trail B (numbers and letters) errors ($U = 793, z = -4.17, p < .001$) than their AD/HD-NK counterparts.

The greatest number of significant differences was found between AD/HD+ODD/CD and Controls, with AD/HD+ODD/CD displaying significantly more task-related impairment. In the Oddball task, Controls made less FPs ($U = 604, z = -4.51, p < .001$) and less FNs ($U = 802, z = -3.33, p = .001$) than AD/HD+ODD/CD. In the GNG task, Controls had larger N1 amplitudes ($U = 868, z = -2.65, p = .008$), made fewer FNs ($U = 859, z = -2.90, p = .004$), and had less reaction time variability ($U = 871.5, z = -2.78, p = .005$) than AD/HD+ODD/CD children. In the EM task, Controls committed less perseverative errors ($U = 499, z = -3.66, p < .001$) in addition to less errors overall ($U = 500, z = -3.65, p < .001$) than their AD/HD+ODD/CD counterparts. In the VIT and the SOAT, Controls made less colour-word errors ($U = 712, z = -3.87, p < .001$) and less trail B (numbers and letters) errors ($U = 608.5, z = -4.46, p < .001$) than AD/HD+ODD/CD respectively. In the CPT, Controls had fewer FPs ($U = 359.5, z = -5.17, p < .001$) than AD/HD+ODD/CD.

Only one significant difference was found between AD/HD-NK and AD/HD+ODD/CD children. Here, AD/HD-NK made fewer FPs ($U = 248, z = -2.84, p = .005$) in the CPT than their AD/HD+ODD/CD counterparts.

No significant differences on any of the variables were found between AD/HD+INT and either AD/HD-NK or AD/HD+ODD/CD, nor were there any significant differences between AD/HD+INT and Controls in the child age group.
### 7.3.5.2 Comorbidity Analysis – adolescents

Table 7.9 below displays the mean rank and 2-tailed asymptotic significance from the Kruskal Wallis Test results between AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control adolescents.

Table 7.9
AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control adolescents: mean rank, median values and significant group effects.

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<th>Task</th>
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<th>Median</th>
<th>Asymp sig (2-tailed)</th>
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* See notes for Table 7.6.
Figure 7.9a Oddball grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control adolescents.
Figure 7.9b GNG grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK, and Control adolescents.
Between Controls and AD/HD-NK adolescents, task performance and accuracy was consistently greater amongst the Controls. In the Oddball task, Controls showed shorter reaction times \((U = 1150.5, z = -2.92, p = .004)\), less FPs \((U = 1118.5, z = -3.23, p < .001)\), and less FNs \((U = 1333, z = -3.05, p = .002)\) than AD/HD-NK. In the EM task, Controls made less perseverative errors \((U = 1034.5, z = -3.08, p = .002)\), less errors overall \((U = 1018.5, z = -3.16, p = .002)\), and took less time to complete the task \((U = 1020, z = -3.18, p = .001)\) compared to AD/HD-NK. In the CPT, Controls had shorter reaction times \((U = 922, z = -3.99, p < .001)\), less reaction time variability \((U = 1489, z = -3.16, p = .002)\), less FPs \((U = 988, z = -3.68, p < .001)\), and less FNs \((U = 1106, z = -3.09, p = .002)\) than AD/HD-NK. And in the SOAT, Controls made fewer trail B (numbers and letters) errors \((U = 1211, z = -2.67, p = .008)\) than their AD/HD-NK counterparts.

A similar outcome was found between AD/HD+INT and Controls, where Controls again scored higher in task performance and accuracy. In the Oddball task, Controls had shorter reaction times \((U = 361.5, z = -3.44, p = .001)\), less reaction time variability \((U = 380.5, z = -3.28, p = .001)\), fewer FPs \((U = 453, z = -2.81, p = .005)\), and fewer FNs \((U = 254.5, z = -6.17, p < .001)\) than AD/HD+INT. In the EM task, Controls required less time to learn the path \((U = 382, z = -3.10, p = .002)\), made less perseverative errors \((U = 429, z = -2.69, p = .007)\), in addition to less errors overall \((U = 334.5, z = -3.53, p < .001)\), were able to complete the task in fewer trials \((U = 405, z = -2.93, p = .003)\), and was able to complete the task in a shorter duration of time \((U = 385, z = -3.07, p = .002)\) than their AD/HD+INT counterparts. In the CPT, Controls had shorter reaction times \((U = 381.5, z = -3.19, p = .001)\), less reaction time variability \((U = 362, z = -3.36, p = .001)\), fewer FPs \((U = 448.5, z = -2.64, p = .008)\), and fewer FNs \((U = 392.5, z = -3.18, p = .001)\), than AD/HD+INT adolescents. In the SOAT, Controls were faster in both trail A (numbers only) \((U = 450, z = -2.68, p = .007)\), and trail B (numbers and letters) \((U = 324.5, z = -3.75, p < .001)\), and made less errors in trail B \((U = 399.5, z = -3.20, p = .001)\) than their AD/HD+INT counterparts. Finally, in the GNG task, Controls displayed greater P3 amplitude \((U = 359, z = -3.46, p = .001)\) than AD/HD+INT.

The greatest number of significant differences was found between AD/HD+ODD/CD and Controls, where Controls displayed less task-defined impairment than
AD/HD+ODD/CD. In both the Oddball and GNG tasks, Controls showed larger P3 amplitudes (Oddball: $U = 954.5$, $z = -3.15$, $p = .002$; GNG: $U = 806$, $z = -234.$, $p < .001$), shorter reaction times (Oddball: $U = 740$, $z = -4.59$, $p < .001$; GNG: $U = 1057.5$, $z = -2.85$, $p = .004$), less reaction time variability (Oddball: $U = 563.5$, $z = -5.56$, $p < .001$; GNG: $U = 575$, $z = -5.50$, $p < .001$), less FPs (Oddball: $U = 779.5$, $z = -4.56$, $p < .001$; GNG: $U = 1015$, $z = -3.11$, $p < .001$), and less FNs (Oddball: $U = 763.5$, $z = -5.97$, $p < .001$; GNG: $U = 676$, $z = -5.29$, $p < .001$). Shorter reaction times were also seen in the Control group for the CPT ($U = 808.5$, $z = -3.75$, $p < .001$), along with less reaction time variability ($U = 620.5$, $z = -4.84$, $p < .001$), fewer FPs ($U = 709.5$, $z = -4.53$, $p < .001$), and fewer FNs ($U = 751$, $z = -4.35$, $p < .001$). In the EM task, Controls made less perseverative errors ($U = 691.5$, $z = -4.33$, $p < .001$), less errors overall ($U = 492.5$, $z = -5.50$, $p < .001$), required fewer trials to complete the task ($U = 905$, $z = -3.08$, $p = .002$), took less time to learn the path ($U = 772$, $z = -3.84$, $p < .001$), and took less time to complete the task successfully ($U = 753$, $z = -3.95$, $p < .001$) compared to AD/HD+ODD/CD. In the VIT, Controls had a higher colour-word score ($U = 986$, $z = -3.25$, $p = .001$), a higher word-only score ($U = 805$, $z = -4.26$, $p < .001$), and fewer word-only errors ($U = 1071.5$, $z = -3.08$, $p = .002$) than their AD/HD+ODD/CD counterparts. Finally, in the SOAT, Controls were quicker to complete trail B (numbers and letters) ($U = 934.5$, $z = -3.52$, $p < .001$), and made fewer errors in this trial ($U = 1074$, $z = -2.83$, $p = .005$) compared to AD/HD+ODD/CD adolescents.

Only one significant difference was found between the AD/HD-NK and AD/HD+INT groups. Here, the AD/HD-NK group displayed significantly less FNs in the Oddball task compared to AD/HD+INT ($U = 189.5$, $z = -2.68$, $p = .007$).

Few significant differences were found between the AD/HD-NK and AD/HD+ODD/CD groups also. AD/HD-NK had less reaction time variability in both the GNG task ($U = 373.5$, $z = -3.22$, $p = .001$) and the Oddball task ($U = 389$, $z = -3.05$, $p = .002$), and also made fewer FNs ($U = 372$, $z = -3.33$, $p = .001$) in the GNG task compared to AD/HD+ODD/CD. In the VIT, the AD/HD-NK group had a higher word-only score ($U = 414$, $z = -2.79$, $p = .005$) than the AD/HD+ODD/CD group.
Only two significant differences were found between AD/HD+ODD/CD and AD/HD+INT, both on the GNG task. Here, the AD/HD+INT group displayed less reaction time variability ($U = 147$, $z = -2.94$, $p = .003$), and fewer FNs ($U = 162$, $z = -2.69, p = .007$) compared to their AD/HD+ODD/CD counterparts.

7.3.6 Compiling Comorbid Profiles: AD/HD+ODD/CD, AD/HD+INT, AD/HD-NK

The following sections focus on compiling a profile for each comorbid group based upon the results from the comorbidity analyses above. Profiles are created for both child and adolescent comorbid groups.

7.3.6.1 AD/HD+ODD/CD Profile – children

The AD/HD+ODD/CD group was found to significantly differ compared with Controls on more variables than either AD/HD-NK or AD/HD+INT, suggesting a more severe symptomatology than the AD/HD alone, or comorbid with internalising symptoms. From an inspection of the tasks where significant differences were found, task-defined impairment was evident in the areas of executive function (EF), response inhibition (RI), sustained attention, and selective attention.

EF deficits were indexed by performance on the EM, VIT, SOAT and GNG tasks. Interestingly, reaction times or performance scores on these tasks did not differ significantly between Controls and AD/HD+ODD/CD, suggesting that there were minimal or no task-processing deficits and hence task performance was unaffected. Impairment appeared in the form of task accuracy or error rate. Here, AD/HD+ODD/CD children made significantly more errors on each of the EF tasks named above, however since this did not affect task performance, such errors can be seen as a result of high novelty-seeking behaviour. On the EM task for example, AD/HD+ODD/CD children were as quick as Control children in completing the task, did not require more trials to complete the task, and took the same amount of time to learn the path. However the number of perseverative and total errors overall was significantly higher than that of the Controls, suggesting that AD/HD+ODD/CD children had greater difficulty controlling their behaviour when errors were made and tended
to perseverate despite a comprehension of the error committed. This observation was also apparent in the VIT and the SOAT where AD/HD+ODD/CD made significantly more colour-word and trail B errors (respectively) however achieved a score that was comparable to that of the Controls.

Interestingly, the AD/HD+ODD/CD children committed more FNs in the GNG task than Control children. Since the GNG task is anchored in the construct of RI, difficulties in RI would typically be indexed by FPs, suggesting an inability to suppress a preponent response. However the presence of FNs suggests a difficulty in attentional re-orienting. That is, once a preponent response is successfully suppressed, the ability to orient attention once again to salient stimuli is impaired or delayed, hence resulting in a FN. This was supported by significantly reduced GNG N1 amplitude in the AD/HD+ODD/CD children compared to Controls, highlighting this difficulty in allocating attention to salient stimuli.

It is worth mentioning that GNG N1 amplitude was the only ERP component to significantly differ between AD/HD+ODD/CD and Control children. This may be seen as supportive of the finding that the two groups did not differ in any complex processing abilities between tasks.

Deficits in attention were indexed by performance on the Oddball task (selective attention) and the CPT (sustained attention). AD/HD+ODD/CD made more FPs on both of these tasks, in addition to more FNs on the Oddball task than Control children, suggesting task-related impairment in both selective and sustained attention. The finding of significantly more FNs than Controls in the Oddball but not in the CPT suggests an attentional deficit specific to the auditory modality.

Overall, it appears that AD/HD+ODD/CD children exhibited difficulties related to high novelty-seeking behaviour that resulted in significantly higher errors on task, however there did not appear to be any task-processing deficits or time-on-task issues. There also didn’t appear to be any problems in RI in the AD/HD+ODD/CD child group, however the ability to re-orient attention following successful inhibition appeared
either impaired or delayed. Auditory selective attention and visual sustained attention appeared to be impaired also, resulting in a higher error rate.

7.3.6.2 AD/HD+ODD/CD Profile – adolescents

Considerably greater task-defined impairment was evident in the adolescent AD/HD+ODD/CD group compared to that found in the child group. Unlike the childhood profile of AD/HD+ODD/CD which centred on novelty-seeking and attentional impairment, there is a noticeable shift in adolescence where task performance is now impaired, suggesting deficits in task-processing.

Probably the most prominent example of task-processing deficits can be seen once again in the EM task. In childhood, there were no differences between AD/HD+ODD/CD in completion time, path learning time, and the number of trials required for successful task completion. Each of these factors were affected in the adolescent group, which showed significantly longer completion times and path learning times, in addition to a larger number of trials required to complete the task successfully compared to Controls. This is in addition to significantly more perseverative errors and more errors overall, which remained unchanged from childhood. Hence, although high novelty-seeking behaviour has persisted with age, it is now accompanied by deficits in task-processing which has affected task performance.

Task performance deficits were seen in each of the six tasks utilised, suggesting impairment in selective and sustained attention, and EF including RI. Complex processing deficits in the Oddball and GNG tasks were highlighted by significantly reduced P3 component amplitudes in both tasks by AD/HD+ODD/CD adolescents. Interestingly, the GNG N1 amplitude differences seen in childhood were no longer apparent in adolescence, suggesting a lack of or comparability of underlying brain abnormalities for this ERP component with Controls and hence an otherwise ‘normal’ process of attention-orienting. Although the presence of significantly more Oddball, GNG, and CPT FNs would appear strongly indicative of a multi-faceted attentional
deficit, it is plausible that AD/HD+ODD/CD did not suffer from attentional impairment, but rather from an inability to adequately process salient stimuli in order to produce a behavioural response in the required time-frame, hence resulting in a FN. This would comply with the reduced P3 amplitudes seen in both the Oddball and GNG tasks mentioned earlier. Reduced GNG P3 amplitude seen in AD/HD+ODD/CD adolescents would also account for the significantly higher rate of FPs, indicative of RI deficits.

Overall, the results show that either the task-defined symptom severity of AD/HD+ODD/CD has significantly increased with age, or that the Control group has improved with age at a significantly greater rate than that of the AD/HD+ODD/CD adolescents.

### 7.3.6.3 AD/HD+INT Profile – children

There were no significant differences between AD/HD+INT and Control children, suggesting a comparable level of performance on all six tasks between the two groups. It may also suggest a diffuse task-defined symptomatology in the AD/HD+INT group, and therefore any differences or task-related impairment that may have existed was not consistent enough to reach significance.

The lack of any significant differences on any of the six tasks suggests that AD/HD+INT children do not suffer from EF, RI, selective or sustained attention deficits that differ considerably from that of the Control group, or that impairment typical of AD/HD+INT lies outside the realm of EF, RI, selective and sustained attention in childhood altogether. The latter appears unlikely, considering the complexity of EF for example, which constitutes a set of cognitive processes that govern self-regulation including purposeful, goal directed behaviour. It is doubtful that deficit(s) in AD/HD+INT children would lie completely outside the umbrella of EF, in addition to outside that of selective and sustained attention. Rather, it appears more plausible that task-defined symptom heterogeneity in AD/HD+INT children has masked any task-related impairment.
7.3.6.4 AD/HD+INT Profile – adolescents

In sharp contrast to the above findings, AD/HD+INT adolescents showed considerable task-defined impairment compared to Control adolescents, suggesting a trend of increasing symptom severity with age. AD/HD+INT adolescents displayed task-defined impairment in the assessed areas of EF, selective and sustained attention.

The most prominent finding centred on deficits relating to attentional processing. AD/HD+INT adolescents showed marked impairment in both the Oddball task and the CPT, with significantly greater reaction times, reaction time variability, FNs and FPs on both tasks, reflecting problems in both selective and sustained attention. Interestingly, no ERP component differences relating to attention orienting were found between AD/HD+INT and Controls in the Oddball task, suggesting no underlying brain abnormalities in neural circuits supporting this task. Since no P3 component differences were found in the Oddball task either, it appears that AD/HD+INT adolescents did not experience any difficulties in orienting their attention to novel stimuli or processing this stimuli to produce a behavioural response, despite their performance on this task. One possible explanation is the type of internalising comorbidity, as the most common internalising comorbid disorder in this group was LD (Learning Disorder) which constituted 65% of all comorbid disorders in the AD/HD+INT adolescent cohort. This result may also be explained if the AD/HD+INT adolescent group were so symptomatically diffuse that any significant ERP component differences on the Oddball task were masked by this heterogeneity; a characteristic that is likely to be a remnant from childhood. It is also possible that AD/HD+INT adolescents have significant difficulty in selectively attending to novel auditory stimuli that is not as a result of any underlying brain abnormality, but rather due to some other neurocognitive factor that is not captured electrophysiologically via the ERP components of the Oddball task.

Significantly reduced P3 amplitude in the AD/HD+INT adolescent group was however, found in the GNG task, although reaction times, FPs and FNs were unaffected. This suggests that despite any complex processing deficits related to RI that the AD/HD+INT
group exhibited, this did not impede their task performance and hence were able to inhibit preponent responses accordingly. Again, it appears that underlying brain abnormalities measured by this task are not catalysts for impaired task performance, or that the variance in task performance scores were too great to allow for any significant differences against Controls. Therefore the AD/HD+INT adolescent group did not display an RI deficit compared to Controls.

There was however, evidence of a general EF deficit in the AD/HD+INT adolescents, as indexed by their performance on the EM task, where impaired performance was apparent in every facet of this task. Since error-rate negatively impacted task performance, the finding of significantly more perseverative errors and cumulative errors can be seen as indicative of an impairment in error monitoring. AD/HD+INT adolescents also required more trials to complete the task successfully, and took longer to learn the path and complete the task, suggesting considerable impairment in planning, working memory, and visuo-spatial learning abilities. Deficits in visuo-perceptual abilities, working memory and error-monitoring were also seen in the SOAT, where AD/HD+INT adolescents took significantly longer to complete both trails A and B, and also made more errors in trail B than Controls. Task performance in trail B in particular, depends critically on the ability to switch between tasks (numbers and letters); the comparatively poor performance of the AD/HD+INT group suggests a strong deficit in this area also.

Overall, AD/HD+INT adolescents appear to suffer predominantly from an attentional deficit, in addition to difficulties in general EF particularly when requiring visuo-spatial abilities. No impairment in RI was evident for this comorbid group.

7.3.6.5 AD/HD-NK Profile – children

Several significant differences were apparent between AD/HD-NK and Control children, predominantly related to attention and novelty-seeking, however task performance indicators such as reaction times, and time-on-task revealed no significant deficit.
Similar to AD/HD+ODD/CD children, AD/HD-NK also showed a tendency to score significantly more perseverative and cumulative errors without any effect on a successful task outcome. That is, AD/HD-NK were able to complete the task in a comparable amount of time, did not require more trials to complete the task, and took the same amount of the time learn the path as did Control children. The presence of perseverative errors suggests high novelty-seeking behaviour.

A similar result was found in trail B of the SOAT, where AD/HD-NK children committed significantly more errors than Controls, however did not require more time to complete the task successfully. Since time-on-task was not affected, this result also appears localised to novelty-seeking, rather than an inability to mentally switch between tasks.

Results from the Oddball and GNG tasks revealed a significant attentional deficit in AD/HD-NK children compared to Controls. The presence of FPs in the Oddball task suggests difficulties in selective attention that may be linked to interference from irrelevant stimuli. This is primarily due to significantly smaller Oddball P2 amplitudes seen in AD/HD-NK children compared to Controls, suggesting a reduced ability to automatically inhibit extraneous sensory input from the environment, hence impeding selective attention and resulting in FPs.

Overall, AD/HD-NK children did not display any significant difficulties in task performance, but rather in task accuracy. Errors on task were considerably higher in AD/HD-NK compared to Controls, suggesting the predominant impairment is as a result of novelty-seeking behaviour and inattention.

7.3.6.6 AD/HD-NK Profile – adolescents

In adolescence, the AD/HD-NK group show similar task-defined impairment in terms of accuracy and attention as was present in the child group, however there appears to be a decline in function with age in both of these areas.
Again, indicators of selective and sustained attention in the Oddball task and CPT respectively, revealed significant impairment in the AD/HD-NK adolescents compared to Controls via increased FPs, FNs and longer reaction times. It appears likely that task-defined deficits in selective and sustained attention were catalysts in impeding error-monitoring, hence resulting in FPs and FNs. This finding was not supported however, by concurrent reductions in ERP component amplitudes in the Oddball task, suggesting that there were no underlying brain abnormalities in the AD/HD-NK group compared to Controls, or that such abnormalities were too variable to allow significant discrimination against Controls.

Errors in the EM task were also apparent, with task performance affected also. Here, AD/HD-NK displayed more perseverative errors and more cumulative errors, and required more trials to complete the task successfully than Control adolescents. Hence, it appears that an impairment in error-monitoring resulted in comparatively poor task performance.

A high error-rate was also evident in the SOAT, however this didn’t affect task performance, with no significance between AD/HD-NK and Controls in the length of time required to complete the task. Therefore, such errors can be seen as indicative of high novelty-seeking behaviour in this task, rather than a deficit in error-monitoring.

Therefore, it appears that the primary impairment in AD/HD-NK adolescents centres on error-monitoring and novelty-seeking, in addition to difficulties in selective and sustained attention. Since deficits in error-monitoring and selective attention were present in childhood, the finding that task performance is now negatively affected suggests an increase in task-defined symptom severity with age.

7.4 Conclusions

The conclusions from this Chapter are discussed in reference to each study conducted. Conclusions from study (i) are discussed first, followed by those from study (ii).
Study (i) Conclusions: The CPRS-Defined Symptom Profiles of AD/HD-NK, AD/HD+ODD/CD and AD/HD+INT

The results showed that there exists a pattern of age-related change in behavioural and cognitive symptoms domains in AD/HD that is rarely linear in nature. Rather, these changes appear to fluctuate with age. In AD/HD-NK and AD/HD+ODD/CD, the only linear relationships found between age and symptom domain were for the Oppositional subscale, which showed a significant increase in oppositional behaviour from childhood to adolescence. This confirms the hypotheses relating to AD/HD+ODD/CD where oppositional behaviour was expected to increase with age, in addition to a general increase in Hyperactivity-Impulsivity, which was also seen in this cohort. The increase in oppositional behaviour in AD/HD-NK was not expected, but suggests the existence of a sub-population within AD/HD-NK that displays sub-clinical levels of ODD/CD symptoms. The hypothesis regarding the age-related dissipation of overt symptoms (Hyperactivity-Impulsivity) was conditionally supported by these results; while there appears to be a decrease in such symptoms from age 6-8 years to 9-11 years, a significant increase in these symptoms was found in later adolescence (from 9-11 years onwards). Again, this may relate to a severe sub-clinical population within AD/HD-NK. The hypothesis regarding the retention of covert symptoms with age in the AD/HD-NK group is supported. In AD/HD+INT, the hypothesis that covert symptoms relating to social interaction would increase with age was partially supported. As hypothesised, a significant (linear) increase in the Social Problems subscale with seen with age, however a significant linear decrease was found for the Anxious-Shy subscale with age. This suggests that the social problems experienced in the adolescent AD/HD+INT group is unrelated, or minimally related, to anxiety and/or shyness.

For AD/HD-NK, significant cubic relationships were found between age and the Hyperactivity-Impulsivity, Anxious-Shy, and the Perfectionism subscales. Hyperactivity-Impulsivity in particular showed two significant increases between the two-year age bands: from 9-11 years to 15-17 years, and also from 12-14 years to 15-
17 years. On inspection of the cubic graph, there appears to be a noticeable decrease in scores with increasing age: from 6-8 years to 9-11 years. Although this decrease was not found to be significant, it supports previous findings of a remission of hyperactive symptoms with age. In addition to this however, was the adjacent finding of a sharp increase in Hyperactivity-Impulsivity around 12 years of age, and again at 15 years of age, which contradicts previous studies. Indeed, studies assessing an age-related change in AD/HD symptoms have measured such change according to the DSM diagnostic criteria, rather than via behavioural rating scales such as the CPRS and hence this may account for the difference in findings. However, since the Conners Rating Scales are frequently used as a confirmatory measure of behavioural diagnosis of AD/HD, in addition to an indicator of dimensional pathology, the use of the CPRS rather than the DSM criteria is not believed to be a methodological confound. Supportive of previous research however, was a general retention of symptoms on the Cognitive Problems-Inattention subscale for AD/HD-NK. This was the only subscale that did not show a noticeable decline in scores at the 9-11 year age-band. This age-band presents an interesting avenue for further research as it appears to be a particularly responsive phase of cognitive/behavioural development. In terms of development, the age range of 9-11 years typically corresponds with puberty, increased social interaction, and an emerging sense of self (Eccles, 1999). A study by Kettunen, Lindberg, Castaneda, Tuulio-Henriksson and Autti (2009) found that the onset of puberty is a developmental phase of particular vulnerability in terms of psychiatric morbidity. In addition to this, an early onset of puberty has been associated with greater hyperactive/impulsive and risk-taking behaviour (Orr & Ingersoll, 1995). It would be of some interest to assess whether treatment methods for AD/HD were more effective if administered during the ages of 9-11 years compared to other stages of development.

AD/HD+ODD/CD also displayed a noticeable drop in scores for the Cognitive Problems-Inattention (quadratic relationship with age) and Social Problems (inverse relationship with age) subscales at the 9-11 year age-band. However the opposite was found for the Psychosomatic, Anxious-Shy, and Perfectionism subscales which showed an increase at that age. Overall however, AD/HD+ODD/CD displayed a general decline in
each of the subscales except for Hyperactivity-Impulsivity, Cognitive Problems-Inattention, and Oppositional, which all showed an increase in scores by age 15-17 years. The increasing scores on these subscales with age is unsurprising and is the expected symptomatic trajectory of ODD/CD (Frick & Nigg, 2012).

In terms of AD/HD+INT, both the Anxious-Shy and Social Problems subscales were found to significantly differ between age groups, showing a decrease and an increase with age respectively. Again, a pattern was found for the 9-11 year age-band which showed a slight decrease in subscale scores for the Oppositional, Cognitive Problems-Inattention, and Hyperactivity-Impulsivity subscales, however this was immediately followed by an increase in scores at age 12-14 and 15-17 years. Perfectionism and Psychosomatic were the only two subscales to show an increase in scores at age 9-11 years, though a general decrease with age was found overall. The decrease in subscale scores for Perfectionism, Psychosomatic, and Anxious-Shy is surprisingly similar to results found for AD/HD+ODD/CD, and quite dissimilar to those of AD/HD-NK. Interestingly, the only subscale to show an age-related pattern that differed between AD/HD+INT and AD/HD+ODD/CD was the Social Problems subscale; while AD/HD+ODD/CD displayed a general decline in Social Problems score with age, AD/HD+INT showed a significant increase with age. Internalising symptoms have previously been linked to social difficulties such as elevated shyness and fear (Oldehinkel, Hartman, De Winter, Veenstra, & Ormel, 2004), and social withdrawal (Rubin, Coplan, & Bowker, 2009). The finding that scores on the Anxious-Shy subscale showed a significant decline with age for AD/HD+INT, despite scores for Social Problems significantly increasing, suggests that such social problems were not directly related to anxiety or shyness.

Overall, both AD/HD-NK and AD/HD+ODD/CD showed significant increases in Oppositional behaviour with age, with AD/HD-NK also displaying elevated Hyperactivity-Impulsivity in mid-to-late adolescence. In keeping with previous findings, AD/HD-NK displayed a general retention of Cognitive Problems-Inattention over time; while Hyperactive-Impulsive symptoms appeared to dissipate, this was only apparent around the age of 9-11 years. AD/HD+INT participants were characterised by
a symptom pattern not dissimilar to that of AD/HD+ODD/CD, though showing significantly elevated Social Problems in adolescence, unlikely to be related to anxiety or shyness. Social problems therefore appear to be a defining characteristic between internalising and externalising pathology. Also, the two-year age-band of 9-11 years appears significant as a particularly reactive developmental period, consistently marking noticeable changes in subscale scores.

Study (ii) Conclusions: The Cognitive-Behavioural Profiles of ADHD-NK, ADHD+ODD/CD and ADHD+INT

The results of this investigation have shown several significant differences between comorbid groups indicative of impairment in some or all of the areas of EF, RI, selective attention and sustained attention. This is the first study to compile profiles of comorbid groups based on psychophysiological data along with behavioural performance on a battery of tasks specialised in measuring these four neurocognitive areas.

The profile of the AD/HD+ODD/CD child group revealed task-defined impairment centred on novelty-seeking and inattention, producing impairment localised to task accuracy rather than task performance. These difficulties did not dissipate with age, but rather became more pronounced, resulting in impaired task performance in adolescence. These results support those found by Purper-Ouakil et al. (2010) who found a high novelty-seeking and low cooperative temperament in their AD/HD+ODD/CD sample aged 10-18 years compared to normal Controls. Increased novelty-seeking behaviour has previously been shown in AD/HD community samples (Yoo et al., 2006) as well as in clinically-referred samples (Cho et al., 2008). Such behaviour is not specific to AD/HD however, as high novelty-seeking has been found in ODD/CD-only populations also (H. W. Kim et al., 2010; Rettew, Copeland, Stanger, & Hudziak, 2004; Schmeck & Poustka, 2001). High novelty-seeking behaviours are akin to impulsivity as one precipitates the other (Cloninger, Svrakic, & Przybeck, 1993; McKinney, Canu, & Schneider, 2012). This can subsequently have a negative influence on selective and sustained attention, as was seen in AD/HD+ODD/CD.
There appeared to be little difference between AD/HD+ODD/CD and AD/HD-NK in childhood, suggesting that the two groups were symptomatically similar in task performance. This result implies that ODD/CD comorbidity has little effect on existing task-defined symptomatology in childhood, and hence did not significantly characterise any behavioural abnormalities beyond that already defined by AD/HD alone.

Adolescence provided noticeably more differences between these two groups, suggesting an age-dependent effect of ODD/CD comorbidity. Here, the consistently poorer outcome in the task performance of AD/HD+ODD/CD compared to AD/HD-NK, shows an increase in task-defined symptom severity that is significantly greater than that accounted for by non-comorbid AD/HD; it appeared that ODD/CD comorbidity in AD/HD resulted in more global deficits in EF, RI and attention, compared to AD/HD-alone. Similar results have previously been found in adult AD/HD populations (R. C. Kessler et al., 2010).

In sharp contrast to the findings for AD/HD+ODD/CD and those for AD/HD-NK, AD/HD+INT exhibited a profile so symptomatically diffuse in childhood that this cohort did not significantly differ from Controls or any other AD/HD group on any of the variables from the six tasks. This may have been as a result of the type of internalising diagnoses that defined the comorbidity in this cohort. In both childhood and adolescence, the most common internalising comorbidity in AD/HD+INT was Learning Disorder (LD), making up 64% and 65% of comorbid diagnoses in childhood and in adolescence respectively. Other internalising comorbidities in this group included Depression and Anxiety. Previous research has shown LD to negatively impact AD/HD symptomatology regardless of age (Shin, Kim, Cho, & Kim, 2003), while the prevalence of other internalising disorders have been shown to increase with age. This has been found for both depression (Connor et al., 2003; Costello, Foley, & Angold, 2006), and anxiety (Connor et al., 2003; Takeda et al., 2012). Therefore, the results suggest a pattern of increasing comorbid pathology with age in the AD/HD+INT group. Given this, the sharp contrast of results between children and adolescents is less surprising.
Between the AD/HD groups, there was a clear indication of increasing task-defined severity with age, suggesting that symptomatology becomes more pronounced in adolescence compared to childhood. Previous research has shown a gradual dissipation of overt symptomatology with age while inattentive symptoms tended to remain (Biederman, 2005; Hart et al., 1995; Hay & Levy, 1996; Spencer et al., 2007). This is due to the fact that children naturally become less hyperactive and impulsive with age; in the absence of hyperactivity/impulsivity, existing inattentive symptoms can seem more prominent (as opposed to more severe). In contrast to this however, the present results found that overt symptoms, such as impulsivity, in addition to inattentive symptoms were more pronounced in adolescence than in childhood. Although comorbidity is typically more prevalent in older cohorts (Takeda et al., 2012), this trend was not simply a product of comorbidity, as this was seen across all groups, even in AD/HD-NK where no known comorbidity was present. AD/HD-NK adolescents, though more impaired than their child counterparts, did however display comparatively less task-defined symptomatology than either AD/HD+INT or AD/HD+ODD/CD adolescents. The finding of greater task-defined impairment with age may have been due to the type of tasks utilised in this study, which focused on specific cognitive domains such as EF and attention, rather than simple behavioural traits per se. Impairment in EF and attention for example naturally become more apparent with age as cognitive demands increase (Frick & Nigg, 2012). Therefore, impulsivity in adolescent AD/HD is perhaps best viewed as relative to cognitive demand, rather than as a ubiquitous behavioural trait.

Task-defined severity was most pronounced in the AD/HD+ODD/CD group irrespective of age. This clinical group showed the largest number of significant differences compared to Controls than any other AD/HD group in both childhood and adolescence. This result is illustrated below in Figure 7.10.
Figure 7.10 Task-defined symptom severity in AD/HD alone (AD/HD-NK), AD/HD comorbid with internalising disorders (AD/HD+INT), and AD/HD comorbid with Oppositional Defiant and Conduct Disorder (AD/HD+ODD/CD). Increasing severity is depicted from left (yellow) to right (red) for both children (top) and adolescents (bottom). Group profiles show the most prominent areas of observed dysfunction based on task performance. Black circles indicate impairment in either task performance (e.g. reaction time), or task accuracy (e.g. error rate), or both.

The most prominent findings focused on task accuracy, where more errors were reflective of greater impairment in the form of novelty-seeking, error-monitoring or inattention. While novelty-seeking is a product of impulsivity, the failure to monitor errors can be seen as resulting from poor working memory, and/or attentional difficulties, both of which have been shown in AD/HD samples previously (Garner, Mrug, Hodgens, & Patterson, 2012; Mevorach et al., 2006). Novelty-seeking behaviour
was a common finding for both AD/HD-NK and AD/HD+ODD/CD children, suggesting a predominance of hyperactivity in the clinical profile for each group. Hyperactivity in turn has been linked to greater severity of AD/HD symptoms in addition to a higher prevalence of comorbidity. Takeda et al. (2012) found AD/HD children with comorbid ODD/CD to exhibit more impulsivity and have greater AD/HD-defined symptom severity than either AD/HD-alone or AD/HD comorbid with internalising disorders; a finding prevalent in prior research on this topic (Connor et al., 2003; Kuhne et al., 1997; Nazari, Wallois, Aarabi, & Berquin, 2011). The present results confirm these previous findings.

In conclusion, a battery of six neurocognitive and psychophysiological tasks were utilised in an attempt to formulate profiles of AD/HD+ODD/CD, AD/HD+INT, and AD/HD-NK. This is the first study to compile profiles of comorbid AD/HD, particularly AD/HD+ODD/CD, in both children and adolescents. The results from this investigation have shown a predominantly novelty-seeking and inattentive profile in AD/HD-NK and AD/HD+ODD/CD children, with deficits in EF and RI appearing in adolescence. AD/HD+ODD/CD were the most impaired in both age groups, suggesting a significant negative impact of ODD/CD comorbidity on AD/HD, irrespective of age.
Chapter 8:


Chapter Overview:

The aim of this experimental chapter is to expand on previous work by Smith, Johnstone and Barry (2003) by utilising an active auditory Oddball task to investigate the utility of ERP component data and psychometric performance data in predicting group membership in AD/HD comorbid groups. The AD/HD same sample as that employed in the previous Chapter (7) were assessed here: of the 64 AD/HD children, 32 were AD/HD+ODD/CD, 11 were AD/HD+INT, and 21 were AD/HD-NK. Of the 88 AD/HD adolescents, 35 were AD/HD+ODD/CD, 17 were AD/HD+INT, and 36 were AD/HD-NK. Results showed modest classification accuracies with a minimum of 50% of all participants being correctly identified in both the child and adolescent analyses. The overall findings from this investigation supports Smith et al.’s contention that an auditory Oddball task may prove beneficial as an adjunct to DSM or ICD based clinician diagnoses. These results suggest that the Oddball task would prove most beneficial as an adjunct to AD/HD-NK and AD/HD+ODD/CD diagnoses, rather than AD/HD+INT which showed the lowest classification accuracy.
8.1 Preamble

At present, clinical diagnosis of AD/HD is based exclusively on subjective measures of behaviour (American Psychiatric Association, 2000), creating a relatively limited conceptualisation of the disorder. Due to the inherent heterogeneity of the condition and the high degree of comorbidity, with around 87% of AD/HD children having at least one other comorbid diagnosis (Gillberg et al., 2004), it is difficult to elucidate causal factors. Identifying psychophysiological markers of AD/HD has been a major contributor to our understanding of AD/HD to date. Techniques providing an objective assessment of brain activity such as ERPs, allow some insight into how neurophysiological correlates of perception and cognition may differ in the AD/HD patient. Such insight could subsequently aid in re-defining AD/HD to enhance diagnostic homogeneity.

Few studies have investigated the discriminant value of electrical brain function or psychometric performance in AD/HD samples (see Section 4.3 of Chapter 4 for a discussion). To summarise, quantitative electroencephalography (QEEG) data has produced accuracy rates ranging from 74% - 94% (Chabot & Serfontein, 1996; Mann et al., 1992), and event-related potential (ERP) data has produced accuracy rates ranging from 77% - 81% (Robaey et al., 1992; J. H. Satterfield & Braley, 1977). Investigations into the discriminant value of psychometric performance data (such as variables relating to attention and language abilities) have produced accuracy rates ranging from 80% - 86% (Lockwood et al., 2001; Pineda et al., 1999).

To date, only one study has been conducted that investigated the utility of both psychometric performance and ERP component data in a discriminant analysis of AD/HD. This study by Smith, Johnstone and Barry (2003) presented novel findings with regard to an age-related (children vs. adolescents) subtype (Predominantly Inattentive vs. Combined) discriminant analysis, which was able to successfully classify 57%-77% of AD/HD and Control participants using an active auditory Oddball task. A summary of their results was provided in Table 4.5 of Chapter 4, and is re-presented below.
## Table 4.5
Summary of discriminant function analyses results from Smith et al.’s (2003) study.

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Chance</th>
<th>AD/HD</th>
<th>Controls</th>
<th>Variables‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD/HD vs. Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 - 12 yr</td>
<td>73.3</td>
<td>54.7</td>
<td>71.4</td>
<td>76.9</td>
<td>Mean RT; PO P3 LS; PO P2 LS; FC N1 LS; PO P3 AS; PO P3 AT; PO P2 AT</td>
</tr>
<tr>
<td>13 - 18 yr</td>
<td>58.7</td>
<td>56.5</td>
<td>56.9</td>
<td>62.5</td>
<td>PO P2 LS; PO P3 AT; FC N1 AT</td>
</tr>
<tr>
<td><strong>AD/HD-I vs. AD/HD-C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 - 12 yr</td>
<td>69.4</td>
<td>50.2</td>
<td>73.9</td>
<td>65.4</td>
<td>PO P3 LS; PO P3 LT; PO P3 AS; PO P3 AT</td>
</tr>
<tr>
<td>13 - 18 yr</td>
<td>64.7</td>
<td>50.2</td>
<td>77.8</td>
<td>45.8</td>
<td>PO P2 LS; F N2 AS; FPs; FC N1 LS</td>
</tr>
</tbody>
</table>

‡ Each variable is presented with three sections representing (1) topography (F = frontal, FC = frontocentral, PO = parieto-occipital), (2) ERP component (N1, P2, N2, P3), and (3) indicators of amplitude (A), or latency (L), combined with target (T), or standard (S); for example PO P3 LS represents parieto-occipital P3 latency to standard stimuli. Mean RT = mean reaction time; FPs = false positives (i.e. errors of commission).
From these results, greater classification accuracies were achieved in the child comparisons, compared to those of the adolescents, which the authors reasoned as being reflective of the gradual decline in symptoms with age, typically seen in AD/HD. Hence, Smith et al. argued that while an auditory Oddball task offers a reasonable correspondence with the clinician diagnosis (and therefore shows potential as a diagnostic aid), this diagnostic correspondence would be expected to decrease as age increases, that is, a lower classification accuracy is expected in older AD/HD cohorts. The authors also emphasise the need to replicate these results in a comorbid cohort in order to confirm the sensitivity and specificity of the auditory Oddball task; hence the aim of the current study is to apply an active auditory Oddball task as a measure of predicting group membership between AD/HD-only (AD/HD-NK), AD/HD with comorbid externalising disorders (Oppositional Defiant/Conduct Disorder: AD/HD+ODD/CD), and AD/HD with comorbid internalising disorders (such as Depression, Anxiety: AD/HD+INT). Both ERP component amplitude and latency data in concert with psychometric performance such as reaction time and error rate will be utilised as predictors of group membership in the current investigation.

As mentioned in Chapter 7, the auditory Oddball task is a well-documented psychophysiological measure of attentional functioning which requires the detection and response to infrequent ‘target’ stimuli, while ignoring frequent ‘standard’ stimuli. The ability to detect and respond to the targets is thought to involve both orienting and allocation of attention, in addition to vigilance in order to maintain task performance (Stevens et al., 2005). The ERP data gleaned from this task allows the inspection of psychometric and cognitive responses to both targets and standards. The Oddball task has become one of the most frequently employed assessments of attention and related cognitive function in studies of AD/HD populations. Results from previous AD/HD research utilising the Oddball task have shown impaired performance (for example reaction time: RT, and number of errors), in addition to deficits (for example, reduced amplitudes, longer latencies) in almost all ERP components compared to healthy Controls. Such previous studies were discussed in Chapter 7 (see Section 7.1.2) and hence will not be repeated here.
8.2 Method

The methods contained within this Chapter were described in detail in Chapter 6 (Methodology), and hence will not be reiterated here. A brief overview will be provided in the Sections below.

8.2.1 Participants

Data from a total of 152 were AD/HD participants\(^9\) (64 children, 88 adolescents) was utilised. Of the 64 AD/HD children, 32 were AD/HD+ODD/CD, 11 were AD/HD+INT, and 21 were AD/HD-NK. Of the 88 AD/HD adolescents, 35 were AD/HD+ODD/CD, 17 were AD/HD+INT, and 36 were AD/HD-NK. See Section 6.1 of Chapter 6 for a more detailed presentation.

8.2.2 Tasks and Procedure

The task employed in this Chapter was an active auditory Oddball task which was described in detail in Section 6.2.1.1 of Chapter 6. Refer to Section 6.2.1 of Chapter 6 for a detailed description of the EEG acquisition protocols. An abridged outline of the salient aspects of the Oddball task and EEG acquisition will be given in the following sections. All participants completed this task as a subset of the larger psychophysiological testing battery.

8.2.2.1 Auditory Oddball Task

To briefly reiterate: 60 target tones were presented at 1000Hz, and 280 standard tones were presented at 500Hz in a quasi-random order (no two targets appeared consecutively). The duration of each tone was 50ms, with an ISI of 1s. All participants were instructed to press two buttons on a button box simultaneously to target tones

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\(^9\) The 152 AD/HD participants is the same sample as that assessed in Chapter 7, and the same as that described in Chapter 6.
only, and to ignore standard tones. The task was preceded by a short practise session to ensure task instructions had been understood. Speed and accuracy in responding were equally stressed in the task instructions. The duration of the entire task was six minutes.

Indicators of psychometric performance consisted of reaction time (RT), reaction time variability (SDRT), false positives (FPs), and false negatives (FNs).

8.2.2.2 EEG Acquisition

EEG data were collected from all 26 scalp sites: Fp1, Fp2, F7, F3, Fz, F4, F8, FC3, FCz, FC4, T3, C3, Cz, C4, T4, CP3, CPz, CP4, T5, P3, Pz, P4, T6, O1, Oz, and O2 (32 channels; Nuamps; 10-20 International system).

ERP component windows were as follows: N1 (70 – 120ms), P2 (120 – 220ms), N2 (120 – 300ms), and P3 (220 – 550ms).

8.2.3 Statistical Analysis

Two separate analyses were conducted using the ERPs and psychometric performance data; (1) a child analysis, and (2) an adolescent analysis. All four performance variables (RT, SDRT, FPs, FNs) were incorporated into the analyses, along with amplitude and latency ERP components (N1, P2, N2, P3) to target stimuli. These ERP components were spatially averaged across scalp sites. Spatial averaging of each ERP component was discussed earlier in Chapter 6 (see Table 6.4 in Chapter 6).

Both analyses were run via a Multinomial Logistic Regression due to normality assumptions being violated by the skewed distributions of both FPs and FNs. All of the variables, or ‘Predictors’, were entered together into the regression equation (main effects model).
8.3 Results

The following sections will display the results according to the type of analysis conducted. Section 8.3.1 below presents the results from the child analysis, while Section 8.3.2 below presents the results from the adolescent analysis. Results from both analyses will be subsequently collated and discussed in Section 8.4.

All of the performance and ERP component variables (12 in total) constituted the Predictors of group membership; ‘group membership’ refers to the statistically determined categorisation of a participant into one of the three groups: AD/HD-NK, AD/HD+ODD/CD or AD/HD+INT. For both the child and adolescent analyses, the AD/HD-NK group was selected as the reference group.

The child and adolescent means and standard errors for the psychometric performance variables are shown below in Figures 8.1a (RT and SDRT) and 8.1b (FPs and FNs) for AD/HD-NK, AD/HD+ODD/CD and AD/HD+INT. The grand average ERP waveforms for the Oddball task for each AD/HD group were shown in Chapter 7, but will be re-presented below in Figure 8.2a for children and 8.2b for adolescents.
Figure 8.1 Means and standard errors for each of the psychometric performance variables: (a) reaction time (RT), and reaction time variability (SDRT), and (b) false positives (FPs), and false negatives (FNs) for AD/HD-NK, AD/HD+ODD/CD, and AD/HD+INT.
Figure 8.2a Oddball grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD-NK, AD/HD+ODD/CD, and AD/HD+INT children.
Figure 8.2b Oddball grand average ERP waveforms (from top): fronto-central N1 and N2, central P2, and centro-parietal P3 for AD/HD-NK, AD/HD+ODD/CD, and AD/HD+INT adolescents.
8.3.1 Child Analysis

The full regression model did not fit the data significantly better than the intercept only model: \( \chi^2(24) = 24.02, p = .46 \). Overall based on these 12 Predictors, group membership was correctly predicted for 53% of AD/HD+ODD/CD, 30% of AD/HD+INT, and almost 70% of AD/HD-NK children in this analysis. These results are shown below in Table 8.1.

Surprisingly, none of the 12 Oddball ERP component and psychometric performance variables were found to contribute significantly to the full regression equation. Only one Predictor (N2A) contributed to the regression model at a trend level \( p < .10 \), therefore, for every unit increase in N2A, the odds of a participant being classified as AD/HD+ODD/CD decreased by 0.18 \( p = .09 \), hence greater N2 amplitudes were more typical of AD/HD-NK than AD/HD+ODD/CD. The significance levels for each of the 12 Predictors including their respective odds ratios are provided below in Table 8.2.

Table 8.1

<table>
<thead>
<tr>
<th>Observed</th>
<th>Predicted</th>
<th>% Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD+ODD/CD</td>
<td>16</td>
<td>AD/HD+INT</td>
</tr>
<tr>
<td>AD/HD+INT</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>AD/HD-NK</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Overall %</td>
<td>37.0%</td>
<td>6.8%</td>
</tr>
</tbody>
</table>

An ‘intercept only’ or ‘null’ model is a model that does not control for any of the predictors (as the full regression model does), and simply fits an intercept so as to predict group membership.
### Table 8.2
Multinomial Logistic Regression results for Predictors in the child analysis, with AD/HD-NK as the reference group.

<table>
<thead>
<tr>
<th>Comorbid Group</th>
<th>Predictor</th>
<th>B</th>
<th>Sig. (p)</th>
<th>Odds Ratio*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD+ODD/CD</td>
<td>RT</td>
<td>-0.01</td>
<td>.12</td>
<td>0.99</td>
<td>0.98 – 1.00</td>
</tr>
<tr>
<td></td>
<td>SDRT</td>
<td>0.02</td>
<td>.38</td>
<td>1.02</td>
<td>0.98 - 1.05</td>
</tr>
<tr>
<td></td>
<td>FPs</td>
<td>-0.03</td>
<td>.31</td>
<td>0.98</td>
<td>0.93 - 1.02</td>
</tr>
<tr>
<td></td>
<td>FNs</td>
<td>0.06</td>
<td>.22</td>
<td>1.07</td>
<td>0.96 - 1.18</td>
</tr>
<tr>
<td></td>
<td>N1A</td>
<td>0.07</td>
<td>.58</td>
<td>1.07</td>
<td>0.84 - 1.38</td>
</tr>
<tr>
<td></td>
<td>N1L</td>
<td>0.00</td>
<td>.96</td>
<td>1.00</td>
<td>0.97 - 1.03</td>
</tr>
<tr>
<td></td>
<td>P2A</td>
<td>0.08</td>
<td>.51</td>
<td>1.08</td>
<td>0.86 - 1.37</td>
</tr>
<tr>
<td></td>
<td>P2L</td>
<td>-0.01</td>
<td>.46</td>
<td>0.99</td>
<td>0.96 - 1.02</td>
</tr>
<tr>
<td></td>
<td>N2A</td>
<td>0.18</td>
<td>.09</td>
<td>1.20</td>
<td>0.97 - 1.48</td>
</tr>
<tr>
<td></td>
<td>N2L</td>
<td>0.02</td>
<td>.11</td>
<td>1.02</td>
<td>1.00 - 1.06</td>
</tr>
<tr>
<td></td>
<td>P3A</td>
<td>-0.06</td>
<td>.43</td>
<td>0.94</td>
<td>0.81 - 1.09</td>
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<tr>
<td></td>
<td>P3L</td>
<td>0.00</td>
<td>.82</td>
<td>1.00</td>
<td>0.97 - 1.02</td>
</tr>
<tr>
<td>AD/HD+INT</td>
<td>RT</td>
<td>-0.01</td>
<td>.36</td>
<td>0.99</td>
<td>0.97 - 1.01</td>
</tr>
<tr>
<td></td>
<td>SDRT</td>
<td>0.02</td>
<td>.52</td>
<td>1.02</td>
<td>0.97 - 1.06</td>
</tr>
<tr>
<td></td>
<td>FPs</td>
<td>-0.04</td>
<td>.50</td>
<td>0.96</td>
<td>0.86 - 1.08</td>
</tr>
<tr>
<td></td>
<td>FNs</td>
<td>-0.02</td>
<td>.82</td>
<td>0.98</td>
<td>0.81 - 1.19</td>
</tr>
<tr>
<td></td>
<td>N1A</td>
<td>0.12</td>
<td>.54</td>
<td>1.12</td>
<td>0.77 - 1.64</td>
</tr>
<tr>
<td></td>
<td>N1L</td>
<td>-0.02</td>
<td>.44</td>
<td>0.99</td>
<td>0.95 - 1.02</td>
</tr>
<tr>
<td></td>
<td>P2A</td>
<td>0.19</td>
<td>.26</td>
<td>1.21</td>
<td>0.87 - 1.66</td>
</tr>
<tr>
<td></td>
<td>P2L</td>
<td>0.02</td>
<td>.44</td>
<td>1.02</td>
<td>0.98 - 1.06</td>
</tr>
<tr>
<td></td>
<td>N2A</td>
<td>0.06</td>
<td>.65</td>
<td>1.06</td>
<td>0.82 - 1.37</td>
</tr>
<tr>
<td></td>
<td>N2L</td>
<td>0.01</td>
<td>.46</td>
<td>1.01</td>
<td>0.98 - 1.05</td>
</tr>
<tr>
<td></td>
<td>P3A</td>
<td>-0.10</td>
<td>.33</td>
<td>0.90</td>
<td>0.73 - 1.11</td>
</tr>
<tr>
<td></td>
<td>P3L</td>
<td>0.01</td>
<td>.52</td>
<td>1.01</td>
<td>0.98 - 1.05</td>
</tr>
</tbody>
</table>

* An odds ratio greater than 1 indicates a greater likelihood that a participant is classified as AD/HD-NK (and vice versa), however the opposite is true for the negative values of N1 and N2 amplitudes. This is because an increase in N1 or N2 amplitude is actually a decrease mathematically. Therefore, odds ratio results for N1 and N2 amplitudes are reversed on interpretation.
8.3.2 Adolescent analysis

In contrast to the child analysis, the full regression model was a good fit to the data, significantly better than the intercept only model: $\chi^2(24) = 43.51, p = .009$. Overall classification based on these 12 Predictors better than that achieved in the child analysis. Group membership was correctly predicted for almost 56% of AD/HD+ODD/CD, 50% of AD/HD+INT, and just over 70% of AD/HD-NK adolescents in this analysis. These results are shown below in Table 8.3.

Of the 12 Predictors, two were found to significantly contribute to the regression model, and two were found to contribute at a trend level. Only one of these four Predictors related to AD/HD+ODD/CD adolescents; for every unit increase in P2 latency, the odds of a participant being classified as AD/HD+ODD/CD decreased by 0.03 ($p = .05$), hence greater P2 latency was more characteristic of AD/HD-NK than AD/HD+ODD/CD.

The other three Predictors related to AD/HD+INT; for every unit increase in N1 latency, P2 and N2 amplitudes, the odds of a participant being classified as AD/HD+INT increased by 0.08 ($p = .01$), 0.21 ($p = .07$), and 0.18 ($p = .06$) respectively. Therefore, greater N1 latency, and greater P2 and N2 amplitudes were more characteristic of AD/HD+INT than AD/HD-NK.

Table 8.3

*Observed and predicted group membership for the adolescent analysis. Correct group predictions are shown in bold.*

<table>
<thead>
<tr>
<th>Observed</th>
<th>Predicted</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AD/HD+ODD/CD</td>
<td>AD/HD+INT</td>
<td>AD/HD-NK</td>
<td>% Correct</td>
<td></td>
</tr>
<tr>
<td>AD/HD+ODD/CD</td>
<td><strong>19</strong></td>
<td>4</td>
<td>11</td>
<td>55.9%</td>
<td></td>
</tr>
<tr>
<td>AD/HD+INT</td>
<td>4</td>
<td><strong>8</strong></td>
<td>4</td>
<td>50.0%</td>
<td></td>
</tr>
<tr>
<td>AD/HD-NK</td>
<td>9</td>
<td>2</td>
<td><strong>26</strong></td>
<td>70.3%</td>
<td></td>
</tr>
<tr>
<td>Overall %</td>
<td>36.8%</td>
<td>16.1%</td>
<td>47.1%</td>
<td>60.9%</td>
<td></td>
</tr>
</tbody>
</table>
Table 8.4
Multinomial Logistic Regression results for Predictors in the adolescent analysis, with AD/HD-NK as the reference group.

<table>
<thead>
<tr>
<th>Comorbid Group</th>
<th>Predictor</th>
<th>B</th>
<th>Sig. (p)</th>
<th>Odds Ratio*</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>AD/HD+ODD/CD</td>
<td>RT</td>
<td>-0.00</td>
<td>.78</td>
<td>1.00</td>
<td>0.98 - 1.01</td>
</tr>
<tr>
<td></td>
<td>SDRT</td>
<td>0.02</td>
<td>.19</td>
<td>1.02</td>
<td>0.99 - 1.05</td>
</tr>
<tr>
<td></td>
<td>FPs</td>
<td>-0.05</td>
<td>.24</td>
<td>0.95</td>
<td>0.87 - 1.04</td>
</tr>
<tr>
<td></td>
<td>FNs</td>
<td>0.30</td>
<td>.20</td>
<td>1.35</td>
<td>0.85 - 2.13</td>
</tr>
<tr>
<td></td>
<td>N1A</td>
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<td>.12</td>
<td>0.86</td>
<td>0.71 - 1.04</td>
</tr>
<tr>
<td></td>
<td>N1L</td>
<td>0.01</td>
<td>.78</td>
<td>1.01</td>
<td>0.97 - 1.05</td>
</tr>
<tr>
<td></td>
<td>P2A</td>
<td>0.07</td>
<td>.50</td>
<td>1.07</td>
<td>0.87 - 1.32</td>
</tr>
<tr>
<td></td>
<td>P2L</td>
<td>-0.03</td>
<td>.05</td>
<td>0.97</td>
<td>0.94 - 1.00</td>
</tr>
<tr>
<td></td>
<td>N2A</td>
<td>0.02</td>
<td>.81</td>
<td>1.02</td>
<td>0.89 - 1.16</td>
</tr>
<tr>
<td></td>
<td>N2L</td>
<td>0.01</td>
<td>.48</td>
<td>1.01</td>
<td>0.98 - 1.04</td>
</tr>
<tr>
<td></td>
<td>P3A</td>
<td>-0.09</td>
<td>.12</td>
<td>0.91</td>
<td>0.81 - 1.02</td>
</tr>
<tr>
<td></td>
<td>P3L</td>
<td>0.00</td>
<td>.97</td>
<td>1.00</td>
<td>0.98 - 1.02</td>
</tr>
<tr>
<td>AD/HD+INT</td>
<td>RT</td>
<td>0.00</td>
<td>.65</td>
<td>1.00</td>
<td>0.99 - 1.02</td>
</tr>
<tr>
<td></td>
<td>SDRT</td>
<td>0.00</td>
<td>.97</td>
<td>1.00</td>
<td>0.96 - 1.04</td>
</tr>
<tr>
<td></td>
<td>FPs</td>
<td>-0.07</td>
<td>.18</td>
<td>0.93</td>
<td>0.84 - 1.03</td>
</tr>
<tr>
<td></td>
<td>FNs</td>
<td>0.37</td>
<td>.12</td>
<td>1.45</td>
<td>0.91 - 2.31</td>
</tr>
<tr>
<td></td>
<td>N1A</td>
<td>0.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.77 - 1.30</td>
</tr>
<tr>
<td></td>
<td>N1L</td>
<td>0.08</td>
<td>.01</td>
<td>1.08</td>
<td>1.02 - 1.14</td>
</tr>
<tr>
<td></td>
<td>P2A</td>
<td>0.21</td>
<td>.07</td>
<td>1.23</td>
<td>0.98 - 1.55</td>
</tr>
<tr>
<td></td>
<td>P2L</td>
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<td>.18</td>
<td>0.98</td>
<td>0.94 - 1.02</td>
</tr>
<tr>
<td></td>
<td>N2A</td>
<td>-0.18</td>
<td>.06</td>
<td>0.84</td>
<td>0.69 - 1.01</td>
</tr>
<tr>
<td></td>
<td>N2L</td>
<td>-0.01</td>
<td>.51</td>
<td>0.99</td>
<td>0.96 - 1.02</td>
</tr>
<tr>
<td></td>
<td>P3A</td>
<td>0.07</td>
<td>.34</td>
<td>1.08</td>
<td>0.93 - 1.25</td>
</tr>
<tr>
<td></td>
<td>P3L</td>
<td>0.01</td>
<td>.26</td>
<td>1.01</td>
<td>0.99 - 1.04</td>
</tr>
</tbody>
</table>

* See notes for Table 8.2
8.4 Conclusions

This chapter aimed to extend previous work by Smith, Johnstone and Barry (2003) by assessing the potential of ERP component data and psychometric performance data from an active auditory Oddball task to predict group membership in a comorbid AD/HD sample. Using a total of 12 Oddball-derived ERP component and psychometric performance Predictors of group membership, the classification accuracy was found to be marginally higher in the adolescent analysis (60.9%), compared to the child analysis (57.5%), with at least 50% of participants correctly identified in each comparison. It is difficult to compare Smith et al.’s results from a subtype analysis to the results of the present study which focused on comorbidity. However, it is possible to compare the individual classification accuracies of ADHD-NK in childhood and adolescence (69.7% and 70.3% respectively), to the individual accuracies of Smith et al.’s non-comorbid ADHD group in childhood and adolescence (71.4% and 56.9% respectively). Although the results for the child analyses are similar, the noticeably higher accuracy achieved in the present study for the adolescent group is undoubtedly an effect of the type of comparison group used, rather than an effect of the Oddball task itself.

The classification accuracies found in the present investigation are slightly different to those of Smith et al. who found that predicted group membership showed a greater accuracy in childhood compared to adolescence. The authors attributed this to the well-known dissipation of symptoms with age in AD/HD, which has been argued in the previous research also (Biederman, 2005; Hart et al., 1995; Hay & Levy, 1996; Spencer et al., 2007). The present results found a noticeably higher classification accuracy was seen in AD/HD-NK adolescents compared to children, however this is not necessarily indicative of a retention or worsening of symptoms with age instead than the commonly observed dissipation. Rather, this result suggests that compared to comorbid groups with externalising or internalising pathology, AD/HD-NK adolescents showed less heterogeneity on the Oddball task, which subsequently allowed greater success in group prediction. The lack of a significant regression model in the child analysis attests to the comparatively greater task-defined psychophysiological and
psychometric heterogeneity in childhood than in adolescence; the commonly observed remission of AD/HD symptoms with age may reduce such heterogeneity, resulting in a more homogeneous profile of AD/HD in adolescents.

Prediction of group membership was the lowest for AD/HD+INT in both the child (30%) and adolescent (50%) analyses, suggesting that the variance in the 12 Predictor variables was too great to allow a clear separation from either AD/HD-NK or AD/HD+ODD/CD. The small sample size of AD/HD+INT is likely to contribute to such results also; a replication of the present study would aid in confirming these findings. AD/HD+ODD/CD on the other hand, showed a modest classification accuracy that was similar between age groups. Hence it appears that existing task-defined heterogeneity remains relatively constant with age. It is interesting that majority of AD/HD+ODD/CD children and adolescents who were misclassified, were misclassified as AD/HD-NK, suggesting that task performance and related cognitive processing were comparable between the two groups. This finding may be task specific however, as previous research has also found performance on an auditory selective-attention task to be similar between AD/HD+CD and AD/HD (Rothenberger et al., 2000).

It is surprising that no psychometric performance variables were found to be significant predictors of group membership in either the child or adolescent analyses. Rather, the child and adolescent regression models were driven by group differences in the ERP component variables. This suggests that while task performance was similar between AD/HD-NK, AD/HD+ODD/CD and AD/HD+INT, the underlying neuro-cognitive processes differed between groups. The predominant differences were seen in ERP components governing automatic sensory or motor inhibition, as indexed by P2 and N2. The theory of an inhibitory deficit in AD/HD is not new (R.A. Barkley, 1997), however the present findings show that AD/HD+ODD/CD also exhibit such deficits.

Overall, the present results indicate that the use of an active auditory Oddball task shows promise in predicting group membership in AD/HD comorbid groups with externalising or internalising pathology. ERP component variables relating to inhibition in particular, appear to characterise comorbid participant groups better than other
ERP components or psychometric performance variables. In contrast to findings by Smith et al., classification accuracy in AD/HD comorbid groups increased with age. Although the classification accuracies were modest, at least 50% of all participants were correctly identified. Given these results, the auditory Oddball task may prove useful as an adjunct to the diagnostic process, though this avenue may be limited in AD/HD cohorts with comorbid internalising disorders, since the lowest accuracies were observed for AD/HD+INT in both children and adolescents. These results do not imply that an auditory Oddball task should replace the DSM or ICD based clinician diagnosis, but rather suggest that this task may prove beneficial as an aid to such diagnoses.
Chapter 9:

The Impact of Comorbid Externalising Disorders on AD/HD

Chapter Overview:
The aim of this experimental chapter is to utilise the same psychometric and psychophysiological variables as in the previous Chapter (7), to assess the relative impact of ODD/CD comorbidity on AD/HD in children and adolescents. The 29 variables were reduced via a Principal Components Analysis (PCA); the significant eigenvectors (6 in total) were then used to determine cluster membership among the Clinical population, via a Two-Step Cluster Analysis. Two clusters were found in the analysis of the adolescent age group - a cluster dominated by Control and AD/HD-NK, while the second cluster was dominated by AD/HD+ODD/CD participants. A similar segregation within the child age group was not found. Further analysis of these objectively determined clusters in terms of their clinical diagnoses indicates a significant effect of ODD/CD comorbidity on a concurrent AD/HD diagnosis. From this, it appeared that comorbid externalising behaviour in AD/HD constitutes a distinct pathological entity in adolescence.

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11 This Chapter was published as an original manuscript by PLoS ONE in 2012.
9.1 Preamble

Although the DSM-IV-TR views AD/HD as a homogenous disorder, this view has been strongly contested. Previous research has repeatedly shown AD/HD to be heterogeneous in its presentation, genetics, severity, comorbidity, and treatment outcome (Brookes et al., 2008; Elia et al., 2009; Steinhausen, 2009; Zhou et al., 2008). In a Swedish study (B. Kadesjö & Gillberg, 2001) with children meeting the full criteria for AD/HD, 87% of their sample had at least one comorbid diagnosis and 67% had two or more comorbid diagnoses (of which Oppositional Defiant Disorder and developmental coordination disorder were the most common). The multidimensional nature of the disorder is also suggested by the numerous theoretical models of aetiology and the variable global prevalence rates. Viewing AD/HD as a homogenous disorder may well account for negative or ambiguous findings in previous research, and it is for this reason that some authors have begun to investigate the existence of AD/HD subtypes or groups that are independent from those defined by the DSM-IV-TR, particularly in terms of comorbidity. In this regard, the World Health Organisation’s International Classification of Diseases (ICD) defines comorbid combinations of disorders. Of particular interest is the ICD diagnosis of Hyperkinetic Conduct Disorder (HCD), which is the diagnostic equivalent to the combination of DSM-IV-TR’s AD/HD and Oppositional Defiant Disorder (ODD) and/or Conduct Disorder (CD). Hence, the ICD considers AD/HD+ODD/CD to represent a distinct pathological entity, rather than a simple “combining of symptoms”. This view has gained some support in the previous AD/HD literature arguing for either the delineation of a distinct subtype of AD/HD comorbid with ODD/CD (Jensen, Martin, & Cantwell, 1997), or that AD/HD+ODD/CD should constitute a separate pathological entity altogether (Albrecht et al., 2005; Banaschewski et al., 2003), similar to that adopted by the ICD.

The argument against a new subtype of AD/HD incorporating ODD/CD comorbidity has stemmed from research findings suggesting that AD/HD+ODD/CD represents a “hybrid” group where the symptomatology is additive (Schachar & Tannock, 1995; Waschbusch, 2002) and does not venture outside the realms of each disorder and
hence does not constitute a distinct pathological entity. This finding was supported by a study by Rommelse et al. (2009) who found that while AD/HD+ODD/CD was a more severe form of AD/HD, it did not produce deficits in executive function (EF) and related motor components beyond the independent effects of AD/HD, and ODD/CD. In sharp contrast to this, Banaschewski et al. (2003) conducted a study utilising a cued Continuous Performance Task (CPT-AX) which found that the ‘hybrid’ concept was not able to account for the symptomatology of AD/HD+ODD/CD, and hence argued for the re-conceptualisation of AD/HD+ODD/CD as a distinct pathological entity. These results were supported by Albrecht et al. (2005) who, using a Stop Task, found inhibitory deficits in AD/HD-only and ODD/CD-only were not additive, and hence did not explain the inhibitory deficits seen in AD/HD+ODD/CD. Hence the authors also argued that individuals with AD/HD+ODD/CD represent a separate clinical entity. Though this debate has remained unresolved, it has fuelled research investigating the possible existence of AD/HD diagnostic groups that deviate from the DSM-IV-TR nomenclature.

Quantitative electroencephalography (QEEG) can play a pivotal role in documenting cerebral dysfunction in attention disordered individuals, and initial research has shown such results with AD/HD populations. A study by Chabot and Serfontein (1996) found two distinct electrophysiological subtypes within their AD/HD population, both indicative of abnormal central nervous system arousal. Similarities in QEEG values were found between the AD/HD subtypes Inattentive (AD/HD-I) and Combined (AD/HD-C), suggesting comparability of underlying aetiology, and consequently providing a new perspective for subtype categorisation. Their study however, did not account for overt comorbidity such as Oppositional Defiant Disorder/Conduct Disorder (ODD/CD) within their AD/HD population. This may explain why later research by Clarke, Barry, McCarthy and Selikowitz (2001b) found conflicting results in terms of the type of QEEG similarities and differences in their AD/HD group. Clarke et al. conducted a within-subtype analysis with children diagnosed as AD/HD-C (combined subtype) with no internalised (i.e. depression, anxiety, etc) or externalised (i.e. ODD/CD) comorbidity. Within this population, the authors isolated three distinct QEEG-defined subtypes associated with cortical hypoarousal, maturational lag, and cortical hyperarousal. An adjunct study focusing on AD/HD-I instead found very similar results.
with two QEEG profiles indicative of cortical hypoarousal, and maturational lag (Clarke, Barry, McCarthy, Selikowitz, & Brown, 2002). Event-related potentials (ERPs) from an Oddball task in the same AD/HD-I cohort showed only the early ERP negativity N1 to significantly differ between the QEEG-defined AD/HD-I subtypes - all other ERPs were comparable (C. R. Brown et al., 2005). Two possible explanations ensue. It may be that the generation of cortical ERPs is primarily unaffected by underlying brain abnormalities, or secondly, both cortical hypoarousal and maturational lag are characterized by largely the same type of brain abnormalities or produce similar task-processing deficits. Since previous research has shown the EEG waveform to fluctuate and change in accordance with physical and mental activity (Ackerman, Dykman, Oglesby, & Newton, 1994, 1995), it is reasonable to assume that any underlying EEG abnormality would be reflected in the task-related ERPs.

These studies suggest the existence of distinct AD/HD subtype groups that are independent of the behaviourally-defined DSM-IV-TR diagnostic criteria. To date, no investigation has been conducted into the ERP and psychometric profiles that may exist between/within Controls, AD/HD, and AD/HD+ODD/CD that lie outside the DSM-IV-TR diagnostic guidelines. This is of particular interest given the continuing debate regarding the classification of AD/HD+ODD/CD as a distinct pathological entity, in addition to the highly publicised symptom heterogeneity in AD/HD groups with and without comorbidity (J. T. Nigg, 2003; Steinhausen, 2009) that can often result in behavioural and/or cognitive overlap between these groups. Therefore, the aim of this study is to ascertain whether the ERP and psychometric performance profiles (from the same six measures utilised in Chapters 7 and 8) of AD/HD with and without ODD/CD comorbidity cluster into meaningful groups that suggest a divergence in the nomenclature of the DSM-IV-TR. Similar to the previous Chapter, a data-driven approach was again adopted in this Chapter.
9.2 Method

The participants, and tasks and procedure presented here are largely the same as that from Chapter 7; any differences will be detailed below. The following sections will provide a brief reiteration, however for detailed methods, refer to the previous Chapter, and also to the Methodology Chapter (6).

9.2.1 Participants

Of the 283 participants, 152 were AD/HD (64 children, 88 adolescents), and 131 were Controls (52 children, 79 adolescents). Of the 64 AD/HD children, 32 were AD/HD+ODD/CD, 11 were AD/HD+INT, and 21 were AD/HD-NK. Of the 88 AD/HD adolescents, 35 were AD/HD+ODD/CD, 17 were AD/HD+INT, and 36 were AD/HD-NK. See Section 6.1 of Chapter 6 for a more detailed presentation.

9.2.2 Tasks and Procedure

Data from the same six tasks from Chapter 7 were utilised in this investigation. These are listed below along with their abbreviations and the primary cognitive and/or behavioural construct measured. Refer to Section 6.2 of Chapter 6 for a detailed presentation of each task.

i. Auditory Oddball Task – selective attention

ii. Continuous Performance “one-back” Task (CPT) – sustained attention

iii. Go/NoGo Task (GNG) – response inhibition (RI)

iv. Verbal Interference Task (VIT) – RI

v. Executive Maze (EM) Task – executive function (EF)

vi. Switching Of Attention Task (SOAT) – EF

All of the above tasks were psychometric except for the Auditory Oddball Task and the GNG Task, which had corresponding ERP components. ERPs were averaged across
scalp sites and topographic location, (refer to Section 6.4.2 of Chapter 6; and Section 6.2.1 of Chapter 6 for details on EEG acquisition).

### 9.2.3 Statistical Analysis

A total of 29 variables were selected for inclusion in a Principal Components Analysis (PCA) (see Table 9.1). Reaction times (RT) were established for oddball and CPT tasks, and ERP data was selected from Oddball and Go-NoGo tasks.

Prior to statistical analysis, square root transformations were performed on all error scores (FPs, and FNs) due to their skewed distributions. Analysis of data in this study was two-fold. Firstly, psychometric performance, and amplitude and latency ERP variables from the six tasks were incorporated into a Principal Components Analysis (PCA) in order to reduce the amount of data. Secondly, a Two-Step Cluster Analysis using the PCA-derived factors was conducted using a log-likelihood distance measure and the Schwarz’s Bayesian Clustering Criterion (BIC). The Cluster Analysis was run for both children and adolescents, with no number of clusters specified a priori. Bonferroni corrections were applied.

Since variables with larger values can have a stronger impact on clustering than those with smaller values (Norusis, 2008), all of the PCA-derived factors were automatically standardised as z-scores ($x = 0$, $SD = 1$) prior to analysis, as part of the two-step Cluster process.

Significant differences between clusters in each age group were determined via Mann-Whitney U Tests due to skewed distributions in the PCA-derived factors. Permutation testing on group centroid distances in Z-space of the most significant predictors was also carried out.
Table 9.1

Final 29 variables included in the Principal Components Analysis.

<table>
<thead>
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<th>Variable</th>
<th>Task</th>
<th>Underlying Construct</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychometric:</strong></td>
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<td></td>
</tr>
<tr>
<td>Incongruent Trial Score</td>
<td>VIT</td>
<td>RI</td>
</tr>
<tr>
<td>Incongruent Error Score</td>
<td>VIT</td>
<td>RI</td>
</tr>
<tr>
<td>Trail Completion Difference*</td>
<td>SOAT</td>
<td>EF</td>
</tr>
<tr>
<td>Maze Trial Time*</td>
<td>EM</td>
<td>visual information processing/ task performance</td>
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<tr>
<td>Perseverative Errors</td>
<td>EM</td>
<td>visual information processing/ task performance</td>
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<td>Non-Perseverative Errors</td>
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<td>visual information processing/ task performance</td>
</tr>
<tr>
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<td>EM</td>
<td>visual information processing/ task performance</td>
</tr>
<tr>
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<td>CPT</td>
<td>sustained attention</td>
</tr>
<tr>
<td>FNs</td>
<td>CPT</td>
<td>sustained attention</td>
</tr>
<tr>
<td>Total FPs</td>
<td>CPT/Oddball</td>
<td>hyperactivity/impulsivity</td>
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<td></td>
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<td>N1A, N1L</td>
<td>Oddball</td>
<td>orienting of attention</td>
</tr>
<tr>
<td>P2A, P2L</td>
<td>Oddball</td>
<td>automatic inhibition</td>
</tr>
<tr>
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<td>Oddball</td>
<td>inhibitory/mismatch process</td>
</tr>
<tr>
<td>P3A, P3L</td>
<td>Oddball</td>
<td>complex information processing</td>
</tr>
<tr>
<td>N1A, N1L</td>
<td>GNG</td>
<td>orienting of attention</td>
</tr>
<tr>
<td>P2A, P2L</td>
<td>GNG</td>
<td>automatic inhibition</td>
</tr>
<tr>
<td>N2A, N2L</td>
<td>GNG</td>
<td>inhibitory/mismatch process</td>
</tr>
<tr>
<td>P3A, P3L</td>
<td>GNG</td>
<td>complex information processing</td>
</tr>
</tbody>
</table>

* ‘Trail Completion Difference’ was measured as the difference in completion times between the two trails of the SOAT; ‘Maze Trial Time’ is the time taken to complete the trial twice consecutively without error; ‘Path Learning Time’ is the time taken to learn the path prior to completing the trial twice consecutively without error (i.e. the time taken from the start of the first trial till the end of the last trial with one or more errors).

* The letter ‘A’ or ‘L’ is added to the end of each ERP component to denote amplitude (A) or latency (L), for example ‘N1A’ denotes fronto-central N1 amplitude.
9.3 Results

The following sections will present the results according to the type of analyses conducted. The results from the Principal Components Analysis will be shown first, followed by those of the Cluster Analysis. Results for both child and adolescent comorbid and non-comorbid groups will be presented.

9.3.1 Principal Components Analysis

The factorability of these 29 variables used (Table 9.1) was supported by both the Kaiser-Meyer-Oklin value (.811) which exceeded the recommended threshold of .60 (Kaiser, 1974), and by a significant Bartlett’s Test of Sphericity ($p < .001$) (Bartlett, 1954). Nine components were found with eigenvalues (proportional to the total variance explained by that eigenvector) greater than one. Since components in the PCA were standardised to a variance of 1, only eigenvalues >1 were retained. However, following a Parallel Analysis (Hayton, Allen, & Scarpello, 2004) with 100 randomly generated replications of the same dataset matrix, only six principal components were finally retained [Parallel Analysis was conducted using the Monte Carlo PCA for Parallel Analysis computer software (Watkins, 2008)].

An exploratory factor analysis was then carried out. Given that each PCA component is considered to represent a different facet of attention and cognition, an oblique rotational method was employed. The six principal components were rotated using a Promax rotation. The pattern matrix from this rotation is shown in Table 9.2.
Table 9.2
*Promax rotated pattern matrix - six eigenvector solution from PCA*

<table>
<thead>
<tr>
<th></th>
<th>EigenV 1</th>
<th>EigenV 2</th>
<th>EigenV 3</th>
<th>EigenV 4</th>
<th>EigenV 5</th>
<th>EigenV 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3L (GNG)</td>
<td>.739</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>N2L (GNG)</td>
<td>.721</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3L (Oddball)</td>
<td>.652</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1A (GNG)</td>
<td>-.593</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EF(SOAT)</td>
<td>.539</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2L (GNG)</td>
<td>.528</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>RT (Oddball)</td>
<td>.493</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Incong. Trial</td>
<td>.451</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.324</td>
</tr>
<tr>
<td>N1L (GNG)</td>
<td>.449</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.240</td>
</tr>
<tr>
<td>RT (CPT)</td>
<td>.409</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Persev. Errors</td>
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<td>.923</td>
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<td></td>
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<tr>
<td>Non-Persev.</td>
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<td>.896</td>
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<tr>
<td>Errors</td>
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</tr>
<tr>
<td>Time per Trial</td>
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<td>.728</td>
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<tr>
<td>Path Learning</td>
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<td></td>
<td>.349</td>
<td>.524</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Total FPs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.788</td>
<td></td>
</tr>
<tr>
<td>FNs (Oddball)</td>
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<td></td>
<td>.661</td>
<td></td>
<td></td>
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<tr>
<td>FPs (GNG)</td>
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<td></td>
<td></td>
<td>.599</td>
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<tr>
<td>FNs (CPT)</td>
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<td></td>
<td>.566</td>
<td></td>
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</tr>
<tr>
<td>Incong. Error</td>
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<td>.531</td>
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<td></td>
</tr>
<tr>
<td>Score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>P2L (Oddball)</td>
<td></td>
<td></td>
<td></td>
<td>.873</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1L (Oddball)</td>
<td></td>
<td></td>
<td></td>
<td>.784</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2L (Oddball)</td>
<td></td>
<td></td>
<td>.366</td>
<td>.655</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1A (Oddball)</td>
<td></td>
<td></td>
<td></td>
<td>-.582</td>
<td>.404</td>
<td></td>
</tr>
<tr>
<td>P2A (GNG)</td>
<td>.551</td>
<td></td>
<td></td>
<td>.767</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2A (GNG)</td>
<td></td>
<td></td>
<td></td>
<td>.628</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P3A (GNG)</td>
<td></td>
<td></td>
<td></td>
<td>-.327</td>
<td>.525</td>
<td></td>
</tr>
<tr>
<td>P3A (Oddball)</td>
<td></td>
<td></td>
<td></td>
<td>.487</td>
<td>.307</td>
<td>.815</td>
</tr>
<tr>
<td>P2A (Oddball)</td>
<td></td>
<td></td>
<td></td>
<td>.487</td>
<td>.307</td>
<td>.815</td>
</tr>
<tr>
<td>N2A (Oddball)</td>
<td>-.484</td>
<td>.384</td>
<td></td>
<td>.582</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Each of the six eigenvectors identified via the PCA comprised of a range of variables originating from different tasks, which renders a sensible naming difficult. Thus, for each eigenvector, the variables that had the highest loadings will be taken as the best representative of any underlying construct(s) (Pallant, 2004). According to Hair, Anderson, Tatham and Black (Hair, Anderson, Tatham, & Black, 1998), a loading of 0.6 or above is considered as “high”, and a loading of 0.7 indicates that roughly half of the variance in that factor is accounted for by that variable.

The largest number of task variables were grouped together to form factor 1. Of these variables, three had loadings at or above 0.6 these were the ERP components P3 and N2 latency from the GNG task, along with P3 latency from the Oddball task. The N2 ERP component has previously been found to be a reliable marker of the inhibitory process (Dimoska et al., 2003; Kok, 1986; Pliszka et al., 2000), in addition to stimulus discrimination or the ‘mismatch detection’ process (Barry, Johnstone et al., 2003; Smith et al., 2004). Given this, it appears that Factor 1 is representative of complex processing related to task difficulty. Since this factor is largely comprised of ERP component latency and RT variables, higher scores would be indicative of greater impairment.

Factor 2 was wholly comprised of variables from the Executive Maze task with 3 variables possessing factor loadings > 0.7 (Preservative Errors, Non-Preservative Errors, and Time per Trial), suggestive of deficits in visuo-spatial abilities as previously identified in AD/HD (Hair et al., 1998; Tirosh et al., 2006) and AD/HD+ODD/CD (Raberger & Wimmer, 2003) cohorts.

The variables that comprised factor 3 were error-related, with only two (Total FPs and FNs from the Oddball task) having a factor loading at or higher than 0.6 (though with FPs from the GNG task giving a factor loading = .599). Together they could be described as relating to error monitoring.

Factor 4 was wholly comprised of ERP components derived from the auditory Oddball task; four in total with three being latency ERPs. Out of these four variables, two
possessed factor loadings above 0.7 (P2L and N1L), and one had a factor loading above .6 (N2L). Previously, these ERPs have been reported as reflective of the initial orienting of attention (N1) (Altenmüller & Gerloff, 1999; Barry, Johnstone et al., 2003; Loiselle et al., 1980; Smith et al., 2004), and the automatic inhibition of irrelevant stimuli (P2, N2) (Banaschewski et al., 2004; Barry, Johnstone et al., 2003; Dimoska et al., 2003; Pliszka et al., 2000; Smith et al., 2004). Note that in a fashion similar to Factor 1, higher scores in Factors 2, 3, and 4 reflect greater impairment.

Factor 5 showed major contributions from four variables, mostly derived from the visual GNG task. Of the four variables, two had factor loadings ≥0.6 (P2A and N2A), with one of out the two having a factor loading above >.7 (P2A). Given that the ERP components P2 and N2 have been suggested to reflect facets of the inhibitory process, this factor may therefore be interpreted as corresponding to response inhibition (Johnstone et al., 2009; Kirmizi-Alsan et al., 2006).

Factor 6 possessed only one variable with a factor loading >.6, though another variable did approach this threshold (N2A: factor loading = .582). As both ERP components here were derived from the auditory Oddball task, this factor may be representative of an auditory selective attention process.

9.3.2 Cluster Analysis

The six rotated factors obtained via the PCA were then subjected to a Cluster Analysis to investigate the possible presence of AD/HD groups that differ from those defined in the DSM-IV-TR.

9.3.2.1 Adolescent Group

In the adolescent analysis, two clusters were identified with 113 participants in the first cluster (Cluster 1), and 54 participants in the second cluster (Cluster 2). Between the two adolescent clusters, Cluster 2 appears to be more of a ‘Clinical’ group due to the comparatively greater populations of AD/HD+ODD/CD and AD/HD+INT
(internalising) than in Cluster 1 which is predominately comprised of Controls (see Table 9.3).

Of the six factors, Factors 3, 2, and 5 all significantly (with Bonferroni corrections) contributed to defining Clusters 1 and 2. Factors 2 and 3 contributed significantly more to Cluster 2 than Cluster 1, and Factor 1 was more prominent in Cluster 2 compared to Cluster 1. As discussed earlier, Factor 1 is thought to represent complex processing related to task difficulty, and Factors 2 and 3 are thought to be indicative of task performance deficits, with Factor 2 being more specific to visuo-spatial processing. Therefore, it appears that Cluster 2 displayed more task performance deficits, and impaired complex processing related to task difficulty, compared to Cluster 1. Figure 9.2 displays the mean factor loadings and standard errors.

Table 9.3
The two clusters produced from the adolescent cluster analysis, and the percentage distribution of Clinical and Control participants in each cluster.

<table>
<thead>
<tr>
<th>Cluster 1</th>
<th>N</th>
<th>Cluster %</th>
<th>Cluster 2</th>
<th>N</th>
<th>Cluster %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>71</td>
<td>63.7%</td>
<td>Controls</td>
<td>7</td>
<td>13.0%</td>
</tr>
<tr>
<td>AD/HD+ODD/CD</td>
<td>11</td>
<td>9.7%</td>
<td>AD/HD+ODD/CD</td>
<td>24</td>
<td>44.4%</td>
</tr>
<tr>
<td>AD/HD+INT</td>
<td>7</td>
<td>6.2%</td>
<td>AD/HD+INT</td>
<td>10</td>
<td>18.5%</td>
</tr>
<tr>
<td>AD/HD-NK</td>
<td>23</td>
<td>20.4%</td>
<td>AD/HD-NK</td>
<td>13</td>
<td>24.1%</td>
</tr>
</tbody>
</table>

*Comorbidities ODD/CD: Oppositional Defiant Disorder/Conduct Disorder; INT: internalising comorbidities; NK: no known comorbidity.*
Figure 9.1 Variable-wise importance charts. Chi-square values for each of the six factors are shown with significant factors (those that exceeded the Critical Value) highlighted for (a) Cluster 1, and (b) Cluster 2, in descending order.
Of particular interest was the greater number of AD/HD-NK adolescents in Cluster 1 than Cluster 2. To see whether this cluster distribution was an effect of AD/HD subtype, a Chi-Square Test was conducted post-hoc (with AD/HD-HI excluded from this analysis since there were only two adolescents in total). The difference in AD/HD subtype distributions between Clusters 1 and 2 did not reach significance ($\chi^2 = 2.096, p = .148$). Therefore, the characteristics of each adolescent Cluster is independent of AD/HD subtype. A second Chi-Square test was conducted to verify that comorbidity significantly differed between the two adolescent Clusters; this was confirmed: $\chi^2 = 46.587, p < .001$. A one-way ANOVA was also conducted to confirm that cluster
distribution was not an effect of intelligence; no significant difference in IQ estimates was found between Clusters 1 and 2 \[ F(1, 166) = .372, p = .543 \]. Importantly, the Z-score data from the three most predicative factors for cluster membership (Eigenvectors 2, 3 and 5) were subjected to a permutation testing routine to test the hypothesis that comorbid diagnosis of AD/HD+ODD/CD would show an objective separation from the group comprising AD/HD without a diagnosis of ODD/CD (a comparison of AD/HD with Externalising comorbidity with other AD/HD participants (with Internalising or no comorbidity)). Visualization of the data via a 3D scatter plot shows a clear separation of the two groups (see Figure 9.3).

![Figure 9.3 3D scatter plot of Adolescent AD/HD+ODD/CD (red dots) and AD/HD without comorbid diagnosis (blue dots) plotted on axes of the most significant factors (2, 3 and 5) from the PCA analysis, scaled as Z-scores (Z-Error Monitoring, Z-Inhibitory processing, Z-Visuospatial learning, respectively).](image)

The Pythagorean distance between centroids of the two groups of points was then calculated. A permutation test was constructed using LabVIEW (National Instruments, Austin USA) based on the null hypothesis that all of the points derive from one population and were thus randomly selected into two groups, of the same sizes as the
experimental groups, 10000 times, and each time the Pythagorean distance between centroids in Z-space was calculated. The experimental datum (1.0856) ranked 4\textsuperscript{th} highest, resulting in an equivalent (two-tailed) probability of $p<.001$.

Testing of the other combinations of clinical AD/HD comorbid diagnoses did not result in significant separation.

\textbf{9.3.2.2 \ Child Group}

Only one cluster was found in the child analysis which comprised all 116 Clinical and Control children. The scores on each of the six Factors from the PCA analysis did not display any pattern that could segregate the children into more than one cluster. It appears that that the variance in the six Factors was too great to result in a significant difference between children from the Clinical and Control groups. This view is borne out by visualization of the 3-factor plot (Factors 2, 3 5) for children with AD/HD+ODD/CD and those with AD/HD without known comorbidity (see Figure 9.4).
9.4 Discussion

The aim of this study was to investigate whether the child and adolescent Clinical and Control populations could be clustered into meaningful groups divergent from that defined by the DSM-IV-TR. This clustering was based on the six Factors from a Principal Components Analysis of 29 data variables derived from a battery of six neurocognitive tasks. The relative impact of ODD/CD comorbidity in AD/HD was also investigated. The results showed a single collective cluster in the child group, and two clusters in the adolescent group which were suggestive of ‘clinical’, and ‘normal/sub-clinical’ populations.
No significant factors were found in the child analysis. In adolescence, three Factors (2, 3, and 5) dictated cluster membership more so than any of the other Factors. Both Factors 2 and 3 are thought to be indicative of task performance, with Factor 2 being more specific to visuo-spatial processing. Factor 5 was thought to reflect response inhibition specific to visual information processing. Factor 1 was also found to significantly discriminate Cluster 2 from Cluster 1, though not vice versa. Factors 2 and 3, which are both thought to be related to task performance, were found to be the two most prominent Factors in this analysis. This is unsurprising given that previous research has found task performance to be significantly more impaired in AD/HD populations, particularly when inhibitory tasks are involved (R.A. Barkley, 1997; Booth et al., 2005; Houghton et al., 1999; Pasini et al., 2007; Pliszka et al., 2000; Quay, 1997; Stins et al., 2005). Therefore, it was also unsurprising to find that Cluster 2, which had the larger Clinical population, displayed substantially more impairment as indexed by these two Factors than Cluster 1. This finding is strengthened by the fact that greater impairment in complex processing relating to task difficulty was a defining characteristic of Cluster 2, rather than Cluster 1. The significant differences in Factor 5 were also strongly indicative of comparatively more impairment in Cluster 2 than Cluster 1.

In the child analysis, only one cluster was found which included all 116 Clinical and Control children. Although AD/HD is typically first diagnosed in childhood, this is also the time when behaviour and development (both physical and cognitive) is the most fluid; any model of “misbehaviour” may be difficult to apply to young cohorts as it may only be representative of a transient phase in development. As a result, any variable dependent on such factors is likely to be applicable only to a more discrete point in time in the child’s development. This highlights the massive scope for variability, which was evident in each of the six Factors. Of the 116 Clinical and Control children, none of the data on the six Factors showed any form of homogeneity that would allow cluster formation due to the substantial amount of variability. Therefore, this result supports the widely held contention in AD/HD research that the overwhelming symptom heterogeneity which is consistently found in AD/HD populations appears to be at its most pronounced in childhood. Given this, a more individualistic approach to
Comorbid subgroups in childhood AD/HD did not cluster into meaningful groups divergent from the core disorder of AD/HD or from Controls, suggesting that overt and covert comorbidity can manifest as highly variable symptomatology that is not dissimilar between groups. Previous research has shown comorbidity such as ODD/CD to be more prevalent in older AD/HD cohorts (Takeda et al., 2012), therefore, AD/HD children diagnosed with comorbid ODD/CD may be more representative of a prodromal comorbid group that are less symptomatic and less impaired than their older counterparts. This result therefore challenges the reliability of comorbid ODD/CD diagnoses in AD/HD children aged 6-12 years, and highlights the need for age-appropriate diagnostic criteria.

The adolescent analysis produced quite different results to that of the children. Two clusters were found; Cluster 1 which resembled a more ‘normal’ or ‘sub-clinical’ group, and Cluster 2 which clearly represented a more ‘clinical’ group. This interpretation was primarily fuelled by the population distributions of the Controls, AD/HD+INT, and AD/HD+ODD/CD. Almost two thirds of the entire Cluster 1 population were Controls, while almost half of Cluster 2 was AD/HD+ODD/CD. There were also slightly more AD/HD+INT adolescents in Cluster 2 than there were in Cluster 1. Given this, it appears that ODD/CD comorbidity in AD/HD is a primary factor in distinguishing behavioural and/or attentional dysfunction against Controls and hence may bias the diagnosis of AD/HD in adolescents. In the absence of such comorbidity, AD/HD-NK displayed a more varied result with 64% of the total population grouped into Cluster 1 with the bulk of the Controls, and 36% grouped into the more ‘clinical’ Cluster 2. Firstly, this suggests some overlap in neurocognitive performance, or some confusion of behavioural diagnosis. Such an overlap can be interpreted as representing dimensional impairment if members of the AD/HD-NK group in Cluster 2 do in fact possess sub-clinical levels of ODD/CD symptomatology. Future research is needed to clarify the dimensional nature of symptomatology and symptom severity between
AD/HD comorbid groups. Secondly, the AD/HD-NK in Cluster 1 may represent the gradual dissipation of overt symptoms with age (Biederman, 2005; Hart et al., 1995; Hay & Levy, 1996; Spencer et al., 2007) and hence, the general decrease in dysfunction and symptom severity. Both of these explanations may be concurrently valid.

The present results in terms of AD/HD-NK can be seen as reminiscent of previous QEEG findings which have typically shown two groups within the AD/HD subtypes that are independent from the DSM-IV-TR definition (Chabot & Serfontein, 1996; Clarke et al., 2001b; Clarke et al., 2002). With the two cluster-defined AD/HD-NK groups, Cluster 2 clearly displayed more impairment than Cluster 1, which was not found to be an effect of intelligence or AD/HD subtype. In the previous research also, two groups (cortical hypoarousal and maturational lag) were found, though analyses did not reveal any significant differences to indicate a more impaired group (C. R. Brown et al., 2005). The concepts of maturational lag and cortical hypoarousal have repeatedly been applied to AD/HD populations in the previous literature (El-Sayed et al., 2003; Lazzaro et al., 1998; Nazari et al., 2011; Shi et al., 2012), with positive results suggesting both theories are equally valid, however some authors argue that AD/HD subjects display deviant maturation, rather than maturational lag per se (Hobbs, Clarke, Barry, McCarthy, & Selikowitz, 2007). Cortical hypoarousal in particular has recently been linked to inhibition (Shi et al., 2012). It is also possible that the two theories are linked, rather than occurring in parallel, that is, one might act as a catalyst for the other. It is difficult to declare that the two AD/HD-NK groups found here displayed signs of maturational lag or cortical hypoarousal as the present results did not incorporate an analysis of quantitative EEG or imaging data. However, an early study linked developmental immaturity to persistent and extreme overactivity (Macfarlane, Allen, & Honzik, 1954), suggesting that clinical levels of hyperactivity and impulsivity were indicative of a maturational lag. Given this finding, it can be reasoned that the more impaired AD/HD-NK in cluster 2 may have displayed a maturational lag compared to the less impaired AD/HD-NK cohort in cluster 1. This contention is based on the type of Factors that were most successful in identifying task-defined symptom severity, and subsequent cluster membership; Factors 2, 3 and 5 represent
components of attention, learning, and inhibition, all of which are strongly influenced by hyperactivity and impulsivity.

Hyperactive and impulsive symptoms have consistently been linked to ODD/CD comorbidity, and greater overall symptom severity in AD/HD samples (Barnett, Maruff, & Vance, 2009; Burke, Loeber, & Birmaher, 2002; Connor & Doerfler, 2007; Drabick, Gadow, & Loney, 2007; Gabel et al., 1996; Hurtig et al., 2007; Newcorn et al., 2001); a study by Decker et al. (2001) for example, found comorbid CD is more likely to be diagnosed in AD/HD subtypes with hyperactive/impulsive symptoms than inattentive symptoms. Given this, the primary distinguishing characteristic between the adolescent clusters 1 and 2 is likely to be task-defined hyperactivity and/or impulsivity, as captured by Factors 2, 3 and 5, which appear to be most pronounced in AD/HD+ODD/CD adolescents.

Task performance as dictated by these three Factors also illustrated a clear distinction between AD/HD-NK and AD/HD+ODD/CD adolescents, suggesting a significant divergence in task-defined symptom severity. Previous research on comorbid AD/HD has repeatedly shown AD/HD+ODD/CD to display significantly greater symptom severity compared to AD/HD-alone (Connor & Doerfler, 2007; Kuhne et al., 1997; Takeda et al., 2012). This result supports previous claims that AD/HD+ODD/CD constitutes a pathological entity different to that of AD/HD-alone (Banaschewski et al., 2003) rather than a ‘hybrid’ group. A hybrid group would be expected to display a noticeable overlap in task performance scores with AD/HD+ODD/CD, suggesting a dimensional increase in symptom severity, however this did not appear to be the case here. Rather, it appears that task-defined symptom severity in AD/HD+ODD/CD adolescents is beyond that defined under the AD/HD-NK umbrella.

From the results found here, the most intriguing was the lack of any Clinical/Control cluster formations in the child analysis. In sharp contrast to the adolescent results, the six Factors did not show any distinguishable pattern between any of the Clinical or Control groups and as a result, all of the children were clustered together. This finding could partly be accounted for by the inherent heterogeneity in AD/HD, however similar variability appeared to be present in the Control children also. This suggests that symptomatology and symptom severity in AD/HD exists on a dimensional scale.
that stems from ‘normal’ cognitive and behavioural function as seen in the Controls, rather than an arbitrary counting of symptoms deemed to be abnormal or maladaptive as per the DSM-IV-TR definition. Given that both physical and cognitive development is at its most fluid state in childhood, the single cluster result found for this age group is contextually unsurprising.

Overall, the adolescent clusters differed primarily in terms of task-related hyperactivity and/or impulsivity as defined by error rate (Factors 2 and 3) and visual response inhibition (Factor 5). The results obtained with these Factors suggest that measures of hyperactivity/impulsivity and visual response inhibition may serve as diagnostic aids in a clinical setting, or as profiling anchors in future research. These Factors indexed greater impairment, particularly when ODD/CD comorbidity was present in AD/HD. Given this finding, the present results support the idea that AD/HD+ODD/CD can be distinguished on a dimensional scale from AD/HD-NK in adolescence. Hence, it may prove beneficial for comorbidity such as ODD/CD to be incorporated into the diagnostic definition of AD/HD and consequently into the diagnostic process, particularly when AD/HD progresses from childhood into adolescence. Such a stance has already been adopted in the ICD, where a distinct diagnosis of Hyperkinetic Conduct Disorder (HCD) is made for AD/HD+ODD/CD (World Health Organization, 1993). The question then arises as to whether or not AD/HD+ODD/CD should be defined as a distinct pathological entity in the forthcoming DSM-V. Although the affirmative has been argued by Banaschewski et al. (2003), others have argued that AD/HD+ODD/CD is more of a ‘hybrid’ group characterised by a greater severity of the same symptomatic domains (Schachar & Tannock, 1995; Waschbusch, 2002), a contention supported by Rommelse et al. (2009) who described AD/HD+ODD/CD symptomatology as “more of the same” (p. 802) rather than a phenotypically distinct subtype. The results from this study indicate that ODD/CD comorbidity has a significantly alters the neurocognitive performance of adolescents diagnosed with AD/HD and hence supports a revision of the current AD/HD nomenclature to allow AD/HD+OD/CD to be seen as a distinct pathological entity, however this appears to be valid only in adolescence; there does not appear to be a similar pattern of results supportive of such nomenclature in childhood. Rather, childhood diagnosis would benefit from a dimensional approach to symptomatology and symptom severity.
Chapter 10:

General Discussion and Conclusions

Chapter Overview:
This chapter will collate and present the major findings of the three experimental chapters which will then be discussed in relation to the thesis aim. The impact these findings have on the current diagnostic conceptualisation of AD/HD in relation to age and ODD/CD comorbidity is discussed. The limitations of this thesis are also outlined along with directions for future research.
10.1 Revisiting the Thesis Aim

The aim of this thesis was three-fold: firstly to investigate the qualitative differences between AD/HD comorbid groups using the behavioural subscales of the Conners Parent Rating Scale – Revised, Long form (CPRS-RL), and also to assess the differences between the AD/HD comorbid groups and Controls on six tasks measuring executive function (EF), response inhibition (RI), selective and sustained attention, and then from these results compile comorbid group profiles. Secondly, to investigate the accuracy of an active auditory Oddball task in predicting group membership of comorbid AD/HD, which was an extension of previous work by Smith, Johnstone and Barry (2003). Thirdly, to assess whether AD/HD+ODD/CD constitutes a distinct pathological entity as compared to AD/HD without such externalising comorbid diagnoses (AD/HD-NK), and which factors (derived from the six tasks) best captured this ‘diagnostic separation’.

These aims were operationalized in the three experimental chapters of this thesis with the CPRS-RL, and the six neurocognitive tasks: Go/No-Go, Continuous Performance task, Auditory Oddball, Executive Maze, Switching of Attention, and Verbal Interference Task. These tasks were selected for their robustness in measuring their respective fields, and hence their ubiquity in the previous AD/HD literature. The results of this thesis represent the first attempt at elucidating symptom and cognitive-behavioural profiles of comorbid AD/HD in both children and adolescents, and also provides supportive evidence for the use of an active auditory Oddball task as a diagnostic aid for AD/HD, in addition to support for the delineation of a new diagnosis for AD/HD+ODD/CD in adolescence. The findings from these investigations, limitations, and possible directions for future research will be discussed in the following sections.
10.2 A Review of the Present Findings

The findings from this thesis provide a stepping stone in the continuing disambiguation of AD/HD with comorbid ODD/CD. To date, no CPRS-defined behavioural profile or neurocognitive profile of AD/HD+ODD/CD in comparison to AD/HD-NK or AD/HD+INT and Controls has been published and as such, this is a necessary endeavour in order to gain a better understanding of the comparative symptomatology, particularly with regard to age differences.

Previous research has repeatedly found that AD/HD+ODD/CD displays a more severe symptom profile than that of AD/HD alone, which was supported by the results of this thesis. Although both AD/HD-NK and AD/HD+ODD/CD displayed an increase in Oppositional behaviour with age, when assessing the areas of EF, RI, selective and sustained attention, AD/HD+ODD/CD were found to perform more poorly than Controls, AD/HD alone (AD/HD-NK), and AD/HD with internalising comorbidity (AD/HD+INT). This result was found in both childhood and adolescence.

In childhood, AD/HD+ODD/CD displayed a profile centred on novelty-seeking behaviour, difficulties in re-orienting of attention, in addition to selective and sustained attention deficits. In adolescence, there appeared to be a shift towards greater task-defined impairment in each of these areas.

AD/HD-NK displayed a child profile primarily focused on novelty-seeking and deficits in selective attention. Impairment that characterised the child AD/HD-NK profile was also present in adolescence, alongside deficits in error-monitoring and impairment in sustained attention.

In sharp contrast to the results of AD/HD-NK and AD/HD+ODD/CD, the profile of AD/HD+INT children was so diffuse that no significant differences were found against Controls or any other AD/HD group. In adolescence however, AD/HD+INT were characterised by inattention and a general EF deficit specifically relating to visuo-spatial abilities.

These results consistently showed an age-related trend of increasing task-defined symptom severity. This was primarily due to the finding that task performance was
significantly impaired in all adolescent AD/HD groups compared to Controls, whereas no such result was found in the child comparisons, which is in sharp contrast to previous research that has found a gradual dissipation of overt symptoms with age. Task-defined symptom severity was found to be a product of novelty-seeking behaviour, poor error-monitoring, and inattention. This was primarily due to the finding that variables relating to error-rate and accuracy were consistently found to be the most significant between groups. Novelty-seeking in particular was associated with a more immature profile and is a behavioural manifestation of hyperactivity and/or impulsivity. This trait was found to be a defining characteristic of both the AD/HD+ODD/CD and AD/HD-NK child profiles, though was comparatively more prominent in AD/HD+ODD/CD. A significantly more impaired profile was found for AD/HD+ODD/CD compared to AD/HD-NK in adolescence also, hence it appeared that novelty-seeking, poor error-monitoring and inattention were markedly more pervasive in the presence of ODD/CD comorbidity at this age, producing global deficits in EF, RI and attention. Overt behaviour such as hyperactivity and impulsivity were not found to be a prominent factor of the AD/HD+INT child or adolescent profiles, albeit the lack of externalising symptomatology is unsurprising in this comorbid group. While no obvious task-related impairment was observed in childhood, age-related changes revealed impairment in AD/HD+INT adolescents to be a derivative of inattention and poor visuo-spatial abilities.

Chapter 8 presented an extension of previous work by Smith, Johnstone and Barry (2003) which assessed the diagnostic utility of an active auditory Oddball task in predicting group membership of child and adolescent AD/HD subtypes. The present results lend support to Smith et al.’s original findings, with comparable accuracy rates achieved in the childhood comparisons. Noticeably higher accuracy rates were obtained in the adolescent comparisons however, which is in sharp contrast to findings by Smith et al. who found higher rates in their child analyses. This divergence in results however, is due to the type of comparison groups employed, rather than any negative indication regarding the predictive utility of the Oddball task itself. The higher adolescent accuracy rates show an effect of comorbidity with age as defined by the Oddball task; rather than the gradual dissipation of symptoms with age (as is
typically seen in AD/HD), the opposite appears to be true for comorbid groups, where task-defined psychophysiological and psychometric heterogeneity declines. This may be due to maturation of comorbid symptoms (with a possible concurrent increase in symptom severity) with age. Overall, the present results support and extend Smith et al.’s contention that an active auditory Oddball task could prove useful as an adjunct to DSM- or ICD-based clinician diagnosis of AD/HD, and AD/HD with externalising or internalising comorbidity.

The differences in task-defined symptom severity between AD/HD-NK and AD/HD+ODD/CD were exemplified further in the results of Chapter 9, where two distinct groups were found when comparisons were made on task-derived factors assessing visuo-spatial learning (Factor 2), task performance (Factor 3), and visual response inhibition (Factor 5). When AD/HD+ODD/CD adolescents were compared to AD/HD-NK adolescents on these three factors, AD/HD+ODD/CD formed a discrete pathological entity, symptomatically distinct from AD/HD-NK. Since there was no overlap between these two adolescent groups on the three factors, the relationship in symptomatology did not appear to simply be an ‘additive effect’ of comorbidity and hence, a dimensional increase in severity. Rather, the impact of ODD/CD comorbidity on AD/HD resulted in a neurocognitive profile that was phenotypically distinct from AD/HD without such externalising comorbidity. This result lends validation to the proposition of a new diagnostic definition that specifically categorises the AD/HD+ODD/CD symptom profile. Such a stance has already been recognised and adopted by the ICD-10 as Hyperkinetic Conduct Disorder (HKD).

Without ODD/CD comorbidity, AD/HD-NK adolescents appeared to form two distinct groups (in Clusters 1 and 2), one of which may be representative of maturational lag. The more impaired group was found in Cluster 2, which displayed greater task-defined impairment than the AD/HD-NK cohort in Cluster 1, based on scores from Factors 2, 3, and 5. The impairment in cognitive performance defined by these Factors are undoubtedly associated with behavioural hyperactivity and impulsivity. Such overt behaviour, as mentioned above, is associated with a more immature behavioural profile, therefore suggestive of maturational lag.
Symptoms of hyperactivity and impulsivity dominated as indicators of impairment; such overt behaviour formed a fundamental component of the primary discriminators between the two Clusters in adolescence. Specifically, hyperactivity and impulsivity within the context of visuo-spatial learning (Factor 2), task performance (Factor 3), and visual response inhibition (Factor 5) show considerable promise in providing a more objective measure of impairment in older AD/HD patients and hence may serve as diagnostic aids in a clinical setting. These factors can also serve as profiling anchors to improve the understanding of comorbid AD/HD and hence influence future nomenclature.

10.3  The Influence of Age and ODD/CD Comorbidity on AD/HD

Age and comorbidity are two crucial factors that are not currently addressed in the present DSM-IV-TR diagnostic criteria for AD/HD, despite the tremendous influence of both factors in the aetiology and presentation of the disorder. Therefore, the patterns of impairment that are associated with age and ODD/CD comorbidity in AD/HD and how these complicate diagnosis, must be addressed. The influence of both age and ODD/CD comorbidity in AD/HD were investigated in the experimental Chapters of this thesis; these findings will be discussed in relation to the previous AD/HD literature in the following sections below.

10.3.1 The Influence of Age on AD/HD

The results of both experimental Chapters revealed that task-defined symptom severity in AD/HD was at its lowest in childhood, compared to adolescence. This was found across all AD/HD groups and is likely due to symptom heterogeneity at this age. When compiling profiles of each AD/HD group for example, task performance was not found to be affected compared to Controls in childhood. However in adolescence, a clear trend of task-defined impairment was apparent, regardless of comorbidity. This
highlights the significant age-related variations that occur in the symptomatology of AD/HD. When investigating the CPRS-defined profiles, the age-band of 9-11 years consistently marked a particularly reactive developmental phase.

Such age-related changes can be a direct consequence of the multitude of developmental changes seen between children and adolescents despite the presence of developmental disorders. Piagetian theory dictates that the vast majority of cognitive developments such as those pertaining to sensorimotor, pre-operational, and logical reasoning all occur prior to 11 years of age, while abstract reasoning typically occurs at or after this age (Berk, 2009; Bukatko & Daehler, 2001). In an early developmental study by Harcherik, Carbonari and Cohen (1982), results showed greater variability in scores attained by their normal child groups aged between 4-11 years than in their older group aged 12-14 years on cognitive, fine motor, gross motor, perceptual-motor, vigilance, and neurological tasks. They also found younger children (particularly those aged around 7 years) to be far more prone to distraction that their older counterparts. Similarly, Drechsler, Brandeis, Foldenyi, Imhof and Steinhausen (2005) found significant differences on attentional tasks between AD/HD and Controls to be most pronounced around 12 years of age. Such findings are substantiated by functional imaging (e.g. fMRI) studies of cognitive processes such as language, executive functioning, and emotion regulation that have shown more varied patterns of brain activation in children compared to adults; a finding that is attributed to neuroanatomical changes associated with brain maturation that does not occur until adolescence (Marsh, Gerber, & Peterson, 2008). Therefore, brain maturation and related cognitive development play a vital role in the expression of AD/HD symptoms and impairment; preschool children deemed ‘hyperactive’ for example, do not always differ from Controls on tests of attention and impulse control (Campbell, Breaux, Ewing, & Szumowski, 1984). Even in a recent longitudinal study of preschool children who exhibited considerable dysfunction and were predicted to meet AD/HD or ODD/CD criteria three years later using a DSM-IV-based checklist and rating scales, a sizable minority (27% for AD/HD and 42% for ODD/CD) did not (Harvey, Youngwirth, Thakar, & Errazuriz, 2009).
Diagnosis of developmental disorders, such as AD/HD, would therefore benefit from a dimensional approach in childhood rather than the current categorical one adopted by the DSM-IV-TR which at present does not account for age-related variations in aetiology and presentation of the disorder. Assessments of mental health must incorporate assessments of emotion and cognition and how these factors affect procedural learning and development. In childhood, these factors are continuously changing, updated, and applied to the learning environment. As such, the application of a categorical description of symptomatology in childhood would only be arbitrarily valid, if at all. A dimensional approach to diagnosing AD/HD in childhood would allow for changes in presentation and severity across a broader symptom spectrum, and how these changes affect susceptibility for comorbid disorders such as ODD/CD in adolescence. Since ODD/CD is more prevalent in older AD/HD individuals, a dimensional approach to comorbid AD/HD would allow AD/HD+ODD/CD to be viewed more as a prodromal group in childhood, rather than one displaying symptomatology equivalent to an older, more impaired sample. This can be applied to internalising comorbid disorders also, which typically become more prevalent with age as well.

The results of this thesis strongly suggest that the much documented heterogeneity often seen in child AD/HD populations may be more of a developmental phenomenon (neurophysiological and neuropsychological) rather than a symptomatic one. Given this, childhood disruptive behaviour disorders such as AD/HD would be better conceptualised on a dimensional scale of symptom severity, particularly when comorbid with other disorders such as ODD/CD or internalising symptomatology.

10.3.2 The Influence of ODD/CD Comorbidity on AD/HD

It is well known that ODD/CD comorbidity has a considerable negative effect on the presentation, duration, and outcome of AD/HD. In the present analyses, AD/HD in the presence of ODD/CD produced significantly more task-defined impairment in adolescence, than AD/HD alone. A distinct neurocognitive profile was found for AD/HD+ODD/CD in comparison to AD/HD-NK, that warranted a revision of current disruptive behaviour nomenclature to allow the singular diagnosis of such a comorbid
group, similar to that currently adopted by the ICD-10. Without ODD/CD comorbidity, the level of impairment in AD/HD-NK was somewhat ambiguous; two groups were found, the more symptomatic possibly representative of maturational lag.

The complex interplay between ODD/CD and AD/HD has sparked debate over whether the comorbid condition comprises enough symptomatic uniqueness to be defined as a separate pathological entity, as is the case in the ICD-10 (diagnosed as ‘Hyperkinetic Conduct Disorder’). While some authors argue the affirmative (Albrecht et al., 2005; Banaschewski et al., 2003), others have contended that AD/HD+ODD/CD is more of a ‘hybrid’ group characterised by a greater severity of the same symptomatic domains (Schachar & Tannock, 1995; Waschbusch, 2002). This proposition was reinforced by Rommelse et al (2009) who described AD/HD+ODD/CD symptomatology as “more of the same” (p. 802) rather than a phenotypically distinct subtype. Since around 42-90% of AD/HD suffers also meet criteria for ODD/CD (Angold, Costello, & Erkanli, 1999; Gillberg et al., 2004; Jensen et al., 1997), it is not surprising that the two conditions share some fundamental similarities. The diagnostic dilemma is whether or not the combining of AD/HD and ODD/CD encompasses enough symptomatic uniqueness to warrant a new diagnostic category. The findings from the present thesis support a new concept that is somewhat a consolidation of those previous; AD/HD+ODD/CD in adolescence constitutes a significant worsening of symptoms compared to AD/HD-NK, which, in some ways, can be considered as ‘more of the same’ or a hybrid group. However, the level and type of task-defined impairment (global deficits in EF, RI and attention) were clearly outside that defined by AD/HD-NK, hence the symptom profile incorporated a component unique to this comorbid group. In other words, AD/HD+ODD/CD resulted in a level of impairment that produced deficits in broader neurocognitive areas compared to AD/HD-NK in adolescence. Given this, the contention that argues for the creation of a new diagnostic category for AD/HD+ODD/CD is supported by the results of this thesis, however only in adolescence.
10.4 Cognitive Markers of AD/HD: Possible Diagnostic Aids

Three factors were found from the analyses of this thesis that captured task-related impairment in adolescence. Visuo-spatial learning (Factor 2), task performance (Factor 3), and visual response inhibition (Factor 5), were found to significantly differ between Clinical and Control groups, and also between AD/HD-NK and AD/HD+ODD/CD in adolescence. Factor 1, representing complex processing related to task difficulty, was also found to be significantly impaired in Cluster 2, supporting the plethora of previous research that has found similar results between AD/HD and Controls. The auditory Oddball task also proved beneficial in predicting group membership among AD/HD comorbid groups in both childhood and adolescence, hence may serve as an adjunct to the DSM- or ICD-based diagnostic process, with inhibitory-related ERP components (P2 and N2) from this task proving most effective.

In childhood, novelty-seeking behaviour and inattention were found to be the most prominent elements of cognitive and behavioural performance. While Inattention appeared to linger into adolescence, novelty-seeking behaviour appeared to be a marker for the later development of EF or RI deficits in adolescence, consequently impeding task performance at this age. Since task-related impairment increased with age, it is thought that hyperactivity and impulsivity associated with these cognitive-behavioural elements become more pronounced with the greater cognitive demand, typically seen as development and maturity progress. As such, hyperactivity and impulsivity in AD/HD may not be a ubiquitous behavioural trait in adolescence, but perhaps more reflective of compensatory behaviour due to deficits in complex information processing abilities.

The age-related development of EF and RI deficits thought to stem from childhood novelty-seeking behaviour, alongside age-resistant inattention, were further defined by Factors 2, 3 and 5 in adolescence. Deficits in general task performance have repeatedly been shown in the previous research (refer to Chapter 4 for a discussion). Specific to Factors 2 and 5, these results support those previous that have found deficits in visuo-spatial learning (Aman, Roberts, & Pennington, 1998; Armstrong,
Hayes, & Martin, 2001; Carter, Krener, Chaderjian, Northcutt, & Wolfe, 1995b), and visual response inhibition (Albrecht et al., 2005; Brandeis et al., 1998; Johnstone & Clarke, 2009; Oosterlaan et al., 1998) in AD/HD populations compared to normal Controls.

The finding that task-related hyperactivity and impulsivity as relating to Factors 2, 3 and 5 didn’t successfully distinguish Clinical from Control groups in childhood, show that the inherent heterogeneity commonly viewed in AD/HD populations, is most pronounced in childhood, rather than in adolescence. The constant changes seen in the developing child around the ages of 6-12 years is undoubtedly a confounding factor in the search for what constitutes abnormal or maladaptive behaviour at this age. From the present results, there did not appear to be any consistent pattern of impairment in AD/HD children aged 6-12 years in complex processing related to task difficulty, visuo-spatial learning, error-monitoring, orienting of attention and automatic inhibition, visual response inhibition, or auditory selective attention. This result was found irrespective of comorbidity. It is tempting to argue that such a result is due to the inclusion of AD/HD+INT which were by far the most heterogeneous group in childhood, however a post hoc Two-Step Cluster Analysis with this cohort removed produced a comparable 1-cluster result. Given this, it appears that the impairment commonly seen in childhood AD/HD either: (1) lies outside the above named domains, or (2) is not adequately captured by the tasks employed in this thesis. With respect to the latter, given that the six tasks utilised here are robust markers of their respective neurocognitive domains and have previously shown deficits in AD/HD compared to Control populations, it is doubtful that the lack of significant results in childhood is task related. Rather, it appears that impairment in childhood is highly variable, making it difficult to generalise maladaptive behaviour at this age. Therefore, childhood AD/HD diagnosis would benefit from a dimensional approach to impairment and diagnosis. This would not only allow a more comprehensive understanding of age-related impairment, but also allow ‘at-risk’ or prodromal individuals to be identified and treated more effectively. The latter is of particular importance as the current DSM operates according to an ‘extensiveness threshold’, which requires the presence of an arbitrary number of symptoms for AD/HD diagnosis. However it is well known that
severity is not simply a matter of counting symptoms, as severe impairment on few symptoms can result in poorer outcomes than mild impairment on many symptoms. A meta-analysis by Faraone et al (2003) for example, found that the rate of AD/HD diagnosis diminished dramatically when accounting for impairment, rather than just the number of symptoms present (16.1% vs. 6.8%, 15.8% vs. 0.2%, etc). This finding was supported by Gordon et al. (2006) who found the number of participants diagnosed with AD/HD based on symptoms alone decreased by 77% when accounting for impairment. In an adult sample, Solanto, Marks, Wasserstein and Mitchell (2011) found that the six symptom threshold for AD/HD hyperactivity/impulsivity failed to capture almost half of significantly impaired adults who reported overt behaviour at least 1.5 standard deviations above the population mean. Given this, a modification to the current AD/HD nomenclature to allow a dimensional approach to classifying impairment in childhood would allow the heterogeneity typically seen in this age group, to be meaningful as an indicator of age-related severity and neurocognitive development, rather than as a confound.

In summary, a dimensional perspective with emphasis on novelty-seeking behaviour and inattention would enhance the conceptualisation and the subsequent effective diagnosis of AD/HD in childhood. In adolescence, cognitive-behavioural factors governing visuo-spatial learning, general task performance, and visual response inhibition can provide an objective measure of functioning and impairment. Taken together, these factors may serve as adjuncts or supportive measures in the diagnostic process of adolescent AD/HD, or as markers of impairment in longitudinal studies of AD/HD.

10.5 Limitations of the Present Thesis

There were a number of limitations in the methodology employed in this thesis. These limitations will be discussed in the following sections with regards to participants (both Clinical and Control groups), and methodological design.
10.5.1 Participant Limitations

Probably the most notable limitation pertains to the Clinical group and refers to the methods by which each participant was diagnosed and recruited into the study. Since the AD/HD cohort was recruited from multiple sites, this resulted in independent diagnoses being made from multiple diagnosticians. Although efforts were made to maintain inter-rater reliability, each AD/HD and comorbid diagnosis was not cross-checked with each clinician. The cross-checking of each diagnosis (though ideal) was not practical given the distance between sites (interstate), and the number of AD/HD participants. However, as stated in the Methodology chapter of this thesis (Chapter 6), the Diagnostic Interview for Children and Adolescents (DICA) was used to support each diagnosis and the Conners’ Parent Rating Scale – Revised, Long form (CPRS-RL) was also used to establish the level of symptom severity in the Clinical group. Therefore, despite the methods of diagnosis, these supportive measures allow the reliability of each AD/HD diagnosis to be maintained.

The AD/HD sample employed in this thesis was recruited from a clinical rather than a community setting. This may have biased the sample towards those that are more severely impaired (Gadow, Sprafkin, & Nolan, 2001) and hence somewhat limit the generalisability of the results. In addition to this, Clinical participants who had undergone a 48-hour washout period from medication were accepted into the study alongside those that were medication naïve. Washout participants were accepted into the study to avoid bias towards those that may be less severely impaired, and hence increase the generalisability of the results. If the participant sample assessed in this thesis is in fact significantly more impaired than other AD/HD samples reported in previous research, then this would in part explain the level of severity seen across age groups. The present findings show significant task-defined impairment in addition to the retention of overt pathology into adolescence, while previous research has argued a general dissipation of symptoms with age. The findings of this thesis require replication in community samples with AD/HD, in addition to samples that are medication naïve, in order to confirm these results.
The recruitment methods also present a potential limitation in the Control group. Although a diagnosis of AD/HD was an exclusionary criterion, whether or not such a diagnosis was present was based solely on the parent’s report and results from the SPHERE-12 (refer to Chapter 6, Section 6.1.3), rather an assessment by a clinician. As a result, there is a possibility that a small sample of the Control group had undiagnosed AD/HD or AD/HD-like symptoms. If the currently reported prevalence rate of AD/HD in the general population is adopted, this would imply that around 10% of children in the Control population (n = 13) have undiagnosed AD/HD. If this were in fact true, it would explain the n = 7 Control participants who were grouped into the more severe Cluster 2 (Chapter 9), in addition to the single cluster result found in the child group. In order to counteract such confounds, future research should screen the Control group for undiagnosed AD/HD pathology using behaviour rating scales such as the CPRS-RL. Ideally, a ‘pure’ Control sample would be free of sub-threshold AD/HD symptoms also.

A second limitation pertaining to the participant groups lies with the Clinical group AD/HD-NK. Upon initial assessment, children and adolescent AD/HD-NK participants did not present with comorbid pathology as per each respective diagnostician’s report. Importantly, no participant in the AD/HD-NK group met diagnostic criteria for ODD/CD, which was the main focus of this thesis. However, this does not rule out comorbidity altogether in this group, since not all comorbidity was tested for. Given this, coupled with the well-documented high incidence of comorbidity in AD/HD, the possibility of some sub-threshold comorbidity within this Clinical group is possible. However, since ODD/CD comorbidity in AD/HD was the focus of this thesis, the possibility of comorbidity other than ODD/CD in the AD/HD-NK group is not a significant confound.

In terms of ODD/CD comorbidity; there is some debate whether the two disorders - ODD and CD - should be combined when investigating their impact on AD/HD. The considerable commonality between the two disorders, particularly given that ODD is considered an antecedent to CD, has resulted in their combination in the overwhelming majority of the previous literature. However, there are some authors who believe that ODD and CD should be assessed independently in AD/HD cohorts.
(Connor & Doerfler, 2007). It may be possible that the ‘ODD/CD’ comorbidity in AD/HD children was more related to ODD than CD based purely on the nature of the diagnostic characteristics of CD. Although a child diagnosis of CD is not uncommon, the diagnostic criteria is noticeably geared towards older children and adolescents (for example ‘has forced someone into sexual activity’, ‘has broken into someone else’s house, building, or car’, ‘often stays out at night despite parental prohibitions’, etc), therefore it is less likely that a child aged 6-12 years would commit these acts than those aged in their teenage years. Given this, there appears appreciable benefit in assessing the influence of ODD and CD in AD/HD separately. Unfortunately, the sample size in the comorbid AD/HD group assessed in this thesis limited this avenue of investigation.

Also, in terms of the AD/HD+INT cohort, there may be some benefit in excluding Learning Disorder (LD) from the ‘internalising’ category. There has been some debate over whether or not learning problems are associated with internalising pathology. While some research has shown a positive association (Becker & Langberg, 2012), others have not (Garner et al., 2012). Given the considerable heterogeneity seen in AD/HD+INT children (see results of Chapter 7), it may be more methodologically valid to exclude LD when investigating comorbid internalising disorders.

Finally, there is a small possibility that the measured deficits in the AD/HD group were context specific. That is, symptomatology can change in response to such factors as the testing environment, the perceived difficulty of the task, motivation, etc. Therefore, the deficits measured by each task may in fact be a product of the context rather than AD/HD itself. If this is the case, then context-specific variability may play a large role in accounting for symptom heterogeneity.

10.5.2 Limitations in Methodological Design

There were two limitations concerning the methodological design of the present thesis. The first relates to data reduction, while the second relates to the cross-sectional design.
Data reduction (PCA) was used in order to maintain adequate statistical power; it is impractical to incorporate every ERP (amplitude and latency) and corresponding psychometric variable from six different tasks into the analysis. The results from the PCA clearly indicated the existence of distinct factors however it is the interpretation of these factors that may house some uncertainty. The factors that significantly contributed to each classification were discussed in terms of which cognitive or behavioural constructs they may represent. This was established based on the nature of the highest loading variables on each factor [with a “high” loading defined as at or above .6 (Hair et al., 1998)], which were seen as the best determinants of the underlying functionality. Despite this, there is still some possibility that the factors do not measure the hypothesised underlying constructs. Given this, the findings obtained using the factors from PCA require replication in future research.

The cross-sectional design of the study meant that the influence of comorbidity on the developmental course of AD/HD could not be examined. Therefore, the results obtained in this thesis pertain only to task-related impairment and the influence of ODD/CD comorbidity in AD/HD at two age-specific time points in development.

10.6 Directions for Future Research

There are numerous possible directions for future research given the findings of this thesis, though since this is the first investigation into the neurocognitive profiles of comorbid AD/HD - particularly AD/HD+ODD/CD - in two age groups, the primary direction for future research would be in replicating these results. There are three fundamental aspects of the present thesis that present opportunities for replication in future research: (1) the neurocognitive profiles of child and adolescent comorbid AD/HD groups, (2) the comparative uniqueness of the AD/HD+ODD/CD phenotype in adolescence, and (3) the three neurocognitive factors as possible markers of impairment in adolescent AD/HD.
The aetiology of AD/HD has taken multiple paths in the previous research however none have effectively encapsulated the entire disorder. This is not due to any lack of investigative effort, but rather due to the inherent heterogeneity of the symptomatology in AD/HD, combined with the high prevalence of comorbidity, which have become so characteristic of the disorder. As such, the present findings represent a first endeavour into constructing neurocognitive profiles of AD/HD with comorbid externalising and internalising disorders. In order to validate the reliability of these profiles, future studies should aim to replicate these results with other robust measures of executive function, response inhibition, and selective and sustained attention, to those utilised here.

The greater symptom severity of AD/HD+ODD/CD compared to AD/HD-alone has been well reported in the previous literature, however such research has only skirted around the concept of AD/HD+ODD/CD as an additional AD/HD subtype or distinct pathological entity in the DSM nomenclature for Disruptive Behaviour Disorders. Comorbidity has become so ubiquitous in the AD/HD picture, that it is now uncommon to diagnose AD/HD without comorbidity. Comorbidity between AD/HD and ODD/CD is by far the most common, and typically produces the most debilitating outcomes (see Chapter 3 for a detailed discussion). From this, the logical question is whether or not AD/HD+ODD/CD encompasses enough symptomatic uniqueness to warrant a separate diagnosis in the DSM. It is well known that this approach has been adopted by the ICD-10, in their diagnosis of Hyperkinetic Conduct Disorder (HCD). The present results support the adoption of a similar nomenclature in the DSM. A comparative analysis of AD/HD+ODD/CD and HCD would help in establishing the validity of a separate diagnosis for AD/HD+ODD/CD in future updates of the DSM.

The three neurocognitive markers found here represent task-related anchors of impairment in adolescent AD/HD. Previous research has shown general task performance deficits, visual response inhibition deficits, and visuo-spatial learning deficits in AD/HD, hence the validity of these factors as characteristics of AD/HD-associated impairment appear robust. However, the specificity of these factors to adolescent AD/HD impairment requires validation in future studies. Future research
could also assess the usefulness of these factors as adjuncts to the diagnostic process for AD/HD, and whether these factors provide an objective and reliable measure of age-related impairment.

Finally, the limitations of the present thesis should be addressed in future research to support the validity and reliability of the results found here.

### 10.7 Conclusions

This thesis presents both hypothesis-driven and data-driven investigations of comorbid AD/HD; the symptom behaviour profiles, the cognitive-behavioural profiles, the diagnostic utility of an auditory Oddball task, the impact of ODD/CD comorbidity in AD/HD children and adolescents, and possible diagnostic aids. Data from an auditory Oddball Task, Continuous Performance Task (CPT), Go/No-Go (GNG) task, Executive Maze task, Switching of Attention (SOAT) task, and Verbal Interference Task (VIT) were utilised as measures of executive function, response inhibition, and selective and sustained attention.

An investigation into the predictive utility of the auditory Oddball task in discriminating between AD/HD comorbid groups showed some promise as a diagnostic adjunct to the DSM- or ICD-based clinical assessment. An extension of previous work by Smith et al., the Oddball task showed modest accuracy in classification that increased with age, suggesting that the commonly seen dissipation of symptoms with age is not a prominent feature when comorbidity is present. Classification was primarily based on indices of cognition, represented by ERP components thought to underlie inhibitory processes.

The neurocognitive profiles of AD/HD+ODD/CD and AD/HD-NK children both involved high novelty-seeking behaviour coupled with attention difficulties. Impairment in re-orienting of attention appeared specific to AD/HD+ODD/CD children, compared to
AD/HD-NK. AD/HD+INT children however, displayed a symptomatically diffuse profile that suggested significant task-defined heterogeneity. All groups, irrespective of comorbidity, showed greater task-defined impairment in adolescence compared to childhood, as indexed by poor task performance. AD/HD+ODD/CD were unsurprisingly the most impaired group irrespective of age, suggesting that the impact of ODD/CD comorbidity produced greater task-defined impairment that either AD/HD-alone, or AD/HD with internalising comorbidity, and this impairment was age-resistant.

The impact of ODD/CD comorbidity on AD/HD was further emphasized when investigating data-driven cluster formation. In adolescence, two clusters were found that appeared representative of a ‘normal’ or ‘sub-clinical’ Cluster 1 that comprised majority of the Controls and AD/HD-NK, and an impaired Cluster 2 which comprised majority of the comorbid AD/HD groups, particularly AD/HD+ODD/CD. It is thought that the two cluster solution was primarily based upon task-defined levels of impulsivity and hyperactivity. A permutation analysis revealed a unique neurocognitive profile of AD/HD+ODD/CD compared to AD/HD-NK in adolescence, based on the three most significant factors that determined cluster membership: visuo-spatial learning (Factor 2), task performance (Factor 3), and visual response inhibition (Factor 5). These results lend support to the contention that AD/HD+ODD/CD represents an entity that is pathologically distinct to AD/HD-NK; however this appeared valid only in adolescence, and not in childhood. Also, the three significant factors (2, 3, and 5) represent neurocognitive constructs that may help to objectively measure impairment in adolescent AD/HD, and hence serve as adjuncts in the diagnostic process.

The childhood analysis produced only one cluster, highlighting the significant task-defined symptom heterogeneity, which appeared most pronounced at this age compared to adolescence. Heterogeneity may be best explained on a dimensional scale of increasing symptom severity, rather than the existing categorical one adopted by the current DSM. Therefore, a dimensional approach to identifying impairment and the resultant diagnosis of AD/HD and associated comorbidities is urged in childhood.
In summary, the results of this thesis urge a re-visit of the diagnostic methodology for AD/HD employed by the current DSM; specifically that pertaining to age-related changes in impairment, and the impact of externalising pathology such as ODD/CD. It is hoped that these findings, taken together, will not only aid in the continuing disambiguation and future nomenclature of AD/HD, particularly that of AD/HD+ODD/CD, but will also motivate further research to replicate these results.
References


Kell, D. B., & Oliver, S. G. (2004). Here is the evidence, how is what the hypothesis? The complementary roles of inductive and hypothesis-driven science in the post-genomic era. *BioEssays, 26*(1), 99-105


Kohn, A. (1989). Suffer the restless children: Though nearly a million children are regularly given drugs to control "hyperactivity", we know little about what the disorder is, or whether it is really a disorder at all. *The Atlantic, 264*(5), 90-98.


Evidence from an event-related functional magnetic resonance imaging study. *Biological Psychiatry, 59*, 643-651.


Shi, T., Li, X., Song, J., Zhao, N., Sun, C., Xia, W., et al. (2012). EEG characteristics and visual cognitive function of children with attention deficit hyperactivity disorder (ADHD). *Brain and Development.*


Multimodal Treatment Study of Children with ADHD. Archives of General Psychiatry, 56(12), 1073-1086.


Appendices
Appendix A: Somatic and Psychological Health Report 12 (SPHERE-12)

Somatic Symptoms:

- Muscle pain after activity?
- Needing to sleep longer?
- Prolonged tiredness after activity?
- Poor sleep?
- Poor concentration?
- Tired muscles after activity?

Psychiatric Symptoms:

- Feeling nervous or tense?
- Feeling unhappy or depressed?
- Feeling constantly under strain?
- Everything getting on top of you?
- Losing confidence?
- Being unable to overcome difficulties?

Response scoring:

0 = Never or some of the time
1 = A good part of the time
2 = Most of the time

Scores of 2 or more on the Psychiatric Symptoms set in addition to a score of 3 or more on the Somatic Symptoms set is suggestive of a depressive, somatic, or anxiety disorder. These individuals are labelled “SPHERE-12” cases.
Appendix B: Computer-Based Questionnaire - Areas of Assessment

The following is the list of psychological and demographic questionnaires and areas of assessment contained within the computer-based questionnaire. This questionnaire was administered to both Clinical and Control participants prior to undertaking the psychophysiologica}nal and psychometric tests.

- Personal details
- Vision
- Hearing
- Mobility
- Handedness
- Mobile phone use
- Learning difficulties/Dyslexia
- Psychiatric history
- Neurological history
- Sleep history
- Eating habits
- Smoking history
- Alcohol history
- Marijuana use
- Recreational drug use
- Relevant surgery
- Physical trauma
- Overall health (SPHERE-12)
- Wellbeing (Depression Anxiety Stress Scale: DASS)
- Emotional intelligence (Emotional Quotient: EQ)
- Prescription drugs
- Early life stress
- Traumatic experience
List of Publications:

Chapter 9 of this thesis has been formatted for publication and has been submitted to PLoS ONE (an ERA A ranked journal). The paper was accepted for publication by PLoS ONE on 25\(^{th}\) of June 2012; see below for citation. This information is given as a footnote on the title page of Chapter 9 (p. 188).