An exploratory study of links between ADHD and a chromosomal mutation in a single family

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Acknowledgments

This study came about through the perseverance of someone who cared very much about her family. I would like to thank her for offering me the opportunity to help her find some answers, and all those members of the family who participated in the study. It was difficult to face the possibility that there may be some problem in their family, particularly for those adults who saw this passed onto their children.

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Genetics and ADHD:
Defining and measuring a complex phenotype

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The aim of this paper is to review evidence of genetic factors in the aetiology of Attention Deficit Hyperactivity Disorder (ADHD). The review examines our current understanding of ADHD, including behavioural criteria, development, and cognition. It is concluded that there are a number of limitations in our current understanding of ADHD, stemming from high levels of co-morbidity, qualitative differences among subtypes, variable research methodology and a heavy reliance on a top down approach to research. The research literature contains a large amount of variation in measurement associated with defining ADHD as a behavioural phenotype, hampering genetic research. It is concluded that there is strong evidence supporting a genetic component to ADHD. Family, twin and molecular studies suggest ADHD may be part of some continuum, with a number of disorders having common genetic vulnerability, and that many genes interacting with environmental variables may be involved. It is suggested that future research should be longitudinal and family based in order to link behavioural, cognitive and genetic characteristics of ADHD as they emerge across the lifespan, and thereby inform our understanding of ADHD on a number of levels.
There is a large body of evidence to suggest that psychopathology runs in families, and that family history is a strong predictor of psychopathology (Rende & Plomin, 1993). However, the interplay between nature and nurture in psychiatric conditions is complex. It is therefore not clear to what extent this familial aggregation is due to genetic or environmental factors.

As quantitative and molecular genetic methods of investigation have developed, genetic factors have become the subject of increasing study in the psychiatric literature. Some extremists have taken the view that molecular genetics may hold the key to fitting psychiatric syndromes “into standard biological moulds”, and potentially offer a precise diagnostic system (Reiss, Plomin & Hetherington, 1991, p. 290). Research to detect a putative genetic contribution to the development of diagnostic conditions has been attempted for most psychiatric conditions. As we can never prove the biological substrate for psychiatric conditions is not there, we end up with a lot of research that is simply fishing for answers. Correspondingly, most diagnostic categories are supported by findings implying there is some genetic influence (Pam, 1990).

Although demonstrating the familial transmission of a psychiatric syndrome is often seen as validation of the syndrome as a diagnostic entity, there are many different levels of explanation for psychiatric conditions. Anatomical, physiological, biochemical and genetic findings cannot be considered in isolation from behavioural, cognitive, developmental and sociological levels of explanation. The difficulty in psychological research lies in conceptually linking biological and psychological levels of explanation. To formulate hypotheses that link biological and psychological states each level of description must be as accurate as possible. Studies in behaviour
genetics are complicated by the measurement error associated with defining psychiatric conditions or specific behaviours as a phenotype (Hay, 1985).

The aim of this paper is to review evidence of genetic factors in the aetiology of Attention Deficit Hyperactivity Disorder (ADHD)\(^1\). However, the validity of the ADHD diagnosis (Prior & Sanson, 1986; Rutter, 1983) and ethics behind the diagnosis (Rasch, 1994) have both been questioned. This suggests that there may be a high level of measurement variability in defining ADHD as a behavioural phenotype for genetic research. Moreover, genetic vulnerability may be dimensional, rather than categorical in nature. The review therefore firstly examines our current understanding of ADHD.

Psychiatric conditions are assessed by observer or self ratings of cognitive, physiological and behavioural symptoms outlined in clinical diagnostic systems such as the Diagnostic and Statistical Manual, 4th edition (DSM-IV, APA, 1994) or ICD Classification of Mental and Behavioural Disorders, 10th edition (ICD-10, WHO, 1993). The DSM-IV defines ADHD as a maladaptive pattern of inattention and/or hyperactivity-impulsivity, inconsistent with developmental level, and being manifested before age seven (APA, 1994). Although considered a childhood disorder, ADHD is beginning to be understood as a pervasive condition that continues into adulthood. The review examines the research on developmental courses and predictive factors for outcome in individuals with ADHD, as this may have a significant impact on diagnosis, as well as how we conceptualise the aetiology of ADHD. According to DSM-IV and ICD-10, ADHD is defined using a behavioural paradigm (impairments in functioning rather than operationally defined definitions). Diagnosis is based on parent and teacher reports of behaviour, i.e. clinical history. Implicit in the literature

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\(^1\) For simplicity the term ADHD will be used as a generic term to refer to the DSM-IV diagnosis and its predecessors (DSM-II, DSM-III, DSM-III-R) unless otherwise specified.
is tacit acceptance that children with ADHD have a cognitive impairment, an “attention deficit”. However, the DSM-IV and ICD-10 do not define ADHD as a disorder of cognitive processing. The distinction between the psychological understanding of attention and the behavioural presentation made in diagnosis is therefore not clear. The review looks at the cognitive functioning of individuals with ADHD. Studies examining attention and response inhibition, which are believed to reflect the clinical constructs of inattention, distractibility and impulsivity, are highlighted.

Research indicating that ADHD symptoms may result organically through brain injury (Max et al., 1998), or genetically as part of another syndrome such as Fragile X (Hagerman, 1996), and the effective treatment of ADHD with stimulants, all suggest there can be a strong biological basis to ADHD. This review focuses on the evidence for a genetic basis, looking specifically at family, twin and molecular studies, and the possible impact of our current understanding of ADHD on this research.

Understanding ADHD

While once essentially unheard of, ADHD is now the most frequently diagnosed childhood psychiatric condition (Halperin et al., 1993). Prevalence rates are in the order of 3% - 5% in school-age children, with males being affected more often than females, with a ratio of approximately 4:1 (APA, 1994).

ADHD is characterised by a persistent pattern of inattention and/or hyperactivity (APA, 1994). Children with ADHD have a lack of direction and control that leads to symptoms including not finishing tasks, switching from one task to another, being easily distracted, forgetful, not following rules, acting before they
Attention-Deficit/Hyperactivity Disorder: Diagnostic criteria

A. Either (1) or (2) to a degree that is maladaptive and inconsistent with developmental level for past 6 months:

(1) Six (or more) symptoms of inattention:
   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 in tasks or play in which remaining seated is expected.
   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.
   e) Often has difficulty organising tasks and activities.
   f) Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort.
   g) Often loses things necessary for tasks or activities.
   h) Is often easily distracted by extraneous stimuli.
   i) Is often forgetful in daily activities.

(2) Six (or more) symptoms of hyperactivity-impulsivity
   a) Often fidgets with hands or feet or squirms in seat.
   b) Often leaves seat in classroom or in other situations in activities.
   c) Often runs about or climbs excessively in situations in which it is inappropriate.
   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.
   g) Often blurts out answers before questions have been completed.
   h) Often has difficulty awaiting turn.
   i) Often interrupts or intrudes on others.

Some hyperactive-impulsive or inattentive symptoms that caused impairment must have been present before age 7 years, present in two or more settings and be associated with clear evidence of clinically significant impairment in social, academic or occupational functioning.

Subtypes:
Attention-Deficit/Hyperactivity Disorder, Combined Type: both Criteria A1 and A2 are met
Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive Type: Criterion A1 is met but not Criterion A2
Attention-Deficit/Hyperactivity Disorder, Predominantly Hyperactive Type: Criterion A2 is met but not Criterion A1
Note: For individuals who currently have symptoms that no longer meet the full criteria, "In Partial Remission" is specified.

Changing diagnostic criteria complicate understanding of ADHD. The symptom cluster initially fell under the rubric of Minimal Brain Damage or Dysfunction, implying an organic aetiology. This terminology was replaced by Hyperkinetic Reaction of Childhood in the DSM-II (APA, 1968), which emphasised a behavioural description of the condition (Schaughency & Hynd, 1989). Attention Deficit Disorder (ADD) first appeared in the DSM-III (APA, 1980), and shifted the
emphasis to a cognitive deficit, and hyperactivity became a criterion for distinguishing a number of subtypes (ADD with hyperactivity (ADD/H), ADD without hyperactivity (ADD/WO), and ADD residual type). In DSM-III-R (APA, 1987) the subtypes were removed and a unidimensional diagnostic category was adopted, this time termed Attention Deficit Hyperactivity Disorder (ADHD). ADHD, as defined by the DSM-IV, now lies conceptually between the multi-dimensional model in DSM-III and the uni-dimensional model used in DSM-III-R. In DSM-IV (APA, 1994) inattention and overactivity are considered equal contributors to ADHD, although children may show one type of symptom only. Impulsivity is considered one of the core features of ADHD, however factor and cluster analysis support the presence of only two separate factors, hyperactivity/impulsivity and inattention, not three (Schaughency & Hynd, 1989). More recently, research on female twins has found three dimensions, reflecting the three subtypes of ADHD described in the DSM-IV (Hudziak et al., 1998).

The ICD-10 (WHO, 1993) criteria for Hyperkinetic Disorder are essentially the same as those for ADHD, however the child must exhibit six symptoms of inattention, three symptoms of hyperactivity (criteria 2a-2e in table 1) and one symptom of impulsivity (criteria 2f-2i in table 1). They are therefore diagnosed with combined type of ADHD and possibly a more severe form of the disorder (Faraone, Biederman, Weber & Russell, 1998). The ICD-10, unlike the DSM-IV, does not allow multiple diagnoses. It does however have a separate category, Hyperkinetic Conduct Disorder, which reflects the high level of co-morbidity between ADHD and Conduct Disorder. ADHD is often co-morbid with Oppositional Defiant Disorder or Conduct Disorder, and there is a high rate of co-morbidity with Mood, Anxiety, Learning, Communication and Tourette’s Disorders (APA, 1994).
Although once believed to fade with age, ADHD is increasingly accepted as a pervasive condition. Prevalence rates in adults are estimates only, but place it conservatively at 0.3% (Shaffer, 1994) and as high as 2% (Biederman, Faraone, Spencer et al., 1995).

It has recently been argued that the DSM-IV subtypes could represent developmental phases of ADHD (Barkley, 1997; Faraone et al., 1998). The field trials for DSM-IV on children aged between 4-17 years found that inattentive individuals were the oldest, followed by the combined type, and finally the hyperactive-impulsive subtype which was present mostly in pre-school children (Lahey et al., 1994). This pattern has been replicated in some but not all studies (Faraone at al., 1998). Suggestions that the hyperactive-impulsive subtype is “a developmental precursor to the combined type” (Barkley, 1997, p.67) need to be established through longitudinal studies that consider development into adulthood, as well as different rates of psychopathology among the subtypes (Faraone et al., 1998). This pattern may reflect the interaction of symptoms with environmental demands as they change over time. It has further been argued that the inattentive subtype of ADHD may be so qualitatively different from the hyperactive-impulsive subtype as to constitute a separate disorder (Barkley, DuPaul & McMurray, 1990). The inattentive subtype is reported to differ from the hyperactive/impulsive subtype in a number of areas including age and gender prevalence (Lahey et al., 1994), association with poorer academic achievement (Lamminmaki, Ahonen, Narhi, Lyytinen & Todd de Barra, 1995), cognitive deficits such as impaired perceptual motor speed (Barkley, DuPaul & McMurray, 1990), and patterns of associated psychopathology such as more anxiety disorders among relatives (Barkley, DuPaul & McMurray, 1990).
differences have not been consistently replicated (Faraone et al., 1998), and more research is required to confirm such a distinction.

Reviews of retrospective and prospective outcome studies have concluded that there are three broad developmental courses of ADHD which are shown in Table 2. It is difficult to estimate the percentage of cases likely to fall into each of these groups due to the overlap between them (Weiss & Hechtman, 1993). Although the majority of adults experience either developmental delay or continual display of symptoms, the potential for children with ADHD to experience developmental decay and possibly require psychiatric hospitalisation or spend time in jail is concerning.

Table 2. Developmental Courses of ADHD (based on Cantwell, 1996 and Weiss & Hechtman, 1993).

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<td>Type of Course</td>
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<td><strong>Continual display</strong></td>
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<td><strong>Developmental decay</strong></td>
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Adolescent Outcome

Adolescence brings with it increased cognitive, academic, personal and social demands. Children with ADHD greet adolescence with pre-existing difficulties including learning gaps, poor social relationships and low self-esteem (Weiss & Hechtman, 1993). Research reveals an overall picture of children diagnosed with
ADHD going on to experience significant academic, social and conduct difficulties in high school (Weiss & Hechtman, 1993), including significantly more grade retention, suspension and dropping out (Barkley, 1991). The core symptoms of inattention and impulsivity appear to abate with age, although scores on tests of both symptoms remain significantly poorer compared to scores of normal controls (Fischer, Barkley, Edelbrock & Smallish, 1990). Hyperactivity on the other hand appears to decline almost completely, with only residual restlessness apparent, such that "rebelliousness" rather than "overactivity" is the greater concern of people in the adolescent's life (Weiss & Hechtman, 1993). Evidence of continual symptoms of ADHD along with antisocial and drug abuse disorders presents the worst outcome for the adolescent (Manuzza, Klien, Bessler, Malloy & LaPadula, 1993).

**Adult Outcome**

The adult with ADHD is seen as disorganised, impatient, distractible, impulsive, easily bored, procrastinating, having poor concentration, difficulty following through, low frustration tolerance, mood swings, and low self-esteem (Cantwell, 1996; Hallowell & Ratey, 1997). Prospective studies have shown that while many children with ADHD outgrow the disorder, at least 11% (Manuzza et al., 1993) and as many as 36% (Weiss, Hechtman, Milroy & Perlman, 1985) continue to experience at least one residual symptom of ADHD that significantly impairs their functioning. The discrepancy in these findings may be due to methodological differences, for example the study by Manuzza et al., (1993) used parental reports while the study by Weiss et al., (1985) used self-reports.

Weiss et al., (1985) found that adults with childhood ADHD had more symptoms of psychopathology, poorer social skills and lower self-esteem than
controls. While they were employed, they experienced difficulties at work as evidenced by having had more job changes, been laid off more often, having lower status jobs, and were rated by employers as being poorer at fulfilling work adequately, working independently and getting along with supervisors. Weiss & Hechtman (1993) suggest the research indicates there is a trend toward greater alcohol and drug use due to a small group who may be heavily involved in drugs. However other studies have found a significantly higher rate of substance use disorders (Biederman, Faraone, Spencer et al., 1995), particularly when there is a concurrent diagnosis of Antisocial Personality Disorder (Manuzza et al, 1993). The significant risk of Antisocial Personality Disorder is of great concern, with research indicating that 18% (Mannuzza et al., 1993) to 23% (Weiss et al, 1985) of adults have Antisocial Personality Disorder at follow up.

Predictive factors

Given the possibility of a severely impairing outcome for perhaps as many as 30% of children diagnosed with ADHD (Cantwell, 1996), the identification of predictive factors is essential. Antisocial activity and IQ predict antisocial behaviour and poor academic achievement respectively, as well as impacting on overall functioning in both adolescents and adults (Barkley, 1991; Weiss & Hechtman, 1993). Family factors including socioeconomic status (SES), mental health of family members and emotional climate of the home, appear to have a global effect on functioning rather than leading to specific outcomes (Weiss & Hechtman, 1993; Barkley, 1991). While it seems clear that the interaction between social and individual factors influences outcome, many of the specific pathways and connections remain unknown. Evidence that parent personality traits such as agreeableness and
neuroticism may impact on the development of behavioural problems in the child with ADHD is now emerging (Nigg & Hindshaw, 1998). Adults who experience the poorest outcome, that is ongoing symptoms of ADHD, Antisocial Personality Disorder, or other psychiatric diagnoses, have been found to exhibit behavioural problems as children (Herrero, Hechtman & Weiss, 1994). At present it is not clear why some children outgrow these symptoms, while others continue to deteriorate, or develop other problems. However, family mental health has been shown to serve as a protective factor (Herrero, Hechtman & Weiss, 1994). Another possibility is the role of genetic influences on ADHD. Male siblings of probands with ADHD and Conduct Disorder, or ADHD probands with a parent with Antisocial Personality Disorder, have been reported to be at greater risk for ADHD (Faraone et al., 1995). Furthermore, persons with a familial case of ADHD have been shown to have poorer neuropsychological functioning on the Wisconsin Card Sorting Test, and Stroop Colour and Word Test (Seidman, Biederman et al., 1995). This suggests that a family history not only puts a person at risk for ADHD, but may put them at risk for a more severe form.

Summary

ADHD is not limited to childhood. The majority of children with ADHD continue to experience functionally impairing symptoms in adolescence and adulthood. The developmental course of ADHD has only been broadly characterised, perhaps due to the small number of prospective longitudinal studies examining children into adulthood. It is clear that the presentation of ADHD varies considerably with age. It is not clear whether these changes primarily reflect the development of ADHD or the cumulative impact of symptoms as they interact with environmental
factors over time. The emergence and impact of co-morbidity with conduct
deficits/hyperactivity and conduct problems/aggression are partially independent
domains, there is still considerable overlap (Hindshaw, 1987). Establishing co-
morbidity in adolescents and adults may be particularly difficult as diagnosis of
ADHD is currently made retrospectively, and hence with poor accuracy. Alterations
in the criteria for both adolescents and adults have been proposed (Barkley &
Biederman, 1997), though perhaps prematurely, and have met with criticism (Levin,
1998). Further elucidation of the adult phenotype of ADHD, through longitudinal
and genetic studies will be essential in clarifying the developmental course of ADHD
and associated diagnostic issues (Hay & Levy, 1996).

**Cognitive Functioning**

Studies looking at ADHD from a cognitive perspective have examined global
cognitive functioning (intelligence), as well as aspects relating to behavioural
presentation of inattention, distractibility and impulsivity. This includes *sustained
attention* (ability to maintain attention over an extended time), *selective or focussed
attention* (ability to selectively direct information processing toward relevant stimuli in
the presence of irrelevant stimuli), *divided attention* (ability to process relevant
information simultaneously), and *response inhibition* (delay of immediate
responding). Furthermore, some of the tests used are potentially useful in the
diagnosis of ADHD (Barkley & Grodzinsky, 1994), and should provide external
validation for parent and teacher symptom ratings of inattention, hyperactivity and impulsivity.

Intellectual functioning

While some studies have shown that the IQ scores of children with ADHD are below those of normal peers (Barkley et al., 1990), others have not been able to replicate these findings (Lamminmaki et al., 1995). Low IQ scores may reflect impaired attention on test performance, rather than a global cognitive deficit. There is evidence for a negative relationship between hyperactivity and intellectual functioning (Sonuga-Barke, Lamparelli, Stevenson, Thompson & Henry, 1994), however inconsistency in the research methodology and findings, suggests that ADHD as defined by the DSM-IV can occur in children of any intellectual level. Children with ADDH have been shown to have decreased vigilance, increased impulsivity and more delayed reading even when IQ is statistically controlled (Levy, Horn & Dalgish, 1987), suggesting the impairment is not a result of low intellectual functioning. However, there is a high rate of co-morbidity with specific learning disorders, which in some cases may be the result of a common genetic influence (Hay & Levy, 1995).

Specific patterns of results within the IQ test show a trend toward lower scores on the Freedom from distractibility (FFD) index of the WISC-R (Ehlers et al., 1997; Lufi, Cohen & Parish-Plass, 1990). This is consistent with difficulties in attention and concentration, although others have argued that this may reflect a deficit in working memory (eg., Barkley, 1997). Children with ADHD have also been found to perform poorly on tests such as The Tower of Hanoi (Weyandt & Willis, 1994), but as with the FFD index, working memory is only one of a number of mental functions required to successfully perform the task.
Attention

Attention is a diffuse and complex concept of which there is no consensual definition. It has been both difficult to define and investigate experimentally (Egeth & Yantis, 1997). Each of the different components is considered to be independent, but come together in performing a cognitive task as an integrated processing system (Sergeant & Van der Meere, 1990). A deficit in any one component therefore affects the overall efficiency of the system and produces poor attentional functioning.

Originally designed to detect brain damage (Rosvold, Mirsky, Sarason, Bransome and Beck, 1956), continuous performance tasks (CPTs) reveal a deficit in sustained attention in right frontal patients, evidenced by longer reaction times and omission of targets (Rueckert & Grafman, 1996). The inability of children with ADHD to stay on task is often described as a deficit in sustained attention. Not surprisingly, poor performance on CPTs by children with ADHD as compared to controls is a consistent finding (Chee, Logan, Schachar, Lindsay & Wachsmuth, 1989; Levy & Hobbes, 1997; Reader, Harris, Schuerholz & Denckla, 1994; Seidel & Joschko, 1991). Corkum and Seigel (1993) reviewing the use of visual CPTs found children with ADHD were less vigilant, but found no compelling evidence for a deficit in sustained attention, which they defined as a decline over time, compared to controls. The research on CPT performance of children with ADHD has shown that the number of omission errors (Reader et al., 1994), and commission errors (Seidel & Joschko, 1991), are significantly higher than those of controls. However, it appears to be slow reaction times and high variability of reaction times which are the most consistently distinguishing performance variables (Greenberg & Dupuy, 1993; Levy & Hobbes, 1997; Reader et al., 1994).
Based on Schneider and Shiffrin’s (1977) model of attention, Sergeant, Van der Meere and colleagues have done extensive research manipulating the CPT task to examine the different components of attention. Sergeant & Scholten (1985b) were unable to find a deficit in selective attention, defined as a limitation in the rate of encoding, search and decision in short term memory in hyperactive children. Their hyperactive subjects did however express a resource strategy limitation, increasing their errors but not their speed in a speed instruction set, suggesting they may not have the energy to rapidly deploy information processing (Sergeant & Scholten, 1985a). As with other studies using CPTs, Van der Meere and Sergeant (1987) have found hyperactive children showed poor task efficiency, they were slower, had more variable reaction times and more frequently made errors than control subjects. This did not appear to be due to a deficit in divided attention (inability to process relevant information simultaneously) or impulsive responding (defined as exchanging accuracy for speed). Furthermore Van der Meere and Sergeant (1988a) have been unable to attribute more variable responding and inaccuracy to the presence of distractors, with no apparent deficit in focused attention, or an inability to develop learning through shifting from controlled to automatic processing (Van der Meere and Sergeant, 1988c). Van der Meere and Sergeant (1988b) also concluded hyperactive children did not have a deficit in sustained attention, either using a CPT or self paced paper and pencil test (Van der Meere, Wekking & Sergeant, 1991). Unable to localise the deficit resulting in consistent task inefficiency in hyperactive children to the encoding (Sergeant & Scholten, 1985b), search, or decision stages of attention (Sergeant & Scholten, 1985a), Van der Meere and Sergeant (1988b), using an energetic model, proposed that children with hyperactivity had an arousal deficit. This was supported by their finding that with a slow presentation rate, children with hyperactivity showed a deficit in sustained attention (Van der Meere, Shalev, Borger & Gross-Tsur, 1995).
This research focused specifically on children with hyperactivity and thus may not generalise to children with ADHD as defined by DSM-IV, particularly the inattentive subtype.

**Response Inhibition**

Significantly higher commission errors on CPTs among ADHD subjects compared with controls is considered to reflect the clinical construct of impulsivity (Greenberg & Dupuy, 1993), which may be evidence of poor behavioural inhibition (Barkley, 1997). Evidence for a deficiency in response inhibition in children with ADHD also comes from poor performance on the Wisconsin Card Sorting Test (WCST, Heaton, 1981), a test that is sensitive to frontal lobe damage (Barkley, 1997). Children with ADHD are reported to perseverate (Boucugnani & Jones, 1989; Chelune, Ferguson, Koon & Dickey, 1986; Gorenstein, Mammatoo & Sandy, 1989; McBurnette et al., 1993), but this is not a universal finding (Reader et al., 1994). Many studies have reported that children with ADHD do not perform poorly on the WSCT and that it is not useful in distinguishing ADD from controls and other groups (Barkley, Grodzinsky & DuPaul, 1992; Fischer et al., 1990).

Keefe (1995) notes that performance on the WCST requires memory, auditory and visual attention, motor skills, abstraction, categorisation and executive control. The literature is not clear on exactly what ability is being tested (O’Donnell, Macgregor, Dabrowski, Oestreicher & Romero, 1994). Factor analysis shows the WCST can be seen as having two components, one relating to problem solving, measured largely by perseveration, and another one relating to attentional processes, measured by failure to maintain set (Greve, Williams, Haas, Littell & Reinoso, 1996). Children’s WCST performance however does not appear to correlate with
behavioural ratings of attention, (Riccio et al., 1994), and principal components analyses have shown the WCST to be a measure of conceptual ability rather than attention (O'Donnell et al., 1994).

Despite the difficulty in interpreting poor performance on the WCST, evidence that children with hyperactivity are less likely to alter responding when they make an error (Sergeant & Van der Meere, 1988) suggests a difficulty in response perseverance. Furthermore, many other tests support the notion of a deficiency in response inhibition including the Letter Cancellation Test (Grodzinsky & Diamond, 1992), and Matching Familiar Figures Test (Weyandt & Willis, 1994). Evidence of poor performance on motor inhibition tasks, higher activity and more vocalisations, and difficulties complying and resisting temptations also support this view (Barkley, 1997).

Similar to the concept of difficulty in delaying immediate responding is resisting interference. Children with ADHD perform poorly on the Trail Making Test (Gorenstein et al., 1989), and have slower performance on the disruption trial of the Stroop Colour and Word Test (SCWT, Golden, 1978; Gorenstein et al., 1989; Lufi et al., 1990; Seidman et al., 1995). The SCWT has been shown to be useful in differentiating disruptive boys with attention deficits from those without (Lavoie & Charlebois, 1994) and discriminating between ADHD and emotionally disturbed groups (Lufi et al., 1990). Furthermore, it appears that the more salient and frequent distractors are, the greater the likelihood is that they will interfere with task performance (Barkley, 1997).
Theories of cognitive functioning

There have been few attempts to bring together research findings in order to formulate a unified theory that links the behavioural symptomatology and cognitive impairment of individuals with ADHD. The work of Sergeant and Van der Meere described earlier is the most extensive body of theoretically driven research. However it is only informative about hyperactivity in children, and does not presently account for the developmental changes or symptom heterogeneity observed among individuals with ADHD.

Douglas (1983) reviewed the literature and proposed that children with ADHD had defective attention, inhibitory, arousal and reinforcement processes, linked to a difficulty in self-regulation (Douglas, 1988). Similarly, evidence of slow reaction times, variable attention, poor memory and learning in adults with ADHD compared with controls led Arcia and Gualtieri (1994) to suggest that adults with ADHD have difficulty in regulating their responses/processing resulting in inattention. However these suggestions of impaired regulation are more descriptive than predictive of ADHD deficits and functional impairments.

Poor behavioural inhibition has more recently been proposed as the central impairment in children with ADHD (Barkley, 1997). Barkley (1997) proposed that the core deficits experienced by children with ADHD were an inability to stop ongoing responses, to control interference, as well as to inhibit prepotent responses. This results in a number of secondary impairments in abilities, which depend on behavioural inhibition for effective functioning. These include deficits in working memory, self-regulation of affect/motivation/arousal, internalisation of speech and reconstitution. This in turn results in decreased motor control/fluency/syntax. These deficits result in observable symptoms, which include poor sustained attention,
distractibility, lack of task persistence, and poor self-control in the child with ADHD. Although the theory has yet to be tested, it provides a useful framework from which to develop hypotheses for future research.

Summary

The research on cognitive deficits in children with ADHD contains many discrepant findings. This reflects both the poor definition of cognitive constructs and the variety of tests used to assess them. A CPT and SCWT may both be cited as measuring distractibility, though they are vastly different tasks. Moreover, CPTs themselves come in a variety of formats, including varying task parameters (length, modality, stimuli, display times, presentation/event rates, task) and output (omission errors, commissions, reaction times, variability, signal detection theory). These tasks are often discussed interchangeably, so what is actually being measured is often not clear. Furthermore, since cognitive ability is not fixed (Hay, 1985), the age range of subjects may affect results.

Research has failed to identify a key core deficit measurable by a cognitive or neuropsychological test that can be used to consistently discriminate children with ADHD from other children. Some cognitive impairment may be a necessary feature, but it does not appear to be sufficient. Thus while there are a number of tests which are potentially useful in evaluating symptoms of ADHD, they could not be recommended as part of a routine assessment (NHMRC, 1995). The large behavioural diversity observed in ADHD may be the result of cognitive deficits interacting with personality features (Korkman & Peltomaa, 1991), in addition to a host of other factors, (attention difficulties, learning problems, low self-esteem, depression, aggressive, oppositional and antisocial behaviour, drug and alcohol abuse,
coercive child behaviours and negative cycles of parenting, family conflicts etc).
Therefore picking a cognitive deficit as a defining key feature may not necessarily be useful (Taylor, 1988). This highlights the need to consider biological, psychological and sociological factors as causative in functional disorders.

**Physiological and anatomical findings**

Symptoms of mild closed head injury including poor attention, organisation and problem solving are similar to those experienced by people with ADD (Arcia & Gualtieri, 1994). More specifically the clinical manifestation of deficits resulting from frontal lobe damage, particularly distractibility and impulsivity (Foster, Eskes & Stuss, 1994), bear striking resemblance to ADHD symptomatology.

Studies of the pathophysiology of ADHD report abnormality in the frontal regions and basal ganglia (Swanson, Sergeant, Taylor, Sonuga-Barke, Jensen & Cantwell, 1998). Functional imaging techniques have revealed the frontal and striatal region to be underactive in children with ADHD (Lou, Henriksen & Bruhn, 1990) and reduced global and regional glucose metabolism in the premotor and superior prefrontal cortex in adults with ADHD, (Zametkin et al., 1990). However the latter research was not replicated in a subsequent study of adolescents (Zametkin et al 1993). Anatomical imaging with MRI has shown a moderate reduction of 10% of volume in the frontal lobes, basal ganglia and corpus callosum (Swanson et al., 1998). Evidence that normal age-related decline in caudate nucleus volume does not occur suggests these changes are developmental abnormalities (Castellanos et al., 1994). Decreased brain activation of frontal and striatal regions is consistent with the deficit in activation found in information processing studies (Van der Meere et al.,1995), and deficits in motor inhibition proposed in Barkley's (1997) model. The distribution of
dopamine also implicates the frontal and basal ganglia regions, consistent with treatment effects seen with stimulant medications that affect dopamine systems.

Due to the heterogeneous nature of ADHD it may be that there are neurobiological subtypes of ADHD corresponding to the various behavioural symptoms. Teeter and Semrud-Clikeman (1995) point out that there are a large number of neuroanatomical hypotheses for ADHD, broadly divided into bottom-up/subcortical theories implicating the thalamic or hypothalamic regions, and top-down theories implicating cortical dysfunction of the frontal lobes and prefrontal/sagittal regions. The literature thus leans toward some sort of anterior-posterior gradient hypothesis to account for the differences between hyperactive and inattentive subtypes. As CT scans and EEG data have not been able to distinguish between subtypes and do not vary with severity of symptoms (Caparulo et al., 1982 in Schaughency & Hynd, 1989), research has yet to confirm such a biological basis.

The aetiology of the neurobiological dysfunction found in these studies is itself likely to be heterogeneous including lesional, particularly pre- and perinatal events, and genetic factors (Lou, 1996). This is further complicated by gene × environment interactions. Pregnancy, delivery and infancy complications including maternal illicit substance use, emotional problems and bleeding, predict ADHD, as well as poor cognitive functioning. These environmental influences however also have a genetic component (Milberger, Biederman, Faraone, Guite & Tsuang, 1997).

The genetics of ADHD

Research strategies used to examine the genetic contribution to ADHD include adoption, twin, family, and molecular genetic studies. Adoption and twin studies are essential to determine the relative genetic and environmental factors
involved. Family studies, while not able to separate genetic and environmental effects, provide important information on the mode of inheritance. Molecular studies are the newest development and consider defects at the level of DNA.

Cytogenetic findings have sometimes lead to establishing the location of genes for single gene disorders (e.g., cystic fibrosis), but this has been less successful in the psychiatric field. Initial reports of linkage between an abnormality of chromosome 5 and Schizophrenia inspired numerous attempts to map a susceptibility locus for Schizophrenia to chromosome 5, with little success (Palmour, Miller, Fielding, Vekemans & Ervin, 1994). Even when a gene is identified in a pedigree, this doesn’t tell us the frequency of that defective gene in the population (Rose, 1995). This is not to say that the identification of such anomalies is not useful. The association between Down’s Syndrome and Alzheimer’s Disease (AD) neuropathology alerted researchers to the role of chromosome 21 in AD. It has since been established that mutation of the APP gene on chromosome 21 is a rare cause of AD, and that there are three genes, which when mutated, can lead to early onset forms of AD (APP, PS1 & PS2), plus a fourth which is implicated as a risk factor (APOE; Lendon, Ashall & Goate, 1997). Mutations in the APP, PS1 and PS2 genes result in an increase in the levels of Aβ found in senile plaques, but we still do not know how this could lead to the neurofibrillary tangle formation or neuronal cell loss associated with AD.

Identification of a gene does not immediately reveal how the gene results in the observed behaviour/condition (Rose, 1995).

Fragile X Syndrome serves as a model of a genetic condition where links are being made between behavioural and cognitive features, and DNA pathology. It also illustrates the complexity of research in behavioural genetics where a high degree of genetic and phenotypic variability is involved. Intellectual functioning is a continuous rather than discrete trait, and levels of mental retardation vary significantly among
individuals with Fragile X, as do other clinical symptoms such as shyness and avoidant behavior. Defining the behavioural phenotype of Fragile X Syndrome is therefore difficult. Furthermore some have argued that the reported autistic-like behaviours and hyperactivity/inattention symptoms are no more common in Fragile X than other intellectually handicapped groups (Einfeld & Hall, 1994), while others have supported features of ADHD and Autism as part of the phenotype (Hagerman, 1996). The categorical approach can be problematic for genetic research, particularly where the category is not well defined or features are diverse and overlap with normal traits. Defining the cut-off point in these cases may be somewhat arbitrary. In such cases it may be useful to also consider dimensional approaches which assume psychiatric symptoms represent one end of a continuum. Differences in the degree of mental retardation, psychopathology, neurocognitive and emotional features among males with Fragile X, and the observed sex differences have lead to hypotheses on the importance of the number of CCG repeats at the site of the FMR-I gene, methylation status of the mutation, and the X-inactivation ratio in females. This begins to explain and clarify the various manifestations of this syndrome (Hagerman, 1996).

Biological parents have been reported to be more likely to be hyperactive than adoptive parents of hyperactive children (Morrison & Stewart, 1973). More recently, biological parents of hyperactive children have been reported to have more attention difficulties than adoptive parents of hyperactive children, but not impulsivity (Alberts-Corush, Firestone & Goodman, 1986). Unfortunately the parents of these hyperactive children also had lower scores of intellectual functioning, and had completed fewer years of education, both of which may be confounding factors. Adoption has become less common and hence less available as a research methodology. Much of the evidence for a genetic contribution to ADHD comes from twin, family and molecular studies.
Twin Studies

Most twin studies have used a dimensional approach to investigate genetic aspects of ADHD, comparing symptoms in monozygotic (MZ) and dizygotic (DZ) twins. Attention problems based on rating scale data have been found to have a significant heritable component with specific figures varying across studies. Gjone, Stevenson and Sundit (1996) reported heritability in the range of 0.73 to 0.79 using the Child Behaviour Checklist (CBCL; Achenbach, 1991), while Sherman, Iacono and McGue (1997) using teacher ratings report heritability to be 0.39. Studies comparing activity levels have also reported a wide range of heritability estimates, from 0.54 (Goodman & Stevenson, 1989) to 0.72 (Zahn-Waxler et al, 1996). Studies vary in the age and size of samples, as well as using different questionnaires, but all support a significant heritable component to ADHD dimensions (Edelbrock et al., 1995; Eaves et al., 1997; Thapar, Hervas & McGuffin, 1995).

The item content of behavioural scales do not explicitly correspond to diagnostic criteria, thus one cannot directly extrapolate results from studies using dimensional approaches to DSM symptoms or diagnostic groupings. Studies using diagnostic interviews such as the Diagnostic Interview for Children and Adolescents (DICA) have confirmed that concordance rates are higher in MZ than DZ twins with heritability estimated at 0.91 (Sherman, Iacona & McGue, 1997; Gillis, Gilger, Pennington & DeFries, 1992). Levy, Hay, McStephen, Wood and Waldman (1997), using a rating scale based on DSM-III-R criteria, also estimated heritability of ADHD at 0.91 (using a 5 symptom diagnostic cut-off). They also considered a dimensional approach, finding that the trait (number of symptoms irrespective of criteria) was not significantly more heritable than the disorder (h²=0.75). This suggests that ADHD is inherited as part of a continuum rather than a discrete disorder.
Heritability estimates appear to vary with the informant used. Hewitt et al., (1997) reported a correlation of 0.35 between ADHD symptoms numbers reported by mothers and fathers of twins. Furthermore, mother’s reports have produced lower DZ twin correlations compared with father and teacher reports on the Rutter scales (Goodman & Stevenson, 1989; Thapar, Hervas & McGuffin, 1995). Although twin contrast effects are significant, heritability remains high when they are removed (Eaves et al., 1997).

Further research in this area is required to investigate inattentive and hyperactive-impulsive symptoms using the DSM-IV criteria. Sherman, Iacona and McGue (1997) separated inattentive and hyperactive symptomatology by factor analysis, finding both dimensions were heritable, and shared a common genetic component, though others have suggested there may also be additional genes specific to inattention (Hay & Levy, 1996). Sherman, Iacona and McGue (1997) reported that the relative shared and non-shared environmental contributions to inattentive and hyperactive-impulsive subtypes may differ, another aspect requiring further study. Unfortunately they only used males in their sample. Males, and twins, have been reported to have a higher rate of ADHD, reading and speech problems than females, or singletons, (Levy, Hay, McLaughlin, Wood & Waldman, 1996). Preliminary reports indicate reading problems and ADHD possibly share around 40% of genetic variance (Levy, 1998).

**Family Studies**

Family studies have used a categorical approach to examine an association between a psychiatric syndrome and patterns of inheritance in families (thus do not distinguish between environmental and genetic effects). The lifetime prevalence rates
of ADHD among first degree relatives of a child with ADHD have been estimated at 0% for female siblings, 21% for male siblings, 6% for mothers and 12% for fathers (Biederman, Faraone, Mick, Spencer, Wilen et al., 1995). Among second-degree relatives prevalence is estimated at 9% for males and 0% for females (Biederman, Faraone, Keenan et al., 1990). Among extended family, prevalence rates of ADHD have been estimated at 4% for aunts, 9% for uncles, 3% for grandmothers, and 5% for grandfathers (Faraone, Biederman & Milberger, 1994). These figures for prevalence rates of ADHD among relatives of probands support significant familial aggregation of ADHD. Furthermore it appears that while not immune to ADHD, female relatives are at a much lower risk than male relatives.

Family studies have shown that there is a higher risk of not only ADHD among relatives of probands with ADHD compared with control probands, but also antisocial disorders, major depressive disorder, substance dependence and anxiety disorders (Biederman et al., 1992). Biederman et al., (1992) found that ADHD and anxiety disorders segregated independently in families, however ADHD and mood disorders appeared to have a common familial vulnerability. They also found that ADHD and Conduct Disorder (CD) appeared to co-segregate (were transmitted together) suggesting they may be a distinct subtype, consistent with the ICD-10 grouping of Hyperkinetic Conduct Disorder.

Morbidity risks for DSM-III ADD increase in a stepwise fashion from controls to ADD probands to those co-morbid with Oppositional Defiant Disorder (ODD) and finally with CD, suggesting increasing familial aetiological factors and severity from ADD to ADD+ODD to ADD+CD (Farone, Biederman, Keenan & Tsuang, 1991). Although ODD is not usually seen as a biologically based disorder, in the case of co-morbidity with ADD it does appear to be transmitted genetically and takes up an intermediate position between ADD and CD. Comparing families in which there was
or was not any antisocial disorder, Faraone et al., (1995) found a lack of elevated conduct problems and substance use in non-antisocial families. They also found differences in the risk for ADHD between genders depending on whether the family was antisocial or not, and could only predict sibling ADHD from maternal depression in antisocial families. This implies the difference is not simply quantitative.

Biederman et al., (1995) reported a much higher rate of ADHD among children of adults with childhood diagnoses of ADHD and current symptomatology meeting DSM-III-R criteria compared to previously reported rates of sibling ADHD, yet with no differences in age of onset, number of symptoms or rates of school failure. They suggested that these findings implied that the aetiological risk factors are stronger in the adult form than the paediatric form. Unfortunately, this study was not double-blind (raters knew of the adults diagnosis when assessing the children), and the use of telephone interviews is questionable, particularly given the high rate of self-diagnosis with ADHD (Diller, Tanner & Weil, 1996).

If ADHD is in fact “a group of conditions rather than a single homogeneous clinical entity, with potentially different aetiological and modifying risk factors and different outcomes” (Biederman et al., 1992, p. 736), as suggested by family studies, understanding its familial transmission will prove quite difficult. Although familial distribution consistent with a single major gene has been reported (Faraone, Biederman & Chen, 1992), other family and twin study data are more consistent with a polygenic model.

**Molecular Studies**

Studies at the molecular level have used clinical samples of individuals diagnosed with ADHD. They have primarily concentrated on two candidate genes:
the dopamine transporter gene (DAT1) and the dopamine D4 receptor gene (DRD4). Approximately 70%-80% of children with ADHD experience symptomatic improvement with methylphenidate (Wilens & Biederman, 1992). Such pharmacological agents (i.e., methylphenidate, dextroamphetamine, pemoline, bupropion) inhibit the dopamine transporter. Furthermore DAT1 knockout mice have been shown to exhibit motor activity (Thapar, 1998). Comings et al., (1991) found an association between ADHD, alcoholism, Tourette's Syndrome, and Autism, and the dopamine D2 receptor gene (DRD2). To address population stratification, Cook et al., (1995) used the haplotype relative risk method (HRR) to test for an association between a variable number of tandem repeats (VNTR) polymorphism at DAT1 (a sequence of DNA able to be identified with a probe) and DSM-III-R ADHD. They found a significant association between ADHD and the DAT1 allele, preliminary evidence for an association between the dopamine transporter gene and ADHD. The association between DRD2, alcoholism and ADHD found by Comings et al., (1991) was not replicated. Their sample size was unfortunately quite small. This association has since been replicated using the same HRR model (Gill et al, 1997). However, it was not replicated by Swanson et al., (1998) who used a refined phenotype, where subjects met criteria for both ADHD and Hyperkinetic Disorder.

Reports of an association between higher novelty seeking scores and the DRD4 7 repeat allele, despite mixed research findings (Thapar, 1998), have inspired interest in DRD4 as a candidate gene for ADHD, because of the overlap between novelty seeking and ADHD behaviours of impulsivity and excitability. DRD4 also displays a high degree of functionally significant variation consistent with the variable symptom presentation of ADHD.

LaHoste et al (1996) reported an association between the 7 repeat allele of DRD4 and ADHD using a case-control method. They also found that the allele was
associated with increased severity. Swanson et al., (1998) replicated LaHoste’s study, finding an association between the DRD4 allele and ADHD using the HRR method. Studies have generally not examined more than one candidate gene in the same population and therefore have been unable to detect contributions from other genes. However in this case no association was found with DAT1 or DRD2 (Swanson et al., 1998). Rowe et al., (1998) also replicated LaHoste et al., (1996) findings with a case control study, and extended the study to a within family analyses. They found an association with inattentive symptoms, but transmission disequilibrium tests (TDT) did not reveal linkage disequilibrium for hyperactive-impulsive symptoms. Smalley et al., (1998) also used the TDT method, finding the 7 repeat allele was differentially transmitted to children with ADHD, resulting in a 1.5 fold increased risk for carriers in developing ADHD over non-carriers. A mean test of identity by decent sharing among affected sibling pair families did not replicate the finding. Furthermore, Castellanos et al., (1998) were unable to replicate the LaHoste et al., (1996) finding in a case control design.

Comings (1997) summarised the research highlighting the concept of disruptive behaviour disorders including ADHD, Tourette’s Syndrome, Learning Disorders, substance abuse, ODD and CD as part of a spectrum of inter-related disorders sharing a number of genes in common and being polygenically inherited. These genes are thought to affect dopamine, serotonin and other transmitters. In particular, he claims an additive effect for three genes: dopamine D2 receptor gene (DRD2), dopamine hydroxylase (breaks down serotonin precursor tryptophan) and dopamine transporter gene. Individuals that inherit all the markers have the highest ADHD scores, then those who inherit two of them, followed by those inheriting one and finally none. This is consistent with twin and family studies that suggest ADHD is
inherited as a continuum, though further clarification of the traits being inherited is required.

Summary

Heritability estimates for ADHD from twin studies vary reflecting various methods of phenotype definition, age and size of samples. All studies support a significant genetic component with high heritability estimates. Twin contrast effects however highlight the need for research to clarify possible rater bias on questionnaires such as the Rutter scales. The difference between inattentive and hyperactive-impulsive subtypes, have yet be clearly established. Family studies indicate there is a significant amount of family aggregation, with a higher risk for males. There is also a higher risk of other psychopathology among ADHD probands, with ADHD and CD co-segregating and possibly being a distinct subtype. Molecular studies have focused one two candidate genes, DAT1 and DRD4, however low power has lead to discrepant findings, and these genes clearly only identify a subset of cases. The genetic literature overall suggests that ADHD is inherited as a continuum, and in a polygenic fashion. The factors found to be involved in any disorder are only valuable to the extent it is a true disorder, thus distinctions between the various externalising disorders, learning disorders and subtypes of ADHD must be clarified. Clearly both dimensional and categorical approaches will be essential to an understanding of ADHD and should not be considered mutually exclusive.
Conclusion

Determining the genetic aetiology of psychiatric conditions depends on accurate definition of the observed phenotype. Phenotypic definition of ADHD appears to be hampered by the impact of co-morbidity and different subtypes.

a) Comorbidity

Symptoms of the externalising disorders overlap (Prior & Sanson, 1986), and studies have not always been able to distinguish between them on the basis of cognition and attentional functioning (Paternite, Loney & Roberts, 1995). Often what appears to be studies about Oppositional Defiant Disorder, Conduct Disorder, or ADHD are broadly only informative about externalising behaviour problems (Paternite et al., 1995), as symptoms of these conditions are moderately to highly correlated (Hewitt et al., 1997), and stringent control over comorbidity in samples is often lacking. Furthermore, there are significant changes in the presentation of ADHD symptoms as individuals age, as well as the appearance of co-morbidity, yet little attention has been paid to what this may mean in terms of either diagnosis or aetiology.

b) Subtypes

Only an extremist would doubt of the existence of an ADHD syndrome, however the convoluted history of changing diagnostic criteria suggests a tacit lack of confidence in the diagnosis of subtypes. Research has found qualitative differences between the hyperactive and inattentive subtypes (e.g., Barkley, DuPaul & McMurray, 1990). It will be some time before a consistent body of research based on the DSM-IV subtype distinctions emerges and clarifies without reasonable doubt whether they are part of the same disorder, perhaps representing part of a developmental course of ADHD, or
are so distinct as to constitute separate disorders. The subtypes may reflect differing aetiology, however at least from a genetic perspective there is little to confirm this. Currently, both subtypes are often combined in samples for research.

One way of avoiding error associated with rating scales and clinical interviews is to find more objective measures to define phenotypes. Research on cognitive functioning and neurophysiology has begun to clarify the deficits that may be resulting in behavioural symptoms of ADHD is, but the findings are often discrepant. Although some inconsistency in performance in ADHD samples is to be expected given the issues highlighted above, the poor link between cognitive impairments and behavioural characteristics of ADHD appears to be exacerbated by variations in research methodology and the lack of a clear theoretical basis in most studies.

a) **Research methodology**

Research methodology in subject definition varies considerably because of changing diagnostic criteria, but also varies in terms of different scales, informants, structured and unstructured interviews and cut-off points for inclusion. Furthermore, the tasks used to measure cognitive deficits vary, and what such tests measure or how that relates to the behavioural features is not always clear. Definitions of constructs, such as inattention are more often than not lacking. The impact of situational specificity on performance should also not be underestimated. Research on the genetic impacts of measures of cognitive dimensions of ADHD (eg CPTs) has yet to be done.

b) **Inadequate theoretical basis**

Ultimately we do not know what the underlying deficit or deficits are, perhaps in part because research has largely failed to base itself upon a strong theoretical foundation
that considers how behaviour may be linked to cognitive, developmental and biological features. Rather it appears research has been exclusively top down in its approach, leaping from behavioural manifestation to an assumed cognitive deficits in attention, without so much as defining inattention in many cases. Similarly biological research has jumped from the effects of stimulants on behaviour to biological substrates and candidate genes. Future research using meta-analysis methodology may help clarify the findings of studies to date to inform a more systematic and bottom up approach to investigating the basis of ADHD.

The literature on the genetics of ADHD is hampered by the measurement variation associated with defining ADHD as a behavioural phenotype. Moreover, diagnostic uncertainty, variability in phenotypic expression, and age dependent penetrance of ADHD, is likely to be resulting in samples with particularly large amounts of genetic and aetiological heterogeneity. These factors reduce the probability of finding a specific deficit or basis for ADHD and reduce the accuracy with which we can pinpoint it (although the chances of finding a genetic basis for externalising disorders as a whole may be higher). Research in molecular studies thus far has used small samples with low statistical power, a problem that will not abate as subtype distinctions are made. From the literature reviewed on the genetics of ADHD it is concluded that:

a) Family, twin and molecular research supports a genetic component to ADHD

b) ADHD appears to be part of a continuum rather than a distinct disorder, with a common genetic vulnerability resulting in an increased risk of other psychiatric disorders.

c) Many genes are likely to be involved in the development of ADHD, and their impact mediated by interactions with environmental factors.
d) There is currently little evidence from a genetic perspective to separate inattentive and hyperactive-impulsive subtypes of ADHD.

e) Measurement variation in the definition of phenotypes, has a significant impact on genetic research.

The present review concludes that our understanding of ADHD continues to have significant limitations. Behavioural criteria and cognitive features associated with ADHD are not well linked. Developmental aspects and the impacts of co-morbidity are largely ignored. Furthermore current definitions of ADHD do not reflect the research in these areas. The genetic research on ADHD to date reflects these limitations suggesting that ADHD is not well defined as a distinct disorder, and may be better conceptualised from a dimensional view.

**Future research**

Longitudinal genetic research appears to provide one way of drawing together research in different fields on ADHD, and providing a link between the different levels of explanation for ADHD symptomatology. The developmental nature of genetic and environmental influences across the life span is often overlooked, though now being more fully acknowledged (Rose, 1995). Genetic and environmental risk factors and influences appear to be variable rather than stable in time (Kendler, 1995; Schmitz, Kulker & Mrazek, 1995). Integrated genetic and longitudinal research would alleviate problems associated with using individuals across generations as this often requires using different dependent measures across ages that may not be comparable (using the same measures may be no better as tests may measure different abilities at different ages). By following the development of families particular pattern of
inheritance can also be observed. Using families with adult probands may prove fruitful as these groups may have a more severe form of the disorder and hence provide a more powerful study.

This type of research allow us to look at ADHD as a category in time, as well as the various psychological dimensions including behaviour and cognition, and psychosocial features across the lifespan as they interact. Thus developmental pathways for both genetic vulnerability and environmental risk can be examined simultaneously. It is often forgotten that genetic contribution to behaviour is probabilistic or pre-disposing, not deterministic (Rende & Plomin, 1993), and not all cases of ADHD will be caused genetically. Fischer, Newby and Gordon (1995) for instance identified a subgroup of ADHD children who performed normally on a Continuous Performance Task (CPT), did not respond to stimulant medication and had more psychosomatic and conduct problems, who may represent a group without a biologically based condition. ADHD is a complicated disorder. While psychopathology appears to run in families, we still have a long way to go to untangle the complex genetic and environmental influences, and their interactions, that result in ADHD.

References


Hyperactivity disorder: Patterns of comorbidity in probands and relatives in psychiatrically and pediatrically referred samples. *Archives of General Psychiatry, 49*, 728-738.


Links between features associated with ADHD and a chromosomal mutation in a single family

Amy Langbein, B.Sc (hons.).
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**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AID</td>
<td>anxiety/depression scale of the CBCL</td>
</tr>
<tr>
<td>Aggr</td>
<td>aggression scale of the CBCL</td>
</tr>
<tr>
<td>Atten</td>
<td>attention scale of the CBCL</td>
</tr>
<tr>
<td>C</td>
<td>colour trial of the VSCWT</td>
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<tr>
<td>Cat</td>
<td>categories achieved on the WCST</td>
</tr>
<tr>
<td>CBCL</td>
<td>Child Behaviour Checklist</td>
</tr>
<tr>
<td>Com</td>
<td>commission errors on the TOVA</td>
</tr>
<tr>
<td>CPT</td>
<td>continuous performance task</td>
</tr>
<tr>
<td>C-W</td>
<td>colour-word trial of the VSCWT</td>
</tr>
<tr>
<td>Del</td>
<td>delinquent scale of the CBCL</td>
</tr>
<tr>
<td>Err</td>
<td>total errors on the WCST</td>
</tr>
<tr>
<td>Ext</td>
<td>externalising scale of the CBCL</td>
</tr>
<tr>
<td>FMS</td>
<td>failure to maintain set on the WCST</td>
</tr>
<tr>
<td>H1</td>
<td>half 1 of the TOVA</td>
</tr>
<tr>
<td>H2</td>
<td>half 2 of the TOVA</td>
</tr>
<tr>
<td>Int</td>
<td>internalising scale of the CBCL</td>
</tr>
<tr>
<td>M</td>
<td>mild deficit (1-2 standard deviations from the mean)</td>
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<tr>
<td>MD</td>
<td>moderate deficit (2-3 standard deviations from the mean)</td>
</tr>
<tr>
<td>MHQ</td>
<td>medical history questionnaire</td>
</tr>
<tr>
<td>NP.err</td>
<td>nonperseverative errors on the WCST</td>
</tr>
<tr>
<td>OM</td>
<td>omission errors on the TOVA</td>
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<tr>
<td>P.err</td>
<td>perseverative errors on the WCST</td>
</tr>
<tr>
<td>P.res</td>
<td>perseverative responses on the WCST</td>
</tr>
<tr>
<td>Q1</td>
<td>quarter 1 of the TOVA</td>
</tr>
<tr>
<td>Q2</td>
<td>quarter 2 of the TOVA</td>
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<tr>
<td>Q3</td>
<td>quarter 3 of the TOVA</td>
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<tr>
<td>Q4</td>
<td>quarter 4 of the TOVA</td>
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<tr>
<td>RT</td>
<td>reaction time on the TOVA</td>
</tr>
<tr>
<td>S</td>
<td>severe deficit (3 or more standard deviations from the mean)</td>
</tr>
<tr>
<td>SCL-90-R</td>
<td>Symptom report checklist -90-revised</td>
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<tr>
<td>Soc</td>
<td>social scale of the CBCL</td>
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<tr>
<td>Som</td>
<td>somatic scale of the CBCL</td>
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<td>T</td>
<td>total scale of the CBCL</td>
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<tr>
<td>Thou</td>
<td>thought scale of the CBCL</td>
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<tr>
<td>TOVA</td>
<td>Test of Variables of Attention</td>
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<tr>
<td>W</td>
<td>word trial of the VSCWT</td>
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<tr>
<td>WCST</td>
<td>Wisconsin Card Sorting Test</td>
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<tr>
<td>Withd</td>
<td>withdrawn scale of the CBCL</td>
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<tr>
<td>WURS</td>
<td>Wender Utah Rating Scale</td>
</tr>
<tr>
<td>Var</td>
<td>variability on the TOVA</td>
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<tr>
<td>VSCWCT</td>
<td>Victoria version of the Stroop Colour and Word Test</td>
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Advanced molecular techniques offer the possibility of identifying genes for psychiatric conditions such as Attention Deficit Hyperactivity Disorder (ADHD). Although there is some difficulty in defining ADHD as a behavioural phenotype and measuring deficits associated with ADHD, the evidence from twin, family and molecular studies supports a strong genetic component in ADHD. The aim of this study was to characterise the difficulties experienced by members of a family identified as having a chromosomal inversion, possibly linked to ADHD type behaviours, and determine if there were significant cognitive deficits associated with carrying this inversion. Family members (8 adults and 9 children, age range 7-63 years) filled out symptom report measures including the SCL-90-R, Wender Utah Rating Scale (WURS) and Child Behaviour Checklist (CBCL), and were assessed on the WAIS-R/WISC-III, a continuous performance task the Test of Variables of Attention (TOVA), the Wisconsin Card Sorting Test (WCST) and the Stroop Colour and Word Test-Victoria version (VSCWT). One family member was able to identify 90.9% of family members carrying the inversion. Testing revealed family members carrying the inversion had significantly lower IQs, than those who did not carry the inversion. Children carrying the inversion had higher scores on the attention, aggression, delinquent, social, externalising, and total problem behaviour scales of the CBCL, than children who did not carry the inversion. They also had lower activities and overall competence. Although significant group differences were not found, family members carrying the inversion performed at levels in the clinical range for omission errors, commission errors, and variability on the TOVA; word and interference trial of the VSCWT; and total errors, perseverative errors and perseverative responses on the WCST. These results and analysis of individual profiles suggest members of the family carrying the inversion may have a deficit in focused attention, high intra-individual variability in attention and poor cognitive flexibility. Interpretation of results was complicated by evidence of family dysfunction, comorbid problems in conduct, anxiety and depression, and confounding of test results due to low intellectual functioning. Strong conclusions were also limited by low subject numbers and lack of experimenter and participant blindness. It is suggested further investigations of the family clarify the presence of comorbid conditions and test results through diagnostic interviewing, and psychophysiological measures.
In the ongoing nature-nurture debate, scientists search for both biological and environmental factors that lead to psychopathology. Can we find a genetic basis for complex human behaviour? While quantitative genetics has clearly shown many disorders have a genetic contribution, molecular methods now offer the possibility of directly linking psychiatric syndromes, such as Attention-Deficit/Hyperactivity Disorder (ADHD\(^1\)), to specific genes.

**ADHD across the lifespan**

While once essentially unheard of, ADHD is now the most frequently diagnosed childhood psychiatric condition (Halperin et al., 1993), with prevalence rates in the order of 3% - 5% in school-age children (APA, 1994). Although once believed to fade with age, outcome studies have revealed that children diagnosed with ADHD may go on to experience significant academic, social and conduct difficulties in high school (Weiss & Hechtman, 1993). Prospective studies have found that while many children outgrow the disorder, at least 11% (Mannuzza, Klien, Bessler, Malloy & LaPadula, 1993) and as many as 36% (Weiss, Hechtman, Milroy & Perlman, 1985) continue to experience at least one residual symptom of ADHD that significantly impairs their functioning. Furthermore, research indicates 18% (Manuzza et al., 1993) to 23% (Weiss et al., 1985) of adults have Antisocial Personality Disorder at follow up. Three developmental courses of ADHD have been broadly characterised, based on the small number of prospective longitudinal studies that have been carried out (Cantwell, 1996; Weiss & Hechtman, 1993):

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\(^1\) The term ADHD will be used to refer generically to the DSM-IV diagnosis and its predecessors (DSM-II, DSM-III, DSM-III-R) unless otherwise specified.
1) Developmental delay (30%-40%) - functionally impairing symptoms of the original syndrome disappear in the young adult;

2) Continual display (40%-50%) - functionally impairing symptoms persist with social, interpersonal and emotional difficulties; and

3) Developmental decay (10%-30%) - continual display of core symptoms and development of serious psychopathology (e.g., Alcohol Abuse, Antisocial Personality Disorder).

The emergence and impact of co-morbidity with conduct problems/aggression appears to be particularly significant. ADHD is often co-morbid with Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD), and there is a high rate of co-morbidity with Mood, Anxiety, Learning, Communication and Tourette’s Disorders (APA, 1994). Antisocial activity and IQ predict antisocial behaviour and poor academic achievement respectively, as well as impacting on overall functioning in both adolescents and adults (Barkley, 1991; Weiss & Hechtman, 1993). Adults who experience the poorest outcome have been found to exhibit behavioural problems as children (Herrero, Hechtman & Weiss, 1994). At present it is not clear why some children outgrow these symptoms, while others continue to deteriorate, or develop other problems.

One possible explanation for different developmental courses is the role of genetic influences on ADHD. Male siblings of probands with ADHD and Conduct Disorder, or ADHD probands with a parent with Antisocial Personality Disorder have been reported to be at greater risk for developing ADHD (Faraone et al., 1995). Furthermore, persons with a familial case of ADHD have been shown to have poorer neuropsychological functioning on the Wisconsin Card Sorting Test, and Stroop Colour and Word Test (Seidman et al., 1995). This suggests that a family history not
only puts a person at risk for ADHD, it may put them at risk for a more severe form. Further elucidation of the adult phenotype of ADHD, through longitudinal and genetic studies will be essential in clarifying the developmental course of ADHD and associated diagnostic issues (Hay & Levy, 1996).

**Evidence for a genetic contribution to ADHD**

Twin, family and molecular genetic studies all support a strong genetic contribution to ADHD. Twin studies using a dimensional approach (rating scale data), report heritability of attention problems ranging from 0.39 (Sherman, Iacono & McGue, 1997) to 0.79 (Gjone, Stevenson & Sundit, 1996). Reports on the heritability of activity levels ranges from 0.54 (Goodman & Stevenson, 1989) to 0.72 (Zahn-Waxler et al., 1996). The reported variation in heritability estimates may reflect the use of different rating scales and informants. Studies using a categorical approach (diagnostic interviews) confirm that concordance rates for monozygotic twins are higher than for dizygotic twins, with heritability estimated at 0.91 (Sherman, Iacono & McGue, 1997; Gillis, Gilger, Pennington & Defries, 1992). Levy, Hay, McStephen, Wood and Waldman (1997), using a rating scale based on DSM-III-R criteria estimated heritability of ADHD at 0.91 (using a 5 symptom cut off). Furthermore, they found that the trait (number of symptoms irrespective of criteria) was not significantly more heritable than the disorder (h2=0.75). This suggests that ADHD is inherited as part of a continuum rather than a discrete disorder.

Studies that have examined the rates of ADHD among relatives of children with ADHD have found an increased risk of ADHD among first-degree (Beidernan et al., 1992) and second-degree relatives (Faraone, Beiderman & Milberger, 1994), that is not accounted for by psychosocial factors (Beiderman et al., 1992). Furthermore,
Beiderman et al., (1995) found a significantly higher rate of ADHD in children of adults with childhood onset ADHD than is found among siblings of children with ADHD, suggesting that adult forms of the disorder may have a stronger familial aetiological risk than paediatric forms of the disorder. Family studies have also shown that there is a higher risk of antisocial disorders, Major Depressive Disorder, Substance Dependence and anxiety disorders (Biederman et al., 1992) in ADHD probands. Biederman et al., (1992) found that ADHD and anxiety disorders segregated independently in families, however ADHD and mood disorders appeared to have a common familial vulnerability. They also found that ADHD and CD appeared to co-segregate (were transmitted together) suggesting they may be a distinct subtype. Morbidity risks for DSM-III ADD increase in a stepwise fashion from controls to ADD probands, to those co-morbid with ODD, and finally to those co-morbid with CD, suggesting increasing familial aetiological factors and severity from ADD to ADD+ODD to ADD+CD (Farone, Biederman, Keenan & Tsuang, 1991). Although ODD is not usually seen as a biologically based disorder, in the case of co-morbidity with ADD it does appear to be transmitted genetically and takes up an intermediate position between ADD and CD.

Molecular genetic studies have primarily concentrated on two candidate genes: the dopamine transporter gene (DAT1) and the dopamine D4 receptor gene (DRD4). Approximately 70%-80% of children with ADHD experience symptomatic improvement with methylphenidate (Wilens & Biederman, 1992). Such pharmacological agents (i.e., methylphenidate, dextroamphetamine, pemoline, bupropion) inhibit the dopamine transporter. Comings et al., (1991) found an association between ADHD, Alcoholism, Tourette's Syndrome, Autism, and the dopamine D2 receptor gene (DRD2). To address population stratification, Cook et al., (1995) using the haplotype relative risk method (HRR), found a significant
association between DSM-III-R ADHD and the DAT1 allele, preliminary evidence with a small sample size, for an association between the dopamine transporter gene and ADHD. The association between DRD2, alcoholism and ADHD found by Comings et al., (1991) was not replicated. The DAT1-ADHD association has since been replicated (Gill et al, 1997), but not with a refined phenotype, where subjects met criteria for both ADHD and Hyperkinetic Disorder (Swanson et al., 1998).

Reports of an association between higher novelty seeking scores and the DRD4 7 repeat allele, despite mixed research findings (Thapar, 1998), have inspired interest in DRD4 as a candidate gene for ADHD, because of the overlap between novelty seeking and ADHD behaviours of impulsivity and excitability. DRD4 also displays a high degree of functionally significant variation consistent with the variable symptom presentation of ADHD. LaHoste et al., (1996) reported an association between the 7 repeat allele of DRD4 and ADHD using a case-control method. Swanson et al., (1998) replicated LaHoste's study using the HRR method. Studies have generally not examined more than one candidate gene in the same population and therefore have been unable to detect contributions from other genes. However in this case no association was found with DAT1 or DRD2 (Swanson et al., 1998).

Rowe et al., (1998) also replicated the LaHoste et al., (1996) finding with a case control study, and extended the study to a within family analyses. They found an association with inattentive symptoms, but transmission disequilibrium tests (TDT) did not reveal linkage disequilibrium for hyperactive-impulsive symptoms. Smalley et al., (1998) also used the TDT method, finding the 7 repeat allele was differentially transmitted to children with ADHD, resulting in a 1.5 fold increased risk for carriers in developing ADHD over non-carriers. A mean test of identity by decent sharing among affected sibling pair families did not replicate the finding. Furthermore, Castellanos et al., (1998) were unable to replicate the LaHoste et al., (1996) finding in
a case control design. Sample sizes in molecular studies have been small. Larger studies will be required to maximise power and confirm these findings.

Comings (1997) suggested that the disruptive behaviour disorders (ADHD, Tourettes Syndrome, Learning Disorder, ODD, CD, Substance Abuse) were part of a spectrum of disorders sharing three genes in common: the dopamine D2 receptor gene (DRD2), dopamine hydroxylase (breaks down serotonin precursor tryptophan) and dopamine transporter gene. The more of these markers that are inherited, the more severe the ADHD. This is consistent with twin and family studies that suggest ADHD is inherited as a continuum. While it has been suggested the familial distribution of ADHD points to a single major gene (Faraone, Biederman, Chen & Krifcher, 1992), a polygenic form of inheritance would appear to be more parsimonious with both the genetic and outcome research.

**Defining a behavioural phenotype**

Although demonstrating the familial transmission of a psychiatric syndrome is often seen as validation of the syndrome as a diagnostic entity, there are many different levels of explanation for psychiatric conditions. Anatomical, physiological, biochemical and genetic findings cannot be considered in isolation from behavioural, cognitive, developmental and sociological levels of explanation. The difficulty in psychological research lies in conceptually linking biological and psychological levels of explanation. To formulate hypotheses that link biological and psychological states each level of description must be as accurate as possible. The studies in behaviour genetics described earlier are complicated by the measurement variation associated with defining ADHD as a phenotype using different methodology (e.g., rating scales, diagnostic interviews, different informants). A high rate of co-morbidity, particularly
with ODD and CD, exacerbates the difficulty in distinguishing ADHD from other forms of psychopathology that have similar or overlapping symptomatology.

Fragile X Syndrome serves as a model of a genetic condition where links are being made between behavioural and cognitive features, and DNA pathology. It also illustrates the complexity of research in behavioural genetics where a high degree of genetic and phenotypic variability is involved. Intellectual functioning is a continuous rather than discrete trait, and levels of mental retardation vary significantly among individuals with Fragile X, as do other clinical symptoms such as shyness and avoidant behaviour. Defining the behavioural phenotype of Fragile X Syndrome is therefore difficult. Furthermore some have argued that the reported autistic-like behaviours and hyperactivity/inattention symptoms are no more common in Fragile X than other intellectually handicapped groups (Einfeld & Hall, 1994; Einfeld, Levy & Hall, 1991), while others have supported features of ADHD and Autism as part of the phenotype (Hagerman, 1996). The categorical approach can be problematic for genetic research, particularly where the category is not well defined or features are diverse and overlap with normal traits. Defining the cut-off point in these cases may be somewhat arbitrary. In such cases it may be useful to also consider dimensional approaches which assume psychiatric symptoms represent one end of a continuum\(^2\). Differences in the degree of mental retardation, psychopathology, neurocognitive and emotional features among males with Fragile X, and the observed sex differences, have lead to hypotheses on the importance of the number of CCG repeats at the site of the FMR-I gene, methylation status of the mutation, and the X-inactivation ratio in females. This

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\(^2\) As a genetic condition may have variable expression or incomplete penetrance (meaning the probability of the phenotype or trait being manifested is less than one), a continuous distribution of traits is possible rather than a distinct condition. Variety in manifestations (phenotypes) of a genetically based psychiatric condition may thus not be captured by its categorical definition.
begins to explain and clarify the various manifestations of this syndrome (Hagerman, 1996).

ADHD is defined using a behavioural paradigm thus there is no straight-forward test for ADHD. Diagnosis relies on parent and teacher reports of behaviour through diagnostic interviewing. Although checklists do not correspond directly to diagnostic criteria, they are useful screening devices (Hewitt et al., 1997) and are recommended as part of an assessment for ADHD (NHMRC, 1995). In adults diagnosis is even more complicated as DSM-IV requires onset to occur before age seven. Some measures have now been designed to aid in making retrospective diagnoses, such as the Wender Utah Rating Scale (WURS; Ward, Wender & Reimherr, 1993).

The behavioural problems outlined in rating scales and diagnostic criteria are presumed to reflect some underlying deficit. Although there is tacit acceptance of an attention deficit, research has failed to identify a key core deficit measurable by a cognitive or neuropsychological test. Deficits in attention, inhibition and arousal have all been implicated (Douglas, 1983). Barkley's (1997) theory is the most extensive to date. He proposes that a central impairment in behavioural inhibition results in secondary impairments in working memory, self-regulation of affect/ motivation/ arousal, internalisation of speech and reconsititution. Not surprisingly deficits also appear to differ between subtypes (Goodyear & Hynd, 1992 in Lamminmaki, Ahonen, Narhi, Lyytinen & Todd de Barra, 1995; Matazow & Hynd, 1992 in Reader, Harris, Schuerholz & Denckla, 1994). How some inherited deficit is manifested in the phenotype will reflect how it interacts with the person's genetic make-up (eg personality, intelligence) and environmental factors (eg family environment, peer relations) at any given time. Measuring the presumed deficit or trait thus may be one
step closer to measuring what is inherited than measuring the expressed behaviour or
symptoms described by diagnostic criteria appear to change over time.

Measuring deficits associated with ADHD

Studies of problem behaviours in children and adolescents have identified
attention as one of the problems for which genetic effects are greatest (Edelbrock,
Rende, Plomin & Thompson, 1995; Van Den Oord, Boomsma & Verhulst, 1994).
One of the major criticisms of ADHD has been that the attention deficit has not be
adequately characterised (Prior & Sanson, 1986). Part of the problem is that there are
a wide variety of definitions of attention, referring to different capacities (Lezak,
1995), such that there is no single correct definition of attention (Van Zomeren &
Brouwer, 1992), and many ways of measuring it. Data on the developmental nature
of attention is also lacking, thus it is difficult to assess the appropriateness of attention
levels in children suspected to have ADHD.

A number of studies have tried to identify cognitive features of ADHD, as a
means of both validating and providing a way of assessing ADHD, using measures
that do not share variance with teacher and parent report scales of behaviour. In
some studies IQ scores of ADHD children are lower than their peers (Barkley,
Fischer, Edelbrock & Smallish, 1990), but this is not always found (Lamminmaki et
al., 1995). The similarity between ADHD and impairments following frontal lobe
injury, including attention (Arcia & Gualtieri, 1994; Foster, Eskes & Stuss, 1994);
have lead researchers to investigate the performance of subjects with ADHD on
neuropsychological tests such as continuous performance tasks (CPTs), the Wisconsin
Card Sorting Test (WCST) and the Stroop Colour-Word Test (SCWT), on which
patients with frontal lobe injuries have been found to perform poorly (Golden, 1978;
Heaton, 1981; Rueckert & Grafman, 1996), and which reflect the clinical constructs of inattention and impulsivity.

Continuous performance tasks (CPT) are considered measures of sustained attention and are widely used in research to compare ADHD to control groups, as well as being increasingly used in clinical practice. A CPT paradigm requires a subject to respond to certain target stimuli while refraining from responding to non-target stimuli. The number of omissions is believed to give a measure of attention while the number of commissions provides a measure of impulsivity and relates to hyperactivity and oppositional behaviour (Lassiter, D'Amato, Raggio, Whitten & Bardos, 1994). Children with ADHD are found to perform poorly on CPTs. They make more errors of omission (Reader et al., 1994), and commission (Seidel & Joschko, 1991), than controls, but perhaps more consistently distinguishing are slower reaction times and greater variability in their reaction times to stimuli (Greenberg & Dupuy, 1993; Levy & Hobbes, 1997; Reader et al., 1994). Sergeant, Van der Meere and colleagues have done extensive research manipulating the CPT task to examine the different components of attention described by Schneider and Shiffrin's model (1997). Unable to find a deficit in selective (Sergeant & Scholten, 1985), divided (Van der Meere & Sergeant, 1987), focused (Van der Meere & Sergeant, 1988a), or sustained attention (Van der Meere, Wekking & Sergeant, 1991), they concluded that children with hyperactivity had an arousal deficit (Van der Meere & Sergeant, 1988b), such that they would demonstrate a deficit in sustained attention with a slow presentation rate (Van der Meere, Shalev, Borger & Gross-Tsur, 1995). Although poor performance on the CPT is not specific to ADHD, being found for example in children at risk for Schizophrenia (Watt & James, 1984), and varies with different task parameters (as demonstrated in the work of Sergeant, Van der Meere and colleagues), it appears to be the most consistently discriminative cognitive/neuropsychological test when
testing individuals with ADHD against comparison groups. Poor CPT performance may also be a good indication of a biologically based condition as performance appears to related to stimulant medication response (Fischer, Newby & Gordon, 1995) and to be worse in familial cases (Seidman et al., 1995).

Findings using other neuropsychological tests have been less consistent than the results of research using CPTs. The more consistent findings include that ADHD children may make more perseverative errors on the WCST (Boucugnani & Jones, 1989; Chelune, Ferguson, Koon & Dickey, 1986) and may be slower on the disruption trial of the SCWT (Gorenstein, et al., 1989; Lufi, Cohen & Parish-Plass, 1990), with performance being even worse when there is a family history of ADHD (Seidman et al., 1995). Such tests are not always able to distinguish between ADHD and other psychopathology or control groups (Barkley, Grodzinsky & DuPaul, 1992). As is the case with full scale IQ scores and IQ profiles such as a low Freedom From Distractibility (FFD) Index, at a group level we may find ADHD children perform more poorly than a control group, but at an individual level IQ and other neuropsychological tests may be of only minor utility in diagnosing ADHD (Anastopoulos, Spisto & Maher, 1994). This may be partly the result of symptom heterogeneity and co-morbidity, which result in large variations in symptoms and test performance at the individual level (Halperin et al., 1993).

Research on the possible cognitive impairment in adult ADHD is only in its early stages, with ADHD still being considered a disorder of childhood. Evidence of slow reaction times and variable attention on a CPT (Arcia & Gualtieri, 1994), and PET research showing reduced glucose metabolism in the premotor and superior prefrontal cortex (Zametkin et al., 1990) is consistent with the deficits in attention and frontal functioning seen in children. Evidence of ceiling effects for adults on CPTs (Rasile, Burg, Burrright & Donovick, 1995) however suggests that the extent of the
deficit is somewhat different in adults, and may therefore not be tapped by the same measures that are found useful in children.

*Exploring features of ADHD in a single family*

This study examined the psychological functioning of a number of individuals in a single family. Genetic testing of one child in the family suffering from ADHD revealed a chromosomal inversion on chromosome 3 (an inversion is the reversal of a portion of the DNA of a chromosome). Subsequent testing of other family members across three generations identified this inversion in 12 of the 18 individuals tested (see figure 1, note that once an individual tested negative their children were not tested and are presumed negative for the inversion). This raises the possibility that a gene or genes, as yet unidentified, may have been disrupted at either or both ends of this inversion.

*Figure 1. Family Tree illustrating genetic status of members*

(■ = tested positive, □ = tested negative, □ = untested assumed negative, □ = refused testing, status unknown, — = divorced, ✗ = deceased)
Cytogenetic findings have sometimes lead to establishing the location of genes for single-gene disorders (e.g., cystic fibrosis), but this has been less successful in the psychiatric field. Initial reports of linkage between an abnormality of chromosome 5 and Schizophrenia inspired numerous attempts to map a susceptibility locus for Schizophrenia to chromosome 5, with little success (Palmour, Miller, Fielding, Vekemans & Ervin, 1994). Even when a gene is identified in a pedigree, this doesn’t tell us the frequency of that defective gene in the population (Rose, 1995). This is not to say that the identification of such anomalies is not useful. The association between Down’s Syndrome and Alzheimer’s Disease (AD) neuropathology alerted researchers to the role of chromosome 21 in AD.

The process of finding a gene can be long and is not always successful. Furthermore, inversions typically do not alter gene expression, and occur with a frequency of 0.2%-1.2%. The aim of this study was to try and characterise the difficulties experienced by those members of the family with the inversion and determine if indeed there were significant deficits associated with having this inversion, before attempting to identify a gene at the break-point regions of the inversion (gene expression could only be altered if a functional gene was present at one or either end of the inverted piece of DNA, and the codons at one or both ends of the inversion had been disrupted in such a way as to alter the protein being coded for).

One member of this family prior to genetic testing identified almost all the affected members of the family claiming they all had similar problems to one another. She was interviewed by a Neuropsychologist regarding the difficulties the identified family members experienced using the neuropsychiatric status interview. Following the genetic testing parents of the affected children went to see their own doctors and the children were prescribed stimulants. Children in the family were thus believed to have ADHD and were reported to have significant disruptive behavioural problems.
(aggressive and defiant) as well as learning difficulties. A number of problems were identified in the affected adults including problems with concentration, impulsivity, poor communication, learning, irritability, temper outbursts, relationships, lack of friends, obsessive-compulsive type behaviours, depression, anxiety, stress, insecurity and suspiciousness.

Selection of measures for the study was based on balancing the impact of informant bias, small subject numbers, wide age range of subjects, and time constraints. Family members were aware of their genetic status and in some cases already believed it caused ADHD. Neuropsychological tests were used to distinguish between individuals with a rating scale (Child Behaviour Checklist, Achenbach, 1991) to screen symptoms, to minimise the impact of any informant bias. Furthermore, due to the low power of the study, tests were selected on the basis of their ability to differentiate ADHD from comparison groups, as well as being able to be used on children and adults. Although the study was exploratory in nature a number of hypotheses were made based on information gained through the neuropsychiatric interview and the presumption of some link to ADHD or related problems. Directional hypotheses were made where this seemed reasonable but as the symptoms described for the adults were quite broad and non-specific no specific predictions were made about the clinical symptoms adults with the inversion may express currently.
Hypotheses

1) Members of the family with the inversion express a behaviour pattern identifiable as problematic.

2) Members of the family with the inversion (positive group) will show clinically significant levels of problem behaviours or clinical symptoms, and difficulties on tests of intelligence, attention and frontal functioning compared to members of the family without the inversion (negative group). In particular

a) Children with the inversion will have both clinically significant and more behavioural problems in total, externalising problems (aggression and delinquent behaviours), and difficulties with attention than children without the inversion as measured by the Child Behaviour Checklist (CBCL).

b) Adults with the inversion will report more symptoms on the WURS consistent with having ADHD in childhood than those without the inversion.

c) The positive group will have below average IQ and lower IQ than the negative group.

d) The children with the inversion will be less competent at school academically measured by the academic competence scale of the CBCL.

e) The positive group will have clinically significant and poorer attention, (higher omission errors, slower reaction time, higher variability) and greater impulsivity (higher commission errors) than family members without the inversion as measured by a CPT, the Test of Variables of Attention (TOVA, Greenberg & Dupuy, 1993)
f) Adults with the inversion will have clinically significant attention deficits and poorer attention than family members without the inversion measured by the Victoria version of the SCWT (VSCWT, Regard, 1981 in Spreen & Strauss, 1991).

g) The positive group will have clinically significant deficits in frontal functioning and poorer performance than the negative group on the WSCT.

Due to the small number of subjects and exploratory nature of the study individual profiles were also be examined.

Method

Participants

Nineteen of the family members voluntarily underwent genetic testing for the inversion. Participants in this experiment included 17 members from three generations of the family (9 female, 8 male). The overall age range was 7-63 years of age (9 children, 8 adults). Of the 17 participants, ten were positive and seven were negative for the inversion.

The participants agreed to have their phone numbers passed on to the researchers after discussions with one member of the family who acted as a liaison between the family and researchers. She herself was not tested, the inversion having been traced to her husband. Contact with the adults was initially made by the researcher's supervisor to check their willingness to participate, answer any queries they may have and inform them that the person testing them would be blind as to their genetic status. They were then contacted by the testing researcher for an initial
testing session. In addition to the 17 participants, parent report data was collected for two children who were not seen by the researcher.

Materials

Materials differed for adults and children for the symptom reports (adults completing the SCL-90-R and WURS for themselves and the CBCL for their children), intelligence testing (WAIS-R for adults, WISC-III for children) and the VSCWT which was only completed by adults.

1) Symptom reports

a) Child behaviour checklist- parent form (CBCL; Achenbach, 1991): This is a check-list of psychological symptoms and problem behaviours using a three-step response scale (not true, somewhat or sometimes true, very true or often true) reported by the parent. It includes eight problem scales (withdrawn, somatic complaints, anxious/depressed, social problems, thought problems, attention problems delinquent behaviour, aggressive behaviour) and a total problem score. A subset of these problem scales are used to form an internalising (withdrawn + somatic + anxious/depressed) and externalising (delinquent + aggressive) scale. It also includes three competence scales (activities, social and school) and a total competence score. Each raw scale score is converted to a T-score based on separate norms for boys and girls and split into two age brackets: 6-11 years and 12-18 years. The clinical range recommended for the problem scales is above 70 (borderline range: 67-70), for the externalising, internalising and total problem scales above 63 (borderline range: 60-63), for the competence scales below 30
(borderline range: 30-33), and for the total competence score below 37 (borderline range: 37-40).

b) *Wender Utah Rating Scale* (WURS; Ward, Wender & Reimherr, 1993): This scale is designed to aid in the retrospective diagnosis of ADHD. There are 61 items in total, of which 25 are used to distinguish ADHD patients. Items are rated on a 5 point scale (not at all or very slightly, mildly, moderately, quite a bit, very much). Ward et al., (1993) report that a cut off score of 36 or more was found to correctly identify 96% of ADHD adults and normal controls.

c) *Symptom checklist -90-Revised* (SCL-90-R; Derogatis, 1986): This is a self-report check-list of psychological symptoms experienced in the past seven days. It has 90 items that are rated on a 5-point scale of distress (0-4; not-at-all to extremely). There are nine primary symptom dimensions (somatisation, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobia, paranoid ideation, psychoticism) and three global indices (global severity index (GSI), positive symptom total (PST), positive symptom distress index (PSDI)). Each raw scale score can be converted to a standard T score using psychiatric or non-patient norms for males or females. The clinical range recommended is T-scores of 65 and above.

d) *Medical History Questionnaire* (MHQ): This was designed for the purposes of picking up medical conditions that may be producing ADHD like symptomatology after one family member mentioned thyroid problems in the family. It was constructed based on the Clinical Interview Form in Barkley (1991) and also
included information regarding development, school functioning, and therapy. A copy is available in appendix 1.

2) Cognitive measures


b) Test of Variables of Attention (TOVA; Greenberg & Dupuy, 1993): This is a CPT lasting 22.5 minutes. Visual stimuli targets (a coloured square containing a small square in the upper half) and non-targets (a coloured square containing a small square in the lower half) are presented for 100msec every two seconds. In the first half of the test the target to non-target ratio is 1:3.5 (target less frequent, 20% of stimuli). In the second half of the test this ratio increases to 3.5:1 (target more frequent, 60% of stimuli). Subjects respond to targets using a microswitch. Four variables are analysed: errors of omission (failure to respond to a target), errors of commission (response to non-target), reaction time (mean correct response times), variability (standard deviation of response times). Results are analysed for each quarter, half and overall, and a raw score, standard deviation and standard score (100 ± 15) is provided. Standard scores are based male and female norms for each age bracket (4-5 years,...,18-19 years, 20-29 years,...,80+ years). When IQ is not in the normal range it is recommended the norm group is adjusted up or down. Scores with a standard deviation of between one and two are considered mild problems (standard score < 80), standard deviation of two to three a moderate problem (standard score < 70), and standard deviations greater than three a severe attention deficit (standard score < 55). It is suggested that a standard deviation of
greater than one on two or more variables, or greater than 1.5 on one variable be considered indicative of an attention deficit overall.

c) *Wisconsin Card Sorting Test* (WCST; Heaton, 1981): This is a test of abstraction ability sensitive to frontal impairment. Subjects sort 128 response cards varying in form (crosses, circles, squares, triangles), colour (red, green, blue, yellow) and number (one, two three, four), according to one of the four stimulus cards (red triangle, two green stars, three yellow crosses, four blue circles). The subject must infer the principle to which cards must be sort (colour, form or number) based on whether each sort (trial) is deemed correct or incorrect by the administrator. When ten consecutive cards are correctly sorted the principle is abruptly changed and the subject must determine the new principle. The test continues until six categories have been sorted or all 128 cards have been sorted. Dependent variables calculated include number of categories achieved, total errors, perseverative responses, perseverative errors, nonperseverative errors and failure to maintain set (correct run of three or more sorts not reaching ten).

d) *Stroop Colour and Word Test - Victoria version* (VSCWT, Regard, 1981 in Spreen & Strauss, 1991): This is a shortened version of the original SCWT. It includes three trials, naming coloured dots (colour score), reading words (word score) and naming colours of printed words (colour-word trial, interference score). Each trial is made up of 24 items and the time recorded to complete the trial and number of errors is recorded.
Design

The independent variable was genetic status (positive or negative). The dependent variables were symptoms (reported by parent for child participants using the CBCL, self-reported by participants using the SCL-90 and WURS), attention (measured using the TOVA and VSCWT), and frontal functioning (measured using the WCST). Testing was initially begun with the experimenter blind to the genetic status of the participants. Through the course of testing however this was violated as the experimenter became aware which participants were on stimulants and therefore presumably positive, and from this could follow the pattern of inheritance back to their parent. A number of the participants in conversation also made it clear which family members were likely to have the inversion.

Procedure

Participants were tested at a private rehabilitation hospital. In the first testing session participants completed the TOVA, half the WAIS-R or WISC-III (including subtests from which to estimate IQ (vocabulary and block design), and those believed to load highly on an attention factor (digit span, coding and arithmetic) and filled out the SCL-90-R or CBCL as appropriate. The CBCL was filled out by the child’s Mother. In three cases (cases 1, 2 & 5) only the Grandmother was available to provide data (she was also the primary carer of case 1).

In the second testing session participants were given the MHQ and completed the remaining WAIS-R or WISC-III subtests (excluding the symbol search and mazes subtests of the WISC-III), the WCST and WURS (adults only). As ceiling effects with some adults on the TOVA appeared to be a problem in the first session, the
adults were also given the VSCWT in the second session as it is a quick, easily administered, measure of attention.

Each testing session lasted approximately one and a half hours. All child participants were tested in the morning. Those children on stimulant medication completed the tests unmedicated with the exception of the WISC-III, and thus three or four shorter testing sessions were undertaken as needed.

The order of testing was kept constant where possible (TOVA & CBCL, WAIS-R/WISC-III, SCL-90-R, VSCWT, WCST, WAIS-R/WISC-III, MHQ) however due to difficulty in arranging times with participants it was decided that data would be collected whenever subjects became available and the order of testing adjusted to suit the length of time the participant had available when they presented.

The family member who provided the information regarding the problems in the family was interviewed after testing had been completed to construct the family tree and determine which members of the family she had correctly predicted the genetic status of.

Results

Varying amounts of data were collected from each participant due to difficulties getting some subjects to complete the testing session or participate in multiple sessions. Data from the MHQ did not reveal anything unusual medically and was not used in the group analyses.
Family predictions

90.9% of those family members with the inversion expressed a behaviour pattern identified by one member of the family as problematic, $\chi^2 (1, N = 17) = 13.25$, $p = .001$. There was a high correlation between the observed behaviour pattern and the inversion, $\Phi = .883$, $p = 0$.

Group comparisons

One-tailed t-tests for independent samples were used. The positive group was presumed to be of lower functioning compared with both the negative control group and normative samples. Due to the wide age range within the groups raw scores were converted to standard scores or z-scores before statistical analyses were done.

Symptom reports

Children

In one case (case 4) the CBCL filled out by the child’s Mother revealed halo effects (T-scores >70 on all problem scales). This child’s Father was asked to fill out the CBCL and this data was used in the analyses. Data was obtained for 11 children (4 positive, 7 negative).

The parent reports of their child’s behaviour revealed that the children with the inversion had more difficulties with attention, $t (9) = 3.226$, $p < .005$, were more aggressive, $t (9) = 4.45$, $p < .005$, showed more delinquent behaviours, $t (9) = 2.63$, $p < .025$, and had more social problems, $t (9) = 3.10$, $p < .05$ than the children without
the inversion. Children positive for the inversion also had a higher level of 
externalising problems than children negative for the abnormality, \( t (9) = 2.75, p < .025 \), and more problem behaviours overall, \( t (9) = 1.98, p < .05 \). The mean scores of

![Figure 2. Positive and negative group's mean T-scores for each CBCL variable (Som = somatic, Withd = withdrawn, A/D = anxiety/depression, Int = internalising, Thou = thought, Soc = social, Atten = attention, Aggr = aggression, Del = delinquent, Ext = externalising; T-scores above 70 are in the clinical range)](image)

the positive group on these variables were in the clinically significant range (see figure 2). There was no significant difference between the groups on any of the remaining problem scales.

On the competence scales of the CBCL children carrying the inversion had poorer scores for activities, \( t (9) = -2.27, p < .025 \), and were less competent overall, \( t (9) = -2.28, p < .05 \). Scores on the school and social activities scales were lower in the positive group, but did not reach significance. Unlike the scores for the problem scales, none of the mean scores for the competence variables fell within the clinically significant range (see figure 3).
Figure 3. Positive and negative group's mean T-scores for each of the competence scales of the CBCL (T-scores below 30 are in the clinical range)

Adults

Only 2 participants filled out the WURS thus no analysis could be made. Both were positive for the inversion but neither scored above the cut-off point recommended to indicate the presence of ADHD as a child. Similarly only 4 participants filled out the SCL-90-R. In one case a strong effect halo (T-scores > 70 for all scales) was observed. As scores of >60 on PST in non-patient females are considered indicative of augmenting response style or faking bad the validity of this data was highly questionable and therefore excluded. No analysis was made on the remaining three cases.

Cognitive Measures

Intellectual ability

Table 1 lists the means and standard deviation for each IQ variable for the two groups. Where testing was not completed FIQ was estimated as described by Silverstein (1982) for adults (WAIS-R), and Sattler (1992) for children (WISC-III). The mean full scale IQ score (FIQ) for the positive group fell in the Well Below
Average range (x = 76.63), significantly lower than the mean FIQ of the negative group (x = 93.71) which fell in the Average range, t (13) = -2.00, p < .05. Both Performance, t (9) = -1.771, p < .05, and Verbal, t (9) = -1.72, p < .05, IQ scores were significantly lower in the positive group. Of the 11 subtests, mean scaled scores for 5 of them were found to be significantly lower in the positive group compared to the negative group. These were Comprehension, t (10) = -2.82, p < .01, Block Design, t (13) = -2.43, p < .025, Digit Span, t (12) = -2.19, p < .025, Picture Arrangement, t (9) = -2.62, p < .025, and Similarities, t (9) = -1.48, p < .05.

Table 1. Mean scores and standard deviations on the WAIS-R and WISC-III indices and subtests for the positive and negative groups.

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>POSITIVE GROUP</th>
<th>NEGATIVE GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>MEAN (SD)</td>
</tr>
<tr>
<td>Global Indices:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIQ</td>
<td>8</td>
<td>76.63 (12.96)</td>
</tr>
<tr>
<td>PIQ</td>
<td>5</td>
<td>77.00 (17.62)</td>
</tr>
<tr>
<td>VIQ</td>
<td>5</td>
<td>73.60 (12.54)</td>
</tr>
<tr>
<td>Subtests:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary</td>
<td>8</td>
<td>6.63 (2.50)</td>
</tr>
<tr>
<td>Information</td>
<td>5</td>
<td>5.40 (2.51)</td>
</tr>
<tr>
<td>Comprehension**</td>
<td>5</td>
<td>4.60 (3.29)</td>
</tr>
<tr>
<td>Similarities*</td>
<td>5</td>
<td>4.60 (3.36)</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>8</td>
<td>5.88 (2.75)</td>
</tr>
<tr>
<td>Digit Span**</td>
<td>8</td>
<td>6.63 (2.50)</td>
</tr>
<tr>
<td>Coding</td>
<td>8</td>
<td>7.13 (3.18)</td>
</tr>
<tr>
<td>Block Design**</td>
<td>8</td>
<td>4.88 (2.75)</td>
</tr>
<tr>
<td>Picture Completion</td>
<td>5</td>
<td>7.80 (4.66)</td>
</tr>
<tr>
<td>Picture Arrangement**</td>
<td>5</td>
<td>4.20 (2.17)</td>
</tr>
</tbody>
</table>

Note:  
* p < .05  
** p < .025.
The TOVA

As the normative group for males in the 30-39 age bracket consisted of only four subjects, the adult male normative groups were collapsed and norms for males aged 20-70 years used. Lower standard scores indicate more errors of omission, or commission, slower reaction times and higher variability.

Only mean total omission errors were appreciably different between the groups, \( t(15) = -1.42, p < .1 \). Individuals carrying the inversion made more omission errors in total (\( x = 74.90 \)) than those who did not have the inversion (\( x = 91.57 \)). More specifically, the positive group made more omission errors in the second but not first half of the test compared to the negative group, \( t(15) = -1.84, p < .05 \), and more errors in the third quarter in particular, \( t(15) = -1.80, p < .05 \).

The mean for the positive group fell in the clinically significant range for total omissions, commissions and variability, while that of the negative group fell in the normal range. Both groups had reaction times in the normal range (see figure 4).

There was some indication of a difference between the groups on variability. The positive group had higher variability (\( x = 78.50 \)) in the first half of the TOVA than the negative group (\( x = 97.00 \), \( t(15) = -1.54, p < .1 \)). The group with the inversion (\( x = 73.20 \)) had higher variability than the normal group (\( x = 96.57 \)) in the first quarter in particular, \( t(15) = -1.59, p < .1 \).
As TOVA scores may be related to IQ (Greenberg & Dupuy, 1993), and significant differences were found between the groups on IQ the correlation between the TOVA variables and IQ was examined. Full scale IQ was correlated with total commission errors, $r = .658$, $p < .005$, and variability, $r = .650$, $P < .005$, indicating that lower IQ score were associated with lower commission and variability standard scores (therefore more commission errors and higher variability). In order to determine if any residual differences were present between the groups once IQ was taken into account, the children’s scores were calibrated against their IQ by converting their raw scores to standard scores using the norms for their mental age rather than their chronological range. Their mental age was calculated by determining their age equivalent for each subtest and averaging these. No norms were available to adjust the adults scores for IQ.

Figure 5 illustrates the differences between the groups after IQ adjustments had been made. The same pattern of results was found. The positive group made more total omission errors compared to the negative group, $t(15) = -1.35$, $p < .1$. The negative group’s mean total omission errors standard score ($x = 93.43$) fell in the normal range, the positive group’s ($x = 77.5$) fell in the clinical range. Again the
The largest difference between the groups was in quarter three (see figure 6) where the positive group had a much lower mean standard score ($x = 67.3$) than the negative group ($x = 91.14$), $t(15) = -1.70$, $p < .01$.

![Mean total standard scores](image)

**Figure 5.** Mean standard scores for the positive and negative groups for total omissions, total commissions, reaction time (RT) and variability on the TOVA after adjusting for the children's IQ.

![Quarterly mean standard scores](image)

**Figure 6.** Mean standard scores of omission errors for the positive and negative groups over each quarter of the TOVA.

The difference between the groups in variability remained small with the positive group having a lower standard score ($x = 82.2$) than the negative group ($x = 103.43$) in the first half of the test, $t(15) = -1.66$, $p < .1$. Again this was largely due to the difference between the groups in the first quarter when the positive group's standard score ($x = 76.6$) was much lower than that of the negative group ($x = 102.71$), $t(15) = -1.70$, $p < .1$. This pattern of results is illustrated in figure 7. The positive group's total variability ($x = 79.4$) was on the borderline of the clinical range, while the negative group's mean total variability ($x = 87.86$) was in the normal range.
The positive group showed a sharp drop in mean standard score of commission errors from quarter one ($x = 84$) to quarter two ($x = 51.2$) as illustrated in figure 8 (thus an increase in errors). The negative group's mean standard score remained stable across the four quarters. While not significantly different, the positive group's mean standard score of commission errors ($x = 78.4$) fell just within the clinical range, while the negative groups' ($x = 84.0$) fell just within the normal range (see figure 5).
Six subjects completed the VSCWT (4 positive, 2 negative). So that the clinical significance of scores could be ascertained raw scores were converted to z-scores using normative data from Spreen & Strauss (1991). The positive group performed worse than the negative group (x = -.23 SD) on the colour-word trial of the VSCWT, t (4) = 1.94, p < .1. As illustrated in figure 9, the positive group’s word and colour-word (interference) scores were both in the clinically significant range. Given the impact of IQ on the TOVA and WCST one-tailed correlations were calculated between the VSCWT variables and IQ to see if higher IQ was associated with better performance. None of the correlations were significant.

![Figure 9: Mean z-scores of adults on the VSCWT.](image)

**WCST**

In order to be able to compare participants across the large age range WCST raw scores were converted to z-scores using adult norms (Heaton, 1981) or age norms (Rosselli & Ardila, 1993) as appropriate. For the child norms the lower of the two SES groups provided in Rosselli & Ardila (1993) were used. Twelve participants completed the WCST (six positive, six negative).
Participants carrying the inversion performed more poorly than the negative group on all of the WCST variables with the exception of failure to maintain set (FMS). The positive group made more errors in total ($x = 2.39$), than the negative group ($x = 1.54$), $t(10) = 1.80, p < .1$, including more nonperseverative errors ($x = 1.73$) than the negative group ($x = .23$), $t(10) = 1.41, p < .1$, and more perseverative errors ($x = 2.31$) than the negative group ($x = 1.11$), $t(10) = 1.63, p < .1$. Taking scores 1.5 standard deviation above the mean as a clinically significant, the positive group scored in the clinically significant range on four of the six variables, total errors, nonperseverative errors, perseverative errors and perseverative responses ($x = 2.66$). The negative group performed within the normal range on all variables. Group mean z-scores for each variable are illustrated in figure 10.

As WCST performance is likely to be related to IQ (Heaton, 1981), and significant differences were found between the groups on IQ the correlation between the WSCT variables and IQ was examined. Full scale IQ was significantly correlated with categories achieved, $r = .587, p < .05$, total errors, $r = -.573, P < .05$, perseverative errors, $r = -.746, p < .005$, and perseverative responses, $r = -.746, p < .05$. This indicates that lower IQ scores were associated with making more errors in total, more perseverative errors, more nonperseverative errors, more perseverative

![Figure 10. Mean z-scores for the positive and negative groups on the WCST variables (Cat = categories achieved, FMS = failure to maintain set, Err = total errors, NP.err = nonperseverative errors, P.err = perseverative errors, P.res = perseverative responses)](image)
responses, and achieving fewer categories. In order to determine if any residual
differences were present between the groups once IQ was taken into account, the
children’s scores were calibrated against their IQ by converting their raw scores to z-
scores using the norms for their mental age (calculated as described earlier, see
section on TOVA) rather than their chronological age.

Once scores had been adjusted for IQ none of the differences between the
groups remained significant even at the .1 level. The group carrying the inversion
continued to have a mean z-score in the clinical range however for total errors (x =
1.67) and perseverative errors (x = 2.05). The negative group also scored in the
clinical range for one variable, failure to maintain set (x = 1.88). The mean
differences between the groups after IQ adjustments are illustrated in figure 11.

Figure 11. Mean z-scores for the positive and negative groups on the WCST variables after
adjusting children’s scores for IQ (Cat = categories achieved, FMS = failure to maintain set, Err =
total errors, NP.err = nonperseverative errors, P.err = perseverative errors, P.res = perseverative
responses)
Individual case profiles

CBCL

Problem Scales

As illustrated in figure 12, all the positive cases had clinically high levels of aggressive problems. Furthermore two of the cases (1 & 2) also had high levels of delinquent and social problems. Scores on the attention scale were very high for case 1, borderline for cases 3 and 4, and in the normal range for case 2.

Figure 12. Individual profiles of children with the inversion on the problem scales of the CBCL.

Figure 13 illustrates scores on the problem scales for the negative group. Five of the cases have scores falling within the normal range on all the scales. The remaining two cases (6 & 11) while both having thought problems, have quite different profiles. Case 11 shows a pattern of externalising problems with high scores on attention, aggression and delinquency, similar to the profile’s of the positive cases. Case 6 shows a profile of internalising problems with a high score on anxiety/depression.
Figure 13. Individual profiles of children without the inversion on the problem scales of the CBCL Competence Scales

Only cases 1 and 2 showed clinically low levels of competence. Case 1 had poor school competence, case 2 had poor competence in the general and social activities areas (see figure 14). None of the negative group had competence scores in the clinical range (see figure 15).

Figure 14. Individual profiles of children with the inversion on the competence scales of the CBCL
Figure 15. Individual profiles of children without the inversion on the competence scales of the CBCL

Intellectual functioning

Figure 16 illustrates the IQ profiles for those in the positive group who completed the whole test. Case 1 is quite distinctive in the low scores obtained on each subtest. Cases 2 and 3 show quite variable patterns of scores with a large range (9 & 11 respectively). Even case 12 with a higher score than the others on most subtests overall only had a FIQ in the low average range. Subtests believed to load highly on attention (digit span, arithmetic, coding) did not appear to be performed at any lower level than the other subtests.

Figure 16. Individual profiles of members of the family with the inversion on the WAIS-R (12 & 13) or WISC-III (cases 1, 2 & 3).
Figure 17 illustrates the profiles for the negative group. There is quite a large spread of scores from case 5 with very low scores (FIQ borderline) to case 14 with quite high scores (FIQ above average).

![Figure 17. Individual profiles of members of the family without the inversion on the WAIS-R (14 & 15) or WISC-III (cases 5, 6, 8 & 9).](image)

**TOVA**

**Omission Scores**

Figure 18 illustrates the profiles of omission scores for the positive group. There are three cases which show no difficulties with the task, cases 1, 13 and 19. Cases 16 and 18 show mild difficulties in quarter three, cases 3 and 4 quite significant difficulties in quarter three. Case 12 shows a continual drop in the second half. Case 2 has variable performance at a level well below normal at all stages. Case 17 while maintaining attention in the first quarter dropped significantly for the remainder of the test. Figure 19 shows the profiles of the negative group. Only case 6 stands out performing at a level significantly below normal.
Figure 18: Profile of omission scores across the three quarters of the TOVA for individuals with the inversion.

Figure 19: Profile of omission scores across the three quarters of the TOVA for individuals without the inversion.

Commission scores

As shown in figure 20, most of the positive group performed at close to normal levels for commission errors. Cases 4 and 16 showed an increase in errors in quarter two only, while cases 3, 12 and 18 showed an increase in errors in quarter three only. Case 19 made a significant number of errors throughout the first half of the test but performed in normal level in the second half. Cases 1 and 2 showed extreme levels of commission errors in the first half of the test. While both were assigned scores of zero in quarter two to aid visual interpretation of the profiles, both had negative standard scores (-149 and -55 respectively). While they improved considerably in the third quarter they still performed at a level well below normal.
Among the negative group two cases, 5 and 8, had clear difficulties with impulsivity (see figure 21). Case 9 made more errors in the second half of the test but only at the borderline clinical range. Case 15 started with a high level of errors in the first quarter but recovered considerably for the remainder of the test.

Reaction Time

Most of the members of the positive group had reaction time scores within the normal range throughout the test. Cases 12 and 17 had slower reaction times in the second half only. Case 4 showed quite a different pattern with significantly slow reaction times throughout the test (see figure 22).
Among the negative group, case 8 had a slow reaction time in quarter two only. Case 15 while having normal reaction times in the first half, in the second half had quite slow reaction times reaching the clinically significant range in the fourth quarter. Case 6 had clear difficulties throughout the test, with reaction times in the clinical range throughout (see figure 23).

Variability

Among the positive group cases 13 and 18 maintained a normal level of variability throughout the test. Cases 1 and 3 had higher variability in the second half though only at borderline levels. Case 17 showed a similar pattern of increased variability in the second half, with clinically significant levels in the second half. Case
19 while starting with high variability, settled down and had normal levels for the remainder of the test. Cases 12 and 16 had exactly the same pattern, starting with high variability in quarter one but dropping in quarter two to within the normal range and maintaining borderline levels for the final two quarters. Only cases 2 and 4 had significantly high variability throughout the test (see figure 24).

![Figure 24: Profile of variability scores across the three quarters of the TOVA for individuals with the inversion.](image1)

Among the negative group cases 5 and 15 showed an increase in variability in quarter four only. Case 8 showed significantly high variability throughout the test (see figure 25).

![Figure 25: Profile of variability scores across the three quarters of the TOVA for individuals without the inversion.](image2)
VSCWT

Figure 26 illustrates the individual profiles for the adults who completed the VSCWT in both the positive (cases 12, 13, 16 & 17) and negative (cases 14 & 15) groups. Only case 16 showed significantly deviant scores on all three variables. Case 12 had high scores on both the word and interference trials, while case 17 had a high score on the interference trial only. Case 13 although positive for the inversion performed within the normal range.

![Figure 26](image)

*Figure 26. Individual profiles for both positive and negative family member’s performance on the VSCWT (Cases 12, 13, 16 & 17 positive, cases 14 & 15 negative).*

WCST

Among the positive group cases 12 and 17 showed quite significantly poor performance on all but the failure to maintain set variable of the WCST. Cases 1 and 2 made a lot of perseverative errors but were not deviant on any other variable (see figure 27).
Among the negative group case 9 made a significant number of total errors, perseverative errors, perseverative responses and achieved fewer categories. Case 5 made significantly high numbers of perseverative responses and errors. Finally case 8 made high numbers of all error types, perseverative responses and had an extremely high failure to maintain set score (see figure 28).

Table 2 summarises the findings on each dependent measure on a case by case basis. Each dependent measure produced a number of sub-scale scores. It is recommended that a moderate deficit on one variable on the TOVA (e.g., omissions), or a mild deficit on two variables (e.g., omissions and commissions), be considered suggestive of a clinically significant problem or deficit overall (Greenberg & Dupuy, 47)
1993). A similar principle was applied to scores on the other dependent measures. Cases which appear to have clinically significant problems overall are highlighted in bold.
Table 2. Clinically significant findings for each case on symptom measures (CBCL or SCL-90), attention (TOVA, VSCWT), and frontal functioning (WCST).

<table>
<thead>
<tr>
<th>CASE</th>
<th>IQ</th>
<th>SYMPTOMS</th>
<th>TOVA</th>
<th>VSCWT</th>
<th>WCST</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive cases:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 1</td>
<td>Intellectual deficiency (IQ &lt; 50)</td>
<td>Soc, att, agg, del, intern, extern, total</td>
<td>S: Com.T MD: Var.Q3</td>
<td>M: Cat, P.err, FMS</td>
<td></td>
</tr>
<tr>
<td>Case 2</td>
<td>Borderline</td>
<td>Soc, att, agg, del, intern, extern, total</td>
<td>S: Om.T, Com.T, Var.T</td>
<td>M: P.err</td>
<td></td>
</tr>
<tr>
<td>Case 3</td>
<td>Borderline</td>
<td>Att, agg, del, intern, extern, total</td>
<td>S: Om.Q3 M: Om.T, Var.T, Com.Q3</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Case 4</td>
<td>Low average*</td>
<td>Thou, att, agg, extern, total</td>
<td>S: RT.T, Om.Q3 MD: Var.T, Om.H2, Com.Q2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 12</td>
<td>Low average</td>
<td>IS, PSY, PST.</td>
<td>S: Om.T MD: Var.Q1</td>
<td>S: W, C M: P.err, P.res</td>
<td></td>
</tr>
<tr>
<td>Case 13</td>
<td>Low average</td>
<td>All scales</td>
<td>S: Om.T MD: Var.Q1</td>
<td>S: C, W, CW M: Cat, Err, NP.err</td>
<td></td>
</tr>
<tr>
<td>Case 16</td>
<td>Borderline*</td>
<td>-</td>
<td>S: Om.T MD: Var.T, Var.H2</td>
<td>M: C-W M: Cat, Err, P.err, P.res</td>
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<td>Nil</td>
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<td>M: Var.T</td>
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<td>Case 19</td>
<td>Low average*</td>
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<td></td>
</tr>
<tr>
<td>Negative cases:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case 5</td>
<td>Intellectual deficiency</td>
<td>Nil</td>
<td>S: Com.T MD: Var.Q4</td>
<td>S: P.err, P.res M: Cat</td>
<td></td>
</tr>
<tr>
<td>Case 6</td>
<td>Average</td>
<td>Som, thou, A/D</td>
<td>S: Om.T MD: RT.Q3</td>
<td>M: RT.T, RT.Q3 Nil</td>
<td></td>
</tr>
<tr>
<td>Case 7</td>
<td>Average*</td>
<td>Nil</td>
<td>Nil</td>
<td>S: FMS MD: Err, NP.err M: P.err, P.res</td>
<td></td>
</tr>
<tr>
<td>Case 8</td>
<td>Average</td>
<td>Nil</td>
<td>S: Com.T, Var.T MD: Om.Q4</td>
<td>M: P.err M: Cat, Err, P.res</td>
<td></td>
</tr>
<tr>
<td>Case 9</td>
<td>Low Average</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Case 10</td>
<td>-</td>
<td>With, A/D, thou, att, agg, del, intern, extern, total</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Case 11</td>
<td>-</td>
<td>With</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Case 14</td>
<td>Superior</td>
<td>IS, Dep, Par, GSI, PST.</td>
<td>Nil</td>
<td>Nil</td>
<td></td>
</tr>
<tr>
<td>Case 15</td>
<td>Average</td>
<td>Nil</td>
<td>MD: Com.Q1, Var.Q2 MD: Var.T, RT.Q4</td>
<td>M: W Nil</td>
<td></td>
</tr>
</tbody>
</table>

Note: *Cases in italics are children.

Variables are reported as either severe (S), moderate (MD), or mild (M). (OM = omissions, Com = commissions, Var = variability, RT = reaction time, Q1-Q4 = quarters 1 through 4, H1-H2, half 1 or 2, T = total)

**Cases in italics are children.**

b Som = somatic, Withd = withdrawn, A/D = anxiety/depression, Int = internalising, Thou = thought, Soc = social, Att = attention, Aggr = aggression, Del = delinquent, Ext = externalising

c Clinically significant variables reported as either severe (S), moderate (MD), or mild (M) (Cat = categories achieved, FMS = failure to maintain set, Err = total errors, P.err = nonperseverative errors, P.err = perseverative errors, P.res = perseverative responses)

d Clinically significant variables reported as either severe (S), moderate (MD), or mild (M) (Cat = categories achieved, FMS = failure to maintain set, Err = total errors, P.err = nonperseverative errors, P.err = perseverative errors, P.res = perseverative responses)

*Estimate of FIQ only
Discussion

One family member was able to identify, prior to genetic testing, all but one of the family members (case 13) who carry the inversion, supporting the first hypothesis that there is some identifiable set of behaviours or problems in individuals carrying the inversion. Differentiating members of the family carrying the inversion from those who do not using more quantifiable measures was less successful.

Symptom reports

Children

As expected parents considered children carrying the inversion had more behavioural problems in total, more externalising problems (aggression and delinquent behaviours), and had poorer attention than children without the inversion (hypothesis 2a). The group means for these variables were in the clinical range (T-scores > 70), suggesting family members with the inversion experienced symptoms of clinical significance. Though it was not specifically predicted, it is perhaps not surprising to find that the children had social problems and were less competent overall, given the high level of aggressive and delinquent behaviour problems.

At an individual level two of the children (cases 1& 2) with the inversion were distinguishable by very high levels of delinquent, aggressive and social problems (figure 12). These children were reported to have a number of behaviours consistent with Conduct Disorder. The other two children with the inversion had much lower levels of problem behaviours overall, but similarly had high externalising problems.
Their behaviour problems thus appeared to be of a similar nature but less severe than those of the other two children.

**Adults**

There was not enough data to analyse scores on the WURS. Data on the SCL-90-R was similarly too scarce to make conclusions regarding the presence of any psychopathology linked to the inversion. Medical History Questionnaires filled out by the mother of two adults who did not fill out the WURS or SCL-90-R revealed school problems including being under special instructions, held back a grade, difficulty getting along with others, and suspension. Both had been in therapy as children. In one case this related to hyperactivity and conduct problems. In the other case there were indications of substance abuse, anxiety and depression as an adult. High levels of depression and anxiety were reported for one child on the CBCL (case 6) and medical histories for two other individuals with the inversion also indicated anxiety problems. Thus there appears to be some family history of depression/anxiety as well as conduct problems. This suggests that in some cases childhood symptoms disappear, while in other cases there is a continual display of symptoms or possibly even a developmental decay.

**Cognitive Measures**

**Intelligence**

As predicted individuals carrying the inversion had lower IQs than individuals without the inversion (hypothesis 1c). This was the strongest finding in the study. None of the individuals carrying the inversion had IQ scores reaching the Average
range. This had a significant impact on the study overall due to the high correlation between IQ and performance on the other tests (TOVA, WSCT). Only children's scores were adjusted to try and examine any residual differences. Had adult norms been similarly adjusted the residual differences between the positive and negative groups may have disappeared entirely. These results strongly illustrate the need for norms that account for variation in general intelligence.

While scores on the FFD index were not analysed, individual profiles did not suggest those subtests believed to load highly on an attention factor (coding, digit span, arithmetic) were performed more poorly than the other subtests. This is perhaps surprising given the group differences found for omission errors on the TOVA and colour-word scores on the VSCWT suggestive of the presence of attention deficits. Omission errors, reaction times and the VSCWT variables were not significantly correlated with FIQ. This suggests attention plays little part in intellectual functioning as measured by the WAIS-R and WISC-III. This is consistent with other findings that the FFD index is not a pure measure of attention (Anastopoulos, Spisto & Maher, 1994).

The hypothesis that children would be less competent at school was surprisingly not supported given the group differences in IQ. Significant school problems were reported for only one child, who had extremely low IQ (case 1). As the CBCL asks parents to compare their child to average, this suggests that their level of performance is not particularly low within their school environment.
Attention

TOVA

Omission errors

Partial support was found for the hypothesis that individuals carrying the inversion would show evidence of poorer attention on a CPT. Their mean total commission error standard score on the TOVA was in the clinical range, but not significantly different from the negative group's mean. Any difference overall was largely due to individuals carrying the inversion making more omission errors than family members without the inversion in the third quarter of the TOVA. Omission errors are said to represent short periods of phasic changes in alertness (VanZomeren & Brouwer, 1992), thus lack of alertness does not appear to have been a problem except perhaps in quarter three. The overall pattern of omission scores across the four quarters does not show a gradual decline that would indicate a significant problem in sustained attention (maintenance of information processing over time). The pattern of increased omission errors from the second to third quarter, when the ratio of targets to non-targets increased (see figure 6) may represent difficulty in shifting between the low and high frequency modes (Greenberg & Dupuy, 1993), as performance was back in the normal range in quarter four. This suggests that members of the family carrying the inversion may have difficulty with cognitive flexibility.

At the individual level there was quite a lot of variation in the pattern of responses, from cases there was no evidence of any problem missing targets, to cases where performance was extremely poor for most of the test. Although the individual
profiles show a confusing picture of different response patterns among the family members with the inversion, this is strikingly different from the almost consistent normal performance of the family members without the inversion (with the exception of case 6). This suggests that while individuals carrying the inversion may be inattentive, there is a wide variety in the severity of this deficit.

*Reaction time*

The hypothesis that reaction times would be slower in the group with the inversion was not supported, with both groups performing well within normal limits. This suggests that any deficit in attention is not the result of slowed processing. Two cases did show a clear pattern of slow reaction times, one was positive and one was negative for the inversion. In the case of the individual without the inversion a clinically significant level of anxiety and depression was also reported (Case 6, see figure 13). It has been suggested when this is the only affected variable, depression may be the cause of impaired performance (Greenberg & Dupuy, 1993).

*Variability*

The hypothesis that the positive group would have higher variability was partially supported as the positive group’s mean standard score for variability did fall just within the clinical range. Similar to the individual profiles for omission scores, the variation in response patterns in the positive group was high. Six of the ten individuals with the inversion had high variability in the clinically significant range for at least one quarter and a further two had borderline scores in two quarters. In contrast the negative group’s showed fairly stable patterns with again one exception.
(case 8). This indicates many of the family members with the inversion had a high level of intra-individual variability in attention, their speed of responding lacked consistency. High variation in performance within the positive group and small subject numbers may have masked any differences between the positive and negative groups overall.

**Impulsivity**

The hypothesis that family members with the inversion would be more impulsive on the TOVA was only partially supported. The positive group’s mean total commission errors standard score was in the clinical range, but not significantly different from the negative group’s mean. Given the description of members of the family as impulsive and the high level of externalising problems suggestive of conduct disorder traits, it is surprising commission errors did not differ significantly between the groups. The individual profiles show commission errors were extremely high for two positive cases (cases 1 & 2), both of whom also had very high externalising problems. This pattern is consistent with findings that commission errors on CPTs relate to hyperactivity and oppositional behaviour (Lassiter et al., 1995).

The positive group’s mean standard score showed a large drop from quarter one to quarter two, that was essentially recovered in quarter three (see figure 8) indicating a decrease in commission errors from the target infrequent condition to target frequent condition. This pattern is unusual as in the second half of the test commission errors on the TOVA are actually expected to increase (Greenberg & Dupuy, 1993). Alterations in the parameters of CPTs have been found to affect responding in ADDH children, including make more false alarms when the event rate is slower (Chee, Logan, Schachar, Lindsay & Wachsmuth, 1989). The drop in
quarter two may similarly reflect a specific response pattern in these participants dependent on the parameters of the TOVA. Impulsive responding may have been related to a lack activity, the participants perhaps becoming increasingly restless and bored with few targets to respond to. When target frequency increased they were kept adequately occupied and the percentage of errors went down. The low frequency condition thus may have given them a large enough window within which to become distracted. These findings certainly suggest further research is required to determine the specific parameters that bring out poor performance in individuals.

Two children without the inversion showed significant commission errors indicating high impulsivity. They also had clinically significant scores on the WCST. No significant problems were reported for either child on the CBCL. This would suggest that while they fall outside the normal range on these measures, any deficit is not causing them any functional impairment in daily life or behavioural problems of concern to their parents. It may also however be indicative of biased reporting on the part of the parents given they were aware these children did not have the inversion.

\textit{VSCWT}

The hypothesis that adults carrying the inversion would have poorer attention than family members without the inversion on the VSCWT was supported (hypothesis 2f), with the positive group being slower on the colour-word (interference) trial. While the significance level was low (.1) three of the four positive adults tested had colour-word scores in the clinical range (see figure 26). In one case VSCWT performance was significant where the TOVA was not suggesting it may be more sensitive tool than CPTs in assessing attention deficits in adults. The Stroop Tests are said to measure concentration effectiveness, or the ability to block out distractors
Poor performance on the interference trial suggests a deficit in focused attention, the ability to attend to a stimulus while ignoring another. Normal performance on the colour naming trial indicates that the processing speed of family members with the inversion was normal, consistent with normal reaction times on the TOVA. The positive group also performed quite poorly on the word trial, perhaps most likely reflecting their low level of intellectual functioning and poor school achievement.

**WCST**

The prediction that individuals with the inversion would have poorer frontal functioning than members of the family without the inversion (hypothesis 1g) was not supported. As the WCST is a test of higher mental processing, largely of conceptual ability (O'Donnell, Macgregor, Dabrowski, Oestreicher & Romero (1984), it is perhaps not surprising to find IQ accounted almost completely for performance on the WCST. Total errors and perseverative errors were however in the clinical range in the positive group. To the extend this may reflect a pattern of responding in the positive group it suggests that they have difficulty with shifting cognitive set. This is consistent with omission scores on the TOVA which also were suggestive of difficulties with mental flexibility. As only one of the subjects showing the increase in omission errors from quarter two to three also completed the WCST the possibility of poor cognitive flexibility could not be confirmed at the individual level.

The mean FMS z-score was in the clinical range for the negative group. This appears to be largely the result of an extremely high score for one subject (case 8), who also showed extremely high commission errors suggesting this may have been the result of a high level of impulsivity. The other children who had high levels of
commission errors on the TOVA did not have significant FMS scores. These cases (1, 2 & 5) all showed an increase in commission errors in quarter two and a decrease in quarter three. Thus they may have been highly distractible rather than lacking in impulse control.

Heaton (1981) suggests using a raw score of 18 on perseverative responses as a cut off point for predicting brain damage, and 13 on perseverative errors. This would correspond to z-scores of .21 and .04 respectively for adults using the norms reported by Heaton (1981). This suggests the criteria for clinical significance used in this study may have been too stringent increasing the likelihood of false negatives. Examination of the individual profiles suggests that while reducing the criteria for clinical significance would identify more cases with apparent frontal impairment it would increase the number of cases in both the positive and negative group and therefore not offer any insight into the difference between these two groups.

The overall picture

The percentage of individuals who had clinically significant problems was well above what would be expected in a normal population, however the percentage of individuals in the negative group with significant problems was also well above what would be expected in a normal population (see table 3). A subset of individuals with the inversion did not have any difficulties and a number of children without the inversion showed signs of having similar problems in attention, impulsivity and cognitive flexibility to those children with the inversion, although their parents did not consider them inattentive or difficult to manage.

Clear conclusions regarding a possible attention deficit are impossible with the small numbers of participants combined with the differences between adults and
children. There is no evidence of a sustained attention deficit, that is poor alertness or slowed processing. There was evidence of a selective attention deficit in focused attention in adults that would need to be confirmed in children. There was suggestive evidence of high intra-individual variability in attention and cognitive inflexibility, but more data would be required to confirm these hypotheses.

Table 3. Percentage of individuals with and without the inversion showing clinically significant deficits overall.

<table>
<thead>
<tr>
<th></th>
<th>Inversion</th>
<th></th>
<th>No inversion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Children</td>
<td>Adults</td>
<td>Total</td>
</tr>
<tr>
<td>Symptomatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CBCL)</td>
<td>4/8 (50%)</td>
<td>4/4 (100%)</td>
<td>2/9 (22%)</td>
<td>2/7 (29%)</td>
</tr>
<tr>
<td>Attention Deficit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(TOVA)</td>
<td>6/10 (60%)</td>
<td>4/4 (100%)</td>
<td>2/6 (30%)</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>Attention Deficit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(VSCWT)</td>
<td>3/4 (75%)</td>
<td>3/4 (75%)</td>
<td>0/2 (0%)</td>
<td>0/2 (0%)</td>
</tr>
<tr>
<td>Frontal impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(WCST)</td>
<td>4/6 (67%)</td>
<td>2/3 (67%)</td>
<td>2/3 (67%)</td>
<td>3/6 (50%)</td>
</tr>
</tbody>
</table>

Symptom report data suggests the children have a hyperactive subtype of ADHD that would need to be formally confirmed by a structured diagnostic interview. The children also appear to have aggressive traits and in some cases a comorbid Conduct Disorder. Anecdotal data for adults suggests Conduct disordered traits, poor school functioning and achievement consistent with studies of adults with ADHD (Biederman et al., 1993) and a family history of anxiety and depression. Combined with low intellectual functioning the symptom picture in this family is difficult to clarify, and interpretation is further complicated by indicators of family dysfunction (high level of divorce, changes in primary carer of children and residence). The high level of externalising behaviours reported for the children and family disruption are consistent with other findings that children with ADDH + CD have parents with a higher rate of psychopathology, families more dysfunctional and
more characterised by adversity compared with ADDH alone (Chee et al., 1989). It is
difficult to tease out what problems may be caused by the disruptive family
background and what by the inversion. As genes and environments interact and
change over time (Rose, 1995) both are probably contributing to the symptoms, and
to different extents depending on the person’s age. This may explain the large
variation in symptomatology and test performance between individuals. There
appeared to be different levels of severity on the behaviour measures, and a wide
variety of response patterns in omission and variability on the TOVA. Both
aggression and anxiety have been found to alter ADHD symptomatology (Halperin et
al., 1993). This study did not find any measure that would come as close to
predicting genetic status as one family member was able to. Any common deficit
seems to be hidden by the interacting variables and small number of subjects, with low
IQ being the only common vulnerability among members of the family with the
inversion.

Limitations of the study

There were a number of significant limitations to this study, many of which
resulted from the exploratory nature of the study and unusual circumstances
surrounding its conception. Low subject numbers limited the power of the study and
conclusions that could be made about the individuals carrying the inversion as a
group. As participants were pre-selected by family membership, this was unavoidable.
Participants could not be recruited elsewhere. In addition, subjects unwilling to
participate in the study further reduced the total subject numbers and resulted in
varied amounts of data for each subject. A subset of the family were not willing to be
tested for the inversion to begin with (see figure 1) and among those who were tested
some were not interested in pursuing the possible significance of the inversion. Discussions with family members through the course of the testing period suggested denial that the inversion caused any problem, embarrassment that they were somehow abnormal, anxiety that they would perform poorly on tests, and guilt on the part of parents that some problem was being passed down to their children, were all factors in their lack of cooperation. The impact such factors would have on the study was underestimated as initial discussions with family members suggested they were willing to participate.

The large variation in age range made subjects difficult to compare. While CPTs have good discriminant validity with ADHD children (Levy & Hobbes, 1997), ceiling effects in adults pose a problem (Rasile et al., 1995). Tests such as the WCST and VSCWT may be more useful for adults particularly once norms accommodating low IQ are developed. As ADHD has variable developmental courses (Cantwell, 1996), we would expect there to be differences in the difficulties experienced by members of the family at the different ages (occurring through altering genetic or environmental impacts with age). The possible effects over time could not be examined as further fragmenting the small sample would have reduced numbers to levels below what could be statistically examined.

Members of the same family without the inversion acted as the control group due to the practical problems in finding subjects that could be adequately matched to the positive group. This however meant there were differences between the groups in both absolute numbers and the ages represented, including different proportions of children and adults. This may have been particularly problematic with the developmental differences in presentation and sensitivity of the tests to the presumed deficit at the different ages. Inclusion of a matched control group (particularly for age and IQ) may have clarified the extent of the positive group’s deficits, as they did not
in many ways represent typical normative groups. The negative group could not
countrol for the possible cumulative and interactional effects of psychopathology
through the generations that might have been achieved with a control group with
some other known psychopathology.

Participants (or their parents) were not blind to their genetic status. This
poses a significant problem for the validity of the data. By virtue of how the inversion
was discovered this was not possible. How this effected test performance is hard to
predict. Unlike in standard research where the outcome of the study has little impact
on the individual participants, in this case the participants are stakeholders in the
research and each have their own reasons for wanting the results to turn out one way
or another. In some cases there was evidence suggestive of faking bad (eg SCL-90
data for case 13). Only one of the children with the inversion was on stimulants prior
to genetic testing, after testing the remaining three were prescribed stimulants. The
parents of these children were convinced of the problem before the study began, and
furthermore believed it was ADHD. This would have had the largest effect on the
symptom report data and not surprisingly group differences were strong on the
CBCL. The CBCL data however did not show halo effects (except case 4), nor were
attention problems specifically high, providing some validity for the results. In other
cases however there appeared to be the opposite effect, with participants giving the
impression they did not believe there was in fact any problem, and that the children’s
problems could be explained by environmental factors. Overall it may be that the
opposing opinions minimised any bias toward either augmenting or minimising
symptom reporting and test performance. Diagnostic interviewing may have provided
clearer information on the problems being experienced by participants and alleviated
any effects caused by literacy demands of the rating scales.
The study was further limited by the lack of blindness on the part of the experimenter. Again this to some extent reflected the nature of the study. Family members were concerned about the inversion and its possible effects and were keen to discuss either their own problems or their children's. Knowing the genetic status of other members of the family they were also keen to share their hypotheses regarding the problems in others. The impact of lack of experimenter blindness was minimised by the design in that formal diagnoses were not made, rather participants were asked to perform tests that could be scored against normative data.

Finally it must be noted that significance levels of 0.1 were accepted due to the unusual nature and size of the sample. This is likely to have increased the probability of false positive results. Furthermore the significant intellectual disability of case 1 identifies this as an outlier although it could not be removed due to low subject numbers. His level of functioning may have impaired performance beyond the attempts to control for IQ differences and skewed the positive groups mean scores.

Conclusion and future directions

The difference in IQ between the groups, a high level of family disruption and indications of concurrent aggression, anxiety and depression paints a confusing picture from which it is difficult to determine whether there is any underlying commonality between the family members carrying the inversion. This was further compounded by a small number of participants that prevented separating out the sample into groups based on age. Given that the course of the condition is likely to change with age combining the whole age range undermined the possibility of findings significant differences between those who carry the inversion and those who did not.
This was further exacerbated by the lack of sensitivity of measures to symptoms in the adults and confounding due to low levels of intellectual functioning.

There are a number of options in trying to tease these variables out. Information from third parties such as teachers would provide information on the children outside their family environment and perhaps be more objective. It would not however help in clarifying the adult’s problems. Structured diagnostic interviewing may tease out the various comorbidities, providing a clearer picture of their symptomatology. From a practical point of view however the lack of cooperation on the part of many family members may still result in small numbers from which to try and discern any pattern of inheritance. A longitudinal study would perhaps be ideal in clearing up some of the interacting variables over time, as the course of the symptoms, cognitive deficits and environmental factors could be charted (small numbers may still limit the strength of any conclusions). Measuring family variables would be of particular interest given the indications of family dysfunction.

This study used only self-report and neuropsychological measures. EEG and event-related potentials (Lubar, 1991), brainstem auditory evoked potentials (Lahat et al., 1995) and steady state probe topography (Pritchard, 1996) have all been found to distinguish between ADHD samples and controls. Like neuropsychological tests they are not dependent on subjective impressions of behaviour and are believed to reflect the presumed pathogenesis of the disorder in question. They have the added advantage of excluding any impact of behavioural responses. Investigations of this nature may prove the only way to avoid the impact of biased responding resulting from the individual’s knowledge of their genetic status.
References


Appendix 1

Medical History Questionnaire

Name.................................................................................................................. Filled out by .................................................................................................
Date of birth........................................................ Relationship to subject/client:.................................................................
Age...................................................... Sex.................................

This questionnaire asks for information about your, or your child’s developmental and medical history. If any of the conditions listed have been a problem, we are interested in when it was a problem, how long it lasted, how severe it was and how it was treated. Please fill free to write on the back of the questionnaire or in the space provided at the end if you need more room. If there are any problems that we have not covered in the questionnaire please make a note of these at the end. If you have any questions please ask.

Developmental history

Pregnancy

Were there any difficulties with the pregnancy or delivery? eg caesarean, breech, premature birth

Did you use any of the following substances while pregnant?

- Alcohol................................................. Coffee/caffeine products............................................
- Cigarettes................................................... Valium.................................................................
- Tranquillisers.............................................. Anti-seizure medications.................................
- Treatment for diabetes............................... Antibiotics........................................................
- Sleeping pills.............................................. Other, please specify ........................................

Infancy

Were there any problems with:

- Feeding.......................................................... Colic..............................................................
- Sleeping........................................................ Responsiveness.............................................
- Alertness........................................................ Health..........................................................
- Crying .......................................................... Activity level.................................................
- Temperament................................................

Developmental milestones

At what age did your child complete the following milestones? Please note any difficulties experienced in mastering these activities:

- Sit-up.......................................................... Crawl..............................................................
- Walk.......................................................... ...........................................................
- Speak single words (other than mum or dad) ..............................................................
- String two or more words together?..............................................................
- Toilet trained?.............................................. How long did toilet training take?..............
School/social history

Please give details for any of these situations if they apply:

Suspended from school? ................................................................. Expelled? .................................................................
Held back a grade? ................................................................. In special classes? .................................................................
Under special instructions? .................................................................
Difficulty getting along with other children? .................................................................
Difficulty making friends? .................................................................
Difficulty keeping friends? .................................................................

Health during childhood

Please tick the best description for each category:

<table>
<thead>
<tr>
<th>General health</th>
<th>Vision:</th>
<th>Hearing:</th>
<th>Fine motor co-ordination:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>Good</td>
<td>Good</td>
<td>Good</td>
</tr>
<tr>
<td>Good</td>
<td>Fair</td>
<td>Fair</td>
<td>Fair</td>
</tr>
<tr>
<td>Fair</td>
<td>Poor</td>
<td>Poor</td>
<td>Poor</td>
</tr>
<tr>
<td>Poor</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Medical history

Any chronic health problems?

Asthma? ................................................................. Diabetes? .................................................................
Heart condition? ................................................................. Endocrine condition? .................................................................
Epilepsy? ................................................................. Other? .................................................................

Other illnesses:

Mumps? ................................................................. Chicken pox? .................................................................
Measles? ................................................................. Whooping cough? .................................................................
Scarlet fever? ................................................................. Glandular fever? .................................................................
Pneumonia? ................................................................. Encephalitis? .................................................................
Otitis media? ................................................................. Lead poisoning? .................................................................
Seizures? .................................................................

Accidents resulting in:

Broken bones? ................................................................. Severe lacerations? .................................................................
Head injury? ................................................................. Severe bruises? .................................................................
Stomach pumped? ................................................................. Eye injury? .................................................................
Lost teeth? ................................................................. Stiches? .................................................................
### Surgery or problems with any of the following conditions:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonsillitis?</td>
<td>Adenoids?</td>
</tr>
<tr>
<td>Hernia?</td>
<td>Appendicitis?</td>
</tr>
<tr>
<td>Eye, ear, nose, throat?</td>
<td>Digestive disorder?</td>
</tr>
<tr>
<td>Urinary tract?</td>
<td>Cardiac difficulties (heart)?</td>
</tr>
<tr>
<td>Blood pressure?</td>
<td>Stroke?</td>
</tr>
<tr>
<td>Leg or arm?</td>
<td>Back?</td>
</tr>
<tr>
<td>Glands? eg thyroid, adrenal?</td>
<td>Burns?</td>
</tr>
</tbody>
</table>

### Any problems with:

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headaches?</td>
</tr>
<tr>
<td>Sleeping?</td>
</tr>
<tr>
<td>Bowel control?</td>
</tr>
<tr>
<td>Hormones?</td>
</tr>
<tr>
<td>Alcohol/drug use?</td>
</tr>
<tr>
<td>Migraines?</td>
</tr>
<tr>
<td>Bladder control?</td>
</tr>
<tr>
<td>Appetite control?</td>
</tr>
<tr>
<td>Physical/sexual abuse?</td>
</tr>
</tbody>
</table>

### Psychological:

<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression/suicidal thoughts?</td>
</tr>
<tr>
<td>Anxiety/nerves/panic attacks?</td>
</tr>
</tbody>
</table>

### Treatment

**Please give details of any prescribed medications past or present**

<table>
<thead>
<tr>
<th>Category</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants?</td>
<td>Tranquillisers?</td>
</tr>
<tr>
<td>Anticonvulsants?</td>
<td>Antihistamines?</td>
</tr>
<tr>
<td>Antidepressants?</td>
<td>Other?</td>
</tr>
</tbody>
</table>

**Non-prescribed drug use:**

<table>
<thead>
<tr>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine?</td>
</tr>
<tr>
<td>Marijuana?</td>
</tr>
<tr>
<td>Pain killers?</td>
</tr>
<tr>
<td>Cigarettes/tobacco?</td>
</tr>
<tr>
<td>Alcohol?</td>
</tr>
<tr>
<td>Other? eg speed, cocaine, heroin, ecstasy...</td>
</tr>
</tbody>
</table>

### Ever had any psychological treatment?

**Please give details eg what treatment was for was it successful, how long were you in treatment**

<table>
<thead>
<tr>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual therapy?</td>
</tr>
<tr>
<td>Group therapy?</td>
</tr>
<tr>
<td>Family therapy?</td>
</tr>
<tr>
<td>In-patient treatment?</td>
</tr>
<tr>
<td>Residential treatment?</td>
</tr>
</tbody>
</table>

Please write down any extra details or any other information that has not been covered by the questionnaire: