Neuropsychological tests and functional impairment in adult Attention Deficit Hyperactivity Disorders – with special reference to memory disturbance

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Niels Dige

Stockholm 2010
T. T. T.

Put up in a place
where it’s easy to see
the cryptic admonishment

T. T. T.

When you feel how depressingly
slowly you climb,
it’s well to remember that

Things Take Time.

Piet Hein

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ABSTRACT

Aim: To investigate the possible use of different neuropsychological tests for diagnosis of adult patients with Attention Deficit Hyperactivity Disorder (ADHD), with specific reference to memory tests.

Methods: Patients were referred from psychiatric out-patient units as part of routine clinical assessment. 158 adults were diagnosed with DSM-IV-TR, median age 32 years. A clinical interview was conducted together with four self-report questionnaires. The patients were neuropsychologically assessed before possible treatment, and were followed-up three years later. A group of 13 standard neuropsychological tests and a dichotic memory test were administered. At telephone follow-up three years later, the patients were interviewed with ASRS v1.1 to assess their ADHD symptoms, and some new questions were posed about functional impairment.

Results: A significant reduction was found in memory tests, including dichotic memory, in the study group after analysis for the covariance (ANCOVA) effects of IQ, sex, age, and years of education; the effects of depression and anxiety on the HAD scale had been removed. Profound reduction was found on the working memory capacity tests with distracters: the Consonant Trigram test, the Dichotic Memory test and the Benton VRT. Reductions were also found in learning and delayed recall on the Rey Auditory Verbal Learning test and the modified Diagnosticum für Cerebralschädigung. Minor but significant reductions were found on Digit Span Backward (WAIS), Arithmetic Capacity (WAIS), Raven SET I, WCST Number of Perseverations and in the Trail Making B test, compared with controls. At follow-up, an ADHD medicated group showed a significant reduction in their symptoms compared with non-medicated patients, and also better self-confidence. The rate of employment was low; in total, 58 % were without employment, even after medication.

Conclusions: In adult patients with ADHD, neuropsychological testing using working memory capacity tests with distracters, demonstrate a reduced working memory capacity. In a follow-up, patients on medication showed fewer symptoms and better self-confidence, but many continued to be unemployed.

Key words: Adult, ADHD, neuropsychological tests, working memory, follow-up interview.
PAPERS INCLUDED IN THIS THESIS

The present thesis is based on the following studies, which will be referred to in the text by their Roman numerals.

I Niels Dige and Gustav Wik: Adult Attention Deficit Hyperactivity Disorder identified by neuropsychological testing.

II Niels Dige, Eija Maahr and Gunnel Backenroth-Ohsako: Memory tests in subgroups of adult Attention Deficit Hyperactivity Disorder reveal simultaneous capacity deficit.

III Niels Dige, Eija Maahr and Gunnel Backenroth-Ohsako: Reduced capacity in a dichotic memory test for adult patients with Attention Deficit Hyperactivity Disorder.
Published ahead of print in Journal of Attention Disorder, 2009.

IV Niels Dige, Jerker Hetta and Gunnel Backenroth-Ohsako: A naturalistic 3-year telephone follow-up study of outcomes in adults diagnosed with Attention Deficit Hyperactivity Disorder.
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADD</td>
<td>Attention Deficit Disorder</td>
</tr>
<tr>
<td>ADHD</td>
<td>Attention Deficit Hyperactivity Disorder</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>Analysis of Covariance</td>
</tr>
<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
</tr>
<tr>
<td>APA</td>
<td>American Psychiatric Association</td>
</tr>
<tr>
<td>ASRS v1.1</td>
<td>Adult Self-Report Scale version 1.1 from the World Health Organization</td>
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<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
</tr>
<tr>
<td>CAADID</td>
<td>Conner’s Adult ADHD Diagnostic Interview for DSM-IV</td>
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<tr>
<td>CANTAB</td>
<td>Cambridge Neuropsychological Automated Battery</td>
</tr>
<tr>
<td>CAPD</td>
<td>Central Auditory Processing Disorder</td>
</tr>
<tr>
<td>CD</td>
<td>Conduct Disorder</td>
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<tr>
<td>COMT</td>
<td>Catechol O-methyltransferase Gene</td>
</tr>
<tr>
<td>COMT val158MET</td>
<td>Valine/methionine polymorphism at codon 158</td>
</tr>
<tr>
<td>CONCERTA</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>CVLT-C</td>
<td>California Verbal Learning Test – Children’s version</td>
</tr>
<tr>
<td>DICHOTIC</td>
<td>A list of verbal nouns to be remembered is presented alternately to one of the two ears at a time. In the opposite ear, the ear not receiving the list of words to be remembered, a distracter is presented simultaneously.</td>
</tr>
<tr>
<td>D-KETS</td>
<td>Delis-Kaplan Executive Function System</td>
</tr>
<tr>
<td>DMTS</td>
<td>Delayed Matching to Sample</td>
</tr>
<tr>
<td>DSM-IV-TR</td>
<td>Diagnostic and Statistical Manual of Mental Disorder - text revision from the American Psychiatric Association</td>
</tr>
<tr>
<td>DRD4 and DAT1</td>
<td>Dopamine Synapse 4 and Dopamine Transporter 1</td>
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<tr>
<td>DUDIT</td>
<td>Drug Use Disorder Identification Test</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogram</td>
</tr>
<tr>
<td>FDA</td>
<td>U.S. Food and Drug Administration</td>
</tr>
<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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<tr>
<td>GLM</td>
<td>Generalized linear Logistic regression Model</td>
</tr>
<tr>
<td>ISE</td>
<td>Irrelevant Sound Effect test (Dichotic memory)</td>
</tr>
<tr>
<td>MBD</td>
<td>Minimal Brain Dysfunction</td>
</tr>
<tr>
<td>Acronym</td>
<td>Full Form</td>
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<td>-----------</td>
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<tr>
<td>MANOVA</td>
<td>Multivariate Analysis of Variance</td>
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<tr>
<td>MANCOVA</td>
<td>Multivariate Analysis of Covariance</td>
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<tr>
<td>M.I.N.I.</td>
<td>Mini – International Neuropsychiatric Interview</td>
</tr>
<tr>
<td>NEPSY</td>
<td>Neuropsychological Examination Form - Young Children</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Health and Clinical Excellence</td>
</tr>
<tr>
<td>ODD</td>
<td>Oppositional Defiant Disorder</td>
</tr>
<tr>
<td>RITALIN</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>TOVA</td>
<td>Test of Variables of Attention</td>
</tr>
<tr>
<td>WAIS-III</td>
<td>Wechsler Intelligence Scale for Adults</td>
</tr>
<tr>
<td>WASI</td>
<td>Wechsler Abbreviated Scale of Intelligence</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WISC</td>
<td>Wechsler Intelligence Scale for Children</td>
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<tr>
<td>WM</td>
<td>Working Memory</td>
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<tr>
<td>WMC</td>
<td>Working Memory Capacity</td>
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<tr>
<td>WURS 25-item</td>
<td>Wender Utah Rating Scale</td>
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1. INTRODUCTION

The research started from a practical question: What procedural tests are necessary to participate in good diagnostics for adult ADHD? The number of patients has increased every year since the start of the neuropsychological unit in 2002, and the study had to reduce the number of investigation hours for each patient. The choice of study population was made from the demands on the health care psychiatry system in which more and more patients asked for an ADHD investigation. At the beginning of our work, there was still a question about which neuropsychological tests were best suited for the diagnostic procedure in adults. Since neuropsychology is time consuming, and there is limitation to the numbers of tests or questions each investigation is able to answer, the testing was concentrated, and started with a specific reference to memory problems. This was because most patients complained about memory problems, and memory is also addressed in four of the criteria for the 18 symptoms of ADHD (see below) in DSM-IV-TR (APA, 2000). In an effort to study deficits in working memory in adults with ADHD, the studies investigated how to assess working memory and its clinical and scientific implications.

1.1 Historical perspective

Attention Deficit Hyperactivity Disorder (ADHD) achieved its status as a specific diagnostic entity about 20 years ago (Doddson, 2005). The first descriptions of children were published by Still (1902), who recognized his subjects as having impaired inhibitory volition, a marked inability to concentrate, and a reduced capacity to sustain-attention. Benzedrine medications have been used in the U.S. since 1934 for severe post-spinal-tap headaches in behavior-disordered children (Bradley, 1937). This amphetamine compound was not helpful for the headaches, but teachers reported dramatic, though short-lived, improvements in the children’s learning, motivation, and behavior while on the medications (Bradley & Green, 1940).

According to Dykman (2005), ADHD had been designated as a brain stem syndrome, and had also been called organic driveness (Kahn & Cohen, 1934). Strauss et al. (1947) were the first to use the Minimal Brain Damage Syndrome terminology (IQ > 85, with hyperactivity and learning disability). In 1962, Clements and Peters proposed the term Minimal Brain Dysfunction (MBD) for specific learning deficits, perceptual-motor deficits, general
coordination deficits, hyperkinesias (extreme over-activity), impulsivity, emotional lability, short attention span and/or distractibility, equivocal neurological signs, and borderline abnormal electroencephalogram (EEG). The U.S. Food and Drug Administration (FDA) gave approval for methylphenidate (Ritalin) treatment in 1968 while at the same time the disorder was named Hyperactivity (Werry, 1968) or Hyperkinetic Syndrome (Rutter et al., 1970). From 1970’s onwards, attention problems were included in the diagnosis, called Attention Deficit Syndrome (Dykman et al., 1971), Intention Disorder (Dykman & Ackerman, 1976), Attention Deficit Disorder (ADD) by the American Psychiatric Association (APA, 1978) and later ADHD by the APA (1987). In the mid-1990’s, research provided valid diagnostic criteria for ADHD, and clearly demonstrated significant adverse consequences of non-treatment (Goldman et al., 1998). Today, there are more than 16,500 publications in PubMed under the heading ADHD (see Table1).

Table 1. Number of references to ADHD in PubMed by time period.

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of publications in PubMed</th>
</tr>
</thead>
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<tr>
<td>1950 – 1960</td>
<td>0</td>
</tr>
<tr>
<td>1961 – 1970</td>
<td>25</td>
</tr>
<tr>
<td>1971 – 1980</td>
<td>834</td>
</tr>
<tr>
<td>1981 – 1990</td>
<td>1,830</td>
</tr>
<tr>
<td>1991 – 2000</td>
<td>3,508</td>
</tr>
<tr>
<td>2001 – 2009</td>
<td>10,363</td>
</tr>
</tbody>
</table>

1.2 Prevalence

It is estimated that between 3% and 5% of children suffer from ADHD (Weiss & Murray, 2003). Although ADHD is perceived by many to be a North American disorder, the prevalence of ADHD in school-aged children is, in many other countries, about the same as in the U.S. (Faraone et al., 2003). In the UK, a survey covering 10,438 children between the ages
of 5 and 15 years, found that 3.62% of boys and 0.85% of girls had ADHD (Ford et al., 2003). The more restricted diagnosis of hyperkinetic disorder in ICD-10 (1997), representing a severe sub-group of DSM-IV-TR (APA, 2000), i.e. combined type ADHD, is naturally less common; prevalence estimates are around 1.5% for boys during the primary school years (Ford et al., 2003). Today, it is not uncommon to find adults self-referring themselves for an ADHD evaluation without having been diagnosed as children. Some data suggest that only 25% of adult ADHD cases had been diagnosed in childhood or adolescence (Faraone et al., 2004a).

A Mental Health Survey (Fayyad et al., 2007) undertaken on the initiative of the World Health Organization (WHO), consisted in ADHD screening of adults, aged 18–44 years, in ten countries in the Americas, Europe and the Middle East (n = 11 422). Estimates of adult ADHD prevalence was on average 3.4% (range 1.2 – 7.3%), with lower prevalence in lower-income countries (1.9%) than in higher-income countries (4.2%). No significant between-country differences were found with regard to gender or education. The Kessler et al. (2006) study of a U.S. sample of 9 200 adults aged 18 – 44, found a prevalence of 4.4%. The National Comorbidity Survey Replication (NCS-R, Kessler et al., 2006) suggests that sex differences are less pronounced in adults who present themselves for diagnostics (Biederman et al., 2004a).

The prevalence of strictly applied operational definitions of ADHD declines with age. In a review of longitudinal follow-up of individuals diagnosed with ADHD as children Faraone et al. (2006a) found that only 15% retained a full diagnosis of ADHD at the age of 25. However, a much larger proportion (65%) fulfilled criteria for either ADHD or ADHD in partial remission, indicating the persistence of some symptoms associated with clinical impairments in the majority of cases. Applying these figures to the prevalence range (3 – 5%) commonly seen in children, it would be expected that 0.6 – 1.2% of adults would acquire the full diagnosis by the age of 25, and a larger percentage (2 – 4%) would fulfil the criteria for ADHD in partial remission.

1.3 Etiology

Although evidence supports neurobiologic and genetic origins, the etiology of ADHD has not been established, (Biederman, 2005). ADHD is usually genetically determined (Faraone & Khan, 2006b), although there are other predisposing factors in less than 20% of cases. One such factor is brain injury acquired during pregnancy or in the first years of life, i.e., alcohol
exposure during pregnancy, bleeding in pregnancy, low birth weight, lead contamination or delivery complications (Faraone & Khan 2006b). Family (siblings or parents), twin studies (monozygotic 78% and dizygotic 35%) and adoption studies have provided evidence for a genetic etiology of the disorder with a mean heritability for ADHD of 0.77 (Biederman, 2005; Weyandt, 2005). The genetic influences appear to affect the distribution of ADHD symptoms across the whole population, not just in clinically defined sub-groups.

The most replicated findings in the literature concern changes in dopaminergic neurotransmission. No single gene of large effect has been identified in ADHD; rather, several DNA variants of small effect – each increasing susceptibility by a small amount – have been associated with ADHD (Brookes et al., 2006). A genome-wide scan has identified six chromosomal loci suggestive of linkage 7p, 10q26, 12q23, 15q, 16p13 and 17p11 (Shastry, 2004). Animal studies suggest the involvement of dopamine pathways in ADHD, but there are at least 20 candidate genes of small effect, none of which account for more than 5% of ADHD symptom variation (Shastry, 2004).

Thus, the specific genes involved in ADHD have not yet been identified (Faraone & Khan, 2006b), although catechol-O-methyltransferase gene (COMT) valine/methionine polymorphism at codon 158 (COMT val^{158}MET) has been associated with phenotypic variation among children with ADHD (Caspi et al., 2008). The human COMT gene is located on chromosome 22Q11 and the Met allele is associated with a 40% reduction in enzymatic activity in the prefrontal cortex where it plays a major role in modulating dopamine. This association has been shown to exhibit less efficient prefrontal cortex processing, as indicated by worse performance on measures of executive functioning and working memory (de Frias et al., 2009; Tunbridge et al. 2006). The covariation between ADHD and oppositional-defiant disorder/conduct disorder (ODD/CD) has also been shown to be accounted for, in part, by common genetic factors (Nadder et al., 2002; Thapar et al., 2006). The genetic association with ADHD is also seen in specific medical treatment responses (Spencer et al. 2005), and in abnormalities in brain structure and function in affected individuals (Bush et al., 2000; Fischman & Madras, 2005; Castellanos et al., 2002). The results suggest that genetic or early environmental influences on brain development in ADHD are fixed, non-progressive, and unrelated to stimulant treatment.

The most replicated brain alterations in ADHD childhood include significant patterns of frontal hypoactivity, affecting the dorsolateral prefrontal cortex, anterior cingulated, prefrontal cortices, and also related regions, including basal ganglia, thalamus, corpus
callosum, cerebellum and parietal cortex (Valera et al., 2007; Volkow et al., 2009; Dickstein et al., 2006; Seidman et al., 2005). According to Schneider et al. (2006), patients with ADHD show a total reduction in cerebral volume, most marked in the right hemisphere. The right hemisphere is hypothesised to dominate in decision-making, inhibitory control and selective attention. More specifically, volume reductions have been observed mainly in the dopamine and noradrenaline-rich areas of the inferior portions of the dorsal prefrontal cortex (Schneider et al., 2006). This area plays an important role in attention, working memory, and the planning and organisation of a task (Posner & Peterson, 1990; Valera, 2007). Reduction in time perception has also been demonstrated in children with ADHD, which is probably due to the involvement of a dysfunctional fronto-striato-cerebellar network (Yang et al., 2007). Time perception is an important function that facilitates the ability to predict, anticipate, and respond efficiently to coming events (Pollak et al., 2009). Research in macaque monkeys has demonstrated a connection between prefrontal cortex and striatum (basal ganglia), a timestamp encoding strikingly similar to that required in models of working memory and learning, and in the structuring of motor and cognitive actions (Jin et al., 2009).

Many studies of adverse family-environments have found risk factors, such as severe marital discord, low social class, large family size, foster care placement, and oppositional and conduct problems, which provide powerful evidence for the importance of psychosocial adversity in ADHD (Biederman et al., 1993). However, such factors tend to emerge as universal predictors of children’s adaptive functioning and emotional health, rather than as specific predictors of ADHD (Biederman, 2005). These factors can thus be conceptualized as nonspecific triggers of an underlying predisposition, or as modifiers of the course of illness.

1.4 Diagnostic procedures in ADHD

The main symptoms of ADHD are characterized by a combination of overactive and poorly modulated behavior, with marked inattention and lack of persistent task involvement, and early onset in childhood. The diagnosis in adults is established through the use of not only a comprehensive examination assessing 18 symptoms in childhood and currently, but also an interview covering personal history, current behavior observation, functional impairment, and differential diagnosis. The available literature provides converging evidence that ADHD is a valid clinical diagnosis in adults that can be reliable (Rösler et al., 2006). The criteria in DSM-IV-TR, Appendix A (American Psychiatric Association, 2000), are regarded as the gold standard for diagnosing ADHD across the lifespan in the U.S. and are widely used in ADHD research around the world (Farone & Antshel, 2008). The DSM-IV-TR criteria are divided
into: (A) the 18 symptoms, (B) symptoms that must be present before the age of 7 years, (C) an impairment that must be present in two or more settings (e.g., at school/work and at home), (D) an impairment of clear significant, (E) symptoms that do not occur exclusively during the course of a psychotic disorder or developmental disorder and are not better accounted for by another mental disorder (cf. Appendix A). The symptoms criteria require a two-stage process in adults in both DSM-IV-TR (APA, 2000) and in International Code for Diagnosis, - 10th Edition, (ICD-10, 1997), consisting of: A) determining that the adult meets criteria for ADHD in childhood, and B) determining that the adult currently meets criteria for the disorder and has a significant functional impairment. The clinical interview for the 18 symptoms of ADHD, in the DSM-IV-TR, (2000) has three subtypes: A-1 the Predominantly Inattentive subtype (ADD or ADHD-I), A-2 the Predominantly Hyperactive Impulsive subtype (ADHD-H), and A-1 and A-2 the Combined subtype (ADHD-C), see Appendix A. The symptoms of either A-1 inattention or A-2 hyperactivity-impulsivity need to meet at least six or more criteria’s for each subtype, and 12 criteria for the combined subtype. In the DSM-IV-TR (2000), the symptoms must have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level. The ICD-10 (1997) uses a different nomenclature; the same symptoms are described as part of a group of hyperkinetic disorders of childhood. In total, the fulfillments of 12 criteria are required, and inattention, hyperactivity and impulsivity must all be present in more than one context. This means that only the combined-type in DSM-IV-TR ADHD qualifies for an ICD-10 diagnosis (NICE, 2008). In addition, the research diagnostic criteria of the ICD-10 provide an even more restricted set of requirements, where there are quite strict exclusion criteria. Whereas coexisting psychiatric disorders are allowed under DSM-IV-TR, the diagnosis of hyperkinetic disorder cannot be made when criteria for certain other disorders, including autism or anxiety states are met. Thus, it must be evident that the hyperkinetic disorder is additional to the other disorder, and the hyperkinetic disorder is, in the ICD-10 further divided into hyperkinetic disorder with and without conduct disorder (see Appendix B).

1.4.1 DSM-IV Criterion B, symptoms before age 7

Several studies have challenged the validity of the age of onset criterion, with onset prior to age 7 (Karam et al., 2009) established by the DSM-IV and also in the ICD-10. In a series of papers (Faraone et al., 2006c; Biederman et al., 2006a; Faronen & Antshel, 2008) the conclusion has been drawn that early and late onset ADHD subjects have similar symptom magnitude, patterns of psychiatric comorbidity, neuropsychological impairment, substance
use disorders and familial transmission. Although these studies do not provide definitive evidence of a specific threshold, they clearly suggest that the moving of the age of onset into adolescence (e.g., to 12 years) would be valid. Faraone et al. (2006c) conclude that the age criterion is crucial to distinguishing ADHD from later onset psychiatric conditions and, unless care is taken to rule out the existence of other conditions, there may be a high rate of falsely identified cases in the clinical childhood symptom interview. However, because of recall bias, poor memory ability, and poor insight there must be some concern about the reliability of the self-reporting of past ADHD symptomatology (Weiss & Murray, 2003).

1.4.2 DSM-IV Criterion C, symptoms in two or more settings

Criterion C in DSM-IV-TR (2000) requires some significant impairment from the symptoms that are presented in two or more settings, e.g., educational academic or occupational functioning and/or social resistance. In addition, other areas are of interest; including: parenting, child-rearing, managing finances through banking, forming contracts, abiding by laws, maintaining social relationships, and routine health maintenance activities (McGough & Barkley, 2004).

1.4.3 DSM-IV Criterion D, significant functional impairment

The D criterion state that there must be clear evidence of clinically significant impairment and that the functional impairment is central to the diagnosis. Biederman et al. (2006b) compared 500 adults with ADHD with 501 gender- and age-matched controls with regard to functional impairment. The results showed that adults with ADHD were significantly less likely to have graduated from high school or obtained a college degree, and had poorer occupational functioning. They were significantly more likely to have been divorced, were less satisfied with their family, social and professional lives, and were significantly more likely to have been arrested. Over a 10-year period, they also had more job changes and were more likely currently to be unemployed.

1.4.4 DSM-IV Criterion E, comorbidity

Similar to its pediatric counterpart, adult ADHD is associated with a wide range of emotional impairments impacting on all aspects of a person’s life (Biederman & Farone, 2004b). This is why the E criterion excludes mental illness. Thus, ADHD symptoms must not be better accounted for by another psychiatric diagnosis, although there may be other coexisting psychiatric conditions. Most commonly reported psychiatric comorbidities in adult ADHD
are anxiety, mood changes, alcohol misuse, psychoactive substance use disorders, and antisocial personality (Thapar et al., 2007; Kessler et al., 2006; Biederman et al., 2004b). The use of both cannabis and cocaine is relatively common in adults with ADHD (Manuzza et al., 1991), but there does not appear to be frequent abuse by ADHD patients of psychostimulants, such as methylphenidate or amphetamines (Kollins, 2008). With a prevalence rate of around 60%, oppositional defiant and conduct problems in children are more commonly reported and correlate with ADHD (Biederman, 2005). Conduct problems in childhood predict adult antisocial personality disorder (Dalsgaard et al., 2002). Symptoms of irritability and hot temper are more closely associated with problems in the social environment, but may qualify as confounders in cases of ADHD with oppositional defiant disorder, conduct disorder, and possibly the dysphoric form of bipolar disorder (McGough & Barkley, 2004). The total comorbidity rate does not differ as a function of gender in adults (Kessler et al., 2006; Biederman et al., 1994). Comorbidity in adult ADHD also includes assessment and treatment of correctional inmates with a history of substance use disorder, where the reported prevalence of ADHD among prisoners ranges from 9 to 45% (Appelbaum, 2008; Rösl er et al., 2004). A diagnosis of ADHD can provide an individual with a number of benefits, including stimulant medication, disability benefits and academic accommodations, which may motivate adults to exaggerate symptomatology on self-report measures and tests of neurocognitive functioning (Harrison, Edwards & Parker, 2007). Differentiating ADHD from other clinical disorders is therefore often the most difficult part of making an ADHD diagnosis in adults (Farone & Antshel, 2008). Barkley (1997) concluded that the symptoms that best discriminated adult ADHD cases from cases of other forms of psychopathology, were the prevalence in childhood of the following: making decisions impulsively, having difficulty in stopping inadequate activities or behaviors, starting projects or tasks without reading or listening to directions carefully, inability to keep promises, difficulties in doing things in their proper order, and driving at excessive speed. These six items correctly classified ADHD with 85% accuracy and differed from other forms of psychopathology.

1.5 Follow-up

The variation in percentage of adults with ADHD, still having the diagnosis in follow-up studies, is very large 6 – 94% (Mannuzza et al., 1998; Mannuzza et al., 2003; Kessler et al., 2005; Rasmussen & Gillberg, 2000; Weiss et al., 2006; Barkley et al., 2006). In a meta-analysis of 32 publications, Faraone et al. (2006a) found that when the ADHD samples included only those who met full diagnostic criteria for ADHD, the rate of persistence was
approximately 15% at age 25. However, the rate was approximately 65% when individuals fulfilling the DSM-IV definition of “ADHD in partial remission” were included, referring to the persistence of some symptoms associated with significant clinical impairments. A key criterion when defining ADHD is not only the presence of sufficient numbers of ADHD symptoms but also, and maybe more importantly, their association with clinical and social impairments at home, work/school and in other settings (Faraone & Antshel, 2008).

1.6 Treatment

There are today only two types of medication approved by the Swedish Läkemedelsverket (the Medical Products Agency) for the treatment of ADHD; stimulants (methylphenidate, dexamphetamine), and atomoxetine. In children and adolescents, over 200 trial reports indicate around a 70% short-term response rate to methylphenidate treatment with an effect size on ADHD symptoms of 0.47 – 0.94 (Smith et al., 2000; Schachter et al., 2001). A meta-analysis of several adult trials indicates that response rates and effect size of treatment in adults is comparable with, although somewhat lower than, those in children (Faraone et al., 2004b; Reimherr et al, 2007; Nutt et al. , 2007). Several randomized, double-blind placebo-controlled trials have confirmed the efficacy of atomoxetine in children and adolescents with an effect size of 0.35-0.4. Also, there have been two larger trials in adults (Adler et al., 2008; Michelson et al., 2003). Mannuzza et al. (2008) studied a prospective follow-up group of 207 children on medication, diagnosed at ages 6 – 12 and at follow-up. At follow-up of, 176 children during early adulthood (18 – 27 years), it was found that the risk of developing substance use disorder was significantly associated with age at start of methylphenidate treatment. The later the treatment started, the greater was the chance of developing substance use disorder. From a naturalistic controlled 10-year follow-up study of 112 subjects with childhood ADHD, it emerged that 73% had been treated previously with stimulants, but that only 22% was undergoing stimulant treatment at the time of the follow-up assessment (Biederman et al., 2008). The NICE (2008) clinical guidelines in the UK recommend that methylphenidate is first-line treatment for adults with ADHD.

Non-pharmacologic or psychological interventions, including education about the ADHD disorder, that can help to ease frustration and enhance self-esteem, give structure to daily living by providing organizational skills and improving interpersonal skills, also help in the treatment of comorbid psychiatric problems like anxiety and depression (Young et al., 2008). Group cognitive therapy can have similar benefits (Philipsen et al., 2007; Hesslinger et al., 2002). Most psychological interventions in adult ADHD are applications of a cognitive
paradigm, usually as a complement to the use of stimulant medication treatment (Stevenson et al., 2002; Abikoff et al., 2004; Hinshaw, 2007). Although psychological interventions without medication may be effective for some adults with moderate impairment, there are insufficient data to support this recommendation (NICE, 2008).

1.7 A patient perspective

Ms. J. 36 years: “To have ADHD is like having influenza. You are able to cook for yourself and the children; you wash so they have clean clothes, but you are not able to fold their clothes, clean windows or do the planning for big shopping. I have an IQ of 122 but can’t organize my life. Everything floats around at home. I get the simplest work, which I can’t stand; I was fighting with my bosses and with my workmates. After I got the diagnosis and medication, I can manage my life. I am able to sit down and have started to solve crosswords without going outside to keep awake, but I don’t feel that I can return to work in an employment yet”.

1.8 Alternative explanations for ADHD symptoms

It has been proposed that ADHD is the result of sleep disturbance (O’Brien & Gozal, 2005). Parental report studies invariably yield findings of significantly more reported sleep disruption in children with ADHD, but objective assessments (polysomnography, actigraphy, and/or video recording) have found no differences, and stimulant treatment appears to have little effect on sleep quality (Bullock and Schall, 2005). According to Lecendreux and Cortese (2007), the most commonly reported sleep problems are: difficulty falling asleep, bedtime resistance, night awakenings, restless sleep and difficulties waking up in the morning or excessive daytime sleepiness, which may cause problems with mood, attention and behavior. Subjective and objective studies of the effects of stimulants on sleep have produced mixed results, where some investigators have reported polysomnographically determined lengthened total sleep time, increased sleep-stage shifts, and increased number of rapid eye movements (REM), patient-reported longer latencies to sleep onset or higher rates of insomnia, but other studies do not confirm these finding (see Corcum, 1998). In an adult study, Philipsen et al. (2005) found that, similar to children, adults with ADHD show increased nocturnal motor activity, but sleep does not seem to be impaired in ADHD patients, as measured by conventional polysomnography or in sleep electroencephalogram spectral power analysis. Treatment with stimulants is associated with a reduction in activity levels and movement index scores, and also improved sleep quality, in adult ADHD patients (Kooij et al., 2001).
Bipolar disorder and ADHD are characterized by hyperactivity, distractibility, inattentiveness and mood changes. The distinction from bipolar disorder, however, is that the mood state of ADHD is irritable and volatile, rather than containing elements of euphoria, cycling course, compromised judgment, hypersexuality, episodicity and grandiosity with episodes lasting for at least four days, DSM-IV-TR (APA, 2000). The goal-directed over-activity of mania is usually seen to be in contrast with the disorganized and off-task activity of ADHD (NICE, 2008). Individuals with ADHD often have difficulty sleeping but, unlike those with mania or hypomania, they complain about their lack of sleep and often feel exhausted during the day. Individuals with ADHD report that they cannot function effectively, and this is often associated with chronic low self-esteem, which is different from the feelings of heightened efficiency seen in mania.

Cluster B personality disorders (DSM-IV-TR), like antisocial, borderline and emotionally unstable personality disorders, which include symptoms such as mood instability, impulsivity and anger outbursts, are commonly seen to coexist in adults with ADHD (Philipsen et al., 2008). Part of the diagnostic process is to distinguish uncontrolled, impulsive, oppositional and antisocial behaviors that arise in the context of a specific ADHD syndrome from those that do not. It is often useful to make particular enquiries about symptoms that are more specific to ADHD, such as short attention span, variable performance, distractibility, forgetfulness, disorganization, physical restlessness and over-talkativeness, rather than to focus solely on the occurrence of maladjusted and disruptive behaviors like psychosis and paranoia. In cluster B personality disorders, symptoms typically have an onset after the age of 7 years (Philipsen et al., 2008).

Anxiety disorders and ADHD have some problems in common. ADHD mostly involves some sort of anxiety, but an important distinction is to consider whether the symptoms of anxiety disorders have a similar onset and time course to ADHD or whether they arise episodically and in response to stressors. In anxiety, the symptoms of inattention typically have an onset after the age of 7 years, and the childhood history of school adjustment generally is not characterized by disruptive behavior, or teacher complaints concerning inattentive, hyperactive, or impulsive behaviors according to DSM-IV-TR (APA, 2000).

Depression (cyclothymia) may give rise to attention and memory problems if the depression is severe enough (Dalsgaard et al., 2002). Attending to the time course of the symptoms and the psychopathology can help to distinguish the between two. Extreme low or high moods, sustained mood change for long periods of time and recent onset are more indicative of a
primary affective disorder. Early onset, chronic trait-like course, frequent mood swings throughout the day, and no recent deterioration or severe exacerbation frequently accompanies ADHD.

Overactivity and inattention may arise as a symptom of anxiety or from a depressive disorder, and the restlessness that is typically part of an agitated depressive disorder should therefore not lead to a diagnosis of ADHD. If the criteria for one of the anxiety or mood disorders are met, ADHD should not additionally be diagnosed simply because restlessness or concentration is impaired and there is psychomotor agitation. Acute onset of ADHD is more likely to be due to some type of reactive disorder (Murphy & Barkley, 1996). Attention problems are common to many psychiatric disorders and schizophrenia, but time of onset and stability in symptoms often distinguish the residual symptoms of a major mental illness from ADHD symptoms which are persistent (DSM-IV-TR, APA, 2000).

ADHD patients frequently present difficulties in performing tasks that challenge the central auditory nervous system. The relationship between ADHD and Central Auditory Processing Disorder (CAPD) was examined by Chermak et al. (1999) from the perspectives of cognitive neuroscience, audiology, and neuropsychology. They proposed that the most common symptoms in CAPD are difficulty hearing in background noise, difficulty following oral instructions, poor listening skills, and reduced understanding of rapid or degraded speech in the presence of normal peripheral hearing. As a consequence of the primary auditory difficulties, they may have secondary symptoms of language, reading and spelling disorders, as well as inattention and distractibility. Characteristically, patients with CAPD have difficulty comprehending spoken language in competing speech or noise backgrounds and with reverberation. These symptoms seem to be very similar to the DSM-IV criteria for ADHD subtype inattention.

Some authors suggest a linkage between ADHD and CAPD (cf. Cook et al., 1993), whereas others maintain that they are two separate developmental disorders (Bamiou et al., 2001). Riccio and Reynolds (2001) concluded that ADHD and CAPS are distinct entities that may nonetheless both involve deficits in auditory processing. The difference between ADHD and CAPD is, according to Chermak et al. (1999) and Bamiou et al. (2001), that ADHD is typically pervasive and supramodal, impacting on more than one sensory modality. The inattention profile of ADHD involves difficulty in initiating, tracking, and remembering tasks, in addition to sustaining allocation of attentional resources, and a motivational deficit. In many patients there are also symptoms of hyperactivity – impulsivity.
By contrast, individuals with CAPD experience attention deficits that may be restricted to the auditory modality alone; these are primary deficits resulting from input or information processing, which are specific auditory perceptual deficits. Electrophysiological procedures may also differentiate between diagnoses. Children with CAPD present significantly delayed P_{300} latencies and reduced P_{300} amplitudes compared with children with ADHD, whose P_{300} latencies and amplitudes do not differ from those of normal control subjects. Moreover, there is no evidence that the medications used in management of ADHD (Ritalin, Concerta) have any influence on peripheral or central auditory nervous system functioning (Tillery et al., 2000). It also seems that the short-term memory Digit Span subtest from WAIS shows lower forward span performance compared with backward span, when patients are diagnosed with CAPD (Maerlender et al., 2004). The opposite applies when subjects with ADHD are diagnosed; that is the backward span is reduced compared with the forward span (Pennington & Ozonoff, 1996).

In a randomized placebo-controlled, one-way crossover trial, Johnson et al. (2009) investigated the use of omega 3/6 fatty acids in children with ADHD, and found that a majority of their 75 children did not respond to 3 months of treatment. However, a subgroup of 26% of the ADD defined group showed a 25% reduction in their inattention symptoms.

It has also been stated that hyperactivity results from factors such as poor nutrition, sugar level and chocolate consumption, rapid cultural changes and food allergies, but none of these claims are supported by any reasonable scientific evidence (Biederman et al., 2009). The parental conflict common in families with ADHD children does not cause ADHD, but can exaggerate the severity of symptoms (Dykman, 2005). Risk factors do not act in isolation, but interact with one another. An example of this is that the risk of ADHD associated with maternal alcohol consumption in pregnancy may be stronger in children with a dopamine transporter susceptibility gene (Brookes et al., 2006).
2.0 A PSYCHOLOGICAL PERSPECTIVE

2.1 Neuropsychology in ADHD

Several meta analyses (Hervey et al., 2004; Willcutt et al., 2005; Martinussen et al., 2005; Schoechlin et al., 2005; Bekker et al., 2005; Woods et al., 2002) have indicated that adult individuals with ADHD commonly exhibit significant deficits compared with normal control participants on a wide range of executive functions, including sustained attention and working memory and verbal fluency, and also deficits in executive processing speed, verbal learning and complex problem-solving and response inhibition. Intelligence tests or IQ measures have been included in many adult ADHD studies; the findings have been mixed, but, in general, IQ tests do not appear to be reliable in discriminating between adults with and without ADHD (Weyandt, 2005).

The majority of cases with childhood deficits in executive functions will have stable deficits from mid-adolescence to adulthood (Biederman et al., 2007; Barkley, 1997). In a review of neuropsychology in children, Nigg (2005) updated the status of four key domains, i.e., attention, executive functions, state regulation and motivation, and the processing of temporal information. The main finding was with regard to the executive functions, which revealed a reduction in set shifting, interference control, inhibition, planning and working memory. The effect sizes (such as $d$, the magnitude of an observation expressed in terms of the distance between two group means in standard deviation units) were on average .64 for response suppression (stop signal reaction x time slope, measuring sustained attention), and .75 – 1.14, for spatial working memory, with all other task results showing a lower effect size. Similar results have been found by Schoechlin and Engel (2005) on 50 standard neuropsychological tests, where adult ADHD patients $n = 867$ from 24 studies (compared with $n = 806$ controls) scored approximately - 0.5 SD lower than did control participants on abstract verbal problem-solving with working memory, on verbal memory, on focused attention and on sustained attention. The conclusion is that the effect sizes are modest, raising serious doubts as to the ability of any one neuropsychologic hypothesis fully to establish whether the deficit in ADHD is specific to one cognitive domain over and above others. In adults with ADHD, Murphy et al. (2001) found, after controlling for initial group differences in IQ, that only 2 out of 14 scores on measures of executive function were significant differentiated from those of a control group, i.e., on the Stroop interference test and the Conners continuous performance test measuring commission errors and speed. Marcetta et al. (2008) reported a similar finding.
for adult ADHD, again on the Stroop interference test, and on processing speed test, measured using a test similar to The Trail Making Test. Willcutt et al. (2005) performed a meta-analysis of 83 studies in which individuals with ADHD (N = 3734) were compared with those without ADHD (N = 2969), and found that ADHD is associated with significant weaknesses in response inhibition, vigilance, spatial working memory, and planning. However, again, the effect sizes for all measures fell in the medium range (.46 - .69), and correlations between ADHD symptoms and scores on executive function tasks were typically significant but small in magnitude (r = .15 - .35). At the same time, the group difference on ADHD symptom criteria were very large in relation to controls with regard to effect sizes (d = 2.5 – 4.0). The deficits found in executive functions significantly increased the risk of both educational and occupational under-attainment in adults (Biederman et al., 2006a; Marchetta et al., 2008; Swanson et al., 2004).

From a review of 32 studies of adults’ neuropsychological performance, Weyandt (2005) concluded that adults with ADHD may exhibit mild neuropsychological deficits on executive function tasks that measure response inhibition and working memory. These findings do not appear to be accounted for by comorbidity, but may be influenced by intelligence. Also the conclusions appear to have no diagnostic utility, since they do not reliably discriminate adults with ADHD from other clinical groups. Barkley et al. (2007) and Doyle (2006) advocate caution in interpreting test data, since there is no single test or battery of tests that has adequate predictive validity or specificity to make a reliable diagnosis of ADHD.

2.2 Working memory

Memory involves decomposition into processes of encoding/learning, storage, and retrieval, and can be divided into multiple forms or systems - collections of processes that operate on different kinds of information and according to different rules (Schacter, 2004). The distinction between short-term and long-term memory is one of the most studied areas in memory neuroscience, where short-term memory is regarded as depending on alterations in the strength and effectiveness of already existing synapses, whereas long-term memory involves the synthesis of new proteins and the growth of new synapses (Bailey & Kandel, 2004). The working memory (WM) is located in frontal and more posterior parietal or temporal regions, and contains domain-specific processes. The frontal cortex code is for attention and efficiency in working memory and task-switching, and the parietal cortex code for spatial information, whereas regions in the temporal cortex code are for object information, the construction and maintenance of a memory trace, rehearsal, retrieval and
reintegration (Davachi et al., 2004; Gathercole, 1999). Working memory dependent on adequate dopamine neurotransmission, and cortical dopamine release, have been observed in humans during the performance of WM tasks (Schneider et al., 2006; Smalley, 2008). In nonhuman primates, locally applied D1 agonists, as well as antagonists, affect both the performance and neuronal firing patterns of prefrontal neurons when information is kept in WM (McNab et al., 2009). Working memory has become one of the most extensively discussed topics with regard to neurocognitive functioning in ADHD (Stevens, 2005). In children, working memory was found to differentiate between ADHD and control groups on several different working memory tasks in 75% of the studies reviewed by Rapport et al. (2000). However, when those studies were statistically controlled for intelligence (IQ), the differences disappeared (Stevens, 2005). Only a spatial working memory test, the Delayed Matching to Sample (DMTS, Barnett et al., 2005) and a self-ordered visual pointing task (SOPT, Wiers et al., 1998) continued to indicate significant differences. In a PET study of adults with ADHD, Schweitzer et al. (2000) found that the Paced Auditory Serial Addition Task (Gronwall, 1977) showed a significant difference from a control group. ADHD group subjects used compensatory mental and neural strategies in response to disrupted ability to inhibit attention to non-relevant stimuli. Working memory is theoretically assumed to be a hierarchical system involved in short-term memory (STM) representation. The test of working memory may be converted into more sensitive working memory subtests, like different span tests, working memory capacity tests with distracters, and the so-called “irrelevant sound effect” (ISE) test in dichotic memory (Conway et al., 2005; Diamond, 2005).

2.3 Conceptual framework in working memory

Kane and Engle (2002) found that individual differences in working memory capacity (WMC), as measured by tasks such as reading span, strongly predict individual differences on a wide range of fluid cognitive capabilities, including language comprehension, learning, and reasoning (Daneman & Carpenter, 1980). The WMC tasks correlate with fluid intelligence more strongly than do “simple” short-term memory (STM) span tasks, which require only immediate recall of lists. Residual variance from WMC tasks continues to predict fluid intelligence even after STM variance has been removed (Kane & Engle, 2002).

Based on the work of, and inspired by, Conway et al. (2005), Kane and Engle (2002) and my own publications (Dige & Wik, 2001; Dige & Wik, 2005), it is therefore possible to suggest a theoretical hierarchical working memory model for testing adult ADHD (see Table 2).

25
Table 2. Theoretical hierarchical model illustrating levels of short-term and working memory.

<table>
<thead>
<tr>
<th>Theoretical hierarchical level</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term memory/simple working memory</td>
<td>Digit span forward (Baddely, 2002)</td>
</tr>
<tr>
<td>Working memory without disturbance, but with a manipulation of the representation</td>
<td>Digit span backward (Pennington &amp; Ozonoff, 1996)</td>
</tr>
<tr>
<td></td>
<td>Trail Making Test B (Reitan 1979)</td>
</tr>
<tr>
<td></td>
<td>Stroop Test, Interference (Stroop, 1935)</td>
</tr>
<tr>
<td></td>
<td>Continuous Performance Test II (Conners et al., 2002)</td>
</tr>
<tr>
<td></td>
<td>Arithmetic (Wechsler, 1997)</td>
</tr>
<tr>
<td></td>
<td>Benton VRT (Benton, 1974)</td>
</tr>
<tr>
<td></td>
<td>Wisconsin Card Sorting Test (Heaton et al., 1993)</td>
</tr>
<tr>
<td></td>
<td>Paced Auditory Serial Addition Task (Gronwall, 1977)</td>
</tr>
<tr>
<td></td>
<td>Delayed Matching to Sample (DMTS) (Barnett et al., 2005)</td>
</tr>
<tr>
<td></td>
<td>A self-ordered visual pointing task (Wiers et al., 1998)</td>
</tr>
<tr>
<td>Dichotic memory (ISE)</td>
<td>Dual-task dichotic memory (Christianson et al., 1989)</td>
</tr>
<tr>
<td></td>
<td>Dichotic listening (Hugdahl, 1995)</td>
</tr>
<tr>
<td>Working memory capacity tests (WMC)</td>
<td>Consonant Trigram Test (Spree &amp; Strauss, 1998)</td>
</tr>
<tr>
<td></td>
<td>Reading span (Daneman &amp; Carpenter, 1980)</td>
</tr>
<tr>
<td></td>
<td>Operation span (Turner &amp; Engle, 1989)</td>
</tr>
<tr>
<td></td>
<td>Counting span tasks (Case, Kurland &amp; Goldberg, 1982)</td>
</tr>
</tbody>
</table>


With regard to theoretical hierarchical levels in working memory for adults with ADHD, inspired by Conway et al. (2005), Kane & Engle (2002), Dige & Wik (2001), Dige & Wik, 2005), we propose the following:

1. Short-term/working storage memory is defined by the ability to maintain selected information in seconds without being disturbed in the process and is an immediate-memory system in the service of ongoing mental activity. There is no time delay between stimulus presentation and rehearsal.

2. Working memory without distracter, but with a manipulation of representation, refers to the ability to maintain and manipulate active representations, and is a multifaceted faculty. A model of human working memory proposes a three-component model: a buffer for the short-term maintenance of verbal information (the so-called phonological loop), a buffer for the maintenance of the visuospatial sketch pad, and a “central executive” that gates and manipulates the representations held in these buffers (Baddely, 2002). The phonological loop is normally tested with a digit span forward type of test, as described by Baddeley (2002). Arithmetic capacity is also seen as a short-term/working memory test (Wechsler, 1997). The visuospatial sketch pad can be investigated with a test like Benton Visual Retention, where the subject has to create drawings of what they just have seen. There is no time delay between stimulus presentation and rehearsal.

3. In the dichotic memory Irrelevant Sound Effect (ISE) test, the purpose is to learn words simultaneously with a distracter. The ISE may represent the so-called “central executive” system (Baddeley, 2002) that gates and manipulates representations different from the phonological loop and the visuospatial sketch pad. In dichotic memory testing (Christianson et al., 1989), lists of common unrelated nouns (eight lists of 12-items, a total of 96 words) are presented on plug-in type earphones, and presented alternately to the two ears; in the opposite ear, the ear not receiving the list of words to be remembered, a distracter is presented simultaneously. The distracter is non-interpretable speech played backward. The test is performed so that, after the presentation of each 12-item list, the disc is stopped and the patient is asked to give free recall from the list just presented, without a time limit. An unexpected rehearsal test (i.e., incidental learning), as a long-time memory recall test, is finally administered to the participants where, after a delay of some minutes, they have to write down as many as possible of words they have remembered from the total of 96 (Beaman, Bridges & Scott, 2007).
4. The working memory capacity tests were created to require not only information storage and rehearsal, but also simultaneous secondary processing of additional information as a distracter. The span tasks present a list of stimulus targets to-be-remembered of increasing length, such as digits or words, and the secondary processing may include comprehending sentences, verifying equations, arithmetic, or enumerating an array of shapes (Conway et al., 2005). The purpose is to create a substantial delay between stimulus presentation and rehearsal, while at the same time stopping the subject from repeating the to-be-remembered target stimuli (Conway et al., 2005). In the auditory Consonant Trigram Test (Brown – Peterson paradigm), subjects have a stimulus of three letters to remember in the correct presentation order. Simultaneously, they have to count aloud backwards from a number minus three digits at interval delays of 9, 18, and 36 seconds, used at random. Dependent measures are the total numbers of letters in correctly recalled order at each of the three intervals, and also the total number of correct letters but without the correct order. The test is influenced by both proactive and retroactive interference, involves mainly maintenance rehearsal and simultaneous capacity, and places significant demands on central-processing resources (Vallar & Baddeley, 1984, in Spreen & Strauss, 1998).

In the counting-span task (Case, Kurland & Goldberg, 1982) the participant, on each trial, is asked to count the number of blue dots, which appear embedded in a field of yellow dots on the computer screen, touching each blue dot and numerating it. Immediately thereafter, the participant is requested to give the total number of blue dots for all preceding displays in correct serial order. This requires holding information in mind while executing another mental operation (counting), selectively attending to the blue dots while inhibiting attention to the yellow ones, updating the information held in mind on each trial, and keeping track of the order of the totals computed across trials (temporal order memory).

The reading span test (Daneman & Carpenter, 1980) is a word span task (stimulus), with the added component of comprehending of the sentences. Subjects read sentences aloud that are 13 – 16 words in length, which are presented in ascending order (i.e., from smallest to largest). The distracters verify the logical accuracy of the sentences, while the subjects are trying to remember first or the last words in the sentence, one for each sentence presented.

The operation span task (Turner & Engle, 1989) requires that subjects perform mathematical operations (distracters) while trying to remember words lists (stimuli). There are 84
mathematical operation strings, where each string consists of a mathematical equation with two arithmetic operations on one side of the equation and a stated solution on the other. The stated solution is correct in half of the trials and incorrect in the other half, e.g. \((9/3) – 2 = 1\), and \((9/3) – 2 = 6\), respectively.
3.0 AIMS

Study I: To investigate whether memory, as measured by short-term memory tests and tests with a distracter, is reduced in adult ADHD.

Study II: To find out whether there are differences on memory tests within three ADHD subgroups.

Study III: To evaluate whether a dichotic memory test with distracter is enough to reveal a deficit in both short-term working-memory recall and long-term memory recall.

Study IV: To examine outcomes of treatment in a naturalistic prospective study.
4.0 SUBJECTS AND METHODS

4.1 Procedure

Psychiatric out-patient units:

Diagnosed with:

Neuropsychological Investigation Unit:

* See below for references.

4.1.1 Screening

Patients were screened for ADHD at psychiatric out-patient units and referred to the Neuropsychological Investigation Unit. Screening was first performed using Conners’ 10 questions for parents and teachers (Conners et al., 1999), and after 2005 using the M.I.N.I. ADHD module (Sheehan et al., 1998). The patients were also evaluated for personality disorders and for alcohol and drug abuse. All patients were registered and diagnosed in hospital paper journals and after 2005 in the computer medical journal system (Melior).

4.1.2 Diagnosis

Diagnosed patients met the DSM-IV-TR criteria of ADHD, currently diagnosed by a certified psychiatrist (E.M.) in clinical interviews for childhood and adult symptoms at the first visit at the Neuropsychological Investigation Unit. In total, 344 patients were referred for ADHD investigation and 158 were diagnosed with ADHD at the Neuropsychological Investigation Unit. The 186 who did not receive an ADHD diagnosis were diagnosed as follows: 48 patients considered as normal or without a childhood history of ADHD, 34 with a personality disorder diagnosis (mostly borderline), 9 with paranoia/schizophrenia, 38 with other problems
(TBE, mild memory disturbance, low IQ (< 80, sensorimotor handicaps), 29 with Asperger’s syndrome/autism without ADHD, 7 with bipolar disorders, 15 with anxiety or depression, 3 with epilepsy, and 3 with Tourettes syndrome. To be given a diagnosis of adult ADHD, the subject had to: 1) meet the DSM-IV-TR (APA, 2000) criteria of ADHD, 2) have had ADHD problems at least by the age of 7 – 12, with a minimum of 6 symptoms in each diagnostic group (Appendix A), 3) to have described persistent ADHD symptoms from childhood to adulthood, 4) to have currently severe significant functional impairment at work/school, socially, or with close relations.

A semi-structured interview constituted the basis for giving patients their diagnosis. Further, to be included in the studies, the patients had to fulfil diagnostic criteria according to the Conner’s Adult ADHD Diagnostic Interview for DSM-IV, i.e., CAADID (Epstein, Johnson & Conners, 2001). This structure rated formula is divided into Yes and No questions for fulfilling each criteria. CAADID has demonstrated good test-retest reliability for both individual symptoms of inattention and hyperactivity-impulsivity and for the overall diagnosis. Concurrent validity has also been demonstrated for adult and child ADHD subtype symptoms (Epstien & Kollins, 2006).

Table 3. Childhood and adulthood ADHD number of criteria met in the different clinical groups according to CAADID results.

<table>
<thead>
<tr>
<th>Childhood</th>
<th>ADHD</th>
<th>Depression &amp; anxiety</th>
<th>Personality disorder</th>
<th>Aspergers/autism</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD</td>
<td>6.65 ± 2.08</td>
<td>2.70 ± 2.63</td>
<td>3.09 ± 2.41</td>
<td>3.50 ± 2.88</td>
<td>1.82 ± 1.92</td>
</tr>
<tr>
<td>HY-IMP</td>
<td>6.44 ± 2.17</td>
<td>1.57 ± 2.27</td>
<td>2.79 ± 2.76</td>
<td>3.07 ± 2.16</td>
<td>1.38 ± 1.87</td>
</tr>
<tr>
<td>TOTAL</td>
<td>13.05 ± 3.25</td>
<td>4.26 ± 4.67</td>
<td>5.70 ± 4.60</td>
<td>6.57 ± 4.32</td>
<td>3.20 ± 3.24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adult</th>
<th>ADHD</th>
<th>Depression &amp; anxiety</th>
<th>Personality disorder</th>
<th>Aspergers/autism</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADD</td>
<td>6.39 ± 2.16</td>
<td>3.83 ± 1.61</td>
<td>3.66 ± 1.66</td>
<td>3.58 ± 1.67</td>
<td>2.28 ± 1.81</td>
</tr>
<tr>
<td>HY-IMP</td>
<td>6.37 ± 2.01</td>
<td>4.48 ± 2.48</td>
<td>6.89 ± 2.07</td>
<td>5.50 ± 2.53</td>
<td>3.44 ± 2.92</td>
</tr>
<tr>
<td>TOTAL</td>
<td>12.75 ± 3.48</td>
<td>8.30 ± 4.01</td>
<td>10.66 ± 3.43</td>
<td>9.08 ± 4.07</td>
<td>5.72 ± 4.33</td>
</tr>
</tbody>
</table>

ADD = Attention Deficit Disorder, HY-IMP = Hyperactivity-Impulsive type, Total = total number of criteria on DSM-IV (unpublished results).
4.1.3 Neuropsychological investigation

The neuropsychological investigations were conducted over two days. Day 1: all self-rating scales for ADHD, psychiatric self-rating with HAD (Zigmond & Snaith, 1983), SCID II interview and Diagnostic Interview for Borderline personality disorder – Revised (DIB-R, Zanarini et al., 1989), AUDID and DUDID for abuse, and a start on performing the different IQ measurements. Day 2: finishing off the IQ measurements, performing all the neuropsychological memory tests, and repeating of the Conner’s questions for the ADHD index.

4.2 Study population

The empirical studies are based on regular clinical neuropsychological examinations at the Neuropsychological Investigation Unit, Department of Psychiatry, the Hospital, Falköping. The catchment area of the hospital had 256,234 inhabitants in 2008. Of these, 200,040 were 18 years or older. Applying current prevalence data of adult ADHD (as presented above, 3.4%, Fayyad et al., 2007) generates an estimate of 6,801 persons with adult ADHD in the catchment area. In total, 158 adults with ADHD were included in the studies during 2003 – 2005 following examination at the Neuropsychological Investigation Unit. All patients were tested by the same experienced neuropsychologist as part of routine clinical assessment.

None of the patients had been diagnosed with ADHD in their childhood, and none of the patients have or had received medication for ADHD. Men and women between the ages of 18 and 55 were eligible for the study. Potential subjects with a history or signs of other serious psychiatric disorders, autism – spectrum disorder, organic brain disorder, sensorimotor handicaps (e.g., hearing, visual, inadequate command of language), or an estimated full-scale IQ less than 80 were excluded. The patients verified that they had not used illegal drugs or abused alcohol during the last 6 months (patients with a history of abuse were controlled for using random blood samples). The control group (n = 66) consisted of staff members from the hospital, all in full-time employment. Without payment, all controls participated in the testing during working hours. The controls were registered anonymously in the computer system.

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Table 4. Demographic data on patients (n = 158) and control subjects (n = 66), and results on the ASRS and WURS scales.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ADD</th>
<th>H – I</th>
<th>Comb</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>66</td>
<td>46</td>
<td>33</td>
<td>79</td>
</tr>
<tr>
<td>Female/male</td>
<td>44/22</td>
<td>26/20</td>
<td>15/18</td>
<td>32/47</td>
</tr>
<tr>
<td>Age: M ± SD</td>
<td>37.09 ± 12.33</td>
<td>30.98 ± 11.28</td>
<td>35.24 ± 8.85</td>
<td>33.15 ± 8.33</td>
</tr>
<tr>
<td>Education: M ± SD</td>
<td>12.64 ± 2.66</td>
<td>11.63 ± 2.48</td>
<td>11.03 ± 2.83</td>
<td>10.90 ± 2.06</td>
</tr>
<tr>
<td>ASRS v1.1 (n = 33)</td>
<td>22.24 ± 15.60</td>
<td>44.76 ± 9.17</td>
<td>49.24 ± 10.74</td>
<td>52.99 ± 8.63</td>
</tr>
<tr>
<td>WURS 25-item (n = 33)</td>
<td>28.55 ± 24.28</td>
<td>50.67 ± 18.26</td>
<td>55.96 ± 20.73</td>
<td>67.18 ± 17.33</td>
</tr>
</tbody>
</table>

ADD = Attention Deficit Disorder, H – I = Hyperactivity – Impulsive, Comb = Combined ADHD. ASRS v1.1 = Adult Self-report Scale from WHO for ADHD. WURS 25 – item = Wender Utah Rating Scale for retrospective childhood ADHD symptom.

Participants in studies 1 to IV - procedures.

In Study I by Niels Dige and Gustav Wik: Adult Attention Deficit Hyperactivity Disorder identified by neuropsychological testing. All patients who were referred and accepted were included. In total, 50 patients went through the inclusion and ethics procedure. Two patients died during the preparation of the publication, hence their data were excluded. One of these patients died due to a somatic illness, the other patient in a traffic accident. None of the deaths had any connection with ADHD. Altogether, 66 normal controls who had participated in the neuropsychological investigation were included.
In Study II by Niels Dige, Eija Maahr and Gunnel Backenroth-Ohsako: Memory tests in subgroups of adult Attention-Deficit Hyperactivity Disorder reveals simultaneous capacity deficit. All patients diagnosed with ADHD according to the initial procedure (N = 105) were divided into the three groups in DSM-IV-TR according to their type and number of symptoms in the clinical interview. The symptoms of either A-1 inattention or A-2 hyperactivity-impulsivity needed to meet at least six or more criteria for each subtype, or 12 criteria or more for the combined subtype. The first group, the A-1 the predominantly inattentive subtype (ADD), consisted of 27 patients; the second group, A-2 the predominantly hyperactive-impulsive subtype had 26 patients; and, the third group, the combined subtype with 12 criteria had 52 patients.

In Study III by Niels Dige, Eija Maahr and Gunnel Backenroth-Ohsako: Reduced capacity in a dichotic memory test for adult patients with Attention Deficit Hyperactivity Disorder. Included were 69 adult patients with ADHD and 66 controls, to whom a dichotic memory test was administered. 33 controls declined to participate in the ADHD symptoms interview, self-rating scales and the neuropsychological basic investigation. Only data from the dichotic memory test, and information on age, years of education and sex were collected for all the controls. Since the database for the controls is protected by anonymity, it has not been possible to go back for prompting.

Study IV by Niels Dige, Jerker Hetta and Gunnel Backenroth-Ohsako: A naturalistic 3-years telephone follow-up study, outcomes in adults diagnosed with Attention Deficit Hyperactivity Disorder. The study included all adult ADHD patients in who had been diagnosed from 2003 to 2006 (n = 158) in a telephone follow-up. We were able to get in contact with 115 patients.

4.3 Self-rating scales

The patients also performed self-ratings for ADHD on the following scales:

- The Conners’ Adult ADHD rating scale (Conners et al., 1999),
- The Wender Utah Rating Scale for retrospective childhood ADHD symptoms (WURS-25 item; Ward et al., 1993; McCann et al., 2000),
- The Adult Self-Report Scale from WHO (ASRS v1.1; Adler et al., 2003; Kessler et al., 2004) for current symptoms and their magnitude.

For measuring mood states, the Hospital Anxiety and Depression scale (HAD; Zigmond & Snaith, 1983) was used.
After a clinical interview for the 18 childhood symptoms in the CAADID, a diagnosis is often supported by a self-rated retrospective report on ADHD childhood symptoms. The short-version of the Wender Utah Rating Scale (WURS 25-item) (Ward et al., 1993 and McCann et al., 2000) was used in these studies. When using the cut-off of 46 points, as suggested by Ward et al. (1993), and McCann et al. (2000) found in there investigation that 72% of those with adult ADHD were correctly classified on the WURS 25-item, but the scale did not correctly classify approximately half of those who did not have ADHD. In factor analyses of the WURS 25-item scores in the McCann et al. study, only one factor, school problems in childhood, distinguished ADHD from non-ADHD patients. McCann et al. (2000) concluded that the WURS 25-item had reasonable sensitivity, but poor specificity.

Evidence from multiple studies suggests that adults with ADHD underreport their ADHD symptoms and the severity of those symptoms (Barkley et al., 2007; Wender et al., 2001). Unlike childhood disorders, in which parents’ and teachers’ reports are frequently used, adult ADHD is often diagnosed with considerable or sole emphasis on self-report clinical interviews, because other informants are often not available, may be too difficult to question, or are clinically contra-indicated to the approach (Faraone and Antshel, 2008). Murphy and Schachar (2000) compared 50 adult ADHD subjects who completed a questionnaire assessing their own ADHD symptoms in childhood, with a parent of each subject who completed a questionnaire on each subject’s rating of their childhood ADHD symptoms. The correlations between the two ratings were significant, both when the ADHD subject were younger than 34 years (r = 0.83), and when they were older (r = 0.77). The same study also found that, when 100 adults rated their own current ADHD symptoms and the subject partners also completed a rating, the correlation was significant (r = 0.69). The study concluded that both self-reporting and retrospective recall of one’s owns symptoms might provide valid and accurate descriptions of ADHD. Manuzza et al. (2002) found a sensitivity of 0.78 and a specificity of 0.89 for retrospective self-rated childhood diagnoses of ADHD symptoms. Kappa was 0.67, suggesting good agreement between retrospective diagnoses made at follow-up and diagnoses made in childhood. Similar conclusions have been drawn by Dias et al. (2008), Murphy & Adler (2004) and O’Donnell et al. (2001), but research has shown that no rating scale alone will provide sufficient evidence reliably to make a diagnosis of childhood ADHD in adults.

There are several different self-rating scales to describe symptoms’ specificity and magnitude; for an overview, see Murphy and Schachar (2000), Murphy & Adler (2004) and Rösler et al. (2006). However, in clinical settings, most clinicians today use the DSM-IV-TR based Adult
Self-Report Scale from the World Health Organization (ASRS v1.1; Adler et al., 2003; Kessler et al., 2004). The 18 symptoms described in DSM-IV-RT are, on the ASRS scale, translated into more adult language and are divided for inattention into questions 1 – 4 and 7 – 11, for hyperactivity questions 5 – 6 and 12 – 15 and for impulsivity into questions 16 – 18, according to DSM-IV criteria (Kessler et al., 2004). In medical research, Conners et al.’s, (1999) self-rating symptom scales are often preferred (Dykman, 2005; Epstein & Kollins, 2006). The ASRS was used in the studies in this thesis.

4.4 Neuropsychological Assessment

4.4.1 Study I: Neuropsychological tests - ADHD vs. controls

The following tests were used:

*Estimated IQ (Intelligence Quotient):* Full Scale IQ was estimated from the Vocabulary and Block design subtest of the WAIS with scaled scores (s.s.), since estimated Full-Scale IQ correlates, at 0.94, with all subtests (Brooker & Cyr, 1986).

*Inductive logic:* From the Raven Advanced Matrices Test (Raven et al., 1998, developed in the 1930s), the Raven SET 1 containing 12 problems with raw scores was used.

*Attention and working memory capacity:* Arithmetic subtest with scaled scores (s.s.) from WAIS (Wechsler, 1981).

*Speed tests:* The WAIS Digit symbol with scaled score (s.s) (Wechsler, 1981). From the Halstead Reitan Battery: the Trail Making Test A and B in seconds (Lezak et al., 2004). Verbal fluency: Category Animals and letter fluency F.A.S./COWAT with raw scores (Gladsjo et al., 1999).

*Speed in information processing:* Stroop word in black ink, color ink and word-color incongruence (Golden, 1978).

*Conceptual flexibility:* Wisconsin Cart Sorting Test (WCST), 64 cards, computer version (Heaton et al., 1993).

*Verbal short-term memory and simple verbal attention:* Digit span forward (FW) and backward (BW), total score with raw scores and with WAIS scaled scores (s.s) (Wechsler, 1981).
Verbal working memory/simultaneous capacity: Two different methods of evaluation were used: (1) Correct order of recalled items on each delayed period and also a total score; the patient has to recall the three letters in exactly the same order as they were presented. Maximum 5 points/items per trial and in total 15 points. (2) Total number of recalled items without correct order of recalled letters, maximum 45 letters. For instructions, see Lezak et al. (2004, p. 416), Mitrushina et al. (1999, p. 101), and Spreen and Strauss (1998, p. 263).

Visual short-term working memory and simple visual attention: Benton Visual Retention Test (BVRT) (Benton, 1974), administration A; form C with raw scores. Number of correctly recalled complete pictures and number of errors were calculated.

Verbal learning and long-term memory: Rey Auditory Verbal Learning Test (RAVLT), total learning (maximum 75), immediate and delayed recall (maximum 15 on each scale) and recognition trail, with raw scores (Schmidt, 1996).

Visual Learning and long-term memory: Modified Diagnosticum für Cerebralschädigung (mDCS) (Dige & Wik, 2001; Dige & Wik, 2005) is a visual learning and memory test consisting of three consecutive learning trials with 15 abstract designs in a consecutive fixed order on each representation trial, and a delayed recall after 30 min. Total learning (maximum 45) and delayed recall (maximum 15) with raw scores were calculated.

The neuropsychological tests were administered according to their test manuals. The tests have all been validated and, except for the mDCS and the dichotic working memory test, are described by Lezak et al. (2004).

4.4.2 Study II: Subdivision in ADHD and test results

All significant reduced test results from Study I were used to find differences between the three subgroups of symptoms in ADHD according to DSM-IV-TR.

4.4.3 Study III: Dichotic memory

Dichotic memory: The dichotic working memory test (Nilsson et al., 1984; Christianson et al., 1989) contains a list of verbal common unrelated nouns (eight lists of 12 nouns, in total 96 words), which are presented on plug-in earphones and presented alternately to the two ears. In the opposite ear, the one not receiving the list of words to be remembered, a distracter is presented simultaneously. The distracter is non-interpretable speech played backward. The test is performed so that, following the presentation of a 12-item list, the disc is stopped and
the patient is asked to give free recall from the list just presented without time limit. An unexpected rehearsal test (i.e. incidental learning) as a long-term delayed memory recall is finally requested when the subject has finished the 96 words. The participant has to write down as many as possible of the total of 96 words.

4.4.4 Study IV: Telephone follow-up 3 years later

Neuropsychological tests were not used, but a clinical interview using the ASRS self-rating scale was conducted.

4.5 Statistical methods

Differences in parametric data were calculated using the Student’s t-test. One-way analysis of covariance (ANCOVA) was used to assess group differences, after the covariance effects of sex, age, education, IQ and level of depression were statistically controlled for. Statistical tests were two-tailed, and an alpha level of 0.05 was used to assert statistical significance. Non-parametric Wilcoxon/Kruskal-Wallis tests (rank sums) were used for differences on ordinal data. Statistical models were fit using the JMP software, version 7.0, for Windows (SAS, 2007).

In Study 1 and in Study 3, a step backward one-way discriminant function analysis with linear common covariance was performed on all variables in order to determine the contributions of each variable to predicting membership of the ADHD and the control groups. In Study 2, a secondary analysis based on Generalized linear Logistic regression Model (GLM) with covariance was applied to the memory tests on the ADHD three subtypes to reduce the demographic influences of gender, estimated IQ level, and depression and anxiety (HAD total score). The decision to use logistic GLM analysis was made since the data were not normally distributed inside all three subgroups and the variances of the data were not constant for all observations. Principal component correlation factor analyses with Varimax rotation on correlations, with an Eigenvalue of minimum 1 and 5 percent explained variance, were performed for the memory tests and for the ADHD symptoms to detect multicorrelation inside the data. Factor analyses were used to validate a set of variables by demonstrating that constituent items load on the same factor, and by dropping items that cross-load on more than 1 factor. Cronbach’s alpha was used to evaluate internal consistency (Cronbach, 1951). In Studie 3 and 4, Spearman’s (rho) correlations coefficients were used to evaluate the relation between outcomes and ADHD symptoms.
5.0 ETHICAL ASPECTS (and permission)

The subjects were given an oral and written description of the study. Written informed consent was obtained from each patient in all studies. The study was approved by the Local Ethics Committees in Sahlgrenska Universitetet in Gothenburg (Ö 541-03 Papers I and II), and later by Etikprövningsnämnden in Gothenburg (Paper III Dichotic memory test T 525-03, Paper IV telephone interview T 538-07).
6.0 RESULTS

6.1 Study I: Neuropsychological tests - ADHD vs. controls

The purpose was to find neuropsychological test indicators for adults with ADHD compared with controls. Out of the scores on 13 neuropsychological tests, 9 were significant reduced for the ADHD group (n = 48) compared with the control group (n = 48). This applied after variations in IQ level, sex, years of education, age and mood state were removed in an ANCOVA analysis. Four memory tests correctly classified 86% of the ADHD group and 75% of the control group in a best-fitting step-backward discriminant analysis including all significantly reduced scores. The memory tests were the working memory capacity tests Consonant trigram correct numbers (F27.35) and Benton VRT error (F21.07); the learning and long-time memory tests were Rey Auditory Verbal Learning for total learning, immediate, delayed recall and recognition (F15.88 - 14.87), and modified Diagnosticum für Cerebralschädigung for total learning and delayed recall (F10.99 - 7.55). The verbal test Digit span forward condition, measuring short-term memory, produced similar scores for patients and controls. In the Digit span backward condition, performance was lower for the ADHD patients than the controls. Moreover, scores on the arithmetic subtest measuring verbal short-term memory were reduced. The logical test Raven SET 1 matrix was reduced in the case of novel problem-solving. Two tests sensitive to the switching of focused attention between tasks generated reduced scores: the WCST number of perseverations and the Test Trail Making B test, which are both sensitive to frontal lobe dysfunction. There were no differences in estimated IQ, in speed tests like verbal fluency, Trail Making A or Stroop test.

The study clearly demonstrates that the ADHD group has problems in the area of memory in cognitive testing, especially in working memory with distracter tests. None of the other significantly reduced test scores were decisive in the discriminant analysis.

6.2 Study II: Subgroups of ADHD

The neuropsychological tests used in Study I were evaluated in relation to the three subgroups with adult ADHD (n = 105). The subgroups, were according to DSM-IV interviewed criteria of childhood and adulthood symptoms, divided into three subgroups according to the interview data, which were also supported by results on self-rating scales like Conners’ Adult ADHD Rating Scales (CAARS) and the Wender Utah Rating Scale (WURS-25 item). An
analysis of a generalized linear logistic regression model (GLM) was used in the different tests to reduce the demographic influences of gender, IQ level and mood (the HAD scale). Only scores on the Benton VRT numbers of errors test (visual WM) and the Rey AVLT total learning test (capacity and long time memory) were reduced, and able to detect a difference between the three subgroups of ADHD. But also on the working memory capacity test, the Consonant Trigram Test, there was a severe reduction in all three groups, which revealed a concentration and working memory capacity disturbance with no difference between the three subgroups. Correlations between memory test results and the DSM-IV subtypes criteria were low < 0.30, but still significant.

The study demonstrated that only the memory tests were able to distinguish between the three subgroups of ADHD.

6.3 Study III: Dichotic memory

Since the working memory/simultaneous capacity tests were best at detecting ADHD disturbances, the study investigated whether a dichotic memory Irrelevant Sound Effect (ISE) test, as a simultaneous working capacity test, would be able to detect a difference between ADHD and non-ADHD subjects. In the dichotic working memory test, a list of words is presented on plug-in earphones alternately to the two ears. In the opposite ear, the ear not receiving the list of words to be remembered, a distracter is presented simultaneously. The distracter is non-interpretable speech played backwards. In an ANCOVA analysis to control for the effects of sex, age, and education, the results for total dichotic learning, learning in left and right ear and delayed recalled were significantly lower (p = .0001) in the ADHD group (n = 69) compared to the control group (n = 66). A backward-step discriminant function analysis correctly classified participants as either having ADHD (80%) or belonging to the control group (76%), in total 78 %. The ADHD group performed at a normal level for short-term memory recall measured on WAIS Digit span with scaled scores, and also on the Rey Auditory verbal learning and delayed recall test compared with normative data. There were low correlations between total dichotic learned words and the on 18 interview ADHD criteria on DSM-IV-TR symptoms (rtt = < .30). The correlations between dichotic presented recalled words and inattention (ADD) and hyperactivity-impulsivity were weaker. There were no differences between the ADD and the hyperactivity-impulsivity groups in dichotic learned or delayed recalled words.
The study demonstrated that dichotic memory learning and delayed recall with a distracter strongly differentiated ADHD patients from the control group.

6.4 Study IV: Follow-up by telephone

In DSM-IV, Criterion D requires clear evidence of clinically significant impairment in areas of educational, academic or occupational functioning and/or social resistance to being given the diagnosis. A telephone interview 3 years after the patients had received their adult ADHD diagnosis was conducted to investigate change in their symptoms and the level of impairment. A semi-structured questionnaire interview at follow-up and the Adult Self Rating ADHD Scale v1.1 at baseline and at follow-up were used. The investigation was able to recruit 115 out of the total of 158 patients for the study, and found that 86 of these had used ADHD medication, of which 51 were still being medicated at follow-up. Further, the investigation found, from demographic data, that 52 patients out of 115 (45%) had earlier in their life had a period of substance dependence, and 14 had returned to abuse at time of follow-up. 19 of the patients had been in prison.

At outset, the ADHD group on average had 1.6 years shorter education (ADHD 11.1 ± 2.4 vs. controls 12.7 ± 3.1, p = .0001). The group being medicated at follow-up (n = 51) reported significantly higher scores (feeling better) on the new items, like self-confidence, quality of life, and sleeping pattern. The medicated group also showed a significant reduction on their symptoms on ASRS total score, with a reduction of 21.2 points between baseline and follow-up, compared with the non-medicated group (n = 64) with a 7.5 points reduction. The rate of employment was low; in total 48/115 (42 %) were in part-or full-time employment, with no difference between the groups, and even after medication, 67 patients were on sick leave or disability/early-retirement pension. The number of patients (n = 50) who were taking other psychiatric medications was similar in the two groups, 24 in the ADHD-medicated group and 26 in the non-medicated group.

At follow-up, the conclusion was that patients with ADHD medication demonstrated an effect in symptom reduction and reported higher scores on self-confidence, but were similar to the non-medicated group with regard to employment at follow-up. As indicated by the low rate of medication and employment at follow-up, adult ADHD patients may need a specialized open psychiatric unit to handle and maintain their medication and treatment.
7.0 GENERAL DISCUSSION

In three investigations a reduction in adult ADHD compared with controls in the ability to concentrate was found in situations that require working memory simultaneous capacity. The most sensitive neuropsychological tests were the Consonant trigram test, the Benton Visual Retention Test and the dichotic memory test, which were compared with 10 other well-known neuropsychological tests used in ADHD research. The findings are revealed after the effects of covariance of sex, age, education, IQ and level of mood state were statistically removed, either in ANCOVA or a Generalized linear Logistic regression Model (GLM).

In the theoretical hierarchical model of working memory, we found no reduction at the first level, short-term memory (Digit span forward test), in Study I. At the second level, in the hierarchical model of working memory without disturbance, but with a manipulation of representation, a reduction was found in Digit span backward, in Arithmetic ability, in Benton VRT, in Trail making test B, and in the Wisconsin Card Sorting Test number of perseverations. The strongest reductions were found on the working memory tests (Study I and Study II). Further, a reduction was found at the third hierarchical level, in dichotic memory test with distracter in Study III, and also at level four, the working memory capacity tests with distracter, the Consonant trigram test (Study I and Study II). The other tests at theoretical hierarchical model level four (Reading span, Operation span, Counting span) remain to be tested in an adult ADHD population. The findings in the theoretical hierarchical model of working memory need replication in different ADHD investigations, and also in psychiatric clinical settings, other than ADHD.

In order to become visible, the reductions in working memory for the ADHD group require a more complex level, than that is required for the short-term memory with the rehearsal of a simple string of digits. The subject has, in working memory, to manipulate the material in one or another way for the test to be sensitive enough to catch the ADHD reduction and demand more of the individual’s concentration capacity. As revealed in studies I and II, the short-term memory test the Digit span test (WAIS) with total raw scores or in scaled scores, did not reveal a reduction; nor, did the Digit span forward span. Only scores on the Digit span backward span were reduced, a finding similar to that in Pennington and Ozonoff’s (1996) study, where a reduction was found in ADHD children in digits backward, as an exemplar of working memory in its relation to Digit span forward from WISC. This is also in line with the findings concerning the so-called “freedom from distractibility factor” with WISC/WAIS.
scaled scores (arithmetic, digit span and coding), which sometimes differentiates between ADHD and control groups. However, the literature regarding ADHD assessment is highly inconsistent with regard to this “freedom from distractibility factor” (Stevens, 2005).

In functional magnetic resonance imaging (fMRI), a reduction has been found in the prefrontal cortex: in left ventrolateral, left mid-ventrolateral, left mid-dorsolateral areas, and also in the dorsal anterior cingulated cortex during working memory, episodic and semantic long-term memory, and cognitive control (Nyberg, et al., 2003; Marklund et al., 2007). These findings are in line with observations of other neural correlates of ADHD, where brain investigations have found significant patterns of frontal hypoactivity, affecting the anterior cingulated, dorsolateral prefrontal and inferior prefrontal cortices, and also related regions including basal ganglia, thalamus, and portions of parietal gyrus (Valera et al., 2007; Volkow et al., 2007). The reduction in working memory and prefrontal areas may increase the risk of both educational and occupational under-attainment in adults.

Study II aimed to investigate whether the three ADHD subgroups of symptoms had a specific memory deficit compared with each other. The investigation found a reduction on the Benton VRT test number of errors and on the Rey Auditory Verbal Learning Test’s total number of learned words, but not on any other tests. To create a subdivision, is difficult since several studies have indicated that patients often report to few symptoms, which may be due to recall bias, poor memory ability or poor insight (Weiss & Murray, 2003). In Study II we found a weak (< 0.30) but significant correlation between the memory test results and the ADHD symptoms criteria according to the interviews. The weak correlation is in line with findings by Stearns et al. (2004) who were unable to find significant relationships between working memory and self-reported symptoms. It may be that people who experience difficulties in attention, concentration, impulse control, hyperactivity and impatience cannot be categorized through the use of a single unifying construct. The etiology and underlying cognitive processes vary considerably among people diagnosed with ADHD (Swanson et al., 1998). If the underlying elements are variable, then a search for meaningful cognitive correlates is likely to end with weak correlations. It is also possible that DSM-IV-TR symptoms do not stringently enough measure the symptoms of reduction in working memory/simultaneous capacity in ADHD. Instead, the DSM-IV-TR criteria are more likely to take into account distractibility and forgetfulness in simple every-day situations, instead of possible disturbances to more complex working memory capacity.
The aim for Study III was to determine whether adult ADHD is associated with dichotic memory deficit. We found a severe reduction in dichotic memory with distracter, a disturbance to the auditory system that in a discriminant analysis, correctly classified the ADHD group to 80% and the control group to 76%. At the same time, the subject were performing normally on the Digit span test from WAIS with scaled scores and also had normal total learning and delayed recall on the Rey Auditory Verbal Learning test, indicating that the reduction in dichotic memory was not due to a general memory disturbance in the ADHD sample, but to a specific disturbance to dichotic memory. This may also be evident in the debate about the relationship between ADHD and Central Auditory Processing Disorder (CAPS, see 1.8, which provide alternative explanations for ADHD symptoms). Since patients perform normally on the Digit span test and Rey AVLT, the reduction is a result of reduced ability simultaneously to process information (working memory), and is not a problem of directing attention at or being uncertain about what has been heard. Thus the results have no connection with the CAPS process. No earlier study has investigated the dichotic memory test in adult ADHD.

In Study IV, reporting on the telephone follow-up interviews three years later, the questions were whether ADHD patients were on medication and, whether they still had a functional impairment. Of the 115 contacted patients, 51 out of 86 were still on ADHD medication after 3 years. The medicated group showed, in comparison with the non-medicated group, a significant reduction in their symptoms measured on the ASRS scale. Among incarcerated women, Hennessey et al. (2009) found that when they met the Wender Utah Rating Scale’s 25-item criteria by scoring >46 points, the women were more likely to have a functional impairment, to be inconsistently employed, to have been recently homeless, to have had lifetime incarceration of more than 90 days, and regularly to use marijuana. In Study IV, the ADHD group had a functional impairment, with a significantly shorter education compared with the control group at baseline. At follow-up, 67 out of 115 (58 %) were without employment and 45 % had had a period of substance dependence, findings similar to those of Barkley et al. (2007) and Biederman et al. (2006b). Faraone and Antshel (2008) concluded that symptom presentation, significant functional impairment and psychiatric comorbidity are hallmarks of adult ADHD.
8.0 CONCLUSIONS

1. Tests with a simultaneous distracter showed reduced working memory capacity in adult patients with ADHD.

2. ADHD patients in all three sub-groups described in the DSM-IV-TR showed reduced working memory capacity with distracter (on the Consonant Trigram Test).

3. The dichotic memory test with a simultaneous distracter demonstrated reduced working memory capacity in ADHD patients compared with controls.

4. In a three year follow-up study patients on ADHD medication demonstrated fewer symptoms than those without.

9.0 FUTURE IMPLICATIONS

Investigation of adult ADHD may in the future be divided into three levels of assessment:

At the first level, there is a need for basic investigation of patients in open wards. There is clear evidence of symptoms, a low level of functional impairment, and a low level of controlled comorbidity. For these patients, no specific neuropsychology investigation is needed, except for those with severe dyslexia or low level IQ.

At the second level, patients may need more extensive investigation for the diagnosis and evaluation of functional impairment. Here, the patients often need to be controlled for drug- and alcohol abuse, and investigated regarding their car-driving capacity. It is suggested that more advanced neuropsychological testing of working memory capacity should be standard in this group. Also, tests of estimated IQ and advanced attention should be performed.

The third level is for patients with complex problems and severe comorbidities, i.e., IQ level of 70 to 80, low education, severe dyslexia, substance abuse during the last three months or prior to that for many years, personality disorder, history of imprisonment, and simultaneous somatic problems. This level requires a special unit with a specialist to perform the investigation. Neuropsychological investigations are required, and EEG, brain MR, and genetic investigation may be necessary.
Sammanfattning

_Syfte:_ Undersöka användningen av neuropsykologiska test med speciell inriktning mot minnestest, hos vuxna med ADHD.


_Resultat:_ Signifikanta nedsättningar i minnestester, inklusive dikotiskt minne framkom i ADHD gruppen. Detta efter ANCOVA analys med borttagning av effekterna för IQ, kön, ålder, år av utbildning och effekt av depression och ångest i HAD-skalan. Påtaglig minskning fanns i arbetsminneskapacitet testen med samtidigt administrerade störningar; Consonant trigram-testet, det dikotiska minnestestet och Benton VRT. Minskning kunde även påvisas i inlärning och fördröjd återgivning i Rey Auditory verbala inlärningstestet och det modifierade Diagnosticum för Cerebralschädigung testet. Mindre men signifikanta förändringar påvisades också i Sifferrepetition baklänges (WAIS), Raven set 1, aritmetisk kapacitet (WAIS), WCST antalet perseverationer och i Trail Making B jämfört med kontroller. Vid uppföljningen hade patienterna som medicinerades med ADHD medicin en signifikant reduktion av sina symptom samt bättre självförtroende jämfört med icke-medicinerade patienter. Graden av sysselsättning var låg; totalt 48/115 (42 %) hade deltids- eller heltidsarbete, även efter medicinering.

_Slutsslutatser:_ Den diagnostiska proceduren för vuxen ADHD bör i de mer komplicerade fallen, kompletteras med neuropsykologiska test innehållande arbetsminnestest med samtidigt administrerade störningar. Patienterna behöver troligen en specialiserad öppenvårdshem för att fortsätta med sin medicinering och förbli i behandling. Patienterna som medicineras har färre symptom och ökad livskvalitet.
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12.0 REFERENCES


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12.0 APPENDIX A: DSM-IV-TR diagnostic criteria for ADHD

A. Either (1) or (2):

(1) Six (or more) of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Inattention

(a) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
(b) often has difficulty sustaining attention in tasks or play activities
(c) often does not seem to listen when spoken to directly
(d) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)
(e) often has difficulty organizing tasks and activities
(f) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
(g) often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
(h) is often easily distracted by extraneous stimuli
(i) is often forgetful in daily activities

(2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

Hyperactivity

(a) often fidgets with hands or feet or squirms in seat
(b) often leaves seat in classroom or in other situations in which remaining seated is expected
(c) often runs about or climbs excessively in situations in which it is inappropriate (in adolescent or adults, may be limited to subjective feelings of restlessness)
(d) is often “on the go” or often acts as “driven by a motor”
(e) often talks excessively
Impulsivity

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

(B) Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7 years.

(C) Some impairment from the symptoms is present in two or more settings (e.g., at school (or work) and at home).

(D) There must be clear evidence of clinically significant impairment in social, academic, or occupational functioning.

(E) The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g., Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Code based on type:

341.01 Attention-Deficit/Hyperactivity Disorder, Combined Type: if both criteria A1 and A2 are met for the past 6 months

314.00 Attention-Deficit/Hyperactivity Disorder, predominantly Inattentive Type: if criterion A1 is met but criterion A2 is not met for the past 6 months

314.01 Attention-Deficit/Hyperactivity Disorder, predominantly Hyperactive-impulsive Type: if criterion A2 is met but criterion A1 is not met for the past 6 months

Code note: for individuals (especially adolescents and adults) who currently have symptoms that no longer meet full criteria, “In Partial Remission” should be specified.

314.9 Attention-Deficit/Hyperactivity Disorder not otherwise specified

This category is for disorders with prominent symptoms of inattention or hyperactivity-impulsivity that do not meet criteria for Attention-Deficit/Hyperactivity Disorder.
Examples include

1. Individuals whose symptoms and impairment meet the criteria for Attention-Deficit/Hyperactivity Disorder, Predominantly Inattentive type but whose age at onset is 7 years or after

2. Individuals with clinically significant impairment who present with inattention and whose symptom pattern does not meet the full criteria for the disorder but have a behavioral pattern marked by sluggishness, daydreaming, and hypoactivity
13.0 Appendix B: ICD-10 criteria for ADHD

ICD-10 research criteria for diagnosis of F90 – F98. Behavioral and emotional disorders with onset usually occurring in childhood and adolescence.

**F90. Hyperkinetic disorders.**

Note: The research diagnosis of hyperkinetic disorder requires the definite presence of abnormal levels of inattention, hyperactivity, and restlessness that are pervasive across situations and persistent over time and that are not caused by other disorders such as autism or affective disorders.

Eventually, assessment instruments should develop to the point where it is possible to take a quantitative cut-off score on reliable valid and standardized measures of hyperactive behavior in the home and classroom, corresponding to the 95th percentile on both measures. Such criteria would then replace G1 and G2 below.

**G1.** Demonstrable abnormality of attention, activity and impulsivity at home, for the age and developmental level of the child, as evidenced by (1), (2) and (3):

1. **(1) At least three of the following attention problems:**
   - (a) Short duration of spontaneous activities;
   - (b) Often leaving play activities unfinished;
   - (c) Over-frequent changes between activities;
   - (d) Undue lack of persistence at tasks set by adults;
   - (e) Unduly high distractibility during study e.g. homework or reading assignment.

2. **(2) Plus at least three of the following activity problems:**
   - (a) Very often runs about or climbs excessively in situations where it is inappropriate; seems unable to remain still;
   - (b) Markedly excessive fidgeting & wriggling during spontaneous activities;
   - (c) Markedly excessive activity in situations expecting relative stillness (e.g., mealtimes, travel, visiting, church);
   - (d) Often leaves seat in classroom or other situations when remaining seated is expected;
   - (e) Often has difficulty playing quietly.
(3) **Plus at least one of the following impulsivity problems:**

(a) Often has difficulty awaiting turns in games or group situations;
(b) Often interrupts or intrudes on others (e.g., butts in to others’ conversations or games);
(c) Often blurts out answers to questions before questions have been completed.

G2. Demonstrable abnormality of attention and activity at school or nursery (if applicable), for the age and developmental level of the child, as evidenced by both (1) and (2):

(1) **At least two of the following attention problems:**

(a) Undue lack of persistence at tasks;
(b) Unduly high distractibility, i.e., often orienting towards extrinsic stimuli;
(c) Over-frequent changes between activities when choice is allowed;
(d) Excessively short durations of play activities.

(2) And by at least three of following activity problems:

(a) Continuous (or almost continuous) and excessive motor restlessness (running, jumping, etc.) in situations allowing free activity;
(b) Markedly excessive fidgeting and wriggling in structured situations;
(c) Excessive levels of off-task activity during tasks;
(d) Unduly often out of seat when required to be sitting;
(e) Often has difficulty playing quietly.

G3. Directly observed abnormality of attention or activity. This must be excessive for the child’s age and developmental level. The evidence may be any of the following:

(1) Direct observation of the criteria in G1 or G2 above, i.e., not solely the report of parent or teacher;
(2) Observation of abnormal levels of motor activity, or off-task behavior, or lack of persistence in activities, in a setting outside home or school (e.g., clinic or laboratory).
(3) Significant impairment of performance on psychometric tests of attention.

G4. Does not meet criteria for pervasive developmental disorder (F84), mania (F30), depressive (F32) or anxiety disorder (F41).

G5. Onset before the age of seven years.

G6. Durations of at least six months.
G7. IQ above 50.

**F90.0 Disturbance of activity and attention**

The general criteria for hyperkinetic disorder (F90) must be met, but not those for conduct disorders (F91).

**F90.1 Hyperkinetic conduct disorder**

Both the general criteria for hyperkinetic disorder (-f90) and conduct disorder (F91) must be met.

**F90.8 Other hyperkinetic disorders**

**F90.9 Hyperkinetic disorder, unspecified**

This residual category is not recommended and should be used only when there is a lack of differentiation between F90.0 and F90.1 but the overall criteria for F90.- are fulfilled.
**Alternative F90 Hyperkinetic disorder (diagnostic criteria for research):**

G 1. Inattention. At least six of the following symptoms of inattention have persisted for at least six months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

(a) Often fails to give close attention to details, or makes careless errors in schoolwork, work, or other activities;
(b) Often fails to sustain attention in tasks or play activities;
(c) Often appears not to listen to what is being said to him or her;
(d) Often fails to follow through on instructions or to finish schoolwork, chores, or duties in the workplace (not because of oppositional behavior or failure to understand instructions);
(e) Is often impaired in organizing tasks and activities;
(f) Often avoids or strongly dislikes tasks, such as homework, that require sustained mental effort;
(g) Often loses things necessary for certain tasks or activities, such as school assignments, pencils, books, toys, or tools;
(h) Is often easily distracted by external stimuli;
(i) Is often forgetful in the course of daily activities.

G 2. Hyperactivity. At least three of the following symptoms of hyperactivity have persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the developmental level of the child:

(a) Often fidgets with hands or feet or squirms on seat;
(b) Leaves seat in classroom or in other situations in which remaining seated is expected;
(c) Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, only feelings of restlessness may be present);
(d) Is often unduly noisy in playing or has difficulty in engaging quietly in leisure activities;
(e) Exhibits a persistent pattern of excessive motor activity that is not substantially modified by social context or demands.
G 3. Impulsivity. At least one of the following symptoms of impulsivity has persisted for at least 6 months, to a degree that is maladaptive and inconsistent with the development level of the child:

(a) Often blurts out answers before questions have been completed;
(b) Often fails to wait in lines or await turns in games or group situations;
(c) Often interrupts or intrudes on others (e.g., butts into others’ conversations or games);
(d) Often talks excessively without appropriate response to social constraints.

G 4. Onset of the disorder is no later than the age of 7 years.

G 5. Pervasiveness. The criteria should be met for more than a single situation, e.g., the combination of inattention and hyperactivity should be present both at home and at school, or at both school and another setting where children are observed, such as a clinic. (Evidence for cross-situationality will ordinarily require information from more than one source; parental reports about classroom behavior, for instance, are unlikely to be sufficient).

G 6. The symptoms in G 1–G 3 cause clinically significant distress or impairment in social, academic, or occupational functioning.

G 7. The disorder does not meet the criteria for Pervasive Developmental Disorders (F84.-), Manic episode (F30.-), Depressive episode (F32.-), or Anxiety Disorders (F41.-).

Comment. Many children with sub-threshold disorders show (e.g., only the whom or only the classroom situation) other syndromes (such as oppositional defiant disorder, F91.3) and should be classified in the appropriate category.

F90.0 Disturbance of activity and attention.

The general criteria for Hyperkinetic Disorder (F90) must be met, but not those for Conduct Disorders (F91.-).