Neuropsychological function in adults with attention-deficit/hyperactivity disorder

Larry J. Seidman, PhDa–f,*, Alysa Doyle, PhDa,f, Ronna Fried, PhDa,f, Eve Valera, PhDa,b,f, Katherine Crum, BAa, Lauren Matthews, BAa

aPediatric Psychopharmacology Unit, Massachusetts General Hospital, 15 Parkma Street, WACC 725, Boston, MA 02114, USA
bPsychiatric Neuroscience Program, Department of Psychiatry, Massachusetts General Hospital, 13th Street, CNY 149, 9th Floor East, Charlestown, MA 02129, USA
cCommonwealth Research Center, Massachusetts Mental Health Center, 25 Shattuck Street, Boston, MA 02215, USA
dLaboratory of Neuropsychology, Massachusetts Mental Health Center, 25 Shattuck Street, Boston, MA 02215, USA
eLaboratory of Psychiatric Epidemiology and Genetics, Massachusetts Mental Health Center, 25 Shattuck Street, Boston, MA 02215, USA
fDepartment of Psychiatry, Harvard Medical School, 25 Shattuck Street, Boston, MA 02215, USA

Although most current knowledge about attention-deficit/hyperactivity disorder (ADHD) developed from clinical observations and research with children, understanding of the disorder in adults is growing rapidly. It is being discovered that adults and children with ADHD share similar clinical features, comorbidities, and failures in major life domains (eg, academics and work) [1–4], and possibly brain abnormalities (see article by Seidman et al in this issue). It has become clear that to gain a full understanding of ADHD, the disorder must be studied from a life span perspective, integrating what is known about how it affects both adults and children [5].

Cross-sectional data suggest that neuropsychological dysfunctions are a central component of the childhood syndrome [6,7], and a growing literature suggests the same for adults [4]. This article reviews the current state of the literature pertaining to the neuropsychological dysfunctions that are found in children and adults with ADHD. Because considerable controversy has existed about the nature and validity of adult ADHD, this

* Corresponding author.
E-mail address: larry_seidman@hms.harvard.edu (L.J. Seidman).

0193-953X/04/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
article will aid clinicians in developing a better understanding of the empirical literature on neuropsychological function in ADHD throughout the lifespan.

Development of the concept of attention–executive dysfunction in attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder, formerly called hyperactivity, hyperkinesis disorder of childhood, or minimal brain dysfunction, first was described 100 years ago as a childhood disorder found mainly in boys [8]. Revisions in the diagnostic construct have been made a number of times over the past century [9]. The most important shift occurred in the 1970s, when the concept of attention dysfunction was introduced as the core defining feature [10], and the disorder was renamed accordingly. The key symptoms needed for the diagnosis, however, were behavioral descriptions of motor and attentional problems rather than direct cognitive measures of inattention.

The diagnosis of ADHD is made on the basis of developmentally inappropriate symptoms of inattention, impulsivity, and motor restlessness [11]. Three subtypes are recognized: inattentive, hyperactive–impulsive, and combined (reflecting a combination of the other two types). Symptoms must be: observed early in life (before age 7), pervasive across situations, and chronic. The clinical presentation has suggested that ADHD is a neuropsychological disorder, and current theories emphasize the central role of attentional and executive dysfunctions and disinhibition [6,12].

In considering these theoretical ideas, it is important to recognize that behavioral studies of normal persons and of brain-injured and psychiatric patients have emphasized that attention and executive functions are not unitary processes [13–15]. Attention refers to a complex set of mental operations that includes focusing on or engaging a target, sustaining the focus over time using vigilance, encoding stimulus properties, and disengaging and shifting the focus. Executive functions regulate behavioral output; typically, they involve inhibition and impulse control, working memory, cognitive flexibility, and planning and organization [16]. Working memory has been defined as the temporary maintenance, manipulation, and storage of information for use in other cognitive operations, such as reasoning [17]. It is analogous to a mental clipboard that holds information on line for short periods of time.

These attention and executive functions have become the focus of current theories concerning the neuropsychological basis of ADHD. Unlike 10 years ago, when cognitive neuropsychological research in ADHD concentrated on attention deficit (eg, vigilance or distractibility), today’s studies examine multiple dysfunctions in the executive processes that control subordinate cognitive processes. Although there is a lack of consensus about the taxonomy of executive processes, there is some agreement that these processes
Neuropsychological dysfunctions in childhood attention-deficit/hyperactivity disorder

Neuropsychological studies in children with attention-deficit/hyperactivity disorder

The neuropsychological functioning of children with ADHD has been studied extensively since the early 1970s, beginning with the pioneering work by Douglas on vigilance deficits [10]. Numerous clinical studies have compared groups of boys with ADHD, typically aged 6 to 12, with normal controls. These studies indicate that children with ADHD exhibit subaverage or relatively weak performance on various tasks of vigilance, verbal learning (particularly encoding), working memory, and executive functions such as set-shifting, planning and organization, complex problem solving, and response inhibition [12,22–27]. Deficits on the Stroop color–word test appear to be among the most significant neuropsychological impairments [23]. This task, requiring suppression of interference arising from conflictual information (response inhibition) has been shown to be abnormal in large samples of boys and girls with ADHD (Seidman, unpublished data, 2004).

Paralleling the large number of clinical neuropsychological studies, paradigms from experimental psychology and cognitive neuroscience have also been employed. For example, experimental investigations of response inhibition or interference control [28] have demonstrated excessive sensitivity to processing irrelevant information in Stroop paradigms [29]. Asymmetrical...
performance deficits on a covert orienting task implicating abnormal right hemisphere processing [30] also have been observed.

Neuropsychological studies in adolescents with attention-deficit/hyperactivity disorder

It is striking and somewhat surprising that despite the plethora of studies of children aged 6 to 12, there is remarkably little data on teenagers with the disorder. The authors have demonstrated in their research that the executive dysfunctions that characterize the disorder in childhood also are found in teenagers [26] (Seidman, unpublished data). These data demonstrate that samples of healthy control children and children with ADHD both improve their performance as they get older, but the deficit between groups remains significant. This persistent picture, and the presence of relatively stable structural brain abnormalities in children aged 4 to 18 [31] supports the notion that these abnormalities will be present in adults with ADHD. In the only published longitudinal study of neuropsychological function, Fischer et al [22] demonstrated results consistent with those just described. Before turning to a review of the adult neuropsychological data, it is important to address the important effects of psychiatric comorbidity, learning disabilities (LDs), and gender on the child data.

Are neuropsychological abnormalities accounted for by comorbidity?

Psychiatric Comorbidity

Children and adults with ADHD frequently have comorbid antisocial, substance abuse, mood, anxiety, or learning disorders [32]. Although spurious comorbidity can occur because of referral and screening artifacts, the review by Biederman et al [32] demonstrated that these artifacts cannot explain the high levels of psychiatric comorbidity. Family studies of comorbidity by the Biederman research team also dispute the notion that artifacts cause comorbidity; rather, they show a causal role to etiological relationships among the disorders [33–35]. In addition, studies in children [7,25,27,36] and adults [4,37] showed that neuropsychological deficits in ADHD remained robust after statistically adjusting for the presence of psychiatric comorbidities. Thus, the existing data suggest neuropsychological abnormalities in ADHD can be demonstrated independent of psychiatric comorbidity. Further research is needed to address whether particular subgroups of persons with ADHD (eg, ADHD plus bipolar disorder) are especially or distinctively impaired.

Learning disabilities

A more complex obstacle in identifying the underlying neuropsychology of ADHD pertains to the overlap between ADHD and various kinds
of learning disabilities, which by definition are neurocognitive disorders. The literature on ADHD consistently has documented that a substantial minority of children with ADHD also have LDs, such as reading or arithmetic disability [38–40]. Rates vary depending on the definition and type of LD, with estimates ranging from 10% to more than 90% [41], although a rate of approximately 30% using both reading and arithmetic as comorbid LDs has been suggested more realistically [42]. LDs, when combined with ADHD, have a specific role in school failure [42]. Because LDs (without ADHD) also can manifest neuropsychological deficits in attention and in components of memory [43–45], more work is needed to evaluate whether neuropsychological deficits in ADHD children with comorbid LDs are caused by ADHD or by LDs.

Learning disabilities are neuropsychological disorders characterized by specific processing problems. For example, dyslexia (ie, reading disability) is characterized especially by specific impairments in single word reading, reading fluency, and reading comprehension, usually resulting from deficient phonological processing [46]. Although the authors documented that executive function deficits in youth with ADHD remained significant after statistically controlling for the presence of LD [26], questions remain as to the nature of the association between ADHD, LD, and executive deficits. For example, in a pilot study of ADHD boys, the authors found that youth diagnosed with ADHD and LD were significantly worse than those with ADHD without LD on the Rey–Osterrieth Complex Figure organization score (a measure of executive functions) and on rapid naming on the Stroop test [25]. Because initial results were based on a small sample, however, the authors could not address specific types of LDs, such as those associated with arithmetic or reading, which were lumped together. An understanding of the role of the specific LDs combined with ADHD is important for clarifying the nature of neuropsychological deficit in ADHD.

In conceptualizing the complex relationship between ADHD and LD in ADHD children, several hypotheses can be formulated. One possibility is that the comorbidity of LD within ADHD represents a qualitatively distinct condition, as suggested by family studies relevant to genetic transmission of the disorders [47]. There is also support for this model from several studies that demonstrate that reading disability and ADHD are characterized by separate deficits, namely phonological processing deficits in the former and executive function deficits in the latter [46,48]. This leads to the hypothesis that persons with ADHD plus LD would not have worse executive function deficits than persons with ADHD without LD.

An alternative hypothesis is that persons with ADHD and comorbid LD have more severe executive deficits than persons with ADHD without LD [25] because of the additive effect of combining two cognitive disorders that both include attentional and memory dysfunctions. There is some support for this hypothesis. Several studies have compared ADHD children with and without accompanying reading disabilities (RDs) on a range of
neuropsychological measures. August and Garfinkel [49] reported that their combined ADHD plus RD group performed significantly worse than the ADHD group (which also was impaired relative to normal controls) on a range of measures in the areas of attention, vocabulary, degraded word recognition, and memory for letter sequences. A similar pattern of findings emerged in a study of memory functioning [50], in which ADHD and ADHD plus LD groups displayed subaverage recall of sequential/ordered auditory and visual information, with the comorbid group showing greater difficulty. Tarnowski et al [51] found that the ADHD plus LD group was significantly worse on perceptual discrimination on a Continuous Performance Test (CPT). In a large recent study, Willcutt et al [52] found that ADHD plus RD was impaired on virtually all measures of neuropsychological function compared with persons with ADHD without RD. Not all studies, however, have found ADHD children with learning problems to be more impaired on measures of memory, attention, and visual–motor functioning [53].

Because these findings were obtained in studies composed mainly of preadolescent, elementary school boys (aged 6 to 12), questions remain regarding the relationship of ADHD and LD in adolescents. Moreover, almost all research attention has been devoted to studying the impact of comorbid RD, while the relevance of comorbid arithmetic disability (AD) has been neglected. The authors could find no published papers addressing the specific role of AD and ADHD on neuropsychological function, nor had prior studies evaluated the neuropsychological consequences associated with combined RD, AD, and ADHD. These results strongly suggested that additional analysis of specific LDs associated with ADHD is important.

An additional issue has to do with the definition of LD. There are no rules for the definition of LD accepted by all investigators, and definitions vary, at least in part, in relation to educational criteria, state regulations, and neuroscientific models [54,55]. In previous work on LD and ADHD [7,25,27,37,41,42,47] the authors used a regression-based approach correcting for the correlation of IQ and achievement as recommended by Reynolds [56] and Frick [57] to define LDs. Nonetheless, there is evidence suggesting that low achievement is an equally valid method of classifying persons with LD [54,55] and that alternative methods of classification need to be compared [58].

The authors tested several hypotheses regarding the relationship of ADHD and LD to neuropsychological dysfunctions [58]. First, they hypothesized that comorbid LDs contribute to a general increase in neuropsychological dysfunction, including executive dysfunction. Second, the authors expected that the more severe neuropsychological dysfunction in the comorbid groups would be independent of psychiatric comorbidity. Third, they considered the role of the specific type of LD on neuropsychological dysfunctions in ADHD (RD alone, AD alone, AD plus RD). Fourth, the authors predicted that results would be comparable using a regression-based classification for LD and classification combining regression-based formulas.
and low achievement. Participants were 148 males diagnosed with Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R)-defined ADHD, with (N = 69) and without (N = 79) LD, and 127 non-ADHD, non-LD male controls of similar age (range 9 to 22 years). LD was defined by a combined regression based plus low achievement classification. Analyses adjusted for the effect of psychiatric comorbidity, age, and socioeconomic status on neuropsychological function. Participants who had ADHD plus LD were significantly more impaired on both executive and nonexecutive functions than ADHD subjects without LD. Neuropsychological performance was impaired most in ADHD with combined arithmetic and reading disability. These data indicate that comorbid LD, especially AD, significantly increases the severity of executive function impairment in ADHD. These results lead to a number of conclusions. First, a substantial component of the variance of neuropsychological deficit in ADHD is explained by LD contributions. Second, having LD plus ADHD predisposes to a particularly severe form of executive dysfunction that requires careful attention in clinical assessment and psychoeducational interventions.

Heterogeneity of attention-deficit/hyperactivity disorder and neuropsychological abnormalities

This article already has addressed the fact that ADHD is a heterogeneous clinical disorder with substantial psychiatric and cognitive comorbidity. It, however, has not investigated the issue of whether neuropsychological deficits are present in all or most individuals with ADHD, or whether the observed group differences can be applied easily to the individual case. To some, this may seem confusing; if ADHD is named “attention-deficit/hyperactivity disorder, should not all cases with the disorder have attention deficits? This would be true if the attention-executive functions measured by psychological laboratory tests are synonymous with the behaviors and symptoms that make up the diagnostic criteria. It is possible that there is substantial method variance (differing methods potentially yielding different results) in the numerous measures of assessing attention, and that attention-executive function neuropsychological deficits will not characterize all persons with the diagnosis.

In fact, the results suggest that neuropsychological and behavioral assessments of ADHD executive functions may not be measuring the same thing. Variability across studies has been noted by comprehensive reviews of the literature [12,23,59]. For example, Sergeant et al [59] found that many but not all studies found Stroop interference deficits, Wisconsin Card Sorting Test (WCST) impairments, and reduced verbal fluency using letters in ADHD samples. Although in their 1992 review, Barkley et al [23] speculated that the variability could be caused by methodological differences and small sample sizes, the fact that heterogeneity continues to emerge.
across large-scale studies and within studies suggests that other factors may
account for this variability. Performance differences within ADHD samples
have been documented by studies that have examined whether various
measures of executive functions could be used as diagnostic tools for
ADHD. These studies have examined male [60,61] and female [62] youth
and adults [63] and found that most measures of executive functions have
good positive predictive power for ADHD but poor negative predictive
power. That is, abnormal scores on measures of executive functions are
generally predictive of the diagnosis; however, normal scores cannot rule
out the diagnosis. This pattern is because not every subject is impaired on
every test, and some individuals with ADHD perform within the normal
range on all or most measures. The authors’ work suggests that
approximately 40% to 50% of persons with ADHD can be considered to
be neuropsychologically abnormal in the context of approximately 5% to
10% abnormality in controls [61]. This result may be a function of true
variability in neuropsychological dysfunctions, or some methodological
aspects of the tests or testing situation that limits their sensitivity.

**Effects of gender on neuropsychological abnormalities in
attention-deficit/hyperactivity disorder**

Although ADHD affects both genders, most of the research literature,
including studies evaluating neuropsychological functioning, is devoted to
males [64,65]. Gaub and Carlson’s review [65] indicated that few studies
included sufficient numbers of female subjects to warrant gender-based
conclusions. Nevertheless, there are data supporting the presence of a valid
syndrome of ADHD in girls. A previous study of girls with Diagnostic and
Statistical Manual of Mental Disorders, Third Edition (DSM III)-defined
attention-deficit disorder [66] documented the same patterns of comorbidity
and familiality in girls that had been observed in boys. Recent work by the
authors [67], reporting on the largest dataset to date on girls with ADHD,
identified more similarities than differences in the core features of ADHD,
with a few notable exceptions. Girls were more likely than boys to have
a somewhat higher rate of predominantly inattentive type of ADHD
(although the combined type was the leading type in both genders), a lesser
likelihood to have a LD, a lesser likelihood to manifest problems in school
or in their spare time, and a lower risk for comorbid conduct disorder and
oppositional–defiant disorder [67]. The authors also demonstrated that the
familial transmission of ADHD and comorbid disorders was similar in boys
and girls [68,69].

Some research suggests girls with ADHD are more neuropsychologically
impaired than boys with ADHD [65]. This observation, while receiving
some support for measures of intelligence, may not generalize to executive
functions, which only partially overlap with intelligence [12]. In fact, most
studies suggest, that, although there are neuropsychological impairments in
girls with ADHD compared with control girls, there are no differences between girls and boys with ADHD on executive functions. For example, DeHaas [70] showed that both girls and boys with ADHD scored significantly below controls on digit span and all subtests of the Stroop. There were no significant differences, however, between girls and boys with ADHD. Similarly, Houghton et al [71] found differences between girls with ADHD and controls on the Stroop and WCST, but they failed to find differences between girls and boys with ADHD. Several studies [72–76] failed to find any gender differences on CPT measures (the last studying a large sample of children, teenagers and adults). Castellanos et al [77] demonstrated that girls with ADHD performed more poorly than healthy controls on delayed response and go-no-go oculomotor tasks, consistent with executive function impairments that have been noted in boys, but they did not examine gender differences. Nigg [20], using a stop signal task measuring inhibition, showed that girls with ADHD were slower to respond than were controls. In contrast, in a pilot study, the authors reported that girls might have a milder neuropsychological syndrome than that observed in boys with ADHD, although they did not compare girls and boys with ADHD directly [78].

Only two studies found significant gender differences between boys and girls with ADHD on attention and executive tasks. Rucklidge and Tannock [79] found that both girls and boys with ADHD (aged 13 to 16) were impaired in processing speed compared with normal teenagers, but the boys with ADHD were slower in processing speed than girls with ADHD. Newcorn et al [80] found that girls with ADHD made significantly fewer CPT impulsivity errors than did boys with ADHD, although no normal controls were studied.

Our literature review suggests there are executive function impairments in girls with ADHD, but it provides limited data about gender differences on measures of executive functioning. Moreover, methodological limitations impede conclusive interpretations. These include:

1. Small sample sizes that do not provide enough power to be conclusive
2. Failure to routinely include a substantial group of male and female controls to address normal sex differences [81]
3. Relatively limited sets of executive function measures that may not enable an evaluation of an appropriate range of measurement
4. Failure to control for the common psychiatric comorbidities and learning disabilities [41,42,58]

These data suggested the need for a well-controlled study using a large sample of boys and girls with ADHD using a range of well-accepted measures of executive functioning. The authors performed such a study, evaluating whether girls with ADHD have executive function impairments compared with healthy controls, whether their neuropsychological features are similar to those found in boys, and whether there are systematic sex
differences (Seidenman, unpublished data). Subjects were 140 girls and 98 boys with DSM-III-R-defined ADHD and 122 comparison girls and 70 boys without ADHD, aged 6 to 17 years. Information on neuropsychological performance was obtained in a standardized manner blind to clinical status. Primary analyses controlled for age, socioeconomic status, learning disability, and psychiatric comorbidity. Girls with ADHD were significantly more impaired on executive functions than comparison girls. Relative to healthy comparisons, girls with ADHD were significantly more impaired on all Stroop subtests, the WCST Perseverative Errors score, and a measure of verbal learning. Deficits were more pronounced in unmedicated girls with ADHD; additional impairments were observed on the Rey–Osterrieth organization score and on CPT errors. This pattern was quite similar to that found in boys with ADHD. With the exception of one test score, there were no significant sex-by-diagnosis interactions. The authors concluded that girls with ADHD have significant impairments in executive functions and that neuropsychological measures of these functions are impaired equally in girls compared with boys with ADHD. As with boys, the observed neuropsychological deficits were not accounted for by psychiatric comorbidity or LD.

Neuropsychological dysfunctions in adult attention-deficit/hyperactivity disorder

Over the past decade, research on clinical neuropsychological dysfunctions in adult ADHD has intensified, and the evidence for such deficits in adults with ADHD is mounting. Recently, a meta-analysis was conducted of neuropsychological deficits in adults with ADHD [82]. They included only samples with persons 18 years and older, and with a control group. They reviewed 33 published studies and found that neuropsychological deficits are largely consistent with those described in children. Impairments were observed relatively consistently in attention, behavioral inhibition, and memory. Similar results were derived from a qualitative review [83]. The adult literature is similar to the child literature described earlier in terms of tests used and other methodological features. Most research is based on the criteria described in the Diagnostic Statistical Manual [12] after a diagnostic interview. Because ADHD is a developmental disorder considered to begin by age 7, ADHD symptoms have to emerge by that age, and, in adults, this is necessarily a retrospective report. Hervey et al [82], point out that not all studies report the age of the subjects. According to their review, for those studies reporting this important variable, the range is between 19 and 41, with a mean age of approximately 32 years. Thus, the literature is based largely on young adults.

Neuropsychologists have literally hundreds of tests to choose from in composing an assessment battery. In the authors’ review of the adult literature, they counted more than 70 tests used to compare ADHD adults and controls. Many of these tests were used in only one or two studies,
however, and their sensitivity cannot be determined. The following discussion will focus on the five tests that differentiated persons with ADHD from controls most consistently and were used in at least seven studies: versions of the CPT, the Stroop, Trail Making, Verbal Fluency (FAS), and the Wechsler Adult Intelligence Scale (WAIS). The WCST, which consistently yielded nonsignificant results, is also addressed.

The CPT, originally published in 1956 by Rosvold et al [84], is actually an experimental method that can be varied endlessly to examine different components affecting vigilance and sustained attention [13–15]. Thus, there are many different versions of the CPT in clinical use, some of which are published commercially. Moreover, like many neuropsychological tests, the CPT produces multiple dependent variables, which can reflect different components of mental abilities (eg, reaction time, errors of omission, and errors of commission). Reference will be made to particular variables as needed. The authors found that different versions of the CPT significantly differentiated adults with ADHD in 13 studies (78%), whereas four studies yielded negative results. The Conners CPT was significantly different in five studies [85–89] and negative in two [90,91]. The Gordon Diagnostic System [92] was significantly different in the three studies in which it was used [93–95]. A number of other home-grown visual CPTs have discriminated ADHD subjects from controls successfully [96–99], and a few studies have been negative [91,100], the latter with the Tests of Variable Attention (TOVA). One study discriminated the groups with a home-grown auditory CPT [37]. According to Hervey et al [82], the effect size [101] discrimination between persons with ADHD and controls was generally in the moderate- (d = 0.50) to-large range (0.75). Commission and omission errors had roughly the same discriminating power. The authors’ results on a relatively simple “X” version of the auditory CPT are consistent with a moderate effect [27] (Seidman, unpublished data).

The Stroop task, generally considered to be a task of inhibition (at least for the color–word conflict condition) has been used in 15 studies, 11 of which showed significant discrimination (73%). Most of the Stroop studies have used Golden’s version [102], and 8 of 12 of these were impaired significantly in ADHD [87,89,94–96,103–105]. Four studies using the Golden version had negative results [37,106–108]. Two other versions of the Stroop task were impaired significantly in adults with ADHD [63,83,109]. Hervey et al [82] reported a medium effect size of approximately 0.45 for the color–word test, which is the most discriminating subtest. Thus, while it is a consistent finding in adults and children, the effect is modest.

The Trail Making test [110], a measure involving connecting circles on a page, has two versions. Trails A essentially measures some combination of visual search and perceptual motor speed. Trails B adds an executive component, shifting set. Hervey et al [82] reported a moderate effect size for Trails A (approximately 0.50 to 0.55) and a slightly larger effect size for Trails B (0.68). The authors found that 7 out of 10 studies (70%) show that...
adults with ADHD perform significantly worse than controls \[63,83,93–95,99,103\]. Three studies found no effect \[87,106,108\]. Thus, while Trails B seems to be a bit more sensitive to the deficits associated with ADHD, the improvement in sensitivity is small, suggesting that processing speed itself is an important component of the deficit.

The Controlled Word Association Test (COWAT) \[111\] measures verbal fluency in response to single letters (FAS), which taps into phonological associations, and category fluency (eg, “name all the animals you can”). This measure seems to combine rapid access to the lexicon, persistence, and processing speed. Seven of eight studies (87%) demonstrated impairment in adults with ADHD \[63,83,89,94,95,105,108\], with only one negative result \[85\]. According to Hervey et al \[82\], most studies have used COWAT total words, and the effect size is moderate (0.60).

There is a long tradition of using subtests or factors from Wechsler intelligence scales for children and adults in the assessment of ADHD. Most of the published adult research literature is based on the WAIS-R \[112\], which is less sophisticated in its factor structure than the recently renormed WAIS-III \[113\]. Clearly, measures of perceptual motor output speed as assessed by the digit symbol coding test are impaired commonly in adults with ADHD \[93,96,97,106,107\]. Digit Symbol has a moderate-to-large effect size of 0.62 \[82\], and along with the arithmetic subtest, which taps into working memory, it is the most discriminating subtest. Estimated full-scale IQ, which typically is calculated as a matching variable between ADHD and control groups, is usually lower in patients with ADHD than in controls, with a more modest effect size of 0.39 \[82\]. Thus, general cognitive impairments account for a significant proportion of the variance of cognitive deficit in adults with ADHD, similar to that observed in children \[7\]. Overall, the authors found significant impairments in 13 of 18 (72%) studies using the WAIS \[96\], the WAIS-R (11 positive reports \[32,63,83,85,87,91,95,98,103,106,114\] and four negative results \[37,95,99,108\], and the WAIS-III \[89\]. Conceptually, the Working Memory and Processing Speed indexes of the WAIS-III are most likely to be impaired in persons with ADHD, and the authors expect more studies of these indexes to emerge soon with the increased use of the WAIS-III.

The WCST is quite ineffective in distinguishing adults with ADHD from controls. The WCST has long been considered, in the general neuropsychological literature, to be one of the premiere measures of executive functions. The first factor of the WCST, perseveration \[115\] is a classic measure of dorsolateral prefrontal cortical function. In the authors’ review of studies with adults with ADHD, however, only one study showed a positive result \[103\], and seven did not \[37,93–95,99,100,114\]. Consistent with the authors’ summary, Hervey et al \[82\] reported trivial effect sizes of 0.02 for categories completed and 0.12 for perseverative errors. Given that the WCST discriminates reasonably well in children with ADHD, two possibilities can be considered to explain this difference in sensitivity:
1. The test is simply too easy for adults, because it has a low ceiling. That is, normal children can achieve approximately adult levels by ages 10 to 12 [116].

2. Adults with ADHD improve on this task relative to controls from childhood to adulthood.

Although this latter possibility can be answered definitively only by a longitudinal study, the authors favor the former interpretation. The WCST was developed in an era [117] when the major focus was on evaluating adults with significant brain damage, such as structural damage to prefrontal cortex as a result of tumors [118]. It simply was not developed to assess persons with subtler neurodevelopmental disorders. Other tasks of problem-solving and abstract reasoning that have higher performance ceilings and have better psychometric features (such as various Tower tasks, or more difficult sorting tasks) may turn out to be effective at discriminating adults with ADHD from controls.

The tests described previously are well-studied clinical instruments and may be less (or possibly more) sensitive to underlying cognitive impairments in adults with ADHD than are a newer generation of information processing and experimental neuropsychological tests [119]. Given the hypothesized deficits in attention and executive function, especially inhibition, several tests hold considerable promise, but too little research has been published to summarize the results. The tests that may turn out to be very useful include measures of inhibition such as the Stop-Signal test [18] and the multi-source interference test [120], tests of working memory such as the Paced Auditory Serial Addition Test [121] and the Delayed Oculomotor Response Task [77], and problem-solving tasks such as Tower tasks.

In summary, the neuropsychological difficulties found in adults with ADHD (in subjects up to approximately age 40) appear to be qualitatively similar to those seen in children with the disorder; thus, they support the notion of syndromatic continuity. Nevertheless, additional research is needed, because not all studies demonstrate impairment of the same tasks or functions, nor do all studies control for the various confounds (eg, psychiatric comorbidities) associated with the disorder. Moreover, there is a paucity of longitudinal neuropsychological research from childhood into adulthood, and this type of design is necessary to determine the full extent of neuropsychological continuity. Finally, newer and more appropriate tests of the hypothesized cognitive functions underlying ADHD need to be tested in multiple carefully designed studies.

**Relating brain structure, function, and neuropsychological dysfunctions**

The analysis of attention and executive functions into subcomponents—and the mapping of attentional functions onto different brain regions—supports the proposition that response inhibition and other executive deficits
in ADHD will be associated with structural and functional brain abnormalities in specific regions. There is limited ADHD research in this area, however. In children, Casey et al [122] found that performance on three response inhibition tasks correlated only with those anatomical measures of fronto–striatal circuitry observed to be abnormal in ADHD (ie, the prefrontal cortex, caudate, and globus pallidus, but not the putamen). The significant correlations between task performance and anatomical measures of the prefrontal cortex and caudate nuclei were predominantly in the right hemisphere, supporting the role of right fronto–striatal circuitry in response inhibition and ADHD. Semrud-Clikeman et al [123], also studying children, found a significant relationship between reversed caudate asymmetry and measures of inhibition (as measured by the Stroop) and externalizing behavior. Three small studies of adults, using functional magnetic resonance imaging [124,125] or positron emission tomography [126], provided evidence that the anterior cingulate [124] and prefrontal cortex [125,126] are dysfunctional when performing response inhibition and working memory tasks.

There is some limited evidence from studies of children with ADHD that executive dysfunctions associated with ADHD are correlated with brain volume abnormalities. Poorer performance on sustained attention tasks was related to smaller volume of the right hemispheric white matter [123]. Castellanos et al [127] found that full-scale IQ score correlated significantly with total brain volume and with left and right prefrontal regions. Using the same sample, researchers found in a different report that full-scale IQ correlated with cerebellar volumes in ADHD [128]. The area of the rostral body of the corpus callosum was correlated significantly with scores on the impulsivity/hyperactivity scale of the Conners questionnaire [129]. These studies were conducted on boys with ADHD. The only study of girls demonstrated that the pallidum, caudate, and prefrontal brain volumes correlated significantly with ratings of ADHD severity and cognitive performance [130]. In a larger sample, combining boys and girls with ADHD, Castellanos and colleagues [31], found that frontal and temporal gray matter, and caudate and cerebellar volumes, were significantly and negatively correlated with ratings of symptom severity and attentional problems. In addition, WAIS-III vocabulary scores were positively correlated with all anatomic volumes. The extant data, while limited, suggest that impairment on neuropsychological measures of executive dysfunction are associated with abnormal brain structures in ADHD.

Future directions for research

Although there is growing information that identifies neuropsychological abnormalities in ADHD in childhood through adulthood, many questions remain. First, there is still relatively little systematic neuropsychological information on ADHD throughout life, particularly in teenagers and in
adults over the age of 60. Second, most of the research is cross-sectional. It will be very important to evaluate a child sample longitudinally to determine whether the neuropsychological abnormalities change throughout life. Third, combining neuropsychological, structural, and functional MRI measures will allow an evaluation of structure–function relationships in ADHD. Fourth, there is a need for studies to study the link between the increasing evidence of genetic anomalies in ADHD with measures of brain dysfunction. Although it is premature to identify an association between gene variants and brain abnormalities in ADHD, the authors believe that when ADHD susceptibility genes have been discovered and confirmed, DNA-imaging resources will provide a useful means of testing hypotheses about gene–brain associations.

Additional issues remain important. An important issue in evaluating the significance of neuropsychological deficits in ADHD is whether they are specific to the disorder. Given the emerging pathophysiology of the disorder, involving a widely distributed neural network including prefrontal cortex, anterior cingulate, caudate and possibly other basal ganglia structures, components of the corpus callosum, and the cerebellum [131], it is possible that the disorder would overlap phenotypically with other disorders in adulthood (eg, mood disorders) that have dysfunctions in some of those regions. Although some measures have been shown to be specific in childhood comparisons with other neurodevelopmental disorders [59], it has not been shown that the overall profile of neuropsychological functioning is distinct from other disorders.

Another important theoretical question is how best to explain the clinical and neuropsychological picture associated with ADHD. As noted earlier, a disturbance of attention and executive functions has been the dominant model for explaining ADHD over the past 20 to 30 years. This model has received only partial support [132], however. Although there are substantial group data supporting this model, a substantial proportion of children and adults with ADHD do not show abnormalities on neuropsychological tests [61]. Sergeant et al [132] recently reviewed the strengths and weaknesses of what they consider to be the five models of ADHD. These include: executive function model, the delay–aversion model, the behavioral–inhibition/activation model, the inhibition model, and the cognitive–energetic model. The field will be advanced by integrating these models into a broad research agenda to find the best explanatory power for understanding ADHD.

Clinical understanding of the neuropsychology of ADHD in adults needs to be taken into account to provide a greater opportunity for improved and more integrated treatment approaches. For example, an increased knowledge of both cognitive and affective difficulties in ADHD will inform treatment providers of ways to incorporate complementary psychopharmacological or psychosocial interventions. It also will direct the development of better assessment protocols that might provide a greater rate of sensitivity and specificity in diagnosing ADHD. Moreover, because ADHD is known to be
a heterogeneous disorder with substantial psychiatric and cognitive comorbidity, and because considerable controversy has existed about the nature and validity of ADHD, this article will aid clinicians in developing a better framework for understanding their patients. This greater knowledge of the neuropsychology of ADHD is necessary to help clarify the neurodevelopmental evolution of the disorder, treatment response, and the meaning of the disorder to patients, families, and treating clinicians.

Acknowledgments

This work was supported by grants from NIMH (MH62152) and the March of Dimes Foundation to Larry J. Seidman, PhD, and by grants from the National Institute of Mental Health (Scientist Development Award) to Alysa Doyle, PhD.

References


