

# A Review of Adult ADHD: A Neuropsychological and Neuroimaging Perspective

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## ABSTRACT

*Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder which effects an estimated 3% to 5% of children. Despite estimates that ADHD persists in 30% to 70% of adults having had the disorder in childhood, ADHD in adulthood remains controversial. This report summarizes current thinking in the diagnosis and etiology of adult ADHD. Most theories posit that ADHD is related to anomalies in frontal lobe function and dopaminergic transmission. However, there is debate as to whether ADHD is a unitary disorder with different manifestations, a syndrome, or multiple disorders. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, classifies ADHD into inattention, hyperactivity-impulsivity, and combined subtypes. Although problems with cognition are core ADHD symptoms, self reporting has not been a reliable predictor of neuropsychological test performance. Nevertheless, we suggest that a performance-based diagnosis, including empirically derived, age-sensitive neuropsychological tests, provides the best hope of dissociating ADHD from psychiatric disorders with similar symptoms. We also describe the promise of new neuroimaging technologies, such as functional magnetic resonance imaging, in elucidating the pathophysiology of ADHD and similar psychiatric disorders.*

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## INTRODUCTION

Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder that was once thought to affect only children. However, recent evidence suggests that ADHD often continues into adulthood. Estimates suggest that some form of the disorder persists in as many as 30% to 70% of those having the disorder in childhood, or 1% to 2% of the adult population.<sup>1-4</sup> Still, the diagnosis of ADHD in adults remains controversial. Much of the controversy stems from the lack of specificity of ADHD symptoms, particularly inattention, since problems with attention are present in many psychiatric and physical disorders. Although

acquired brain injury can result in syndromes of cognitive and behavioral problems similar to ADHD, there is no evidence for ADHD onset in adulthood. Thus, by definition, adult ADHD is the continuation of the childhood disorder. It is necessary to diagnose childhood ADHD retrospectively, when no diagnosis has been made previously. This often entails the recollection of distant childhood memories, which may not be accurate. Lastly, while the construct of attention is generally agreed to be central to cognition, it encompasses several dimensions and is difficult to measure directly. The purpose of this article is to review the current diagnostic criteria for ADHD, examine the evidence of its neurological basis, and discuss the role of neuropsychological (NP) assessment and recent advances in neuroimaging as part of a normative-based diagnostic approach. Although the focus for this review is adult ADHD, much of the ADHD literature describes children. Consequently, we sometimes refer to the child ADHD literature as a way of providing context for the adult studies.

## DEFINITIONS AND THEORIES OF ADHD

Barkley<sup>5</sup> describes the primary characteristics of ADHD as inattention, impulsiveness, and hyperactivity. Inattention is defined in terms of difficulty persisting during a task, although other theorists<sup>6</sup> have included being easily distracted in this category. Impulsivity is described as a deficiency in inhibiting an inappropriate response, whereas hyperactivity refers to an inappropriate level of activity for a particular situation. Historically, hyperactivity has been viewed as central to the disorder. Recently, however, inattention and hyperactivity have been accepted as distinct subtypes, with only a subgroup of patients manifesting both an attention deficit and hyperactive/impulsive features.

Theories about the core nature of the disorder have evolved from the belief that the central deficit was Hyperactivity. Then, theories shifted to inattention as the central deficit. Currently, theories have focused on deficits in cognitive control mechanisms that mediate attention and

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executive functions.<sup>7</sup> Barkley<sup>8</sup> has proposed that behavioral disinhibition is the central cognitive deficit in ADHD. Behavioral disinhibition is defined as the failure to inhibit a prepotent response, stop an ongoing response, or maintain a response in the presence of distraction or interference. This core deficit sets the stage for other disrupted cognitive abilities. However, this theory primarily applies to the hyperactive/impulsive form of ADHD. To explain the full range of deficits seen in ADHD, including deficits in initiating and sustaining executive functions, others have postulated that behavioral disinhibition alone is inadequate.<sup>8-10</sup> They have proposed deficits in effort, arousal, activation, or various executive functions.

### DIAGNOSIS OF ADHD

Like many psychiatric disorders, ADHD is defined by behavioral symptoms, with qualifiers stipulating duration and exclusionary criteria. The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*,<sup>11</sup> criteria lists the symptoms of inattention and hyperactivity-impulsivity separately (Table 1). This allows the diagnosis for each subtype to be made independently. At least some symptoms within each category need to have been present before 7 years of age. Impairment must be present in two or more situations, and be clinically significant in social, academic, or occupational functioning. Lastly, the symptoms must not occur exclusively as part of another recognized psychiatric disorder and cannot be better accounted for by another mental disorder.

Epidemiological research shows that the Combined subtype is the most common. This is followed by predominantly inattentive ADHD.<sup>12</sup> This subtyping distinction has recently gained empirical support in research with children,<sup>13</sup> but has yet to be validated in adults. Because it makes many clinicians question the validity of the diagnosis in patients without hyperactivity-impulsivity, some investigators have argued that any link between inattention and the overt behavioral symptoms of the disorder is problematic. Instead, they suggest that attention-deficit and hyperactive-impulsive subtypes represent qualitatively distinct disorders. Thus, there is a continuing debate as to whether ADHD is a unitary disorder or a collection of similarly appearing disorders with different neurobiological substrates.<sup>14</sup>

The criteria that symptoms must not occur exclusively as part of another recognized psychiatric disorder or cannot be better accounted for by another mental disorder can make the diagnosis difficult. This is particularly true for the inattention subtype. ADHD can exist together with other psychiatric diagnoses, but this requires that some symptoms of the comorbid disorder be clinically distinct. Taylor and Miller<sup>15</sup> evaluated 489 consecutive adults self referred for ADHD. Less than half (211) of them met the *DSM-IV* criteria for ADHD. Only 68 subjects met the criteria for ADHD without the presence of a comorbid psychiatric diagnosis. The most common comorbid diagnoses were mood disorders, anxiety, substance abuse, or some combination of these. Patients who

failed to meet the criteria for ADHD typically met the criteria for one or more of these other diagnoses.

Similar studies of self-referred patients also found that about half meet the *DSM-IV* criteria for ADHD,<sup>16</sup> while other investigators report a similarly high percentage of comorbid diagnoses in both referred and self-referred ADHD adults.<sup>17</sup> Therefore, one major obstacle to overcome in order to properly diagnose ADHD is an accurate discrimination of ADHD from other psychiatric conditions—either those that have similar symptoms or are frequently comorbid. Perhaps the only currently valid approach is confirming the cognitive dysfunction that accompanies ADHD using NP testing. However, as will be reviewed later in the article, this approach is fraught with problems of test sensitivity and specificity to ADHD versus other psychiatric conditions that involve attention and behavioral control impairment.

The *DSM-IV* criteria for diagnosing ADHD was intended for use in individuals 16 years of age or younger. To diagnose ADHD in adulthood, it first needs to be established

**TABLE 1. DSM-IV CHECKLIST**

#### ATTENTION-DEFICIT/HYPERACTIVITY DISORDER

1. Either of the following groups:
  - A. At least six of the following symptoms of inattention, persisting for at least six months to a degree that is maladaptive and inconsistent with development level:
    - a. Frequent failure to give close attention to details, or making careless mistakes.
    - b. Frequent difficulty in sustaining attention.
    - c. Frequent failure to listen when spoken to directly.
    - d. Frequent failure to follow through on instructions and failure to finish work.
    - e. Difficulty organizing tasks and activities.
    - f. Avoidance of, dislike of, and reluctance to engage in tasks that require sustained mental effort.
    - g. Frequent loss of items necessary for tasks or activities.
    - h. Easy distraction by irrelevant stimuli.
    - i. Forgetfulness in daily activities.
  - B. At least six of the following symptoms of hyperactivity-impulsivity, persisting for at least six months to a degree that is maladaptive and inconsistent with developmental level:
    - a. fidgeting with hands or feet, or squirming in seat.
    - b. Frequent wandering from seat in classroom or similar situations.
    - c. Frequent running about or climbing excessively in situations in which it is inappropriate.
    - d. Frequent difficulty playing or engaging in leisure activities quietly.
    - e. Frequent "on the go" activity or acting as if "driven by a motor."
    - f. Frequent excessive talking.
    - g. Frequent blurting out of answers before questions have been completed.
    - h. Frequent difficulty awaiting turn.
    - i. Frequent interrupting of or intruding on others.
2. The presence of some symptoms before the age of 7.
3. Impairment from the symptoms in at least two settings.
4. Significant impairment.

DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*  
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that ADHD was present in childhood. This determination is typically based on retrospective reports. Faraone and colleagues<sup>2</sup> reviewed the research literature in order to examine the validity of the diagnosis in adult ADHD. Although hyperactivity may decrease with age, inattention, impulsivity, and hyperactivity appear to be the core features of the disorder in both children and adults. ADHD adults, like children, are more prone to significant psychosocial problems. For adults, these include fewer years of education, lower socioeconomic status, more frequent job changes, and a higher incidence of marital problems. ADHD adults also have a higher rate of comorbid psychiatric problems, most often substance abuse. Like children, it is also expected that adults with ADHD will have more comorbid learning disorders than nonaffected adults.<sup>17</sup>

### **TREATMENT FOR ADHD**

The use of amphetamine drugs to treat hyperactive children was first reported in 1937,<sup>18</sup> and psychostimulant medications continue to be the treatment of choice for both children and adults.<sup>5</sup> These medications are structurally similar to brain catecholamines and are thought to mimic the actions of these neurotransmitters.<sup>19</sup> Currently, methylphenidate, dextroamphetamine, and magnesium pemoline are the most commonly prescribed drugs in the treatment of ADHD. Spencer and colleagues<sup>20</sup> reviewed 150 controlled studies of 5,768 ADHD children, adolescents and adults, and estimated drug efficacy in 70% of the participants for reducing core symptoms. Although alternatives to pharmacologic treatment have been studied, these have not shown the same efficacy as stimulants. Furthermore, a recent controlled study found no clear additive effect of behavioral interventions to the efficacy of stimulant treatment.<sup>21</sup> However, more research is needed to establish whether combining psychotherapy approaches with psychostimulant drugs will increase treatment efficacy. A combination of treatment approaches may improve outcome when ADHD occurs with comorbid conditions.

### **GENETIC RISK FACTORS**

Epidemiological studies show that there is a greater likelihood that ADHD adults will have ADHD children. Twin studies lend support to a genetic vulnerability hypothesis. Monozygotic twins show higher rates of concordance for an ADHD diagnosis and symptomatology than dizygotic twins, who show higher rates than expected in the normal population.<sup>22-24</sup> There also is evidence to suggest that both ADHD subtypes (predominantly hyperactive-impulsive, predominantly inattentive) exist as continuous traits in the general population,<sup>25</sup> with diagnoses assigned to persons at the extremes of each distribution. Although some studies have examined the interaction of genetic and environmental factors, such as socioeconomic status or parenting, these data typically suggest that environment is less important in determining ADHD than genetic vulnerability.<sup>26,22</sup> Nevertheless, not all studies are

consistent. More evidence is needed before definite conclusions can be made.

The enhanced response to psychostimulants in ADHD has led molecular genetic studies to focus on those genes involved with dopamine (DA) neurotransmission. The involvement of several DA genes have been identified as possible factors underlying ADHD behaviors, including the *D2* receptor gene, the DA transporter gene (*DAT*), and the *D4* DA receptor gene.<sup>28</sup> A variation of the DA transporter gene (*DAT1*) common to families with ADHD<sup>27-29</sup> has also been found in ADHD adults. These studies suggest that DA abnormality in the ADHD brain function may represent one vulnerability to the disorder in children and adults.

### **BRAIN CORRELATES OF ADHD**

Although the pathophysiology of ADHD remains unknown, several lines of evidence point to anomalies in frontal lobe function. Measurements of brain regions based on magnetic resonance imaging have shown anatomical differences between brain structures in patients with ADHD compared with nonaffected controls. In ADHD, the prefrontal cortex is reduced in size, particularly in the right hemisphere.<sup>30,31</sup> Similar decreased volumes have been described for the basal ganglia, but these results have varied across studies with respect to laterality. Most studies find that ADHD individuals have smaller caudate head and globus pallidus volumes compared with normal controls, but the results vary as to which hemisphere is most affected.<sup>30-34</sup> White matter tract volumes have also been found to be reduced in right anterior brain regions (ie, prefrontal cortex) in ADHD<sup>31</sup> and in the corpus callosum.<sup>35-37</sup> Other studies find significantly smaller cerebellum volume in ADHD boys and girls.<sup>30,38</sup>

Electrophysiological studies of event-related potentials (ERP) in ADHD children have found reduced amplitude of an evoked brain surface electrical component thought to measure attention allocation and memory cognitive processes.<sup>39-43</sup> ERP are time-locked to the stimulus and represent the brain's response to stimulus as well as cognitive processes engaged by a specific target stimulus that are defined by the context of the task. The ERP findings were among the first to link abnormal brain activity directly to specific types of cognitive functions known to be impaired in ADHD persons.

Zametkin and colleagues<sup>44</sup> pioneered the use of positron emission tomography to study ADHD. They demonstrated reduced glucose metabolism in anterior brain areas during the performance of an executive function task in unmedicated ADHD adults relative to controls. Other investigators failed to replicate this finding in adolescents<sup>45</sup>; however, Schweiter and colleagues<sup>46</sup> recently reported similar reductions in anterior brain activity in a study of ADHD adults.

To date, there have been only three published studies examining brain activity in ADHD that use high spatial resolution of functional magnetic resonance imaging (fMRI). fMRI produces detailed measurement of brain activity

through the use of blood-oxygen level change that occurs naturally in the brain following neural activity. Pursuing the idea that response inhibition is an important aspect of the cognitive deficit in hyperactive-impulsive ADHD, Rubia and colleagues<sup>47</sup> reported less activation on a motor control “stop task” in the right superior-lateral prefrontal cortex, right inferior prefrontal cortex, and left caudate nucleus in unmedicated ADHD adolescent boys compared with controls. Another study reported similar findings were obtained for ADHD children.<sup>48</sup> Finally, Bush and colleagues<sup>49</sup> failed to find the normal activation of the anterior cingulate in unmedicated ADHD adults during a cognitive interference test, which they interpret as suggesting deficits in stimulus selection or response selection.

The efficacy of psychostimulant medications in attenuating ADHD symptoms has also led to studies of DA and other catecholamine pathways in the basal forebrain. Ernst and colleagues<sup>50</sup> showed diminished left and medial prefrontal cortex dopaminergic neurotransmission. Other studies have found that psychostimulants appear to normalize electrophysiological abnormalities. In those studies, medicated ADHD subjects showed comparable ERP signal amplitudes to normal controls,<sup>51-53</sup> and altered activity in basal ganglia.<sup>48</sup> This and other frontal brain areas are widely known to involve DA in extracellular signaling.<sup>54</sup> Psychostimulant medications like methylphenidate have been shown to increase extracellular DA.<sup>55</sup> Differences in DA receptor density in individuals with ADHD, particularly in young boys, may help to explain the gender prevalence of the disorder.<sup>56</sup> These studies and others have led to the suggestions that catecholamine dysregulation may be important to ADHD pathophysiology.<sup>57</sup>

**NEUROPSYCHOLOGICAL ASSESSMENT OF ADHD**

Neurobiological theories of ADHD propose that there are dysfunctions in ADHD patients’ brain areas that underlie the cognitive abilities of attention and executive function. Attention is a multidimensional construct that has been redefined over the years to include many specific cognitive functions, including general arousal, selective attention (inhibiting responses to irrelevant stimuli), sustained attention (vigilance), and shifting attentional focus.<sup>58,59</sup> Related to these abilities are what neuropsychologists refer to as executive functions. Executive functions are defined as supervisory abilities that control and direct the processes of attention and other cognitive abilities in the pursuit of goal-directed behavior.<sup>60</sup> These abilities work closely together, and are thought to have their primary neurological substrates in the same general brain areas (ie, prefrontal cortex and its connections with other brain structures).

Attention and executive function are multifaceted constructs and numerous tests have been developed to measure these abilities both clinically and experimentally. These tests are called NP assessments. NP studies in children with ADHD have consistently shown lower scores or clinically significant deficits on a variety of different tests. These

studies show lower intelligent quotient (IQ) scores and poorer performance on measures of executive functioning, vigilance, and memory. Even ADHD children with above average IQ scores do more poorly than expected on tests of executive functioning.<sup>61</sup> Given that executive functioning is presumed to be mediated by frontal brain regions, these findings provide additional support for frontal lobe dysfunction in ADHD. Attempts to demonstrate similar NP deficits in ADHD adults have yielded mixed results.

Although a few studies comparing ADHD adults to comparable controls show lower IQ scores, many do not. When overall IQ differences and difference in IQ subtest scores have been reported, the differences tend to be small with both group means being in the average range. However, a number of studies have demonstrated that patients with adult ADHD are more likely to be impaired on specific measures of attention, executive functioning, and memory (Table 2). Holdnack and colleagues<sup>62</sup> showed small but significant differences in IQ estimates between ADHD adults and age- and education-matched controls based on the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Information, Digit Span, Vocabulary, and Digit Symbol subtests. No one WAIS-R subtest differentiated the groups. However, they did find differences on measures of reaction time on a visual continuous performance test and memory for a word list from the California Verbal Learning Test. Although ADHD adults performed more slowly their accuracy was the same. Seidman and colleagues<sup>63</sup> found adults with ADHD performed more poorly on tests requiring vigilance, arithmetic, and semantic

**TABLE 2. NEUROPSYCHOLOGICAL TESTS SHOWN SENSITIVE TO ADULT ADHD**

Test	Study
California Verbal Learning Test	Seidman et al <sup>55</sup> Jenkins et al <sup>58</sup> Riordan et al <sup>16</sup> Holdnack et al <sup>54</sup>
Continuous Performance Tests*	Epstein et al <sup>59</sup> Seidman et al <sup>55</sup> Riordan et al <sup>16</sup> Holdnack et al <sup>54</sup>
Stroop Color and Word Tests*	Riordan et al <sup>16</sup> Corbett and Stanczak <sup>56</sup>
Wechsler Adult Intelligence Scale-Revised*	Biederman et al <sup>17</sup> Taylor and Miller <sup>15</sup>
Paced Auditory Serial Addition Test	Jenkins et al <sup>58</sup>
Controlled Oral Word Association Test	Jenkins et al <sup>58</sup>
Test of Auditory Discrimination	Corbett and Stanczak <sup>56</sup>
Wisconsin Card Sorting Test*	Taylor and Miller <sup>15</sup>

\*Other investigators have not found these tests to be sensitive to ADHD. ADHD=attention-deficit/hyperactivity disorder. Kaplan RF, Stevens MC. *CNS Spectrums*. Vol 7, No 5. 2002.

encoding, but similar to controls on IQ tests, tests of academic achievement, and other measures of executive function. These differences could not be explained by either learning disabilities, gender, or comorbid psychopathology. However, ADHD adults in both of the aforementioned studies performed similar to controls on some tests requiring executive functioning (ie, Trail Making Test, Stroop Color and Word Tests, and Wisconsin Card Sorting Test, that are typically impaired in ADHD children. One study did show adults with ADHD to be impaired relative to controls on the Stroop Color subtest, but not the Stroop Interference Test,<sup>64</sup> a measure in which ADHD children typically perform more poorly than non-ADHD children.<sup>65</sup> Thus, while ADHD children and adults have deficits in similar cognitive domains, these findings suggest that cognitive deficits may be attenuated as a function of aging.

Some NP measures have been shown to discriminate patients with ADHD from those with other psychiatric disorders.<sup>15</sup> The indices which best discriminate attentional problems in ADHD from those observed in other psychiatric conditions were failure to maintain set on the Wisconsin Card Sorting Test and WAIS-R Block Design score. ADHD adults with and without comorbid depression showed similar deficits in verbal memory, motor and processing speed, visual scanning, and auditory and visual distractibility.<sup>16</sup> To our knowledge, this is the only study concentrating on the NP effects of methylphenidate treatment in adults, with both groups benefitting from treatment. A comparison of adults reporting difficulties with attention, with and without a history of childhood ADHD, revealed lower scores on measures of sustained auditory attention, delayed recall of a word list, and word fluency in those adults who reported childhood symptoms.<sup>66</sup> Since diagnosis of adult ADHD is often based on self-reported cognitive symptoms rather than test scores, the previous study's inability to show a strong relationship between subjective complaints of attention problems and performances on a NP test (NPT) of attention is noteworthy. When adult ADHD patients were compared with anxiety-disordered patients and controls on a continuous performance test measure of response inhibition, the ADHD group exhibited deficits not shown in the other groups.<sup>67</sup> However, this pattern was not observed on two other measures of response inhibition, one of which had been shown to successfully discriminate ADHD in children.<sup>10</sup> Thus, while deficits in response inhibition are considered central to ADHD, tests sensitive to measuring such deficits in children may not be equally sensitive in adults.

In summary, adults meeting the *DSM-IV* criteria for ADHD, with or without a comorbid psychiatric diagnosis, perform more poorly than non-ADHD adults on some tests requiring sustained attention, executive functioning, and memory. Although the ADHD-related cognitive deficits in adults tend to be in the same cognitive domains as those reported in children, they appear less pervasive and severe. It is possible that brain maturation and the development of compensatory strategies reduce the severity of childhood

deficits, but this hypothesis needs to be investigated in prospective studies. Some NPT measures seem to be able to differentiate ADHD from other psychiatric disorders, which have attentional symptoms. Regardless, these studies have been few and are limited in scope. Lastly, self-reported symptoms of inattention as unreliable indicators of actual performance on objective testing is an important contribution from NP studies in adults with ADHD.

#### **DIRECTIONS FOR FUTURE NEUROIMAGING RESEARCH**

In this article, we present some preliminary findings using fMRI data that highlights differences in the anterior brain, including networks of prefrontal cortex and limbic system areas in ADHD and conduct disorder (CD), two disorders with a high incidence of comorbidity. Using a visual sustained attention task, we have collected data representing areas of the brain that show changes in blood-oxygenation during the detection of target stimuli representing increased brain activity. During the task, subjects are shown single-letter stimuli flashed on a screen. The letters "T," "C," and "X" correspond to frequent standard, rare distracter, and rare target stimuli, respectively. Subjects are instructed to respond only to the rare targets. This rare target paradigm has been shown to evoke a robust brain response, when analyzed using event-related fMRI methods.<sup>68</sup>

Data for four adult male subjects between 18 and 24 years of age are shown in Figures 1 and 2. All subjects provided written informed consent, using procedures approved by the University of Connecticut's Institutional Review Board. Subjects were all unmedicated and showed similar behavioral performance on the task (statistical analyses for four subjects in four groups were not possible). In normal controls, evoked brain activity in response to rare visual target detection has been shown to activate areas of the anterior insulae bilaterally, as can be seen in our control subject. In comparison, the ADHD subject shows additional



**FIGURE 1.** Differences among single subjects to rare targets on the three stimulus visual oddball task. Subjects are variously diagnosed with ADHD, comorbid ADHD/CD or CD alone. Areas of red-yellow show statistically significant activation effects between  $P < .05$  and  $P < .001$ . The left side of the image is the left side of the brain.

ADHD=attention-deficit/hyperactivity disorder; CD=conduct disorders.

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areas of activation in the prefrontal cortex, with less organized insulae activity. An adult subject who meets *DSM-IV* criteria for both ADHD and CD shows relatively typical bilateral insulae activity, but also shows extra areas of visual cortex activation. Finally, a subject diagnosed with CD who does not meet criteria for ADHD shows a lack of insulae response to rare targets. Instead, he shows activation in areas of the medial frontal cortex.

Changes in brain activation occurring within each experimental run were examined using multiple regression-to-model, time-dependent effects. In Figure 2, data for the control and CD subjects show no significant changes in areas of the medial frontal cortex, in response to successive rare targets. The ADHD subject's activity, in response to targets, progressively increased towards the end of the run in areas of the occipital cortex. The CD/ADHD subject showed a large area of activity change from the beginning to the end of the run in one anterior area. Findings for this CD/ADHD subject also included decreasing activity in another part of the medial prefrontal cortex.

These data are very preliminary. No conclusions can be drawn regarding how brain function relates to diagnoses based on single-subject data alone. However, these data are presented to emphasize that there may be empirical differences in brain activity underlying cognitive task performance that are related to symptom profile. Differences and similarities in brain activity patterns among clinical groups has the potential to help researchers better understand the pathophysiology of symptom expression.

### CONCLUSION

Converging lines of behavioral and biological evidence provide support that ADHD can persist into adulthood.<sup>2</sup> What is less clear is the nature of this disorder. Whether ADHD is one disorder with different manifestations, a syndrome, or multiple disorders is still being debated.<sup>5</sup> The *DSM-IV* uses a criterion-based approach to classify three subtypes of ADHD: inattention, hyperactivity-impulsivity, or a combination of the two. Most ADHD adults are diagnosed with the inattention type; however, most ADHD adults carry at least one additional psychiatric diagnosis. Whether an individual meets criteria for any of these diagnoses is most often determined by a clinical interview and symptom checklists. In research studies that strictly adhere to the *DSM-IV* guidelines, only about half the adults self-referred for ADHD meet the criteria. Furthermore, these studies have shown a low correspondence between the perception of cognitive dysfunction (self-reported symptoms) and performance on NPTs of attention and memory.<sup>66,69</sup>

Discrepancies between the self reporting of cognitive dysfunction and objective evidence of impairment are not unique to ADHD. Similar findings have been reported for Lyme disease and other central nervous system disorders.<sup>70-72</sup> In some of these studies, self-reports of cognitive impairment were more related to symptoms of depression than to

actual NPT performance.<sup>71,72</sup> Discrepancies between the perception of cognitive dysfunction and actual test performances provides one explanation for the many NPTs not sensitive enough to the cognitive deficits in ADHD. However, equally important is that most tests in the standard NPT battery were designed to assess more severe deficits in other clinical populations. The cognitive deficits in ADHD adults tend to be relatively specific and subtle compared to deficits in other neurocognitive disorders, such as dementia or head injury. It is therefore not surprising that ADHD patients may perform normally on many NPTs, but more poorly on specific tests like the California Verbal Learning Test and certain vigilance tasks. This makes it imperative for researchers and clinicians alike to use those few measures shown to discriminate the dimensions of ADHD from normal cognition, and to develop new measures more sensitive to the deficits in adults.

Whereas some NPTs may provide the sensitivity to discriminate cognitive deficits from perceived cognitive symptoms and determine the severity of impairment, they may lack the specificity to differentiate ADHD from other psychiatric disorders with similar symptoms. For example, memory for word lists performance and vigilance tasks have been shown to discriminate ADHD adults from controls, but not adults with ADHD and depression.<sup>16</sup> This limits the utility of testing alone in understanding the neural substrate of these disorders. Much of the available evidence points to dysfunction in the anterior brain structures as central to ADHD. Neural networks of the anterior brain comprise the primary neural substrates for mediation of attention and executive functions.<sup>60</sup> The prefrontal cortex is believed to be specifically involved with integrating, executing, and regulating planned behaviors. Damage to this region has long been recognized to result in a syndrome of impulsive and disinhibited behavior.<sup>73,74</sup> Networks of anterior brain areas including both cortical and subcortical structures working in conjunction with the posterior parietal cortex are thought to



**FIGURE 2.** Differences among single subjects to successive rare targets on the three stimulus visual oddball task. Subjects are variously diagnosed with ADHD, comorbid ADHD/CD or CD alone. Areas of red-yellow show statistically significant activation effects between  $P < .05$  and  $P < .001$ . Blue-green areas show deactivation effects within the same statistical threshold. The left side of the image is the left side of the brain.

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mediate selective and sustained attention.<sup>75,76</sup> Although ADHD has been linked to structural and functional anomalies in these brain regions in ADHD, these brain regions are implicated in numerous other neuropsychiatric disorders, such as depression, obsessive-compulsive disorder, mania, and CD—all of which may involve inattention and impaired executive functioning.<sup>54,77-81</sup> Furthermore, many of these disorders are comorbid with ADHD.

Discrepancies between symptom checklists and objective evidence of impairment suggest that there are inherent problems in diagnosing ADHD on the basis of self-report. There is considerable evidence suggesting that the traits that define ADHD exist on a continuum in the general population, rather than as distinct categories,<sup>5</sup> thus lending itself to a performance-based approach. Faraone and colleagues<sup>2</sup> have proposed that the assessment of ADHD be considered like the construct of intelligence using different test batteries to assess different age groups. From this perspective, NPTs that target age-appropriate cognitive deficits would be used to establish the diagnosis, such as those recommended in diagnosing Alzheimer's disease.<sup>82</sup> Similarly, we suggest that new neuroimaging technologies (ie, fMRI) may prove to be promising tools in defining brain anomalies underlying ADHD, when used in the context of normatively-based standards. The aforementioned fMRI case studies were not presented as definitive maps of the pathophysiology of these disorders. Rather, we intended to provide examples of how adults who meet the *DSM-IV* criteria for one or more disorders can differ with respect to anomalies in brain physiology compared to normal controls. We are hopeful that future research will reveal systematic differences between normal controls and patient groups that will help clarify the neurobiological theories of ADHD and other psychiatric disorders. **CNS**

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