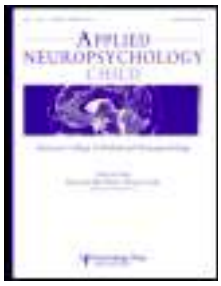

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Neuropsychological Assessment and The Paradox of ADHD

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Neuropsychological Assessment and The Paradox of ADHD

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Attention-deficit hyperactivity disorder (ADHD) is a behaviorally defined diagnosis. Despite the fact that neuropsychological tests have typically been used successfully to investigate the functional neuroanatomy of ADHD in neuroimaging research paradigms, these tests have been of surprisingly limited utility in the clinical diagnosis of the disorder. This article examines this paradox by reviewing the characteristics of the *Diagnostic and Statistical Manual of Mental Disorders* diagnosis versus neuropsychological nomenclature, by reviewing the assumptions about etiologies for ADHD and by demonstrating how an emerging dimensional approach to diagnostic assessment can be combined with large-scale brain network studies to enhance the role of neuropsychological evaluation within clinical settings. This selective topical review is intended to arm practicing neuropsychologists with knowledge of new ideas, theories, and methods related to the causes of ADHD to prepare them for meaningful advances in understanding and assessing the disorder that are possible during the next decade.

Key words: ADHD brain networks, connectivity profiles, neuropsychological testing

NEUROPSYCHOLOGY AND ADHD—THE DIAGNOSTIC PROBLEM

Attention-deficit hyperactivity disorder (ADHD) is a behaviorally defined diagnosis characterized by inappropriate levels of inattentiveness, impulsivity, and hyperactivity. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) lists 18 possible behavioral symptoms for diagnosing the condition (American Psychiatric Association, 2000); there are 9 observations that concern inattention, 6 symptoms concerning hyperactivity, and 3 behavioral symptoms pertaining to impulsivity. This categorical system allows for the classification of three behavioral subtypes of ADHD: The Combined subtype is believed to occur most frequently; the Inattentive subtype is presumably the second most frequent, and it has been proposed that this subtype may be a distinct entity (Diamond, 2005); the Predominantly Hyperactive subtype presumably occurs relatively rarely (Bush, 2010). However, children who present with a diagnosis of ADHD, regardless of subtype, remain a highly heterogeneous population, in part because these 18 symptoms can be "combined" in a variety of ways. In addition, certain ADHD symptoms are not unique to that disorder and can be observed in a variety of other DSM diagnostic conditions. Symptoms in various DSM categories can overlap to such a degree that differential diagnosis becomes extremely problematic. Indeed, many studies of ADHD are by necessity conducted in clinic-referred samples, where comorbidity is the rule and not the exception (Pritchard, Nigro, Jacobson, & Mahone, 2012). In one investigation, children presenting for clinical evaluation simultaneously

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met full DSM-Fourth Edition, Text Revision (DSM-IV) criteria for one to five diagnoses (Yaryura-Tobias, Rabinowitz, & Neziroglu, 2003). In these cases, the primary role of psychological assessment is to identify comorbid disorders. Although diagnostic "checklists" that list the 18 DSM symptoms are typically used to make the diagnosis, it has been demonstrated that this methodology for diagnosing ADHD is unstable and capricious (Valo & Tannock, 2010). It is influenced by the subjective perspectives of the informants, by the informants who are chosen to provide the ratings, by instrumentation or the type of rating scale methodology administered, and by the manner in which information from multiple sources is aggregated.

Although clinical neuropsychology can be argued to have laid important theoretical groundwork for much of current neuroscientific inquiry into ADHD, as a field, it currently struggles in making decisive contributions to the actual diagnosis of the disorder. Neuropsychology is a field that was built upon the study of brain–behavior relationships. Perhaps in part because of this foundation, the field relies upon a descriptive nomenclature for describing cognitive ability and impairment that does not intersect smoothly—or at times at all—with behaviorally defined disorders described by the DSM observational methodology (Lezak & Loring, 2004). For instance, two widely cited reviews of neuropsychological studies of ADHD found that although impairment on various "executive" cognitive tests was conclusively linked to the disorder, impairment on any single test, or even multiple tests, has not yet been proven to reliably differentiate any given person with ADHD from a person who does not have ADHD (Nigg, Willcutt, Doyle, & Sonuga-Barke, 2005; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Although previous studies have tried to correlate the DSM diagnosis with neuropsychological test findings in ADHD, the results have been anything but convincing (Barkley, 2006).

There is no specific neuropsychological test profile for ADHD, other than identifying the frequent co-occurrence of executive dysfunction (Biederman et al., 2004; Brown, Reichel, & Quinlan, 2009). Similarly, neuropsychological test results have not been specifically useful in identifying any of the subtypes of ADHD as defined by the DSM (Doyle, Biederman, Seidman, Weber, & Faraone, 2000; Hinshaw, Carte, Sami, Treuting, & Zupan, 2002). This lack of any specific, practical, clinically useful relationship between the common broad neuropsychological test battery and ADHD diagnosis can be difficult to understand because a large portion of neurobiological research of ADHD is based upon observations on neuropsychological tests of response inhibition, attention, and so forth. Moreover, such research typically employs common "neuropsychological" test paradigms like continuous performance tasks, response inhibition tasks, etc., in functional neuroimaging contexts, or relates such cognitive test performance to brain structure or function measurements as a way of validating various findings of importance to the disorder. How is it, then, that neuropsychological tests fail to achieve any sort of diagnostic utility in ADHD?

Diagnostic Systems and Etiological Models

A central issue involves the mismatch between DSM and neuropsychological systems. Because the behaviorally defined DSM system is not neuroanatomically organized, it becomes difficult to "map" DSM observations on to brain networks and systems. Such neuroanatomical organization likely would facilitate the generation of more readily testable hypotheses regarding brain–behavior relationships that drive the condition using neuropsychological tasks. However, the DSM system is instead based upon a medical model of etiology. In its most general application, this traditional medical model assumes that one disease process typically has a single identifiable cause that can generate a group of symptoms, or a syndrome. Such an approach can be extremely powerful. For instance, when the study of brain–behavior relationships was in its infancy, this type of "lesion" model was useful in identifying the roles that certain brain regions play in certain cognitive functions (Lezak & Loring, 2004). Patients with lesions in specific brain regions were compared to normal control subjects in their performances on neuropsychological tests; differences in test scores and behavior were interpreted as a manifestation of how the brain behaved in the absence of that particular lesioned brain region.

However, this historic model also can be limiting because it assumes a single unitary cause for behavioral abnormality, including the generation of multiple symptoms. A classic example that comes to mind is Gerstmann's syndrome, in which the symptom complex of finger agnosia, right–left disorientation, acalculia, and agraphia was associated with lesions of the left angular gyrus (Mendoza & Foundas, 2007). However, adhering to this model limits and restricts our ability to examine other possibilities. With respect to ADHD, the limitations of this "one cause/one disorder" model for years led theorists to seek a single cognitively based dysfunction that could plausibly explain the symptoms of the disorder. This model led some researchers to conclude that "the implicit assumption of causal homogeneity and the associated empirical search for simple single deficits has shaped the research agenda in much of the [ADHD] field" (Nigg et al., 2005). This criticism underlies the recognition that ADHD itself likely is not a unitary disorder but instead is a behavioral presentation

that arises in any given individual from one (or more) different abnormalities in key neural systems. In the mid- to late-1990s, ADHD theorists began to recognize the futility of such a single-cause approach for understanding ADHD. During this time, Barkley (2006) articulated his highly influential cognitive model that specified deficits in several, albeit interrelated, cognitive functions. Others accepted the now well-recognized dysfunction within the brain's motivation/reward systems and proposed "dual pathway" neurocognitive models (Sonuga-Barke, 2003), or multiple etiology neurocognitive models (Durston, Belle, & Zeeuw, 2010; Sonuga-Barke, Bitsakou, & Thompson, 2010). The role of nervous system arousal also was implicated (Sergeant, 2000).

From nearly three decades of structural and functional neuroimaging research into ADHD, there is now overwhelming evidence that ADHD symptoms are a manifestation of abnormally functioning brain circuitry (Ashtari et al., 2005; Casey, Nigg, & Durston, 2007; Castellanos & Acosta, 2004; Castellanos & Proal, 2012; Mackie et al., 2007; Rubia, 2007; Vaidya, 2011). For instance, brain volume abnormalities are important indicators of pathophysiological processes that likely reflect disorder etiology. ADHD brain structure deficits have been found in grey- or white-matter volume (Ellison-Wright, Ellison-Wright, & Bullmore, 2008; Hutchinson, Mathias, & Banich, 2008; Seidman, Valera, & Makris, 2005; Valera, Faraone, Murray, & Seidman, 2007), cortical thickness (Klein, 2011), and more recently, in white-matter microstructure measured via diffusion tensor imaging (i.e., large white-matter tracts interconnecting major brain regions to form the brain's primary "information superhighway" connections; van Ewijk, Heslenfeld, Zwiers, Buitelaar, & Oosterlaan, 2012). As the result of such research, the field has concluded that ADHD brain volume deficits are consistently found in the cerebellum, the corpus callosum splenium, total and right cerebral volume, and right caudate (Valera et al.). Functional brain abnormalities in prefrontal-striatal-cerebellar brain regions measured are also frequently observed (Castellanos & Proal; Cubillo, Halari, Smith, Taylor, & Rubia, 2012; Durston et al., 2010; Rubia, 2011). Recently, there has been a large handful of informative, useful reviews of this complicated literature (Bush, Valera, & Seidman, 2005; Pastura, Mattos, Gasparetto, & Araujo, 2011; Vaidya, 2011). The interested reader is referred to these valuable summaries of the field for more in-depth information about any given cognitive function/neural system.

The theoretical and empirical work performed since the advent of neuroimaging typically has used neuropsychological test probes to investigate the ways these brain regions fail to function as expected when called upon to perform specific cognitive tasks theoretically linked to ADHD. The justification for these studies comes from decades of clinical and laboratory neuropsychological research that has conclusively linked ADHD deficits to problems with motor and cognitive inhibition or "cognitive control," aversion to delay (Sonuga-Barke, 2003), and more recently, mental timekeeping ability (Durston et al., 2010; Sonuga-Barke et al., 2010). Because it has also been documented that ADHD can result from presumably distinct etiologies, the pressing question these days is no longer whether we can locate a single "smoking gun" brain region in which dysfunction causes ADHD (Barkley, 2006; Swanson et al., 2007; Voeller, 2004). The diversity of cognitive dysfunction found in ADHD and the putative relationships of these various abnormalities to widely different neural systems make this largely implausible. Alternatively and more likely, ADHD in any given individual stems from dysfunction within one or more different neural mechanisms, possibly occurring as the result of several distinct etiological influences, each of which gives rise to a similar constellation of symptoms that represent phenotypic ADHD.

From the perspective of genetic underpinnings, this is best thought of as a "common disease/common variant" model of psychopathology that has gained increasing acceptance in neuroscientific research of psychiatric disorders (Lohmueller, Pearce, Pike, Lander, & Hirschhorn, 2003). Such causal hetereogeneity is ideally addressed by various neuroimaging methods because they are well suited to measure different profiles of structural and/or functional abnormality across the brain regions already implicated in ADHD. Indeed, many ADHD theorists have gravitated toward this latter model—for example, specifying different parts of the ascending mesocorticolimbic dopamine pathways for cognitive control versus delay aversion deficits in ADHD (Sonuga-Barke, 2003). Other studies have sought to characterize such pathways from the genetic level up to measurable cognitive dysfunction, linking specific genotypes (e.g., *DAT1* or other catecholamine-related genotypes) with abnormal structure (Shaw et al., 2007), or function of brain systems related to cognitive control or frontostriatal circuits in ADHD (Bedard et al., 2010; Braet et al., 2011; Brown et al., 2011), or in turn linking behavior on neuropsychological tests to those networks. Therefore, traditional neuropsychological testing approaches remain crucial for disentangling the complex relationships among the possible admixture of different types of cognitive dysfunction that might be present in any given individual with ADHD, even if they currently do not have a critical role for diagnosing ADHD in the clinical practice setting. For instance, several studies have reinforced the use of cognitive tests in differentiating ADHD-related primary impairment with cognitive control and delay aversion (Nigg et al., 2005; Solanto et al., 2001; Sonuga-Barke, Dalen, & Remington, 2003). It may prove that this

dual-pathway distinction ultimately might be found to have prognostic or treatment significance, providing a new use of cognitive tests in the clinical evaluation of ADHD.

REGIONAL FUNCTIONAL SPECIALIZATION VERSUS COGNITIVE NETWORKS

Another important recognition about cognition that has emerged from the past decade of cognitive neuroscience involves the limitation of ideas about "functional specialization." Most neuropsychologists are trained within a model that has emphasized simple brain–behavior relationships pioneered by researchers like Broca, Wernicke, Milner, and Penfield, who along with other notable clinical researchers did much to teach us that certain brain regions had demonstrable and often crucial relationships with specific cognitive functions. Functional specialization can therefore be defined as the degree of processing specificity of a given brain region for a particular cognitive ability or facet of cognitive operations (Friston, 2002; Johnson, 2005). However, no brain region functions alone, in isolation. The general architecture of the brain is characterized by cerebrocortical, cortical-basal ganglia, cerebrocerebellar, and basal ganglia-cerebellar reciprocal connectional profiles (Alexander, DeLong, & Strick, 1986; Blumenfeld, 2002; Bostan, Dum, & Strick, 2010; Schmahmann & Pandya, 1997).

For example, the local cognitive processing that occurs in relatively isolated regions of the brain for vision or visuospatial integration must somehow communicate with other brain regions to effectively implement adapative behavior. In the emerging jargon of this field, "functional integration" of distal brain regions refers to transient, dynamic, context-specific interactions that convey information via subsets of anatomical connections among a limited handful of brain regions engaged by a particular cognitive process. In recent years, there has been an important shift in cognitive neuroscience research of ADHD and numerous other psychiatric disorders away from consideration of single brain regions or even collections of brain regions into thinking about how distributed, functionally integrated neural systems might be more proximately related to symptom expression or disorder etiology (Rosazza & Minati, 2011; Sakoglu et al., 2011). This shift has also played a measurable role in emerging theories about ADHD (Konrad & Eickhoff, 2010).

Large-Scale Brain Systems and Functional Connectivity

Using magnetic resonance imaging (MRI)-measured brain anatomy and functional connectivity from 1,000 healthy adults, Yeo and colleagues (2011) recently observed the remarkable replicability of the same seven patterns of cortical connectivity within the human brain, most of which are believed to be involved in ADHD. These connectional profiles include a frontoparietal network, which is commonly engaged during effortful cognitive task performance requiring information or rules to be held in mind and guide behavior. This network consists of the dorsolateral prefrontal cortex, the anterior cingulate cortex, the anterior prefrontal cortex, the lateral cerebellum, the anterior insula, the caudate nucleus, and the inferior parietal lobe. Aspects of this circuitry have been strongly implicated in ADHD and in motor inhibition (to be discussed below in the section on Dimensional Behaviors and Brain Networks). The dorsal and ventral attentional networks are involved in goal-directed executive control processes and salience evaluations, respectively, which are necessary operations for the control of spatial attention and attentional shifting. The ventral attentional network includes the temporoparietal junction, the supramarginal gyrus, the frontal operculum, and the anterior insula. The dorsal attentional network is anchored in the intraparietal sulcus and the frontal eye fields. The occipital lobe, the lateral temporal region, and the superior parietal lobule, making up the visual network, interact with the dorsal and ventral attentional networks to sustain attention and to suppress attention to extraneous, irrelevant stimuli, which are often identified as a key deficit in ADHD.

The limbic network interacts with these networks to generate motivational and reward influences. The sensory-motor network consists of the primary motor cortex, the primary and secondary sensory cortices, the supplementary motor cortex, the ventral premotor cortex, the putamen, the thalamus, and the cerebellum. These regions are involved in certain motor abnormalities that are observed in ADHD, and the occurrence of these motor abnormalities has been characterized as predictive of positive response to psychostimulant medication in ADHD (Stray, Ellertsen, & Stray, 2010). In addition, a "default network" of which activity is high until active, goal-directed cognitive processing is required is anchored in two regions—the anterior medial prefrontal cortex and the posterior cingulate cortex—as well as in two additional systems, the dorsomedial prefrontal system and the medial temporal-lobe memory system. The default network is less active during the performance of cognitive tasks in normal control subjects. However, in ADHD, these default network regions are recruited; activity is not suppressed, and this has been associated with lapses in attention (Weissman, Roberts, Visscher, & Woldorff, 2006). (For an in-depth review of the specific brain structures that make up these network connectivity profiles relevant to ADHD, see Castellanos and Proal, 2012, from which this summary was abstracted).

Simply put, what this increasingly supported "distributed network" perspective for cognition and psychiatric illness means for clinical neuropsychologists is that it is no longer appropriate to think of ADHD as a simple "frontal-lobe disorder" given not only the complexity of the neural systems involved for cognition but also the indications (as reviewed above) for ADHD causal heterogeneity. Thus, it should be no surprise to anyone these days that a single neuropsychological test cannot be found to be pathognomonic for ADHD. However, this emerging network-based appreciation of the complexity of brain–behavior relationships does not make the typical neuropsychologist's training or perspective obsolete. For one thing, cognitive neuroscientists are evaluating whether large-scale networks or even smaller, more modularized subnetworks might be shown to have strong degrees of specialization for certain cognitions. On the one hand, this would merely replace a strict localizationist perspective (i.e., one brain region = one cognitive function) with a similar framework that replaces a single brain region with a group of regions. On the other hand, as this field matures with more examples of how certain broad classes of cognitive functions are indeed related to either the frontoparietal or the frontostriatal cognitive control systems, default mode networks, etc., neuropsychological testing might again contribute its diversity and precision of behavioral quantification.

Another continuing role for neuropsychologists derives from the important change in how mental illnesses are being conceptualized as we move away from the DSM "disease-centric" perspective into a more dimensional approach. The National Institutes of Health have emphasized a dimensional approach to understanding most mental disorders (Cuthbert & Insel, 2010; Insel et al., 2010; Sanislow et al., 2010). This research domain criteria perspective emphasizes measureable behavior from cognitive tests as possible end-products of a line of genetic, physiological, and neural system functions/dysfunctions that converge from a variety of sources to manifest as ADHD or another disorder. Such measurements might more closely reflect a meaningful profile of genetic variation that cuts across disorders with similar forms of cognitive dysfunction (i.e., "endophenotype"; Gottesman & Gould, 2003). As this type of research progresses, it could be that demonstrable links between aspects of behavior measured on neuropsychological tests will have newly found important roles in understanding various disorders like ADHD.

ADHD FROM A DIMENSIONAL PERSPECTIVE

Some have argued that a dimensional approach to ADHD can be just as easily employed as a categorical one (Chabernaud et al., 2012; Marcus, Norris, & Coccaro, 2012; Shaw et al., 2011; Voeller, 2004). In this approach, a single symptom class can be identified, while its severity can be measured. For example, a symptom such as impulsivity can first be identified, while its severity can be estimated. Although it is most likely that all kinds of impulsivity are not alike (Aragues, Jurado, Quinto, & Rubio, 2011; Dannon, Shoenfeld, Rosenberg, Kertzman, & Kotler, 2010; Humby & Wilkinson, 2011; Kim & Lee, 2011; Potenza & de Wit, 2010; Swann, 2010), this unidimensional approach allows for investigating how different types of impulsivity might "map" on to different brain networks or circuitries. For example, a person might be impulsive because of insufficient inhibition when presented with any stimulus; because of lack of inhibitory control when multiple stimuli are presented; or because of insufficient inhibition when presented with a single stimulus because of lack of anticipatory control; or a person might be impulsive when presented with rewarding stimuli because of an inability to inhibit reward systems. Therefore, impulsivity can be heterogeneous in its own right, but by identifying and characterizing its "behavior" under different circumstances, a dimensional approach to understanding ADHD etiology and severity allows for identifying brain systems and circuitry connectional profiles that underlie the diversity and degree of impulsivity on any given measure. Identification at this level is critical in understanding the heterogeneity of behavior and in potentially generating appropriate treatment. For example, Whelan and colleagues (2012) have identified distinctly different cortical and subcortical networks underlying successful inhibitions and inhibitory failures in adolescents with ADHD symptoms and adolescents with drug use. Therefore, it is possible that such a dimensional approach might provide the means to directly link observable behavior with its neuropsychological underpinnings—by definition, the study of brain–behavior relationships.

Dimensional Behaviors and Brain Networks

The following provides three examples of how traditional neuropsychological tests can be used in neuroscience studies to not only understand the complex neural system basis of specific cognitive functions relevant to ADHD, but also to understand how they provide examples of ways to explore the possible dimensional basis of ADHD pathophysiology. From the practicing clinical neuropsychologist's perspective, impulsivity and inhibition can be defined in many ways and quantified using a battery of commonly employed tests. Withholding a prepotent response is often measured clinically using the Stroop Color Word Task, various inhibition paradigm tasks on the NEPSY-II (a

Developmental Neuropsychological Assessment) and the Delis-Kaplan Executive Function System, the Test of Variables of Attention, or the Connor's Continuous Performance Test (CPT), to name just a few procedures. Using one example (a Go/No-Go variant of the CPT paradigm), neuroimaging data have been very clear in identifying frontal-basal ganglia-thalamic circuitry as an integral node in the cognitive and motor networks responsible for inhibitory control (Koziol & Budding, 2009).

However, Stevens and colleagues provided the first description of how multiple neural network dynamics are associated with response inhibition in normal control adolescent and adult subjects in the performance of a Go/No-Go task (Stevens, Kiehl, Pearlson, & Calhoun, 2007). In that study, it was seen that successful response inhibition did not rely on just a single frontostriatal network. Instead, three response inhibition networks formed an interdependent, hierarchically organized system by which thalamic modulation of input to the premotor cortex by frontostriatal regions resulted in response inhibition. A frontostriatal-thalamic network, consistent with the indirect pathway of the basal ganglia, recruited activity within the caudate and bilateral dorsolateral prefrontal cortex while reducing activity in premotor regions known to be activated in conditioned response tasks. Therefore, this circuit inhibited the premotor region's response to learned motor responses. An additional network demonstrated decreased activity within the precentral gyri and inferior temporal cortex, which are typically engaged in object recognition, polymodal sensory integration through the anterior insula, and successful response inhibition involving the right inferior frontal cortex; these regions are proposed to be involved in translating sensory information into certain actions. The third response inhibition component revealed that correct No-Go responses activated a network consisting of the inferior right frontal gyrus, the right dorsolateral and bilateral frontopolar prefrontal cortex, the bilateral inferior parietal lobule, the pre-SMA (Supplementary Motor Area) region, the thalamus, and the cerebellum; these brain regions have been associated with increased activity during performance of tasks requiring executive control over attention and working memory, so that activation of this network seems to bias or recruit activity in other brain regions to accomplish goal-directed behaviors. All three networks were described as functioning in concert for successful response inhibition through the effects of the direct and indirect pathways of the primary frontostriatal-thalamic network.

Importantly, this configuration of networks was sensitive to developmental differences in performance. Adults had quicker response reaction times and fewer errors or disinhibited responses in comparison with adolescents, suggesting a relatively slow maturational process in the development of these circuits (see Stevens et al., 2007, for a comprehensive account of these functional circuitries). Two significant features of this study concern the identification of regionally connected networks and their dynamics in prepotent inhibitory control as well as developmental differences in these dynamics in healthy humans. In ADHD, one might surmise that disturbance in the primary inhibitory network could easily lead to a variety of cognitive, executive function, and impulse control deficits based upon this study of functional connectivity. For example, impairment in the frontostriatal-thalamic circuitry profile would not only lead to disinhibition but also to distractibility, difficulties staying on task as a manifestation of failure in goal-directed behavior, and deficits in working-memory functions (Awh & Vogel, 2008; Frank, Scheres, & Sherman, 2007; Hazy, Frank, & O'Reilly, 2007; McNab & Klingberg, 2008).

This example shows how complex network behavior can be meaningfully linked to neuropsychological testing typically performed in clinical practice. Such links not only aid practitioners in the psychoeducation of patients but also represent an ongoing need for new and more theoretically distinct tests to be developed to be used as probes of brain function. Impulsivity as a behavioral dimension also can be conceptualized as a relative insensitivity to error, inability to effectively monitor ongoing behavior for errors, or difficulties adjusting behavior once neural systems signal the presence of an error. Brain network dynamics during correct responses and error commission on a Go/No-Go task were also investigated in a subsequent study by Stevens and colleagues with normal control participants between the ages of 11 and 37 years (Stevens, Kiehl, Pearlson, & Calhoun, 2009). Errors engaged the premotor, motor, and cerebellar regions, as these are critical regions of the motor execution system. However, striatal brain regions that are typically associated with response execution were not recruited, and the right inferior frontal cortex and dorsolateral prefrontal cortex were not engaged. In fact, there were decreases in activity in the caudate nucleus and dorsolateral prefrontal cortex—brain regions typically associated with successful response inhibition.

Therefore, with commission errors, there was a decoupling of aspects of the motor system from the higher-order, executive control system. These findings are consistent with the interpretation of errors of commission as reflecting a disturbance within the brain's action/intention systems (Denckla & Reiss, 1997; Heilman, Voeller, & Nadeau, 1991; Koziol & Budding, 2009). For example, people with ADHD frequently demonstrate deficits in knowing when to start, when not to start, when to persist, and when to stop a behavior. Disturbances in these intention programs may underlie commission errors on the type of CPT

Go/No-Go task employed by Stevens and colleagues (2007, 2009). In any event, this "error network" may be preferentially engaged in a variety of impulse control disorders characterized by impetuous, reckless decision making or an inability to anticipate logically important, future considerations for the purpose of guiding behavior as is frequently observed in ADHD. Similarly, these "correct identification" and "error networks" demonstrated a slower maturational developmental trajectory as suggested by very early studies (Beck, Bransome, Mirsky, Rosvold, & Sarason, 1956; Kelly, 2000; Rebok et al., 1997). Therefore, the findings also provide support for the possibility of interpreting ADHD as a manifestation of maturational delay (Rubia, 2007).

Our third example concerns the cognitive control of working memory. This executive function is typically defined as the ability to temporally hold and mentally manipulate information, in the absence of stimuli. Many, but not all, children with ADHD have this problem. Similarly, many children with this problem do not meet DSM diagnostic criteria for ADHD. Brain regions engaged in working memory include the dorsolateral and ventrolateral prefrontal cortex, the posterior parietal cortex, the anterior and middle regions of the cingulate, the inferior temporal lobe, the direct and indirect pathways of the basal ganglia, and the cerebellum (Hayter, Langdon, & Ramnani, 2007; Hazy, Frank, & O'Reilly, 2006; Hazy et al., 2007; Owen, McMillan, Laird, & Bullmore, 2005). However, functional connectivity studies have demonstrated that brain regions involved in working memory are organized into distinct functional networks (Curtis, Sun, Miller, & D'Esposito, 2005; Gazzaley, Rissman, & D'Esposito, 2004; Miller, Deouell, Dam, Knight, & D'Esposito, 2008). The well-known frontal- and parietal-lobe brain region connections are engaged for working memory regardless of information encoding or retrieval demands and therefore serve as a primary node or hub supporting the working-memory system (D'Esposito, Postle, & Rypma, 2000; Wager & Smith, 2003). Wong and Stevens (2012) recently used the Sternberg Item Recognition task for investigating the effects of psychostimulant medication on working-memory functional connectivity. Older children and adolescents with ADHD were studied both on and off medication using functional MRI. The main findings included the identification of six frontoparietal networks that were recruited during the encoding, maintenance, or retrieval phases of the task. Within the on-medication condition, three of these networks demonstrated a significant increase in activation. Medication strengthened the connectivity of some frontoparietal regions. Medication also led to the recruitment of additional brain regions that were not previously engaged in these networks. Many of these connectivity changes were directly related to improved working-memory reaction time. The study supports our belief that neuropsychological tests can be used to understand a specific cognitive executive function relevant to ADHD, that these tests assist in the investigation of the dimensional basis of the neuroanatomy of ADHD, and that a dimensional approach to diagnosis might lead to effective symptomatic treatment.

DISCUSSION

So why are neuropsychological tests so inadequate in the diagnosis of ADHD? The primary issue concerns our current conceptualization and understanding of brain network functional connectivity. Behaviorally defined criteria in ADHD do not easily "map" on to functional brain networks. Moreover, different psychiatric disorders share features of the same connectional profiles so that the diagnosis of "uncomplicated" ADHD becomes the exception, while comorbidity with other conditions becomes the rule. The same principle holds true for diagnosing the disorder with neuropsychological testing. Many existing neuropsychological tests "map" on to different aspects of different brain networks, while these networks do not respect the neuroanatomic boundaries and interactions of the newly identified patterns of functional connectivity that have been described above. Tasks that presumably measure executive control processes are not all the same. For example, the Wisconsin Card-Sorting Test (Heaton & Psychological Assessment Resources, 1993), the Tower of London Test (Culbertson & Zillmer, 2001), and the Tower of Hanoi, all understood as "frontal-lobe" tasks, simply do not assess the same aspects of executive functioning. Indeed, with the advent of functional neuroimaging, it was seen conclusively that these sorting and planning tasks should not fairly be considered "frontal" tests at all (except in the recognition that frontal-lobe injury often causes impairment), as complex profiles of frontal- and parietal-lobe activation consistently underlie these sorts of paradigms. These tests all engage a different and dynamically changing neuroanatomy (Goel & Grafman, 1995; Lazeron et al., 2000; Monchi, Petrides, Petre, Worsley, & Dagher, 2001; Schall et al., 2003). Although each of these tasks recruits aspects of the networks we described above, simply put, these assessment instruments were never designed or intended to evaluate the networks and interactions in question. Similarly, these types of tasks were not developed to assess DSM behaviorally defined disorders. This limitation is distinctly problematic when these are the primary tools in the neuropsychologist's arsenal.

The same consideration needs to be given to CPTs, which are sometimes mistakenly considered to be tests for ADHD. There are several commercially available

CPTs, but these tests are all organized differently with respect to the frequency of presentation of targets, the type of target to be identified, and the rate of stimulus presentation, to name just a few variables. Therefore, it should be no surprise that the results of these tests do not correlate very well with one another (Riccio, Reynolds, & Lowe, 2001; Riccio, Reynolds, Lowe, & Moore, 2002). All Go/No-Go paradigms are not the same. The paradigm developed by Luria for which there is a commercially available version is definitely not the same neuroimaging paradigm employed by Stevens et al. in the identification of functional connectivity networks associated with successful response inhibition and errors of commission (Goldberg, Podell, Bilder, & Jaeger, 2000; Stevens et al., 2007). There are many commercially available tests and psychometric indexes that require the subject to inhibit prepotent responses, but once again, it should be expected that different paradigms will not likely recruit the exact same networks simply because of the demand characteristics of the different tasks. Moreover, given the now widely accepted belief of causal heterogeneity in ADHD, it would be difficult to defend the continuing expectation that all ADHD-diagnosed youth or adults should display the same type or profile of behavioral impairment on one of these numerous different types of neuropsychological tests of response inhibition. Although "working memory" is routinely assessed as an executive function, there is no commercially available version of the Sternberg paradigm for clinical application. It is not known how other working-memory tasks that differ in demand characteristics map on to the working-memory connectivity patterns described above. Similarly, there are no commercially available neuropsychological tests to assist the clinical practitioner in evaluating critical reward and motivational circuitry. However, tasks such as probabilistic category learning, used to assess reward preferences in the experimental lab, might be applied for clinical diagnostic purposes.

This does not mean that neuropsychology has no place at the "diagnostic table" with respect to identifying ADHD. Indeed, it is hard to argue against the value of knowing whether or not there is tangible evidence for certain forms of cognitive dysfunction in ADHD. The presence or absence of demonstrable neuropsychological impairment usefully denotes specific problems that might influence educational/vocational recommendations, or ultimately even remediation strategies. However, the ineffectiveness of conventional cognitive testing in the ADHD diagnostic process does present neuropsychology with challenges. To elicit the intended network performance, the field should move toward clinically employing the same paradigm designs that are used experimentally. Although this initially might appear to be a very difficult process in regards to developing traditionally based normative standards, this is not necessarily all that problematic. The purpose of the application of new paradigms is to assist in recruiting the functions of identified brain networks that govern "dimensional" concepts and variables. Therefore, the diagnostic and interpretive emphasis is not upon developing "normal distributions" of test scores, but instead applying pathognomonic sign test interpretation methodologies based upon neuroscientific discovery. This becomes a very manageable task that is in agreement with how these tasks were applied within neuroscience research paradigms. However, it is fair to say that the challenge is a two-way street. The burden on ADHD clinical neuroscientists is to demonstrate that these new ideas about brain organization and dysfunction have concrete, clinical impact. For instance, the challenge to functional neuroimaging is to find a way to effectively "diagnose" ADHD, usefully differentiate neurally heterogeneous subtypes, or measure something that points toward the most optimal treatment strategy using these new network-based, potentially dimensional, endophenotypic tools and concepts. If these advances fail to materialize, it is hard to argue that clinical practitioners should readily adopt experimental paradigms as clinical tools. Instead, clinicians might more profitably seek to develop new tools that might show utility both as clinical and experimental probes in ADHD. However, if the promise of imaging, electroencephalography, or other forms of neuroscientific inquiry into ADHD do pan out as hoped during the next decade, clinicians should be prepared to adopt neuroscientifically validated paradigms as the most useful tools available for meaningful clinical practice.

In sum, the identification of functionally connected neural networks is an emerging area. This represents an opportunity for clinical neuropsychology. The combination of dimensional approaches, applying what is learned about functional connectivity networks, and applying experimental tasks within clinical settings might help us to fully characterize neuropsychologically based subtypes of ADHD. The current application of neuropsychological tests to the differential diagnosis of ADHD focuses upon the identification of different executive function deficits that are frequently part of the disorder and in identifying comorbid conditions such as anxiety disorder, depression, autism, and Tourette's syndrome (Pritchard et al., 2012). However, as our understanding of the networks involved in ADHD increases, interactions between circuits might very well lead to biologically based phenotypic presentations characterized by subtypes with specific impairment in reward circuitry, impulse control, and/or highly specific cognitive deficits. Neuropsychology can establish itself at the "ground floor" in developing methodologies to explore these different dimensions of behavior

experimentally and directly applying these methodological paradigms clinically. In these ways, neuropsychology can become central in both experimental and clinical settings.

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