Understanding the Effects of Stimulant Medications on Cognition in Individuals with Attention-Deficit Hyperactivity Disorder: A Decade of Progress

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The use of stimulant drugs for the treatment of children with attention-deficit hyperactivity disorder (ADHD) is one of the most widespread pharmacological interventions in child psychiatry and behavioral pediatrics. This treatment is well grounded on controlled studies showing efficacy of low oral doses of methylphenidate and amphetamine in reducing the behavioral symptoms of the disorder as reported by parents and teachers, both for the cognitive (inattention and impulsivity) and non-cognitive (hyperactivity) domains. Our main aim is to review the objectively measured cognitive effects that accompany the subjectively assessed clinical responses to stimulant medications. Recently, methods from the cognitive neurosciences have been used to provide information about brain processes that underlie the cognitive deficits of ADHD and the cognitive effects of stimulant medications. We will review some key findings from the recent literature, and then offer interpretations of the progress that has been made over the past decade in understanding the cognitive effects of stimulant medication on individuals with ADHD.

INTRODUCTION

Cognitive deficits and behavioral symptoms associated with attention-deficit/hyperactivity disorder (ADHD) have been studied intensively and are well documented in the literature. Stimulant drugs (methylphenidate (MP) and amphetamine (AMP)) are particularly effective for the clinical treatment of ADHD, and accordingly, pediatricians and psychiatrists have been prescribing them for over seven decades (Bradley, 1937). Clear reductions in symptoms justify treatment with stimulant medications (MTA, 1999b), but the cognitive effects are less clear. Here, we will review the current understanding of some underlying neural processes that may account for the ADHD symptoms of inattention and impulsivity, and we will review evidence from neuropsychological and neuroimaging studies about how stimulant medications may affect these processes. To focus our review, we will not revisit related topics that

are addressed elsewhere: the medical use of non-stimulant drugs to treat ADHD (Dopheide and Pliszka, 2009; Waxmonsky, 2005), the non-medical use of stimulants and non-stimulants for cognitive enhancement (Sahakian and Morein-Zamir, 2007; Stix, 2009), and non-medical alternative treatments based on neurofeedback (Gevensleben et al, 2009) and working memory training (Klingberg et al, 2005) that have recently been evaluated and have gained some support in randomized clinical trials.

In the Diagnostic and Statistical Manual (DSM) of the American Psychiatric Association, Version IV (APA, 1994, 2000), the cognitive symptoms of ADHD are grouped into two domains: inattention and hyperactivity/impulsivity. Currently, nine are specified for inattention (poor attending to details, sustaining attention, listening, organizing and finishing tasks, exerting mental effort, ignoring extraneous, and remembering things and activities), but only three for impulsivity (blurting out answers, cannot wait, and interrupting others), which are grouped with six motor symptoms of hyperactivity (often fidgeting, leaving seat in the classroom, running about, not able to play quietly, 'on the go', and talking excessively).

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These cognitive symptoms have been grouped, ungrouped, and re-grouped in different ways in the serial revisions of the DSM (DSM III, 1980; DSM III-R, 1987; and DSM IV, 1994); hence a variety of subtypes have been proposed and evaluated (respectively, ADD with or without hyperactivity; ADHD without subtypes; ADHD predominately inattentive, predominately hyperactive/impulsive, or combined types). This vacillation suggests great difficulty in understanding the place for cognitive deficits in the clinical diagnosis of ADHD. This may be related to the complexity of definitions of the same domains in the cognitive neurosciences. For example, Winstanley *et al* (2006) described two general types of impulsivity—impulsive choice and impulsive action—and (Posner and Rothbart, 2007) described three general components of attention—alerting, orienting, and executive control. More precise definition and measurement of cognitive deficits related to inattention and impulsivity may help advance the understanding of cognitive deficits in ADHD.

Over the past decade, specific laboratory tasks have been used for this purpose. Here, we will focus on three of the most prominent that use reaction time (RT) as a measure of performance: (a) the Stop Signal Task (STOP) that requires the cued inhibition of response to stimulus after a signal; (b) the reverse continuous performance task (CPT) (Go–NoGo) that requires response to most but not all stimuli in a series; and (c) the attentional network task (ANT) that requires response to central stimuli in the face of temporal, spatial, and conflicting surrounding cues. We will build on reviews that relate these tasks to the brain imaging literature of structure (Krain and Castellanos, 2006), function (Dickstein *et al*, 2006), and connectivity (Bush, 2010), and emphasize advances over the past decade in the conceptualization and evaluation of neural processes and networks that may be abnormal in ADHD, and thus may mediate the effects of stimulant medication on cognition in individuals with ADHD.

BACKGROUND STUDIES ON THE EFFECTS OF STIMULANTS IN COGNITION IN ADHD

Cognitive Deficits

One purpose of clinical treatment is to correct a deficit; this is important to consider in the assessment of cognitive effects of stimulant drugs in light of the current controversy about non-medical use of stimulants and cognitive enhancement (Sahakian and Morein-Zamir, 2007; Stix, 2009). The Yerkes–Dodson Law provides a theoretical framework for this (Diamond *et al*, 2007; Arnsten, 2009). At some doses and on some tasks (Dodds *et al*, 2008), stimulant drugs may have the same direction of effect (cognitive enhancement) in some individuals without ADHD (Clatworthy *et al*, 2009) as well as in those with ADHD. The non-medical use of stimulant drugs for enhancement rather than the medical use for correction of deficit defines an ethical issue addressed elsewhere (Sahakian and Morein-Zamir, 2007;

Swanson *et al*, in press). In this section, we will focus on definitions of cognitive deficits associated with diagnoses of ADHD in children.

A brief history and succinct review of theories of attention in ADHD will set the stage for our review of the recent literature. Sergeant and Scholten (1983) applied a cognitive energetic theory of information processing and found that in ADHD children central processing stage was intact and that deficits are restricted to motor organization and output stages of information processing. Swanson *et al* (1991b) applied a cognitive anatomical theory of attention (Posner and Petersen, 1990), and found that in ADHD children, the posterior system for engaging attention was intact and that deficits were restricted to the anterior system of maintaining (disengaging and moving) attention. Pennington and Ozonoff (1996) proposed that the core deficits of ADHD were linked to the abnormal development of executive functions in childhood. The most prominent and influential theory (Barkley, 1997) was based on the Fuster theory of frontal lobe function (Fuster, 1980), and it proposed that ADHD was characterized by a core deficit in response inhibition, which theoretically would lead to cognitive symptoms as secondary manifestations.

The core deficit theories of ADHD were assessed in comprehensive reviews by Nigg (2005) and Willcutt *et al* (2005). Both used the concept of 'effect size' (es) (defined as the difference between an ADHD and control group, expressed in standard deviation units) to compare cognitive deficits across a variety of neuropsychological tasks. In Table 1, we present their lists of tasks that provide an empirical basis to define cognitive deficits and the relative es. These reviews mark a watershed point in the literature on cognitive deficits of ADHD: they pointed out that few children with ADHD showed pervasive deficits across tests, concluded that executive function deficits were not necessary and sufficient causes of ADHD, and contributed to the shift from core deficit to multiple deficit theories.

Laboratory measures of inattention and impulsivity have been used to assess the pervasive cognitive deficits manifested by children with ADHD across multiple domains. In some studies, multiple tests of executive function and motor inhibition were used (Oosterlaan *et al*, 2005; Scheres *et al*, 2004). In others, standard batteries of neuropsychological tests were used: two prime examples are the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Rhodes *et al*, 2005, 2006) and the Maudsley Attention and Response Suppression (MARS) (Rubia *et al*, 2007). This approach has uncovered ADHD–control group differences (deficits) on tests of temporal and parietal lobe function (spatial recognition and span, pattern recognition, and delayed matching to sample), as well as frontal lobe function (working memory, planning and strategy formation, and set-shifting). Another approach has been to use a specific task to assess cognitive components of inattention and impulsivity in ADHD children, and over the past decade three have emerged as the most prominent in the literature: the Go–NoGo task, the STOP task, and the ANT.

TABLE 1 Tasks Reviewed by Nigg (2005) and Willcutt et al (2005)

Nigg		Willcutt	
Spatial working memory	1.14 to 0.75	Spatial working memory	0.63
Response suppression (Stop Task)	0.94 to 0.61	Stop task	0.61
Signal detection (CPT)	0.72	CPT omissions	0.64
		CPT commissions	0.51
Stroop naming speed	0.69		
Full scale IQ	0.61		
Set shifting (Trails B)	0.55 to 0.75	Trails B	0.55
Planning (Tower tasks)	0.51 to 0.69	Tower of London	0.51
		Tower of Hanoi	0.69
Mazes	0.58	Porteus Mazes	0.58
Verbal working memory	0.51 to 0.41	Verbal working memory	0.55
Fluency	0.27		
Decision speed (Go Task)	0.49		
WCST perseverations	0.36 to 0.53	WCST perseverations	0.46
		R-O copying (Organzation)	0.43
Stroop interference	0.25		
Covert VP orienting	0.20		

Numbers represent effect sizes, which are defined as the difference between an ADHD and control group, and expressed in standard deviation units.

A typical version of the Go–NoGo task requires rapid responding (eg, with a key press) to a series of 'Go' stimuli (eg, letters) and selective inhibition of the motor response to infrequent 'NoGo' stimuli (eg, specific letters). The Conners version of the CPT (Conners et al, 2003) required a key press response to all but one letter (eg, all but X), and in a study to develop population norms (Epstein et al, 2003), about 20% of the commission errors occurred owing to failure to withhold a response. Comparisons of Go–NoGo performance of ADHD and control children revealed significant differences in commission errors, as well as variability of RTs, omission errors, and a derived measure of perceptual sensitivity (d') based on signal detection theory. These performance deficits were associated with differences in brain activation as assessed by fMRI (Dickstein et al, 2006). During the performance of a Go–NoGo task, in the ADHD compared with controls, some important findings were reduced activation of right caudate nucleus, but increased activation in the right inferior parietal lobe and posterior cingulate (Durston et al, 2003); increased activation of the posterior cingulate and dorsolateral prefrontal and parietal brain regions (Schulz et al, 2004; Tamm et al, 2004); attenuated activity in frontostriatal regions when tested off medication, which were increased when tested on medication along with increases in cerebellar regions (Epstein et al, 2006); and disrupted structural connectivity within frontostriatal networks (Casey et al, 2007). These Go–NoGo fMRI studies reveal hypoactivation involving relatively smaller regions within

the inferior frontal cortex, anterior cingulate cortex, and precentral gyrus, as well as hyperactivation in medial frontal gyrus and right paracentral lobule. Reviews of the literature (Dickstein et al, 2006; Fassbender and Schweitzer, 2006) concluded that ADHD children may rely on brain functions based on visual and motor processing of information associated with performance strategies that allow them to compensate for deficits in executive functions.

The STOP task requires the inhibition of the Go response (eg, a key press to visual stimuli) when a Stop signal (eg, a tone) occurs. One version had fixed delays between the Stop and Go signals, which may result in a strategy-related delay in response to Go signals to avoid unsuccessful inhibitions to the Stop signal. To prevent this, another version incorporates a dynamic tracking adjustment of the delay between Go and Stop signals, decreasing it after successful and increasing it after unsuccessful trials to elicit about 50% successful inhibitions to the Stop signal. On the basis of an underlying model of the speed of the two mental processes, the RT to the Stop signal is estimated indirectly. The STOP task has been used in many studies of ADHD children to evaluate inhibition deficits (see reviews by Lijffijt et al (2005), Oosterlaan et al (1998), and Willcutt et al (2005)). A recent review (Alderson et al, 2007) contrasted the es for the Stop-signal reaction time (SSRT, es = 0.63) and mean RT (MRT, es = 0.45), as well as on a measure of Stop Signal Delay (SSD) defined as the difference between them (ie, SSD = MRT—SSRT, es = −0.025), and concluded that children with ADHD

had slower and more variable RTs to primary stimuli (ie, go-stimuli) as well as a Stop signal, and thus they appeared to have '…an underlying attention deficit rather than deficient inhibitory control' (p 755). Studies that combined the STOP task with fMRI also showed differential activation patterns of a distributive nature, which do not support models that hinge on the dysfunction in any one frontal subregion (Dickstein et al, 2006). The interpretation of task-related group differences is complicated by a significant group difference in activity while performing the STOP task in the imaging setting. For example, Pliszka et al (2006) used a visual fixed interval STOP task and reported that more children with ADHD (15 of 32) than without (eight out of 23) were eliminated owing to motion artifacts, and significantly higher scores for allowable movement were present in the remaining censored group of ADHD children than in the control group (2.57 vs 1.71).

The ANT was developed by Posner and his colleagues (Fan et al, 2002) as a simplified variant of the Posner visual–spatial orienting task (Posner et al, 1988; Swanson et al, 1991b) to facilitate the evaluation of components of attention—alerting (elicited by a temporal cue), orienting (elicited by a spatial cue), and executive control (elicited by visual–spatial conflict). It is based on the Eriksen–Flanker Task, using a right or left pointing arrow (or swimming fish for children) surrounded by stimuli pointing in the same (congruent flankers) or the opposite direction (incongruent flankers) to establish cognitive conflict. The speed of each of the three component processes is estimated by differences in RTs for trials with different types of cues or flankers. The ANT has been included in the NIH Toolbox of cognitive tasks for the assessment of attention across the lifespan (Jin-Shei et al, 2010). It has been modified for the assessment of cognitive deficits associated with brain damage as a test for attentional performance (Drechsler et al, 2005). Various versions of the ANT have revealed deficits in ADHD vs control groups on measures of the executive function network, but the observed response patterns (slower RTs and more errors, particularly on conflict trials), did not reflect impulsive responding (Johnson et al, 2008; Konrad et al, 2006). Konrad et al (2006) also used fMRI to evaluate brain regions activated by trials requiring alerting (anterior cingulate gyrus activation was greater in the control than in the ADHD group, but the brainstem activation was greater in the ADHD than in the control group), orienting trials (putamen activation was greater in the ADHD than in the control group), and executive control (frontal activation was greater in the control than in the ADHD group, but brainstem and parietal activation was greater in the ADHD than in the control group). This pattern suggested that some individuals in the control group have the expected activation of the frontal–striatal circuitry, whereas the ADHD group manifest compensatory activation of different brain regions.

In summary, we should emphasize that over the past decade, there has been a shift in the consensus view of cognitive deficits associated with ADHD. Earlier theories had proposed core deficits in the frontal lobe function, but a variety of studies favored multicomponent theories based on various cognitive deficits formulated to account for the observed heterogeneity of cognitive impairments manifested in the clinical samples of ADHD cases. Some fMRI studies of ADHD confirmed a wide range of brain regions with the evidence of deficits (hypoactivation relative to controls), but others suggest that ADHD children may compensate for cognitive deficits by using alternative neural processes to perform these tasks compared with control children, which may produce patterns of hyperactivation as well as hypoactivation in different brain regions.

Cognitive Effects of Stimulants

The evaluation of cognitive effects of stimulants on children with ADHD has a long history (Knights, 1974). The conclusions have become more consistent over time as the literature on this topic increased exponentially (Conners, 2002; Ottenbacher and Cooper, 1983; Rapport and Kelley, 1993; Swanson et al, 1991a). A basic finding is that the percentage of children who benefit depends on the task used to assess improvement, with the highest response rates for the assessment of activity (with decreases considered beneficial) and the lowest response rates for the assessment of learning or problem solving (with increases considered beneficial). An early study of dose-related effects (Sprague and Sleator, 1977) had suggested that the optimal dose for cognitive effects was lower than that for behavioral effects of MP, and in an early study of the effects in non-ADHD individuals, Rapoport et al (1978) suggested that the response in ADHD individuals was not 'paradoxical', but instead was in the same direction for some measures in control (non-ADHD) individuals. Sahakian and Robbins (1977) and Robbins and Sahakian (1979) suggested that this task-dependent pattern of response may be a consequence of the general dose-related effect of stimulants to increase stereotypic behavior, which would improve performance on some tasks (eg, tasks that require sustained attention for repetitive action and thought), but impair it on others (eg, tasks that require reversals in cognitive strategy). Pietrzak et al (2006) provides a meta-analysis of the recent literature on placebo-controlled studies of the effects of MP on a variety of neuropsychological tasks, and in studies comparing effects for more than one clinical dose, higher doses produced greater improvements than lower doses for some tasks (attention, vigilance, memory, and working memory), but no additional improvements on others (planning, cognitive flexibility, inhibitory control, naming, and motor speed).

Dose-related effects of stimulants have been evaluated using batteries as well as specific tasks. For example, Coghill and his colleagues (Coghill et al, 2007; Rhodes et al, 2005, 2006) used the CANTAB to evaluate the acute and chronic effects of MP (0.3 and 0.6 mg/kg doses). In stimulant-naïve children with ADHD, controlling for practice effects in a randomized clinical trial (RCT) with between-subject

comparisons (Rhodes *et al*, 2006), improvement was documented on some tasks without a major executive function (EF) component (complex reaction time, spatial recognition memory reaction time, and delayed matching-to-sample) but surprisingly not those designed to assess the executive function components of neuropsychological performance (inhibition, working memory, strategy formation, planning, and set-shifting). In the follow-up study of chronic (four-week) MP administration (Coghill *et al*, 2007), a significant behavioral response to medication compared with placebo was documented by parent and teacher ratings on the Conners' 10-item rating scale in 59% of the children at some dose, but the effect of dose was not significant and the optimal dose varied across children (33% when treated with a low—0.3 mg/kg—dose and 43% when treated with the high—0.6 mg/kg—dose). The chronic cognitive response to MP was shown on visual memory tests (pattern matching, delayed matching to sample, and spatial memory), but not on EF tests (except the Go–NoGo test). This well-designed and implemented study of the cognitive effects of stimulant medication did not confirm expectations that the response would correct EF deficits, but also did not document a dose-related impairment on any of the tasks in the battery.

Scheres *et al* (2003) provides an example of the use of a specific task (the STOP task) to evaluate dose-response to MP in a double-blind, placebo-controlled, crossover study of three doses (5, 10, and 20 mg). The overall effect of medication was significant owing to faster SSRTs and lower RT variability, but the dose effect was not significant, suggesting that the maximum cognitive benefit may be elicited by a low dose of medication. Spencer *et al* (2009) evaluated the cognitive response of children with ADHD to stimulant medication based on an RT task of discriminating two stimuli (X or O) in a double-blind, dose–response, crossover study of placebo, low (0.9 mg/kg/day) and high (1.8 mg/kg/day) MP doses delivered by controlled-release formulations. Medication produced a significant reduction of the mode and SD from the mode (rather than the mean, which is correlated with SD) for the low as well as high doses, which was not owing to a speed-accuracy tradeoff, but instead reflected an overall increased efficiency of responding (faster and more accurate responses). The evaluation of the effects of dose on mode RT suggests that the full effect of cognitive enhancement was manifested at the low dose.

Overall, the literature suggests some general findings that have been consistent across time and studies. Stimulant-related improvements in ADHD children have been documented across a wide range of cognitive functions. In well-controlled studies using batteries, stimulant-related cognitive enhancements were more prominent on tasks without an executive function component (complex reaction time, spatial recognition memory reaction time, and delayed matching-to-sample) than on tasks with an executive function component (inhibition, working memory, strategy formation, planning, and set-shifting). Dose–response studies of stimulant medications suggest that

the optimal dose varies across individuals and depends somewhat on the domain of function, with high doses tending to produce greater enhancement on some (eg, vigilance) but not others (eg, planning), without clear evidence of completely correcting cognitive deficits associated with ADHD.

Long-term Cognitive Effects of Stimulant Medication

Most studies of the cognitive effects of stimulant medication focused on acute effects, but recently a few follow-up studies have provided some data that have generated speculations about long-term effects. One of the most controversial (BBC, 2010) has been the Multimodal Treatment study of ADHD (MTA). The MTA evaluated a large sample ($n = 579$) in a 14-month RCT of groups assigned to intensive pharmacological treatment with stimulant medication (MedMgt), intensive non-pharmacological treatment with behavior modification (Beh), treatment with the combination of these two modalities of treatment (Comb), or to a treatment in the community for comparison to the treatments-by-protocol (CC). The acute effects of stimulant medication were documented in a double-blind, dose–response titration trial to select optimal starting dose for each participant (MTA, 1999a). At the end of the 14-month treatment-by-protocol phase, the chronic effects of stimulant medication were evaluated by comparison of the treatments with (MedMgt and Comb) and without (Beh and CC) the MTA medication algorithm as a component of the assigned treatment. This RCT comparison documented the relative superiority of stimulant medication on the primary outcome measure (ie, parent and teacher ratings of symptom severity). In parallel with the behavioral ratings of ADHD symptoms, relative superiority of medication on cognitive outcomes evaluated by tests of achievement on reading and math were documented. The clinically optimal dose varied across individuals, but over the 14 months of treatment-by-protocol, increases in dose of about 20% were made to maintain full efficacy (Vitiello *et al*, 2001). The MTA was continued as a prospective observational study. In the naturalistic follow-up at 2, 3, 6, and 8 years, the natural history of medication use was clear: most children who were assigned to treatment with and were actually treated with stimulants did not continue this component of treatment. Current percentage of ADHD cases who were being treated with stimulant medications at the 8 year follow-up was 32.5%. The follow-up assessments revealed that by the 3-year assessment point, the initial relative benefits of assignment to the medication conditions and of current medication use were no longer significant. This suggests that the relative benefits of childhood treatment with stimulant medication, compared with non-pharmacological treatments—improvement in cognitive deficits as well as reductions in symptom severity—may dissipate after a 2- to 3-year period, whether or not the medication component of treatment is continued or withdrawn (Molina *et al*,

2009; Swanson *et al*, 2008a, b). In addition, the expected long-term relative benefits of childhood treatment with stimulants over non-pharmacological treatment on important non-symptom domains, such as substance use or delinquency that often emerge in ADHD individuals as they enter adolescence and adulthood, were not observed in the MTA follow-up (Molina *et al*, 2007, 2009).

Other long-term follow-up studies (Abikoff *et al*, 2004) suggest a different pattern of long-term residual benefits of medication. Powers *et al* (2008) recently reported on a long-term (about 9 year) follow-up of a cohort of 169 children with ADHD. Of these, 90 were assessed at follow-up, and 48 had a history of medication use for more than 1 year (average 5.33 years) and 42 had a history of no treatment or short-term treatment (less than 1 year). The self-selected subgroups differed on three measures of academic achievement and on grade point average, with the medication group outperforming the non-medication group, leading to the speculation that treatment with medication during childhood may improve long-term outcome in these cognitive domains. Biederman *et al* (2008) evaluated adolescent and adults from two large cohort studies of children with ADHD ($n = 140$ boys and $n = 140$ girls, for a total $n = 280$) and without ($n = 120$ boys and $n = 122$ girls, for a total $n = 242$). In the observational follow-up, in which about half of the sample was evaluated, some ADHD individuals were taking stimulant medication at the time of assessment ($n = 26$) and most were not ($n = 94$). The effects of medication were estimated by comparison of these two subgroups to each other and to controls ($n = 133$). The general pattern of performance indicated that, compared with the control group, the subgroup of ADHD not taking medication at follow-up had a more pervasive pattern of significant deficits than the subgroup of ADHD taking medication. A comparison of ADHD subgroups revealed that the subgroup on medication had better performance on sustained attention (measured by the CPT) and verbal learning (measured by the California Verbal Learning Test).

The developmental courses of behavioral manifestations of the disorder (symptoms) and neuropsychological performance (executive function deficits) have been evaluated in prospective studies of children with ADHD followed into adulthood, and some suggested attenuation in executive functioning deficits among patients with ADHD (Halperin and Schulz, 2006). However, the combined reports on neuropsychological testing of ADHD children present a highly inconsistent picture, with several studies failing to find differences on many measures of executive functions. Several meta-analyses designed to determine the degree to which executive function deficits can adequately account for the underlying cause of ADHD have failed to settle this question (see Homack and Riccio (2004), Huang-Pollock and Nigg (2003), and van Mourik *et al* (2005)). One interesting hypothesis is that the lingering ADHD–control discrepancy may be related to underlying heterogeneities in brain maturation trajectories. This hypothesis appears to be consistent with the observation that when a group of

patients with childhood ADHD was subdivided based on their adolescent ADHD status, both persisters and remitters exhibited deficits in perceptual sensitivity and response variability, and fidgetiness (suggestive of an enduring subcortical impairment), whereas executive function deficits, relative to controls, were only seen in persisters (suggestive of a prefrontal cortex (PFC) maturation-related process of recovery) (Halperin *et al*, 2008).

A program of longitudinal brain imaging was established in the child psychiatry branch of the National Institute of Mental Health (NIMH), and the ADHD component of this program has provided evidence of a global reduction in brain volume, as well as multiple regional differences in brain anatomy, suggesting an approximately 10% reduction in prefrontal, basal ganglia, corpus callosum, and cerebellum (Castellanos *et al*, 2002a; Giedd *et al*, 2001; Shaw *et al*, 2006, 2007). Krain and Castellanos (2006) suggested that these brain deficits were non-progressive and associated with the disorder (presumably from the result of early genetic and/or environmental factors), rather than consequences of treatment of the disorder with stimulant drugs. Shaw *et al* (2006) and Shaw *et al* (2007) reported differences in brain development based on measures of cortical thickness, which was reduced in childhood in ADHD cases compared with controls. Both environmental (history of treatment with stimulant medication) and genetic (genotype of the dopamine (DA) receptor *D4* gene) factors affected the developmental trajectory. Surprisingly, the group that had been treated consistently with stimulant medication appeared to show normalization in the trajectory of brain development (for a review see Shaw *et al* (2010)), but this group was self-selected and may differ on other factors related to outcome. The NIMH brain imaging program also provides the essential background of normal brain development in a large cohort of singletons (see Giedd *et al* (2001)) and twins (see Lenroot and Giedd (2008)), which have defined the pattern for typical brain development (ie, roughly linear increase in white matter volumes and inverted U-shaped trajectories for some gray matter structures), and suggest that some childhood onset disorders may be disorders of neuroplasticity (Rapoport and Gogtay, 2008). These reviews emphasize that the journey (trajectory) as well as the destination (end point) are important to consider in the evaluation of brain anatomy, and that the most important differences between normal and abnormal brain development are likely to be dependent on age and stage of development at the time of the evaluation.

In summary, we should note that the literature on long-term benefits of childhood treatment with stimulants is mixed. In some observational follow-up studies of children into adulthood, comparison of self-selected naturalistic subgroups suggest a long-term benefit of stimulant medication on cognition as well as behavior, but selection biases have not been adequately addressed to justify a firm conclusion about this hopeful hypothesis. The MTA study that used RCT methods documented temporary long-term effects that dissipated over time and with developmental

course of ADHD, so that there were no residual relative benefits of childhood treatment with stimulants. As a randomized trial of long-term treatment is impractical, controlled studies of neural adaptations produced by stimulants have been carried out in animals, and some long-term effects have been documented (Jezierski *et al*, 2007; Moll *et al*, 2001). Paired with appropriate cognitive tasks developed for the assessment of attention and impulsivity in animal studies (Winstanley *et al*, 2006), animal models could be developed to provide a rigorous evaluation of the long-term effects of stimulant drugs on brain development and cognition.

THEORIES OF RESPONSE VARIABILITY AND DEFAULT MODE NETWORK

Evaluation of RT Distributions by Ex-Gaussian and Fast Fourier Analysis

An influential review by Castellanos and Tannock (2002b) noted that '…response variability is one of the ubiquitous findings in ADHD research across a variety of speeded-reaction-time tasks, laboratories, and cultures' (p 624). In almost all studies that used RT as a measure of performance, ADHD individuals differ from controls in overall speed (slower average RT) and variability (increased within individual SD). In addition to these usual summary statistics, the shape of the distribution of RTs differs, because it is more skewed to the right in the ADHD individuals owing to an increased proportion of infrequent long RTs.

One hypothesis is that the skewness and infrequent long RTs are the result of periodic lapses in attention (Douglas *et al*, 1995). Leth-Steensen *et al* (2000) evaluated this theory with an innovative 'Ex-Gaussian' analysis of data from a spatial choice RT task. The usual RT analysis is based on a mathematical model of one underlying process, which generates a description of the empirical distribution of RTs provided by the mean and the first (SD) and second (skewness) moments about the mean. The 'Ex-Gaussian' model accounts for the empirical distribution of RTs based on an assumption of two underlying processes, with one generating a normal ('Gaussian') distribution of RTs described by the parameters μ (mu; mean) and σ (sigma; standard deviation) and the other generating an exponential ('Ex') distribution of infrequent long response described by a parameter τ (tau; the tail of the empirical distribution). In this innovative study and analysis, the ADHD and control groups did not differ significantly in comparisons of the normal distribution parameter estimates of μ (575 *vs* 525 ms) or σ (86 *vs* 78 ms), but they did differ for the exponential distribution parameter τ (354 *vs* 134 ms). This suggested that the ADHD children had more lapses of attention marked by long RTs, but otherwise they responded about the same as the control children. The ADHD–control differences revealed by this 'Ex-Gaussian' analysis may depend on the task used. Hervey *et al* (2006) evaluated a group of stimulant-naïve ADHD children in the

MTA follow-up study ($n = 65$) and matched group classmates without ADHD ($n = 65$) using a Go–NoGo task (the Conners' CPT). On the basis of standard analyses, the ADHD group had a longer MRT and greater SD and skewness. However, an Ex-Gaussian analysis revealed that, compared with controls, the ADHD group had lower estimates of μ (ie, faster RTs) but a greater τ (ie, more long RTs). The former analysis would suggest inefficient responding (slow, inaccurate, and variable), whereas the latter analysis might suggest impulsive responding (fast and inaccurate) combined with interspersed long RTs owing to lapses of attention.

The Ex-Gaussian analysis has been applied to evaluate cognitive response to stimulant medication. Epstein *et al* (2006) evaluated the performance of 316 ADHD children in the MTA at the 2-year assessment, who were tested on the Conners CPT. At this assessment, 190 of the 316 (60%) were taking stimulant medication and 126 (40%) were not. A comparison of the self-selected subgroups evaluated by traditional analysis of RT (mean and SD) revealed that the subgroup on medication responded faster and was less variable than the subgroup off medication, but the Ex-Gaussian analysis revealed that this was owing to a reduction in τ (suggesting fewer long RTs in the inattentive state) and an increase in μ (slower RTs in the attentive state). Thus, the modeling of RT distributions by the Ex-Gaussian approach leads to very different conclusions about the underlying effect of stimulant medication on cognitive processing.

Other methods have been developed to evaluate skewed distributions of RTs. Instead of randomly varying owing to either a normal or exponential process, Castellanos *et al* (2005) hypothesized that RTs varied systematically over time with a slow cycle of about 10–20 s that reflected underlying variation at the synaptic level of the DA system (Walters *et al*, 2001). This systematically cyclical variation can be evaluated by using a fast Fourier transform (FFT) analyses of RTs, which also depend on the temporal characteristics of the task, such as the inter-trial interval (ITI) and the total time of a block of trials, that set the upper frequency (1/twice the ISI) and the lower frequency (1/half the duration of each block). Castellanos *et al* (2005) applied FFT analysis to evaluate RTs from the Eriksen–Flanker Task with an ITI 3 s and six trial blocks of 180 s each, which allowed for FFT decomposition into frequencies from 0.17 (1/6) and 0.011 Hz (1/90). The usual summary statistics (mean and SD) suggested that the ADHD group had overall greater variability in responding, but the FFT analysis revealed that the magnitude of the systematic waxing and waning was greater for the ADHD than the control group (ie, oscillations centered at 0.05 Hz were present in both groups, but the power at this frequency was 50% greater for the ADHD than the control group). Following this innovation, others have used FTT analysis of RTs in studies of cognitive deficits of ADHD. For example, Di Martino *et al* (2008) used RTs from an Eriksen–Flanker task with a single 15 min block of trials, Vaurio *et al* (2009) used RTs from a

Go–NoGO task, and Johnson *et al* (2008) used RTs from a sustained attention to response task (SART) that requires response to a fixed sequence of digits (1–9), except for the digit 3. In general, FFT analyses of these studies revealed that the ADHD group differed from the controls owing to an increase in power in the frequency band reflecting periodic cycles about every 10–20 s (as hypothesized by Castellanos) that increase variance of the RT distribution.

The FFT analysis has also been used to evaluate response to stimulant medication. Castellanos *et al* (2009) used FFT analysis to evaluate the effects of stimulant medication on performance on the Eriksen–Flanker task (see above), and showed that the group difference observed at baseline (greater amplitude of oscillations centered at 0.05 Hz in ADHD) was no longer significant with medication. Johnson *et al* (2008) used FFT analysis of RTs from the SART (see above) and showed that treatment with medication (and average titrated dose of 0.51 mg/kg) over 6 weeks produced a decrease in the fast component of variability of RT.

In summary, we should emphasize that one of the most prominent cognitive deficits manifested in RT studies is increased variability, and that models of RT analysis have been applied to investigate underlying processes, such as randomly occurring lapses of attention (the Ex-Gaussian model) or systematic waxing and waning of attention (the FFT model) that affect RT. Task characteristics affect RT distributions and analyses, but this additional source of variation may be informative of the underlying cognitive processes. These models of analysis of RT distributions have been applied to evaluate effects of stimulant medication on cognitive processes such as attentional lapses ('mind wandering') or fundamental cyclical variation related to neurochemical processes and reflected in brain states, which has been addressed in the related concepts of 'resting state' or 'default mode' of brain function.

History of the Concept of the Resting State and Default Mode Network

Sonuga-Barke and Castellanos (2007) proposed that the skewed RT distributions of individuals with ADHD (see above) may be a consequence of interference by the default mode network (DMN) of the brain. Owing to the importance of DMN, as well as controversies about it, we will provide a brief review of this concept here.

Raichle (2010) provides a historical account of PET studies that led to the discovery of a 'constellation of brain regions now generally referred to as the DMN' (p 182). Breakthrough studies are reviewed that link the PET studies of the DMN to fMRI studies, which revealed 'spatial coherence in the spontaneous fluctuations (ie, noise) in the fMRI blood oxygen level-dependent (BOLD) signal'. As shown in Figure 1a, these brain regions—posterior cingulate cortex (PCC)/precuneus, medial prefrontal (MPF), and the lateral parietal cortex (LP)—have correlated increases in BOLD activity during the resting state when a task is not being performed shown in slow wave (0.1 Hz)

cycles. Fox and Raichle (2007) provide a review of resting state fMRI studies, which consistently show within-subject positive correlations of the slow cyclical fluctuations of BOLD signals from the brain regions within the DMN (ie, PCC, MPF, and LP—see the red and yellow lines in Figure 1b).

Brain regions that are typically activated by task performance also show highly correlated cyclical fluctuations in BOLD signals (or functional connectivity), although this activity is out of phase with the waxing and waning of the BOLD signals from the DMN. Fox and Raichle (2007) used as an example a task-positive network related to focused attention and working memory that during the resting state is associated with opposing (anticorrelated) decreases in activity in the intraparietal sulcus (IPS), frontal eye field (FEF), and middle temporal (MT) brain regions (see the blue line in Figure 1a). The intrinsic brain activity in the task-positive network is out of phase with the intrinsic activity of the DMN, so the correlation of the spontaneous cyclical activity in the two networks over time is high—but negative or anticorrelated (see Figure 1b). Dosenbach *et al* (2007) described a dual-process task-positive network consisting of a frontoparietal component that initiates and adjusts control and a cingulate–opercular component that maintains task orientation over time and '…might in part support a basic domain-independent and externally directed 'task mode' in opposition to the brain's
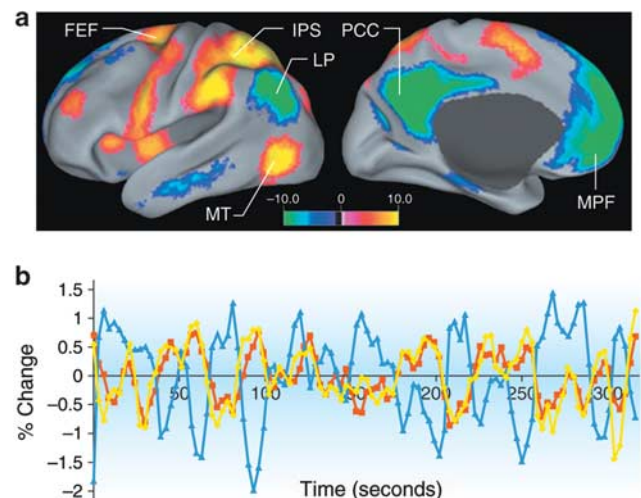

Figure 1. Anticorrelated brain activity in a component of the task-positive network related to externally cued attention. (a) The intraparietal sulcus (IPS), frontal eye field (FEF) and middle temporal (MT) areas are the positive nodes (shown in warm colors) and are significantly correlated with seed regions involved in focused attention and working memory (task-positive seeds). The task-positive seeds are significantly anticorrelated with seed regions that are routinely de-activated during attention-demanding cognitive tasks (task-negative seeds shown in cool colors) and located in the posterior cingulate cortex (PCC)/precuneus, lateral parietal cortex (LP), and medial prefrontal cortex (MPF). (b) The bottom actograms represent the time course for a single run based on the seed region (PCC, in yellow), a region positively correlated with this seed region in the MPF (orange), and a region negatively correlated with the seed region in the IPS (blue). Modified with permission from Fox and Raichle (2007) and Fox *et al* (2005).

default mode' (p 11076). On the basis of this, we will use the label 'task mode network' (TMN) for comparisons to the DMN. Of course, there are multiple TMNs dependent on the cognitive demands of tasks, and each may be related (or anticorrelated) with the same or different DMNs. For example, Fox et al (2006) proposed dorsal–ventral distinctions between a dorsal TMN and ventral DMN. The proposed TMN included the dorsal–lateral and dorsal–ventral prefrontal brain regions that are activated by a variety of cognitive tasks. The proposed ventral network (equivalent to the DMN) included the MPF, posterior cingulate, and lateral parietal brain regions, which are assumed to be activated when not performing a task (in the 'resting state'). Fransson (2006) presented a similar conceptual framework of cognitive control and proposed the brain switches ('toggles') between the DMN and TMN. De Luca et al (2006) identified five resting state networks (RSNs), and one of these (RSN-2) was equivalent to the DMN described by Raichle (2010) and Fox et al (2006a) and depicted in Figure 1.

There is evidence from several studies that spontaneous BOLD fluctuations during task performance are related to trial-to-trial variability in task-related evoked signals (Fox et al, 2006b; Fransson, 2006). This suggested the exciting possibility of linking temporal variation in brain states to variability in behavior or performance on a task, such as variability in force applied in a key press response task (Fox and Raichle, 2007) or variability in RT (Weissman et al, 2006). For the purposes of the current review, the most relevant demonstration of the cyclical anticorrelated fluctuations of BOLD activity in the DMN and TMN is provided by Kelly et al (2008). The brain regions emphasized by Kelly et al (2008) and the pattern of negative correlation between BOLD activity in the DMN and the TMN for the Eriksen–Flanker Task are shown in Figure 2a.
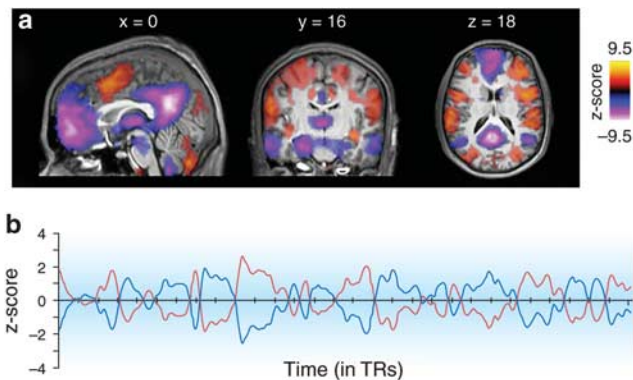

Figure 2. The pattern of negative correlation between blood oxygen level-dependent (BOLD) activity in the default mode network (DMN) (equivalent to RSN-2) and the task-positive network for a component of the attentional network task (ANT) task. (a) Z-score threshold maps of the spontaneously active (task-independent) DMN (purple/pink) and its negatively correlated task mode network (TMN) (red/orange). (b) An individual example of a nearly perfect negative correlation ($r = -0.97$) between DMN and TMN antiphase time series. Reprinted with permission from Kelly et al (2008).

High negative correlations (see Figure 2b for an individual example) were observed for all of the 26 subjects evaluated, with a range from -0.80 to -0.97, and this inter-subject variation in the degree of anticorrelation was related to inter-subject variation in performance measures of the task (RT variance): the subjects with the higher anticorrelations had lower RT variances in performance of the task.

It is important to mention that raw fMRI data from the resting state must be edited to remove contaminating motion artifacts and various other sources of physiological noise. Some experts have suggested that these techniques might introduce spurious negative correlations upon regressing out whole brain signals (Murphy et al, 2009; Van Dijk et al, 2009). Beyond the technical questions, it is necessary to contend with the claim that '…the observation of a difference between a subtraction and a reverse subtraction is not evidence for the importance of the baseline' (Morcom and Fletcher, 2007). Clearly, the use of global regression techniques warrants extra caution when interpreting the directionality, or even the meaning of resting state relationships. On the other hand, it has been pointed out that several of the characteristics of anticorrelated networks (eg, spatial distribution, cross-subject consistency, presence with modified whole brain masks, and existence before global regression) cannot be attributed readily to global signal removal, which supports the notion that these signals represent a true underlying biological phenomenon instead of a statistical artifact (Fox et al, 2009).

Despite these caveats and concerns, in summary we should emphasize that the discovery of the intrinsic organization of brain activity and the development of fMRI methods to characterize networks and functional connectivity offer the exciting possibility of an important new way to map brain organization and to investigate disorders (such as ADHD). It is important to recognize that this can be accomplished without the use of a task (ie, in the so-called resting state) as well as with a variety of tasks. This DMN approach is consistent with a hierarchical organization of brain networks (Raichle, 2010): the DMN may be a 'hub' at the top of a hierarchal organization, which operates '…to organize information for interpreting, responding to, and even predicting environmental events'. In this organization it is assumed that this '…activity is modulated by phase resetting to match incoming information, to increase activity in brain areas associated with goal-directed behavior, and to enhance performance on cognitive tasks.'

Theoretical Approach and Empirical Tests in the ADHD Area

Sonuga-Barke and Castellanos (2007) used the concept of anticorrelated networks (which we have outlined in Figures 1 and 2) to propose an alternative to the traditional top–down model of ADHD based on executive function deficits (which we reviewed in 'Background studies on the effects of stimulants in cognition in ADHD' above). During the

resting state, this theory proposes a recurrent toggling or switching (Fransson, 2005) between a state of self-reflection (an 'Introspective' state) and a state of attentive readiness (an 'Extrospective' state). Sonuga-Barke and Castellanos (2007)) proposed the default-mode interference hypothesis to account for the systematic increased intraindividual variance in RT tasks (which we have reviewed in 'History of the concept of the resting state and default mode network' above). They considered the task-positive and task-negative networks together as a default mode state in which spontaneous fluctuations are synchronized in the opposing (anticorrelated) relationship described in Figure 1. This produces a corresponding cyclical pattern of Introspective and Extrospective states. When a task is initiated, they propose the magnitude of the fluctuations in Introspective and Extrospective states is decreased but, over time, this magnitude increases, crossing a threshold at some point that they label the 'default mode interference threshold'. When this occurs, they propose a lapse of attention results in a long RT. In individuals with ADHD, the recovery and 'default mode interference' is faster and the lapses of attention are more frequent than in non-ADHD individual when performing a task (such as the Go–NoGo, STOP, or ANT), resulting in an increase in the intraindividual variance of RTs that creates a skewed distribution.

A few recent fMRI studies of ADHD and the intrinsic activity in the resting state provide data that can be used to evaluate the default mode interference hypothesis. Tian *et al* (2006) evaluated resting-state functional connectivity in 12 adolescents (11–15 years of age) with ADHD and 12 controls based on correlations with the dorsal anterior cingulate gyrus shown to function abnormally in task-based fMRI studies. The ADHD group had greater resting state connectivity than the controls in multiple brain regions (bilaterally in the dorsal anterior cingulate, pons, insula, cerebellum, and thalamus), which was interpreted as abnormalities in areas involved in autonomic control. Zang *et al* (2007) evaluated 13 adolescents with ADHD and an age-matched control group (average age about 13 years), and reported increased functional connectivity for some brain regions (right anterior cingulate gyrus, left cerebrum/fusiform, right inferior temporal gyrus, left sensorimotor cortex, and bilateral brain stem regions in the midbrain and pons) but decreased on others (right inferior cortex, bilateral cerebrum, and cerebellar vermis). An observed increase in right anterior cingulate gyrus activity in the resting state was particularly interesting because it suggested the opposite of the expected ADHD-related deficit (decreased activity) when performing a task. Similarly, Yang *et al* (2010)) also evaluated children in a resting state fMRI study and reported that, compared to controls, the ADHD group had specific brain regions displaying either higher and lower functional connectivity. Even though these group differences may be compounded by large differences in IQ, the nature of the regions involved could be tentatively interpreted as a reflection of abnormalities in intrinsic brain organization in the frontal cortex in

ADHD children in the resting state. Castellanos *et al* (2008) found that a group of adults with ADHD had reduced negative correlation with a region in the DMN (precuneus/ posterior cingulate gyrus). This decreased functional connectivity during the resting (which partially contradicts Tian *et al* (2006), who reported increased functional connectivity between the dorsal anterior cingulate and widespread regions involved in autonomic control) was interpreted as an abnormality in the interactions between the TMN and DMN. This may underlie performance deficits in the task state—attentional lapses and the periodic long RTs that characterize the performance of individuals with ADHD when they perform a task. Uddin *et al* (2008) also study the DMN in the same sample of adults with ADHD and found that, compared to controls, network homogeneity was lower for one region (the precuneus). This was interpreted as abnormal function of a highly integrative structure with connections to many cortical (eg, anterior cingulate gyrus) and subcortical (eg, striatum) brain regions implicated in ADHD.

Fassbender and Schweitzer (2006) evaluated functional connectivity during the performance of tasks (a visual serial visual search task, an addition task, and a matching to sample task). They investigated the persistence of anticorrelated BOLD activity in task-negative networks (ie, the DMN) during task performance and the ability to deactivate the task-negative DMN during task performance that is reflected in TMNs. They compared the RT performance of 12 ADHD and 12 control children, which by Ex-Gaussian analysis showed the skewness presumed to occur owing to periodic lapses of attention. The groups differed in the degree of deactivation of the DMN: during performance of the most demanding (visual search), the ADHD group showed less deactivation of the medial PFC than the control group. The ADHD group also showed greater intraindividual variability, which was negatively correlated with activity in the PCC. This was interpreted as a relative weakness in the ADHD individuals to suppress activity in the DMN during performance of a working memory task, and it provided support for the hypothesis of Sonuga-Barke and Castellanos (2007) of default mode interference as a cause of periodic attentional lapses and long RTs.

Wolf *et al* (2009) evaluated 12 adults with ADHD and 12 age-matched controls during performance of a three-phase (encoding, delay, and probe) working memory task. The groups did not differ in performance of this task, but they did differ in the patterns of brain activation elicited by the task (ie, in the task-positive networks for working memory) and in the functional connectivity estimates during the delay phase of the task. The ADHD group had less functional connectivity for some brain regions (ventral–lateral PFC, anterior cingulate gyrus, superior parietal, and cerebellum) and greater functional connectivity for other brain regions (right PFC and left dorsal anterior cingulate gyrus, and cuneus). This was interpreted as consistent with the hypothesis of ADHD-related dysfunction of the prefrontal–parietal, anterior cingulate, and cerebellar brain

regions proposed based on anatomical and functional imaging studies that we outlined in the Introduction (Bush, 2010; Castellanos and Tannock, 2002b).

Peterson et al (2009) used the Stroop task in an fMRI study of children without ADHD ($n = 20$) and children with ADHD ($n = 16$) evaluated on and off of their established clinical doses of stimulant medication. They found significant differences in brain activation for the ADHD group off medication compared with the control group, suggesting that the ADHD group was not able to suppress activity in the DMN to the same degree as the control group, and in the ADHD group medication appeared to improve the suppression of DMN activity in the ventral anterior cingulate gyrus.

In summary, we should relate the literature on variability of RTs and the literature on functional connectivity. The literature based on multiple RT paradigms suggests that ADHD individuals have an increased proportion of infrequent long reactions that skew the distribution of RTs and may reflect lapses of attention. The literature on brain states suggests that spontaneous cyclical activity is correlated across brain regions related to cognition, and is organized in opposing TMN and DMN (ie, task-positive and task-negative networks—see Figures 1 and 2). The BOLD activity from fMRI signals may be related to variation in RTs. In ADHD, abnormalities in functional connectivity have been documented, but both increases and decreases relative to controls have been observed. Increased activity in the DMN was present in some studies, which is consistent with the hypothesis that ADHD individuals may have increased intrusions during task performance that are manifested as lapses of attention and variable patterns of response that reflect in part improper deactivation of the DMN. Stimulant medication may facilitate the deactivation of the DMN and alleviate the ADHD symptoms of inattention and their variable manifestation over time.

INTEGRATION OF ATTENTION AND MOTIVATION

Attention

In the previous sections, we discussed this evidence for attentional deficits in ADHD from the perspective of the cognitive neurosciences. We have focused on the impaired ability to suppress ongoing actions or pre-potent responses that is one of the hallmarks of the theory of a core inhibition deficit of ADHD (Barkley, 1997) and is one of the most disruptive aspects of ADHD (Kenemans et al, 2005). In addition, we have also explored a variety of deficits manifested in three cognitive components of attention (alerting, orienting, and executive control) linked to specific neural loci (right frontal, parietal, and anterior cingulate gyrus) and neurotransmitters (norepinephrine, acetylcholine, and DA (see (Posner and Rothbart (2009)). Another model of attention proposes two networks; a dorsal network involved in top-down orienting of attention and a ventral attention network involved in reorienting attention in

response to salient sensory stimuli (Corbetta and Shulman, 2002; Fox et al, 2006a). As discussed above, the ventral attention network orients attention to internal or Introspective processes and is part of the DMN that is activated in the so-called resting state (see discussions in 'Background studies on the effects of stimulants in cognition in ADHD' and 'Theories of response variability and default mode network' and Figure 1). The DMN is deactivated during cognitive operations but not completely suppressed, as the dorsal TMN is activated (see Figure 2), resulting in anticorrelation of BOLD activity even during the task state (Fox et al, 2006a). To evaluate cognitive deficits in ADHD, both Introspective and Extrospective processes appear to be important, and neuropsychological and brain imaging methods are being developed to characterize ADHD-related cognitive deficits and effects of stimulant medication that may correct them (see Sonuga-Barke and Castellanos (2007)).

Motivation

Motivation and reward may represent another 'core' deficit of ADHD (Luman et al, 2005). The notion that ADHD involves an underlying dysfunction in reward and motivation was proposed over two decades ago (Haenlein and Caul, 1987), revived a decade ago (Iaboni et al, 1997), and emphasized in some current theories of ADHD (see below). Several new theories of motivational deficits have been proposed over the past decade. Johansen et al (2002) proposed a theory based on the premise that ADHD children have a steeper than normal delay-of-reinforcement gradient, and Sonuga-Barke (2002) proposed a theory based on the premise that some ADHD children have an aversion to delay of reinforcement.

Luman et al (2005) evaluated the frequency and magnitude of reinforcement on a learning task by contrasting performance of ADHD children ($n = 23$) and controls ($n = 30$), as well as a clinical control group of children with autistic spectrum disorder ($n = 21$). The ADHD group was unaffected by the manipulation of reinforcement by frequency or magnitude of reinforcers. Bitsakou et al (2009) evaluated delay aversion in children with ADHD ($n = 70$), a control group of unaffected siblings ($n = 65$), and a normal control group ($n = 50$). Multiple tasks were administered and an overall index of delay aversion was used to contrast the groups. The contrasts revealed a significant difference between the ADHD and normal control group (es = 0.9), and even though the difference compared to the familial control group was not significant, the average for the sibling control fell midway between the average for the ADHD and the normal control groups. Shanahan et al (2008) evaluated children with ADHD ($n = 25$) and normal controls ($n = 30$) using the STOP task with and without motivation. This study documented significant main effects of motivation on overall RT, variability of RT, and SSRT, but the critical group by motivation interaction was not significant. Shiels et al (2008) tested children with ADHD ($n = 21$) in

a crossover design to evaluate the effects of a behavior modification technique (point system with back-up reinforcers) on a spatial span task that required storage (forward span) and manipulation (backward span). Motivational incentives enhanced performance on the backward span, but not the forward span task. In an epidemiological study of 1156 children, Kuntsi *et al* (2009) used a Go–NoGo task to evaluate RT and RT variability in the 5% of children with the highest ratings of ADHD ($n = 58$) compared with the remainder of the population sample ($n = 1098$). In the baseline task, with a slow event rate (8 s), the ADHD group had longer average RT and higher intraindividual variability (average mean RT = 1018 *vs* 943 ms; average SD = 495 *vs* 404 ms). To improve performance on the task, a fast event rate (1 s) was used and incentives were provided by a point system (1 point earned for correct responses, 1 point lost for omission errors, and 5 points lost for commission errors, with a prize as back-up reinforcement). Compared with the performance on the task with a slow event rate and no incentive, the combination of a fast event rate and the incentive condition normalized speed of response (mean RT = 653 *vs* 648 ms) and intraindividual variability (SD = 217 *vs* 203 ms).

A few recent studies evaluated the effects of medication and motivation (reinforcement) on brain function. For example, Rubia *et al* (2009) evaluated children with ADHD ($n = 13$) and normal controls ($n = 13$) on CPT task performed in an fMRI study of 'cool' attentional and 'hot' motivational brain networks. The CPT had 48 occurrences of two targets (24 each of the letters X and O) embedded in 416 trials, and correct responses to one of the targets was rewarded with money. Off medication, the ADHD group had significant performance deficits on CPT, and reduced activation of a brain network that connected frontal, striatal, parietal, and cerebellar brain regions and increased activation of orbitofrontal and superior temporal brain regions. Medication normalized the attentional network (upregulating activity) and in the motivational network (downregulating reward-induced overactivity). A recent neuroanatomical study (Carmona *et al*, 2009) provided clear evidence of alterations in the ventral striatum of children with ADHD. This finding is consistent with recent fMRI data showing ventrostriatal hyporesponsiveness during immediate and delayed reward processing in adults with ADHD (Plichta *et al*, 2009; Strohle *et al*, 2008). Tripp and Wickens (2008) proposed the DA transfer deficit theory and suggested that children with ADHD have diminished cellular responses of DA cells to cues that precede reinforcement.

In summary, we should emphasize that multiple theoretical approaches have emerged in the literature that suggest that ADHD children manifest impulsive behavior that is characterized by preference for small immediate reinforcers over large delays reinforcers (see reviews by Johansen *et al* (2009) and Luman *et al* (2005)). Recently, the emerging critical issues in this area of motivation or reinforcement deficits in ADHD were addressed at the European Network

of Hyperkinetic Disorders (EUNETHYDIS) 2009 Conference (Sergeant *et al*, 2009) and in an international workshop at Okinawa Institute of Science and Technology (Tripp and Wickens, 2009). Another comprehensive review would be premature, but studies in this area are increasing, and this represents a new direction for the evaluation of cognitive deficits in ADHD and the possible correction of these deficits by stimulant medication.

Neuronal Targets of Stimulant Medications

Several brain regions and circuits are involved in the orchestration of specific cognitive processes that impact attention; these circuits are modulated by the catecholaminergic system and thus are affected and modulated by stimulant medications (Wilens, 2008). Most of our knowledge about the mediation of the therapeutic effects of stimulants derives from studies focused on the PFC and striatum, but there is increasing evidence of the relevance of catecholaminergic modulation in limbic regions such as ventral striatum (perhaps also amygdala and hippocampus) in mediating the motivation enhancing effects of stimulant drugs (Lehmann *et al*, 2003; Wilens, 2008).

As reviews of brain imaging studies document (see Paloyelis *et al*, (2007) for a systematic review), many studies that compare ADHD and control groups have documented a long list of possible anatomical (Krain and Castellanos, 2006) and functional (Dickstein *et al*, 2006) abnormalities associated with ADHD. As reviewed and discussed in 'Background studies on the effects of stimulants in cognition in ADHD', the most consistent patterns include abnormalities revealed by anatomical MRI (ie, reduced global size as well as brain regions in frontal lobes, basal ganglia, and cerebellum (Krain and Castellanos, 2006), and by functional MRI (ie, frontal hypoactivity affecting anterior cingulate, dorsolateral prefrontal and inferior PFCs, portion of the parietal cortex, as well as basal ganglia and thalamus; see Dickstein *et al* (2006)). Moreover, recent studies have shown that disruptions in ADHD affect not only the activity in these brain regions but also the way in which these regions connect with one another to form specific networks. The fMRI methods are highlighted in Figures 1 and 2 and discussed in detail in 'Theories of response variability and default mode network'. In the next section, we will discuss PET methods that address the evaluation of neural mechanisms related to the cognitive deficits in ADHD and their possible correction by treatment with stimulant medication.

PET IMAGING AND COGNITIVE PROCESSES IMPLICATED IN ADHD AND EFFECTS OF STIMULANT DRUGS

Neural Deficits Related to ADHD

Patients with ADHD present with specific cognitive deficits, which may be the consequence of impaired attention or

motivation or both. In previous sections, we based our interpretations on the literatures on neuropsychological performance (see 'Background studies on the effects of stimulants in cognition in ADHD') and fMRI imaging of functional activation and functional connectivity in task-negative and task-positive networks of the brain (ie, the DMN and TMN—see 'Theories of response variability and default mode network'). On the basis of the PET imaging approach, the literature and concepts are somewhat different. Here, we discuss the neurobiological substrates underlying the cognitive processes evaluated by PET imaging, which have contributed considerably to our knowledge on how stimulants may modulate them.

PET studies have investigated the mechanisms of DA transmission and their relationships to the hyperactive-impulsive and inattentive symptoms of children with ADHD. The DA hypothesis of ADHD was proposed decades ago (Levy, 1991; Wender, 1971), based partially on the hypothesis that stimulants acted as DA agonist drugs and that the increase in synaptic DA was a critical factor in the response to stimulant medication. PET study confirmed this hypothesis, first with intravenous doses of MP (Volkow et al, 1995, 1999a) and then with oral clinical doses of MP (Swanson et al, 1999; Volkow et al, 1999b, 2002).

Surprisingly, it is still unclear and debated whether DA activity is enhanced or depressed in individuals with ADHD. For the past decade, a generally accepted under-pinning of biological theories of ADHD has been that this disorder is associated with abnormally high levels of DAT density, which were suggested by studies using single photon emission tomography to evaluate small samples of ADHD adults (Dougherty et al, 1999; Krause, 2008). These studies were based on the hypothesis that high DAT density would accelerate reuptake of synaptic DA and create a DA deficit. Some recent PET studies seem to corroborate these early findings: Larisch et al (2006) reported a modest increase in striatal DAT density in adults with ADHD, and a similar study (la Fougere et al, 2006) reported hetero-geneous distribution, including high DAT densities. In one of the largest studies so far, Spencer et al (2007) evaluated unmedicated ADHD adults and reported striatal binding potential was at 2 SD above the mean for the control group.

Some studies suggest the reverse. For example, in a PET study Jucaite et al (2005) observed reduced DAT binding in the midbrain of adolescents with ADHD. In a series of PET studies using the radioligands C^{11}raclopride and C^{11}co-caine, Volkow et al (2007) assessed the density of DAT and DA D2/D3 receptors in the striatum of stimulant-naïve adults with ADHD. Individual differences in MP-induced increases in synaptic DA were not related to individual differences in DAT density (Volkow et al, 2002), suggesting that DA release rather than the DA reuptake may be a primary factor contributing to a DA deficit in the ADHD brain and the manifestations of deficits in attention. Volkow et al (2009b) found lower DAT and D2/D3 receptor density in the nucleus accumbens as well as the caudate nucleus. In a prospective long-term treatment study of MP (Wang et al,

2009), DAT density was reassessed in a subset of these ADHD patients after 1 year, with a 24-h washout to avoid the confusion of DAT density with DAT occupancy by MP. The formerly decreased DAT density was now increased in the same individuals, suggesting that neuroplasticity may operate in a homeostatic way to maintain DA levels in a narrow range: in response to high synaptic DA that results from blockade of DAT by clinical oral doses of MP (Volkow et al, 1999b, 2002), DAT density may increase and be a consequence of the DA agonist effect of MP. This may contribute to acute tolerance (Swanson et al, 1999; Volkow et al, 1998, 2001, 2002) and possibly long-term tolerance (Coghill et al, 2007; Vitiello et al, 2001) to clinical doses of stimulant medications.

In summary, the literature on PET imaging supports the DA hypothesis of ADHD, but the specific details are not yet clear. Some studies support the DAT excess hypothesis, which results in a DA deficit owing to increased reuptake of synaptic DA, whereas others support the hypothesis of DAT plasticity that resets density based on levels of synaptic DA, which may be low in stimulant-naïve individuals but high in treated individuals with clinical doses of MP as a result of adaptation to treatment rather than the presence of the disorder.

PET Studies of Attention and Motivation

On the basis of PET imaging studies, it has been hypo-thesized that stimulant medications may act by facilitating the engagement of a dorsal task-positive attention network and the deactivation of the ventral resting state network or DMN (Volkow et al, 2008). This may reflect in part improved filtering out of task-irrelevant stimuli by way of stimulant-mediated DA and NE release in the PFC and anterior cingulate gyrus (Arnsten, 2006). Other PET imaging studies of effects of stimulant medications on the brain have shown increased regional blood flow in the anterior cingulate gyrus (Udo de Haes et al, 2007). Also, PET studies have suggested that non-responsiveness to stimulant medications could be partially explained by different patterns of cerebral blood flow in anterior cingulate gyrus (Cho et al, 2007).

As a result of their ability to increase DA, stimulants appear to enhance the motivational saliency of cognitive tasks. On the basis of findings from a PET study that showed a significant association between MP-induced DA increases in the striatum and the perception as to how interesting the task was, Volkow et al (2004) postulated that stimulant's therapeutic effects may be mediated in part by their ability to enhance motivation. Increased interest may explain why stimulants improve performance of a boring task in normal healthy individuals as well as in ADHD individuals (Robbins and Sahakian, 1979; Sahakian and Robbins, 1977) and why unmedicated children with ADHD are able to perform properly when the task is salient to them (Groom et al, 2010).

In summary, we should note that recent findings from PET brain imaging studies have documented that the DA deficits in ADHD were most prominent in the ventral striatum (a crucial brain region for modulating reward and motivation) and in the midbrain (where most DA neurons are located), which highlights the relevance of the reward/motivational circuit in this disorder (Volkow *et al*, 2009b).

PET Imaging Studies of ADHD Adults and Effect of Stimulant Drugs

The effects of MP at its site of action in the brain have been studied extensively with PET. Imaging studies have corroborated the ability of oral MP to induce significant levels of DAT blockade in the striatum, with an estimated ED50 (dose required to block 50% of the DAT) of 0.25 mg/kg (Volkow *et al*, 1999a). Imaging studies have also shown that MP and AMP, at clinically relevant doses, can significantly increase extracellular DA (Villemagne *et al*, 1999; Volkow *et al*, 1999b, 2009a). Imaging studies in non-human primates have also shown significant blockade of the NE transporter at doses that are pharmacologically equivalent to those used in humans, which is interesting in light of the data indicating that enhanced extracellular catecholamine levels in cortical regions, secondary to NE reuptake inhibition, improves multiple aspects of inhibitory control over responding in rats and monkeys (Seu *et al*, 2009). Synaptic levels of DA and NE, under physiological conditions, act primarily as neuromodulators changing the efficacy of other transmitter signals (Keeler *et al*, 1989; Kiyatkin, 2002) as a function of ongoing neuronal activity (Seamans and Yang, 2004). For example, in the striatum, applications of DA decrease the activity of spontaneously active neurons to a greater extent than that of glutamate-stimulated neurons (Kiyatkin and Rebec, 1996). These increases in glutamate-induced excitation relative to baseline are assumed to improve signal-to-noise neuronal activation (Rolls *et al*, 1984). Norepinephrine can also facilitate excitatory transmission by depressing the level of basal activity (Woodward *et al*, 1979). Thus, by virtue of their DA and NE amplifying capacity (Kuczenski and Segal, 1997; Solanto, 1998), stimulants may enhance task-specific signaling in target neurons within specific circuits.

By enhancing signal-to-noise ratio of neuronal activity, stimulant medications may render the brain more efficient.

And there is evidence from brain imaging studies suggesting that this may indeed be the case. For example, using PET and FDG, Volkow *et al* (2008) compared brain glucose metabolism in controls when performing a cognitive task (numerical calculations) with or without MP. As shown in Figure 3, compared with placebo, MP significantly reduced the amount of glucose utilized by the brain when performing the task (the increase was reduced by about 50%). This reflected both a decrease in the magnitude of task-dependent regional activation and greater deactivation of regions from the DMN that has been described in Raichle (2010) and implicated in ADHD (Sonuga-Barke and Castellanos, 2007). This suggests that, compared with placebo, MP reduced (focused) the use of attentional resources in the human brain that are necessary to achieve similar levels of performance on a task. Moreover, subsequent PET studies that measured availability of DAT and functional activation/deactivation (measured with fMRI) during visual attention revealed a positive correlation between DAT and activity in the DMN, such that the higher the DAT, the less the deactivation of the DMN. As stimulants block DAT, this was interpreted to indicate that stimulant therapeutic actions reflect in part their ability to facilitate and sustain the deactivation of the DMN during task performance (Tomasi *et al*, 2009).

These findings are also consistent with those reported by previous PET imaging studies showing reductions with MP in the CBF increases in the dorsolateral PFC and posterior parietal cortex when controls performed a working memory task (Mehta *et al*, 2000). Similarly, imaging studies reported that MP reduced the CBF increases in the PFC when adults with ADHD performed a task of executive function (Schweitzer *et al*, 2004). Moreover, as recent studies provide evidence of deficits in the DMN in ADHD (Uddin *et al*, 2008), this may be a target for the therapeutic effects of stimulants.

Focusing of regional activation during task performance by stimulant medications may be beneficial when neuronal resources are diverted (ie, by 'mind-wandering') by the situation or task (Dodds *et al*, 2008) or by personality (Clatworthy *et al*, 2009), as well as by the presence of the disorder (ADHD). This may lead to an inverted U-shaped relationship between the effect of DA and performance, based on the premise that deficits as well as excesses of DA (and of NE) can impair cognition (see Figure 4). Thus, the
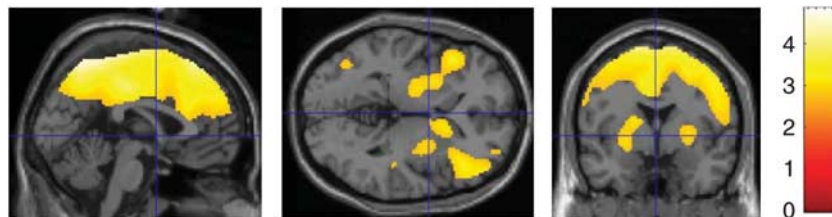

Figure 3. Differences in task activation between placebo (PL) and methylphenidate (MP). Statistical Parametric Mapping (SPM) results showing the areas (in yellow) that had greater increases in metabolism when the cognitive task was given with placebo *vs* when it was given with MP. Comparisons correspond to paired *t*-tests ($p < 0.005$ uncorrected > 100 pixels). None of the brain regions had higher metabolism for the cognitive task when given with MP than with placebo. Reprinted with permission from Volkow *et al* (2008).
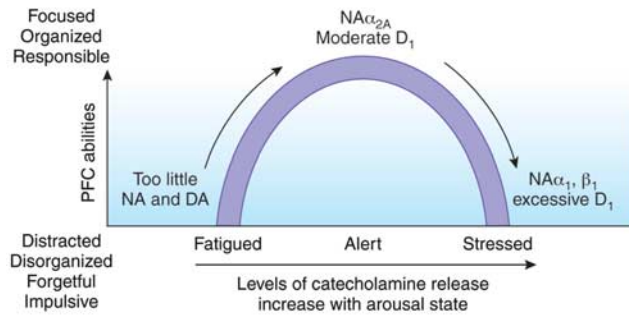
Figure 4. U-shaped curve relating activity on the prefrontal cortex (PFC) to levels of catecholamine release. As noted by Arnsten (2009), the PFC is very sensitive to catecholamine levels, with which it is suffused as a function of the arousal state. As proposed, PFC function is impaired whenever too little or too much catecholamine is released. In this schematic representation, moderate levels of noradrenaline (NA) and dopamine (DA) improve PFC function by optimally engaging their cognate receptors. Reprinted with permission from Arnsten (2009).

effects of stimulant drugs *could be detrimental* when brain activity is already optimally focused. This would also explain why stimulants may have beneficial effects in some individuals and not others, and beneficial effects in certain contexts and detrimental effects in others. Indeed, the inverted U-shaped relationship between cognitive performance and dopaminergic and noradrenergic signaling in frontostriatal circuits has been proposed to account for the intra- and interindividual differences in the effect of stimulant medications in ADHD patients. On the basis of animal models (Berridge *et al*, 2006; Robbins and Arnsten, 2009), the optimum alert state (see Figure 4) appears to be related to more moderate levels of activation of NE α-2A and DA D1 receptors in the PFC, but that stress-related increases of release of NE and DA and results in the activation of NE α-1 and β-1 receptor and excessive activation of D1 receptors (Arnsten, 2009).

Support for this hypothesis is provided by studies in laboratory animals, which have shown consistently that responses to stimulant drugs are determined in part by the state of the DA system (Deminiere *et al*, 1989; Hooks *et al*, 1991). Similarly, in laboratory animals, MP-induced increases in extracellular DA in the PFC are dependent on the conditions of its administration (Marsteller *et al*, 2002).

To the extent that the DA system (and possibly the noradrenergic system as well) is involved in ADHD, this could underlie the differential response to stimulant medications between controls and patients with ADHD. For example, in fMRI studies of children with ADHD (Vaidya *et al*, 1998) and of adults with ADHD (Epstein *et al*, 2007), MP's effects on striatal activation during performance of a task may recruit inhibitory control circuits that differ from those seen in healthy children. In a relevant fMRI study in non-ADHD adults, Dodds *et al* (2008) showed that the effects of MP on the brain depended on the task being performed, with attenuation of BOLD activity in the ventral striatum during phase of a reversal learning task

(after negative feedback) and modulation of the BOLD signal in the PCF in the face of distractions when response set was maintained. The context dependency of stimulant effects has also been shown in humans. For example, a PET study showed MP-induced increases in extracellular DA were greater when healthy subjects were exposed to a salient stimulus (visual display of food in food-deprived individuals or with exposure to remunerated stimuli) than when given with a neutral stimulus (Volkow *et al*, 2002). Also, in a PET study Clatworthy *et al* (2009) documented variability in MP effects on subregions of the striatum and changes in D2/D3 receptor for different tasks requiring reversal learning and spatial working memory.

FUTURE DIRECTIONS AND CONCLUSIONS

As knowledge with regard to human brain function increases, we should gain a better understanding of the various neuronal components implicated in functional deficits in ADHD (attention, inhibition and motivation) and how stimulant medications affect them. This, in turn will permit a much better characterization of the specific deficit(s) in any given ADHD patient. The advances in the definitions of cognitive deficits in ADHD and cognitive effects of stimulant medication (see 'Background studies on the effects of stimulants in cognition in ADHD') set the stage for a future when treatment might be personalized to target the specific deficits of a patient.

The literature suggests a few important directions to pursue. For example, it is intriguing that stimulant medications appear to have different effects depending on the context of administration and the type of task required, as it has been shown for classical neuropsychological tasks that require reversal learning and spatial working memory (Clatworthy *et al*, 2009) or responses within a task such as reversal learning (Dodds *et al*, 2008). It is also likely that fast shifting tasks with rewards (eg, a video game) (Koepp *et al*, 1998) may induce, by themselves, larger DA increases than slower tasks (memory or composition) that require maintenance of attention, so that these two types of tasks are likely to be differentially affected by stimulants. On the basis of the likelihood of a ceiling effect, it is reasonable to propose that stimulant medication would lead to a greater improvement in the performance of the latter compared with the former tasks. Also, the literature of RT distributions clearly shows context effects that alter the peak frequency of slow wave variations over time. Stimulants may also shift the engagement of attentional resources from favoring fast shifting stimuli with rewards to slow, changing stimuli that require maintained engagement. In general, little emphasis has been placed on understanding the energy requirement for cognitive performance and on how stimulant medications may affect this. Raichle (2010) has initiated a discussion of this topic and points out that task activation accounts for only a small proportion of the energy expenditure of the brain measured by glucose

utilization, and that the high-energy expenditure of background activity (in the so-called resting state) likely serves an important purpose. An emerging literature suggests that stimulant drugs decrease the energy requirements to maintain attentional resources engaged, and this could facilitate the engagement of attention for tasks that are energy demanding. Stimulant drugs may also change the cycling of the DMN and the relative predominance of task-negative (Introspective) over task-positive (Extrospective) brain states. Lapses of attention could reflect either a deficit in ability to maintain deactivation of the DMN or to an overactivation of this network. The analysis of RT distributions and the long reactions may provide a practical way to assess the periodic lapses of attention that are presumed to underlie them.

Despite the marked increase in our understanding of the function of the human brain and the neurobiological substrates underlying ADHD, our approach for treating the cognitive deficits that define this disorder has changed little over the past 50 years. However, one can predict that this will change in the next decade as genetic and epigenetic research identifies new targets for medications, and technologies evolve to help strengthen neuronal circuits that are impaired in ADHD. Similarly, this research may help develop personalized interventions that are tailored to an individual's unique impairments and strengths.

As brain imaging capabilities become more widespread, this may allow imaging studies to be part of clinical characterization for the neurobiological deficits in patients with ADHD and, in the future, these may also help optimize and follow treatment interventions.

DISCLOSURE

NV and RB declare that, except for income received from their primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service. JS has received support as an advisor, speaker, and expert witness from pharmaceutical companies (Johnson and Johnson, Shire, and Noven) that manufacture and market stimulant medications for the treatment of ADHD. None of the authors have personal financial holdings that could be perceived as constituting a potential conflict of interest.

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