



## NEWS & VIEWS

# Searching for a neurobiological signature of Attention Deficit Hyperactivity Disorder

**The search for a neurobiological marker of Attention Deficit Hyperactivity Disorder may be narrowed as functional magnetic resonance imaging reveals an atypical striatal response to methylphenidate in children with the disorder.**

Approximately 5% of school-age children in the United States are diagnosed with Attention Deficit Hyperactivity Disorder (ADHD), a neurodevelopmental disorder characterized by age-inappropriate symptoms of inattention, impulsivity, and hyperactivity. The disorder is linked to lower educational and vocational outcomes and increased risk of antisocial disorders and drug abuse in adulthood.<sup>1</sup> The primary form of treatment for ADHD is the prescription of stimulants, such as methylphenidate (Ritalin) and dextroamphetamine, that release and inhibit reuptake of catecholamines. These drugs relieve ADHD symptoms temporarily, but the reasons behind their effectiveness are not well understood.

Misdiagnosis is of significant concern among clinicians and parents because criteria rely on subjective evaluations of children's behaviors reflecting symptoms of inattention, impulsivity, and hyperactivity that, to a lesser degree are seen commonly in many children (eg, 'fidgets with hands and feet'). Furthermore, other disorders (eg, depression, oppositional-defiant disorder) mimic ADHD. The definition of biologically valid diagnostic criteria for ADHD could improve diagnostic accuracy. To date, however, there is no characteristic 'signature' for ADHD, either in the form of a brain landmark or a cognitive profile.

Understanding the neurobiology of ADHD, a first step in developing objective diagnostic criteria, may now be within reach due to advances in functional brain imaging methods. Studies using positron emission tomography (PET) and single photon emission computerized tomography (SPECT) indicate that the frontal lobes and the striatal regions have reduced metabolism in ADHD.<sup>2,3</sup> Further, methylphenidate, the most commonly prescribed drug for ADHD, enhances activity of these hypoactive regions.<sup>2</sup> Methylphenidate binds to dopamine transporter in *in vitro* and *in vivo* animal studies and is taken up primarily in the striatum, in resting-PET studies with healthy adults.<sup>4</sup> The striatum has numerous direct and indirect connections to the frontal cortex.<sup>5</sup> Thus, a working hypothesis about ADHD is that it is characterized by hypoactive frontal-

striatal regions due to deficient dopaminergic transmission. Further, abnormal dopaminergic function may be normalized by stimulant treatments.

This hypothesis is supported by two lines of research. First, direct evidence comes from a PET study that found abnormal dopaminergic presynaptic function in ADHD male adults.<sup>6</sup> Second, indirect evidence comes from structural brain imaging studies that found volumetric differences in frontal cortices and striatal structures (caudate and globus pallidus) between ADHD and control groups.<sup>7,8</sup> Structural abnormalities in these regions may index abnormal neurodevelopmental processes of dopaminergic function. These structural imaging studies, however, disagree with respect to the specific nature of the differences. Furthermore, other regions, such as the cerebellum and corpus callosum, also show abnormalities in ADHD.<sup>7,9</sup> These lines of work have made inroads into the neurobiological basis of ADHD, but they have been unable to provide a diagnostically useful marker. Moreover, these methods have limited clinical potential for several reasons: (1) PET, SPECT and structural MRI rely on group averaging for accurate information; (2) PET and SPECT carry risks associated with exposure to radioactivity; and (3) structural MRI has limited diagnostic use because there are no consistent structural landmarks for ADHD.

A more promising method may be functional magnetic resonance imaging (fMRI) which detects changes in the hemodynamic properties of brain regions participating in cognitive performance.<sup>10</sup> This method does not require exposure to radioactive tracers and can reveal accurate information in individual brains. We used fMRI to examine the effects of methylphenidate on frontal-striatal function during performance of Go/No-Go tasks that require control of impulsive responding, an ability that is impaired in ADHD.<sup>11</sup> The subjects were 8–12 year-old boys, 10 of whom had been diagnosed with ADHD and six of whom were healthy. Subjects had to push a button in response to all visually presented letters (Go trials), but withhold a response to the letter 'X' (No-Go trials). The letter 'X' occurred relatively rarely, and therefore, it was difficult to inhibit the impulse to respond. Two tasks were included that differed in the presentation parameters (rate and number) of the Go trials. By comparing fMRI activation during task-phases that contained No-Go

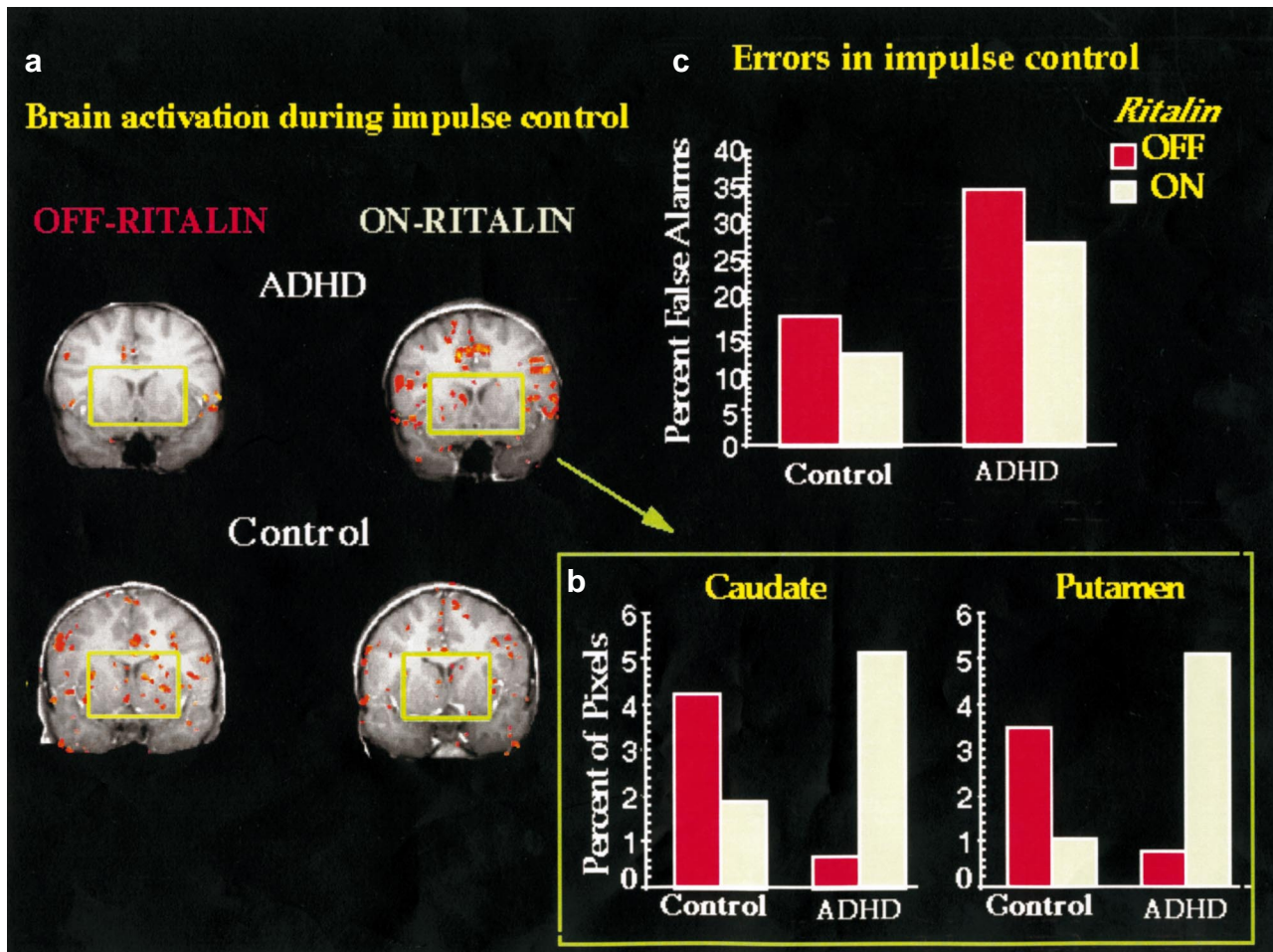
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trials with those that contained only Go trials, we were able to examine frontal-striatal involvement in inhibitory control. All children were scanned once with and once without methylphenidate. Thus, we were able to compare the drug's effects on inhibitory control both behaviorally and neurally.

Our study found some striking differences and similarities between ADHD and control children. Behaviorally, ADHD children had poor inhibitory control on both Go and No-Go tasks. Methylphenidate improved their performance on both tasks. In contrast, methylphenidate improved performance in control subjects only on one task (see Figure 1). Other indirect dopaminergic agonists such as dextroamphetamine also improve performance in healthy children.<sup>12</sup> Methylphenidate did not affect control children's performance on the other Go/No-Go task, perhaps because it was at ceiling levels.

Neurally, the most striking difference between ADHD and healthy subjects was obtained in the head

of the caudate and putamen on one Go/No-Go task: methylphenidate increased activation in ADHD boys but decreased it in healthy boys (see Figure 1). The frontal cortex did not show any differences between the two groups: methylphenidate increased activation in both groups. Thus, improved inhibitory control by methylphenidate in the two groups was subserved by distinct reactions in the striatum. A second difference between ADHD and healthy groups was obtained in frontal regions on the other Go/No-Go task: activation was greater in ADHD than healthy children. Greater activation may reflect increased inhibitory effort because ADHD subjects performed below control levels. Methylphenidate did not affect activation in either group on this task. Thus, our study, the first to use fMRI in ADHD and to compare effects of methylphenidate in ADHD and healthy children, found atypical frontal-striatal function in ADHD and different effects of methylphenidate on striatal activation in ADHD and healthy children.



**Figure 1** Panel (a) shows activation during response inhibition on a Go/No-Go task in two coronal slices located 12 mm anterior to the anterior commissure in a child diagnosed with ADHD (top row) and a control child (bottom row). Green squares highlight the opposite effect of methylphenidate (Ritalin) in the head of the caudate and putamen in the ADHD and control child. Panel (b) shows percentage of active pixels in these striatal structures in ADHD and control groups with and without Ritalin. Panel (c) shows Go/No-Go performance in the two groups with and without Ritalin; higher bars indicate worse impulse control.

Our findings support the possibility that ADHD is characterized by atypical dopaminergic modulation of the striatum. The opposite striatal response to methylphenidate in ADHD and healthy children may reflect differences in baseline dopamine activity because PET imaging of the effects of methylphenidate in resting healthy adults showed that changes in brain metabolism varied in individuals and brain regions as a function of dopamine receptor availability.<sup>13</sup> The specific reasons behind the observed striatal differences can be better understood only with PET and SPECT studies that are able to image neurophysiological properties of dopaminergic transmission in ADHD. Our finding, although a promising first step in the search for biological markers of ADHD, is not without limitations. It remains to be determined what role, if any, prolonged stimulant use played in the observed atypical striatal function. ADHD subjects, unlike controls, had 1–3 year histories of stimulant use. Whether the atypical striatal response to methylphenidate occurs prior to chronic treatment remains unknown. Further, despite the high subject-by-subject consistency of our results (8/10 ADHD and 5/6 controls showed the characteristic striatal response), replication is required in larger sample sizes and also those including females. Upon replication, however, our findings may contribute to the development of biologically-valid diagnostic criteria for ADHD.

Detecting neurobiological markers of ADHD could prove to be challenging for several reasons. First, both abnormally low and abnormally high activation is associated with ADHD. The two Go/No-Go tasks in our study differed in presentation parameters such that one proved to be more difficult than the other. Off-drug activation was abnormally low in the striatum on the difficult task, but abnormally high in the frontal lobes on the easier task. Thus, the same ADHD subjects exhibited both hypoactivation and hyperactivation. Task-difficulty also modulated drug-effects in the two groups such that methylphenidate affected activation only on the difficult task. Studies in adults have noted such modulation of the effects of indirect dopaminergic agonists on brain activation by task-difficulty.<sup>14</sup> Given the task-specificity and region-specificity of our findings, it is important that future functional imaging studies vary task-difficulty parametrically, in order to determine the optimal conditions that most consistently discriminate ADHD from healthy children.

Second, brain abnormalities in ADHD may be necessary but are not sufficient for the manifestation of ADHD. Our study included three additional controls who had ADHD siblings; two of these subjects showed the striatal response characteristic of ADHD. These subjects, however, did not meet behavioral criteria for ADHD but appear to share characteristics of dopaminergic transmission with their affected siblings. Indeed, specific variations in dopaminergic genes have been associated with ADHD.<sup>15</sup> Our findings, therefore, lend biological support to findings of increased familial risk in ADHD. Furthermore, two (of 10) ADHD subjects and one (of six) control subjects did not show the

characteristic striatal response observed in their respective groups. These subjects, however, met behavioral criteria for their respective groups. These outlying cases, therefore, illustrate that relying on a biological marker alone for diagnosis may not be optimal. Rather, the use of converging biological and behavioral diagnostic measures may be more appropriate. In the future, an approach that combines genetic studies with studies imaging neural activation and neurophysiological characteristics of dopaminergic transmission should prove fruitful in identifying diagnostic markers of ADHD.

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