Brain Imaging Data of ADHD

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The past two decades have ushered in a new era of methodological advances in tools for noninvasive imaging of the living brain. The information gleaned from advances in neuroimaging have been used to provide insights into ADHD's etiology, diagnosis and treatment.

In the United States, approximately 2% to 6% of school-age children are diagnosed with attention-deficit/hyperactivity disorder. Data show that stimulant medication is the most consistently successful form of treatment in ADHD, with psychostimulants such as dextroamphetamine (Adderall, Dexedrine) and methylphenidate (Ritalin) exerting therapeutic effects via modulation of the noradrenergic and dopaminergic systems. In the United States, methylphenidate is used to treat over 2 million children with ADHD annually. Methylphenidate acts primarily by blocking the dopamine transporter and increasing extracellular dopamine in the striatum. Despite more than 50 years of clinical and neuroscientific research, appropriate diagnostic and therapeutic interventions for ADHD are still an issue for many people, and although reports summarize the current knowledge (American Academy of Pediatrics Subcommittee on Attention-Deficit/Hyperactivity Disorder and Committee on Quality Improvement, 2001), they use parameters that are still based on the same descriptive determinations that have plagued the field for years. Stimulants are thus widely prescribed for the treatment of ADHD even though the mechanisms subserving their calming effects are not easily understood.

The past two decades have ushered in a new era of methodological advances in tools for noninvasive imaging of the living brain. Brain imaging has forged an impressive link between psychology, psychiatry and neuroscience. The information gleaned from such advances has been used to study both the anatomical and functional aspects of neural processing. Functional neuroimaging methods allow measurement of changes in brain activity associated with simultaneous changes in behavior or in response to a wide variety of stimuli. Event-related potentials, functional magnetic resonance imaging (fMRI), magnetoencephalography, near infrared spectroscopy, positron emission tomography (PET), and single photon emission computed tomography (SPECT) can all measure changes in brain activity. Neuroimaging allows scientists to study the ways in which medications affect neurophysiology and is beginning to provide more precise insights into ADHD--its etiology, diagnosis and treatment.

Neuropsychological studies have implicated the frontal cortical regions of the brain and the circuits linking them to the basal ganglia as critical to executive function, attention and the ability to exercise inhibition. Anatomical assays using quantitative MRI of the brain have provided insights into the neuroanatomical substrate. Early studies suggested that individuals with ADHD had smaller total cerebral volume and showed loss of the normal asymmetry in the size of the caudate nucleus (Castellanos et al., 1996). These data also showed decreased volumes of the right globus pallidus, right anterior frontal region and cerebellum. While PET studies in adult volunteers have provided new knowledge about the pharmacokinetic properties of methylphenidate at its primary site of action in the brain, morphometric and functional neuroimaging have illuminated the neural correlates of abnormalities in both children and adults diagnosed with ADHD (Castellanos and Tannock, 2002; Giedd et al., 2001). Replicable findings using larger samples have implicated brain regions long

suspected to play a role in ADHD, but have also identified neural circuitry not previously considered in the context of pathophysiological models.

Neuroimaging assays have most consistently implicated abnormalities of the dorsal prefrontal cortex and basal ganglia in the pathophysiology of ADHD. Reduced metabolic rates have been reported in the left sensorimotor area in children with ADHD (Lou et al., 1989) and in the premotor and superior prefrontal cortices of adults with ADHD (Zametkin et al., 1990). Positron emission tomography data from 10 adolescents with ADHD found reduced metabolic rates versus healthy controls in, among other regions, the left anterior frontal area, showing negative correlation with numerous symptom severity measures (Zametkin et al., 1993). Smaller volumes of the right prefrontal cortex have been reported in children with ADHD compared with healthy controls (Castellanos et al., 1996). This result has generally been replicated but not always with regard to laterality (Aylward et al., 1996; Filipek et al., 1997). Magnetic resonance imaging data demonstrated smaller right globus pallidus nuclei in boys with ADHD relative to a control group (Castellanos et al., 1996).

More recent data compared regional brain volumes at initial scan and their change over time in medicated and previously unmedicated male and female study participants with ADHD versus healthy controls (Castellanos et al., 2002). Individuals with ADHD had significantly smaller brain volumes in all regions, even after adjustment for significant covariates. This global difference was reflected in smaller total cerebral volumes and in significantly smaller cerebellar volumes. Compared with controls, previously unmedicated children with ADHD demonstrated significantly smaller total cerebral volumes and cerebellar volumes. Unmedicated children with ADHD also exhibited smaller total white matter volumes compared with controls and with medicated children with ADHD. Volumetric abnormalities in total and regional cerebral measures and in the cerebellum persisted with age. Caudate nucleus volumes were initially abnormal for patients with ADHD, but differences disappeared as caudate volumes decreased throughout adolescence. Developmental trajectories for all structures except the caudate remained roughly parallel for patients and controls during childhood and adolescence, suggesting that genetic and/or early environmental influences on brain development in ADHD were unrelated to stimulant treatment.

In line with PET findings showing reduced basal ganglia perfusion in patients with ADHD (Lou et al., 1989), subsequent fMRI studies have reported abnormal activation of the striatum (Rubia et al., 1999; Vaidya et al., 1998), prefrontal cortex (Rubia et al., 1999) and anterior cingulate cortex (Bush et al., 1999). Two ligand-based SPECT studies of adults diagnosed with ADHD reported marked elevations of dopamine transporter levels in the basal ganglia (Dougherty et al., 1999; Krause et al., 2000), which, after four weeks of 5 mg methylphenidate treatment three times daily, decreased to control levels (Krause et al., 2000).

One study compared adults diagnosed with ADHD with healthy controls in a conflict task (Bush et al., 1999). The control participants showed more anterior cingulate cortex activation than those participants with ADHD, probably due to higher attentional efficiency. While the latter group performed only slightly worse than controls, they appeared to activate an entirely different network of brain areas than that seen in the controls: Whereas control participants activated the anterior cingulate cortex, participants with ADHD seemed to rely on the anterior insula--a brain region typically associated with responses in more routine tasks not involving conflict.

Preliminary analyses of findings from a follow-up study seem to indicate that when adults with ADHD had been medicated with methylphenidate, their anterior cingulate cortex activation increased toward levels seen in healthy controls, while their insula activations decreased (Bush et al., 2003). Similar activation trends were observed in children with ADHD following administration of stimulants.

In other recent studies, fMRI was used to assess mean regional task-related signal change in 16

children and adolescents with ADHD, both on and off psychostimulants (e.g., methylphenidate), and 20 healthy controls (Potenza et al., unpublished data). Participants performed the Stroop task--an experimental conflict task requiring proficient readers to name the ink color of a displayed word. Individuals are usually slower and less accurate indicating the ink color of an incompatible color word (e.g., responding "blue" when the word red is inked in blue) than identifying the ink color of a congruent color name (e.g., responding "red" when the word red is inked in red). This difference in performance constitutes the Stroop conflict and is one of the most robust and well-studied phenomena in attentional research (MacLeod, 1991; MacLeod and MacDonald, 2000).

Potenza et al. (unpublished data) found that participants with ADHD were significantly less hyperactive and more attentive on clinical measures of ADHD symptoms when taking psychostimulants than they were when not taking psychostimulants, although they remained more hyperactive and inattentive than controls. They did not differ significantly from controls in measures of performance on the Stroop or other attentional measures, either on or off stimulants, although their performance when taking psychostimulants was consistently intermediate between their off-psychostimulant performance and that of the control group. A brain-region-by-diagnosis interaction was significant in comparing participants with ADHD who were off psychostimulants versus controls, as was a brain-region-by-stimulant interaction when comparing participants with ADHD on versus off psychostimulants. The brain-region-by-diagnosis effect comparing participants with ADHD and controls was no longer significant when the ADHD group was taking psychostimulants. Brain regions previously implicated in the regulation of attention and impulse control contributed to these interactions. In conclusion, using psychostimulants in children with ADHD was associated with improvement in attention and hyperactivity, and concurrently normalized activity in neural systems subserving attention and impulse control.

Neuroimaging data indicated, in addition to smaller prefrontal and basal ganglia structures, a decreased volume of the posterior-inferior vermis of the cerebellum (Berquin et al., 1998; Castellanos et al., 2001; Mostofsky et al., 1998), a region that is thought to be important in attentional processing (Middleton and Strick, 1994). Furthermore, the interpretation of some data proposes increased density of striatal dopamine transporters in adults with ADHD (Dougherty et al., 1999; Dresel et al., 2000). One study, however, reported no significant difference in striatal dopamine transporter density (van Dyck et al., 2002).

Compared to healthy controls, children with ADHD had less striatal activation during a cognitive inhibition task (Vaidya et al., 1998). Methylphenidate increased striatal activation in patients with ADHD but decreased striatal activation in controls. During another inhibitory task, adolescents with ADHD showed reduced activation of the medial prefrontal cortex, right inferior prefrontal cortex and left caudate nucleus, compared to controls (Rubia et al., 1999).

An inverse index of regional cerebral blood flow, T2 relaxometry (an fMRI procedure), was used to indirectly assess blood volume in the striatum (caudate and putamen) of boys ages 6 to 12 in steady-state conditions (Teicher et al., 2000). Boys with ADHD had higher T2 relaxation times bilaterally in the putamen than controls. Relaxation times strongly correlated with both the individual's capacity to sit still and error performance on an attentional task. Daily treatment with methylphenidate significantly changed T2 relaxation times in the putamen of boys with ADHD, although the magnitude and direction of the effect was strongly dependent on unmedicated baseline activity.

Similarly, Anderson et al. (2002) found that methylphenidate decreased steady-state blood flow to the cerebellar vermis of objectively hyperactive boys with ADHD and had the opposite effect on boys with ADHD who were not objectively hyperactive. Objective measures of activity and attention were quantified in children with ADHD on different doses of methylphenidate and placebo (Teicher et al., 2003). Data showed that higher doses altered activity and attentiveness in a rate-dependent manner.

These findings illustrate an inverse association between symptom severity and degree of therapeutic response.

Genetic assays of executive attention (e.g., examining the gene that codes for catechol-O-methyltransferase [COMT]) have been few but with intriguing results (Fan et al., 2003, 2001; Fossella et al., 2003, 2002a, 2002b). For example, control participants with the valine/valine genotype showed somewhat more efficient conflict resolution (i.e., lower Stroop conflict) than participants with the valine/methionine genotype (Sommer et al., 2004). The valine allele of COMT, which confers relatively higher levels of enzyme activity and thus lower relative amounts of extrasynaptic dopamine, has been examined in the context of neuroimaging studies in which it was correlated with lower activity of the dorsolateral prefrontal cortex (Egan et al., 2001). Frontal attentional networks may provide insights into pathologies of higher cognition, but there is already compelling evidence relating these networks to ADHD (Berger and Posner, 2000).

In conclusion, the hypothesis that ADHD is a syndrome with multiple distinct endophenotypes and several different etiological mechanisms (Castellanos and Tannock, 2002) must be constrained by neuroimaging findings and behavioral results. Measures of cognitive inhibition, working memory and temporal processing will likely illuminate the neural bases of ADHD and further operationalize the roles of attention, impulsivity and disinhibition in the formulation of ADHD pathophysiology.

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