EDITORIAL

The Neurobiology of Attention-Deficit/Hyperactivity Disorder

This special issue of *Biological Psychiatry* focuses on attention-deficit/hyperactivity disorder (ADHD), a highly heritable and disabling condition characterized by core behavioral symptoms of impulsivity, hyperactivity, and/or inattention (1). Attention-deficit/hyperactivity disorder is the most prevalent neuropsychiatric disorder of childhood with a prevalence of 4% to 10%. It is often overlooked that some 40% to 60% of these children will still show clinically significant symptoms into adulthood. Attention-deficit/hyperactivity disorder should not be seen as an absolute bar to academic and social success. However, it has been associated with educational difficulties, increased criminality, substance abuse, family breakups, and driving accidents. The excess cost of the condition (in terms of education, occupational impairment, and medical treatment) was estimated at $30 billion in the United States in 2000 (2). Given the disabling and prevalent nature of ADHD, it is important to further our understanding of the neural underpinnings of this condition and the mechanisms by which drug treatments exert their beneficial effects.

Dysfunction of noradrenergic and/or dopaminergic neurotransmission has been widely implicated in the manifestation of ADHD (3–5). Noradrenaline (NA) and dopamine (DA) exert neuromodulatory influences over behavior and cognition via fronto-striato-cerebellar circuitry (6), and pharmacotherapy is thought to target these systems to ameliorate problems with impulsivity, inattention, and hyperactivity. Psychostimulants are widely used for ADHD and act to increase free brain levels of noradrenaline and dopamine by blocking reuptake and triggering release (7). A wealth of evidence shows these agents to be effective in the treatment of ADHD for many patients. For example, Spencer *et al.* (pages 1380–1387, in this issue) investigated the efficacy of extended release dexmethylphenidate in adults, using a double-blind, placebo-controlled, parallel fixed-dose design (20 mg, 30 mg, 40 mg, or placebo daily for 5 weeks). Treatment at all doses was significantly superior to placebo as measured by change from baseline for DSM-IV ADHD Rating Scale scores.

Nonetheless, 20% to 30% of patients do not respond to psychostimulants or cannot tolerate them. Various other potential treatments have been highlighted in the literature, principally drugs acting on NA/DA neurotransmission. The highly selective noradrenaline reuptake inhibitor (SNRI) atomoxetine is licensed by the Food and Drug Administration (FDA) for the treatment of child and adult ADHD. According to animal research, atomoxetine (like psychostimulants) increases free dopamine and noradrenaline in the cortex when administered systemically. However, whereas psychostimulants are associated with addictive potential due to effects on the midbrain dopamine system (8), atomoxetine appears to lack these effects and to have low addictive potential (9,10). Other clinical advantages are emerging, such as benefits for sleep quality over psychostimulants and possible efficacy in the treatment of comorbid tics (11,12). The wake-promoting cognitive enhancer modafinil is another agent with efficacy in the treatment of ADHD (13), although it is not currently licensed. The mechanisms of action of modafinil on the brain are not fully elucidated. The locomotor effects of modafinil were blocked by noradrenergic antagonists in animals, suggesting a key role for noradrenaline (14), parsimonious with the wake-promoting actions of this drug.

How might we investigate the neurocognitive mechanisms underpinning the beneficial effects of ADHD drugs on pathological behavior? One key translational neuroscience approach is to measure cognitive effects following short-term dosing in animal models, in human volunteers, and in patients. Much research has focused on objective tests relating to impulse control, such as stop-signal, continuous performance, and 5-choice serial reaction time (5-CSRT) tasks. Blondeau and Dellu-Hagedorn (pages 1340–1350, in this issue) measured the effects of atomoxetine and methylphenidate on 5-CSRT performance in rats. Atomoxetine decreased premature responses, except in rats that were very efficient at baseline. Methylphenidate increased impulsivity in the rats, with some evidence for deleterious effects on accuracy at higher doses. These methylphenidate results stand in contrast to the human literature, which has typically reported reductions in impulsivity following psychostimulant treatment (e.g., 15). This discrepancy may relate to antifatigue effects of psychostimulants during prolonged neuropsychological assessment in humans, highlighting the need for caution with interpretation.

Eagle *et al.* (16) have also recently shown that modafinil and methylphenidate improved stop-signal response inhibition in rats. Concurrent dopamine receptor antagonism did not affect response inhibition. In human volunteers and ADHD patients, methylphenidate, atomoxetine, and modafinil improved stop-signal response inhibition when given acutely (17–21). Other pharmacological manipulations acting principally on the serotonin system, such as tryptophan depletion and citalopram dosing, had no effect in healthy volunteers (22). Collectively, these proof-of-concept studies reveal that the cognitive mechanisms of ADHD drugs overlap to some degree: all appear capable of enhancing the capacity for response inhibition. Further, data so far suggest that these influences are noradrenergic as opposed to dopaminergic in nature. More research is needed to explore other cognitive functions and to link these early beneficial cognitive effects to longer term clinical outcomes.

Response to pharmacotherapy varies considerably between individuals, not only in terms of changes in symptoms but also in relation to side effects and subjective effects. Genetic factors are likely to play a key role in determining drug response. Dlugos *et al.* (23) explored whether variations in the noradrenaline transporter (SLC6A2) gene modulated subjective increases in positive mood and euphoria following amphetamine (10 mg, 20 mg) in healthy male and female adult volunteers in a double-blind, placebo-controlled design. Euphoric effects are thought to relate to addictive potential (8). The 36001C/C genotype was associated with increased positive mood and elation following 20 mg amphetamine, whereas the A/C and A/A genotypes were not. Follow-up studies in patients, examining genetic influences over clinical outcomes, could ultimately contribute to tailored treatment algorithms.

In addition to the NA/DA dysregulation posited to play a role in ADHD, there is growing evidence for structural abnormalities

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in distributed fronto-striato-cerebellar circuitry, such as reduced brain volumes in frontal regions, the caudate nucleus, and the cerebellum in children (24,25). Valera *et al.* (pages 1361–1369, in this issue) conducted the first meta-analysis of structural neuroimaging findings in children and adolescents with ADHD. This meta-analysis found global reductions in brain volumes, with most prominent reductions affecting total and right cerebral volumes, cerebellar regions, the splenium of the corpus callosum, and the right caudate nucleus. There was substantial variability in the region-of-interest measurements between studies, which made assessment of frontal regions especially problematic.

Relatively little is known about how brain abnormalities in ADHD change over the life span. In a study by Castellanos *et al.* (26), children and adolescents with ADHD were followed over time using magnetic resonance imaging (MRI). Volumetric abnormalities in the cerebrum and cerebellum persisted with increasing age, whereas caudate differences versus control subjects disappeared. These findings appeared to be unrelated to stimulant treatment. Few structural neuroimaging studies have been conducted in adults with ADHD, which hampers our understanding of developmental trajectories. Seidman *et al.* (27) previously reported volumetric reductions in frontal and anterior cingulate cortices in adults with ADHD. It appears from these preliminary studies that subcortical structural abnormalities normalize into adulthood but that cortical abnormalities persist. The implications of these neuroimaging changes for differences between children and adults in cognitive and behavioral symptoms remain to be determined but may relate to decreasing motor hyperactivity with age (28).

Right frontal lobe abnormalities have been linked to response inhibition deficits often reported in ADHD. The volume of damage to the right inferior frontal gyrus (RIFG) in neurosurgical patients was shown to correlate with the magnitude of stop-signal impairment, and transcranial suppression of this region in healthy volunteers led to behavioral deficits (29,30). Clark *et al.* (pages 1395–1401, in this issue) investigated response inhibition and working memory in adult ADHD patients, in comparison with neurosurgical patients with left or right frontal damage and healthy control subjects. Response inhibition deficits correlated significantly with working memory errors in ADHD and right frontal neurosurgical lesion patients but not in left frontal lesion patients and control subjects. These results implicate the right frontal lobe (especially the right inferior frontal gyrus) in the manifestation of both response inhibition and working memory impairments in adult ADHD.

Functional neuroimaging has been used to probe brain correlates of cognition in health and in the context of neuropsychiatric conditions. Krauel *et al.* (pages 1370–1379, in this issue) investigated neural correlates of memory formation in adolescent recruits. Participants observed neural and emotional pictures during functional magnetic resonance imaging (fMRI) and later undertook a recognition test outside the scanner. Attention-deficit/hyperactivity disorder patients tended to be impaired at recognizing neutral but not emotional stimuli. Differential neural activations were reported for the successful encoding of neutral pictures between the study groups. Whereas control subjects showed activation of the anterior cingulate cortex, ADHD patients instead showed (presumably compensatory) activation of the superior parietal lobe and precuneus. By contrast, the successful encoding of emotional stimuli was associated with similar activation of the prefrontal and inferior temporal cortices in both groups. These results implicate cingulate dysfunction and recruitment of other neural regions in the processing of nonemotional stimuli in ADHD.

Collectively, this is a promising time for research into the neurobiology of ADHD. Articles in this issue and elsewhere implicate NA/DA dysregulation in the manifestation of symptoms and cognitive deficits associated with the disorder. Medications with demonstrable efficacy in the treatment of ADHD act mainly on these systems and have been shown to exert beneficial effects on aspects of cognition (such as response inhibition) in proof-of-concept studies. Translational approaches are shedding light on the precise neurochemical mechanisms. The body of evidence also implicates subtle structural and functional abnormalities of fronto-striatal-cerebellar circuitry in the manifestation of the disorder. Pharmaco-fMRI should be used in the future to investigate the effects of ADHD medications on neural activity during cognitive tests and to compare different agents. There is also a need for baseline factors influencing clinical outcomes to be explored. Specifically, it will be critical to examine whether baseline cognitive function and the presence of different genetic polymorphisms modulate treatment outcomes. It is hoped that research in these areas will contribute to the development of improved treatment algorithms for children and adults with ADHD, to reduce harms (side effects and abuse potential) and maximize clinical benefits.

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