

COGNITIVE NEUROSCIENCE OF ATTENTION DEFICIT HYPERACTIVITY DISORDER: CURRENT STATUS AND WORKING HYPOTHESES

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Cognitive neuroscience studies of Attention Deficit Hyperactivity Disorder (ADHD) suggest multiple loci of pathology with respect to both cognitive domains and neural circuitry. Cognitive deficits extend beyond executive functioning to include spatial, temporal, and lower-level “non-executive” functions. Atypical functional anatomy extends beyond frontostriatal circuits to include posterior cortices, limbic regions, and the cerebellum. Pathophysiology includes dopaminergic as well as noradrenergic neurotransmitter systems. We review the major insights gained from functional brain imaging studies in ADHD and discuss working hypotheses regarding their neurochemical underpinnings. © 2008 Wiley-Liss, Inc. *Dev Disabil Res Rev* 2008;14:261–267.

Key Words: executive control; functional brain imaging; dopaminergic; noradrenergic

Application of functional brain imaging methods has brought unprecedented insights into Attention Deficit Hyperactivity Disorder (ADHD), confirming its origins as a condition of altered neurobiological development that particularly impacts higher-order cognition. Symptoms of inattention, distractibility, and impulsivity that define ADHD suggest selective weakness of regulatory or control processes that are subsumed under the label “executive” in psychological theory. Indeed, the locus of most cognitive neuroscience research on ADHD has been component processes of executive control such as response inhibition [reviewed in Bush et al., 2005]. However, increasingly studies are pointing to atypicalities in other cognitive domains and in lower-level “nonexecutive” functions and their underlying brain circuitry. As a result, the developing consensus among researchers supports a model of neuropathological heterogeneity produced by alterations in multiple neurocognitive circuits.

This brief review presents the current status of human research on ADHD that elucidates its neuropathophysiology and yields hypotheses for future investigations. First, we present a synthesis of the main insights gained from studies using functional magnetic resonance imaging (fMRI) that visualizes oxygen-dependent hemodynamic change induced by cognitive activity. Findings from behavioral and structural imaging studies are also included to the extent that they explicate the fMRI findings. Findings are organized by neuroanatomical cir-

cuits—frontostriatal, mesolimbic, motor, and parietal-temporal, distinguished by the functional domain they most critically enable. Second, we discuss pathophysiology that unifies the seemingly diverse deficits and outline working hypotheses and methodological approaches for future investigation.

FUNCTIONAL NEUROPATHOLOGY

Frontostriatal Circuitry

This circuit comprises lateral prefrontal, dorsal anterior cingulate, and dorsal striatal regions such as caudate and is linked to the cerebellum via the thalamus. It mediates task-relevant response selection without affective value, often labeled “cool” executive function and has been evoked with tasks requiring suppression of prepotent actions (e.g., Stop signal, Go/No-go, Stroop), resisting interference from irrelevant stimuli (e.g., Flanker task, Multisource interference task), maintenance and manipulation within working memory (e.g., N-back task, PASAT, mental rotation), and cued switching between responses (e.g., Meiran Switch task). This circuit has been the focus of most fMRI work in children, adolescents, and adults with ADHD and has provided three main insights as described in the following three paragraphs.

First, the frontostriatal network appears to be underactivated in ADHD in most studies [confirmed in meta-analysis by Dickstein et al., 2006]. Across studies, reduced activation was observed in lateral aspects of frontal cortex ventrally (BA 44, 45/47, inferior frontal gyrus) in regions that mediate inhibition and selection of response sets, and dorsally (BA 9/46, middle frontal gyrus) in regions that maintain and manipulate goal-relevant representations in working memory, and medially in the anterior cingulate (BA 24), a region associated with

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monitoring errors and response conflict. Across studies, the caudate has been consistently underactivated in subjects with ADHD. Regarding prefrontal cortex, different tasks draw upon subregions to different extents (e.g., Stroop-tasks activate anterior cingulate, response inhibition activates right inferior frontal regions, and working memory relies on dorsolateral prefrontal regions). The same task (e.g., Go/No-go) also activates subregions of prefrontal cortex to different extents across studies. Further, prefrontal activation varies across individuals by level of performance in some studies; ADHD adolescents with worse inhibitory performance activated inferior frontal (BA 47) and frontopolar (BA 10) cortex to a greater extent relative to controls [Schulz et al., 2004, 2005a,b]. Greater rather than reduced prefrontal recruitment in low performers, particularly in medial regions that are not part of frontostriatal circuitry (BA 10), may reflect use of compensatory strategies. Thus, prefrontal involvement is sensitive to subject and performance-related factors that vary across studies. Convergent evidence for atypical frontal-striatal involvement points to the frontostriatal circuit as a core site of neuropathology in ADHD.

Second, several studies have documented deficits in temporal processing in ADHD that are likely to reflect atypical cerebellar function. Children with ADHD perform worse than controls on time estimation tasks especially at long durations [reviewed in Castellanos and Tannock, 2002]. While no study has imaged temporal processing without motor/executive demands, children with ADHD showed reduced cerebellar involvement on a task involving use of temporal information during response inhibition and selection [Durstun et al., 2007]. Temporal processing deficits could be primary (e.g., atypical temporal coding) or secondary to deficits in executive control (e.g., decision-making demands of estimation task) and motivation (e.g., inability/unwillingness to wait longer durations).

Third, behavioral studies show considerable heterogeneity in the magnitude of executive deficits in ADHD. A meta-analysis of 83 studies involving 6,700 subjects found small to moderate effect sizes for differences between ADHD and control groups on a variety of “cool” executive tasks ($d = 0.4-0.7$ [Willcutt et al., 2005]). Larger effect sizes were observed for spatial working memory tasks ($d = 0.85-1.14$ [Martinussen et al., 2005]) indicating less heterogeneity in spatial working memory function.

In sum, atypical frontostriatal involvement is well documented in ADHD. Individual variability in prefrontal recruitment and magnitude of executive dysfunction suggests that phenotypic heterogeneity is an important functional characteristic of ADHD.

Mesolimbic Circuitry

This circuit includes ventromedial prefrontal regions such as orbitofrontal gyri (BA 10, 11) and anterior cingulate (BA 32), and ventral striatum (nucleus accumbens) as well as medial-temporal limbic regions of amygdala and hippocampus. It mediates task-relevant response selection with affective value, often labeled “hot” executive function and has been evoked using tasks manipulating motivational properties with reward contingencies (e.g., reward anticipation, delay aversion, gambling). Behavioral and fMRI studies in ADHD have led to three main insights as described in the following three paragraphs.

First, many (but not all) behavioral studies indicate atypical sensitivity to reward in children with ADHD, although there are differences in experimental design across studies making comparisons difficult [reviewed in Luman et al., 2005]. In studies showing group differences, children with ADHD showed greater sensitivity to reinforcement on behavior but reduced sensitivity on physiological measures, greater delay aversion, the preference for immediate over delayed rewards, and risky decision-making on gambling tasks. Thus, motivational deficits characterize some children with ADHD.

Second, two fMRI studies suggest altered functional connectivity within components of mesolimbic circuitry in ADHD. During anticipation to reward, ventral striatal regions were less activated in ADHD than control adolescents [Scheres et al., 2006] and adults [Strohle et al., 2008]. Following delivery of reward, however, that region was activated in ADHD but not in control children. Elevated response to reward delivery in ADHD has also been noted using scalp-related electrophysiological potentials [Holroyd et al., 2008]. These findings suggest qualitative differences in encoding of reward information in ADHD. Further, orbitofrontal cortex was activated in control but not children with ADHD [Strohle et al., 2008]. This prefrontal region exerts an inhibitory influence over ventral striatum, and its lack of involvement in ADHD suggests weak “top-down” control signals. Together, these findings suggest atypical reward-

related modulation of the orbitofrontal-ventral striatal network in ADHD.

Third, one fMRI study suggests altered functional connectivity between mesolimbic and frontostriatal circuitry in ADHD. During a gambling task, activation was reduced in the hippocampus but greater in dorsal anterior cingulate in ADHD relative to control adults [Ernst et al., 2003].

In sum, similar to “cool” executive function, deficits of “hot” executive function are often, but not always, found in ADHD, while few fMRI studies suggest an atypical relationship within regions of mesolimbic circuitry as well as in their relationship to frontostriatal regions. Despite interaction between regions of the two circuits, “hot” and “cool” executive dysfunction is dissociated, because it is weakly correlated among children with ADHD [Sonuga-Barke et al., 2003]. Thus, it is important to elucidate the process-specific contribution of component regions to motivational and executive function.

Motor-Execution Circuitry

This section describes findings from studies using tasks requiring simple motor execution involving sensorimotor cortex and associated regions. Behaviorally, children with ADHD show subtle motor abnormalities such as slower and variable response latencies [Leth-Steensen et al., 2000] and excessive motor overflow (i.e., unintentional movements on the other side of the body [Denckla and Rudel, 1978]). In the brain, activation in contralateral primary motor and right superior parietal cortex was reduced in ADHD relative to control children, despite similar self-paced finger-to-thumb sequencing performance [Mostofsky et al., 2006]. These findings may reflect immature motor circuitry as suggested by reduced neural inhibition within the corticospinal tract (measured by transcranial magnetic stimulation) in children with ADHD [Moll et al., 2000]. Further, motor abnormalities relate to executive function, because motor overflow was positively correlated with response inhibition performance [Mostofsky et al., 2003]. These findings are consistent with anatomic organization such that motor-premotor circuits parallel those for goal-relevant response selection. Thus, lower-level motor abnormalities are observed in children with ADHD and may contribute to executive dysfunction.

Parietal-Temporal Circuitry

While traditionally not considered central to cognitive dysfunction in

ADHD, posterior cortices are gaining attention in investigations of visual-spatial functioning and in their contribution to executive control. This work provides three insights as described in the following three paragraphs.

First, right parietal involvement was reduced in children with ADHD relative to controls during a spatial working memory task. During mental rotation, reductions were observed in inferior parietal [Vance et al., 2007] and superior parietal and temporal [Silk et al., 2005] gyri. Thus, underactivation of right parietal cortex may contribute to spatial working memory impairment in ADHD.

Second, parietal-temporal involvement during visual and auditory selective attention was reduced in ADHD relative to control children and adolescents, despite similar task performance. During oddball tasks that examine involuntary attention to novel stimuli, reductions were observed in the precuneus and supramarginal and angular gyri bilaterally [Tamm et al., 2006], superior and middle temporal gyri and posterior cingulate [Rubia et al., 2007], and parahippocampal gyrus and amygdala [Stevens et al., 2007]. During voluntary selective attention, reductions were observed in right superior parietal lobe during a visual search task [Booth et al., 2005] and left posterior middle temporal gyrus during an auditory/verbal task [Shafritz et al., 2004]. Thus, multiple regions in medial and lateral parietal and temporal lobes were underactivated in ADHD.

Third, parietal-temporal regions were more activated in children with ADHD relative to controls on several executive tasks that showed reduced prefrontal activation [reviewed in Fassbender and Schweitzer, 2006]. The specific locus of these increases differed across studies and tasks. Activation was greater in medial parietal cortex during Flanker interference [Vaidya et al., 2005], in posterior superior temporal [Vaidya et al., 2005] and inferior parietal [Rubia et al., 1999; Durston et al., 2003] regions during response inhibition, and in parietal and occipital cortices during working memory [Schweitzer et al., 2000]. Greater posterior activation during executive function may be a product of weak prefrontal inhibition of sensorimotor cortices or use of alternate performance strategies (e.g., reliance on visual-spatial processes during auditory working memory [Schweitzer et al., 2000]).

Thus, convergent evidence supports atypical parietal-temporal involve-

ment in ADHD. Together, evidence from all four circuits indicates that functional neuropathology in ADHD extends beyond frontal-striatal regions and executive control to include motor and posterior cortices and associated sensory functions. In addition to the distributed nature of pathological loci, two themes emerge across studies: (1) individual variability in behavioral performance and functional anatomical findings suggests substantial phenotypic heterogeneity; (2) the nature of atypical activation (i.e., more or less) in regions within and across circuits suggests alteration in functional connectivity.

STRUCTURAL NEUROPATHOLOGY

Findings from structural MRI studies provide some insight into the

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fMRI findings reviewed above. First, subjects with ADHD had reduced volumes or cortical thinning in regions encompassing all four circuits, including medial and lateral prefrontal, premotor, striatal, right parietal, superior and medial temporal, and cerebellar regions [reviewed in Seidman et al., 2005]. Thus, alteration in structural maturation may mediate functional atypicalities observed in fMRI studies. Second, in addition to differences in selective regions, there are global brain differences between ADHD and control children. Lobular volumes and cortical folding was reduced, suggesting early onset of maturational alteration in prenatal development [Wolosin et al., 2007]. Third, longitudinal studies indicate that maturational timecourse was

similar between groups but was delayed in ADHD by ~3 years [Shaw et al., 2007a]. Thus, patterns of functional activation in subjects with ADHD may reflect immature rather than aberrant functional anatomy. Fourth, adults with ADHD had reduced integrity of white matter microstructure in a tract connecting frontal and parietotemporal cortices in the right hemisphere [Makris et al., 2008]. Weak structural connectivity is likely to reduce functional connectivity between those regions. Additionally, there were relative gray matter differences between those regions: gray matter was reduced in prefrontal cortex but greater in posterior temporal and inferior parietal regions in ADHD relative to control children [Sowell et al., 2003]. Together, the white and gray matter findings suggest that weaker top-down control by prefrontal cortex and larger parietotemporal cortices may facilitate the compensatory involvement of posterior cortices observed during executive control tasks in fMRI studies. Fifth, individual variability in structural developmental trajectories predicted symptom progression. Children with ADHD with persisting symptoms in adolescence had thinner medial prefrontal cortex relative to controls, and those with remitted symptoms in adolescence had right parietal cortical thickness similar to controls [Shaw et al., 2006]. Therefore, structural brain differences may mediate, at least in part, phenotypic heterogeneity characterizing ADHD.

NEUROCHEMICAL PATHOLOGY

The developing consensus among researchers is that the anatomically distributed and phenotypically heterogeneous nature of neurocognitive abnormalities in ADHD can be reconciled within dysfunction of catecholaminergic neurotransmitters, dopamine (DA) and norepinephrine (NE). Interaction of the two systems subserves “top-down” control of behavior by increasing “signal” and decreasing “noise” to optimize adaptation to the environment [reviews in Aston-Jones and Cohen, 2005; Brennan and Arnsten, 2008]. Both systems play a modulatory role (e.g., NE in regulating arousal, DA in reward processing) and determine the balance between sensory/reactive and control processes.

While the two systems largely overlap in anatomy, differences in distribution of transporters/receptors subserve functional anatomical selectivity.

Dopaminergic and noradrenergic neurons originate in the midbrain with axonal networks innervating frontostriatal and mesolimbic circuitry as well as parietal cortices. Distribution of transporters differs such that DA transporters are abundant in caudate and low in prefrontal cortex, whereas NE transporters are abundant in prefrontal cortex but absent in caudate [Madras et al., 2005]. Further, D1 receptors are higher in the caudate relative to prefrontal cortex whereas D4 receptors and multiple NE receptors operate in prefrontal cortex but not in striatum. These anatomical differences in the physiological regulation of DA/NE levels influence the pattern of functional neuropathology and effects of medications in ADHD.

Effects of Medication

Catecholaminergic dysfunction as a working hypothesis of ADHD stems from the action of stimulant medication such as methylphenidate (MPH). MPH effectively alleviates ADHD symptoms temporarily following acute administration of small doses (0.10–2.0 mg/kg), in the majority of children with ADHD (60–70%). It enhances synaptic DA in the striatum by inhibiting reuptake by DA transporters and DA and NE in prefrontal cortex by stimulating receptors. Behaviorally, MPH improves performance on “cool” [reviewed in Pietrzak et al., 2006] and “hot” (e.g., gambling [Devito et al., 2008]) executive function and lower-level sensory processing (e.g., auditory [Korostenskaja et al., 2008] and visual [Jonkman et al., 1997]). Thus, pharmacological modulation of catecholamines has widespread effects extending to all circuits affected in ADHD.

Pharmacological fMRI studies suggest that MPH restores functional integrity of regions known to be deficient in ADHD. MPH improved response inhibition but by variable effects in the striatum: increases in children with ADHD but decreases in controls, relative to activation without MPH [Vaidya et al., 1998]. This group difference suggests differences in baseline striatal DA transmission, because striatal MPH effects are mediated by DA rather than by NE. Further, MPH also increased activation in prefrontal cortex, in lateral [Vaidya et al., 1998] and medial [Bush et al., 2008] regions that are hypoactivated during inhibitory functions in subjects with ADHD without MPH. Unlike the striatum, prefrontal modulation by MPH relates to increased DA and NE [Berridge et al.,

2006], by stimulating D1 receptors to enhance DA and alpha-2-adrenoreceptors to enhance NE [Arnsten, 2006]. Thus, while striatal findings in ADHD reflect DA dysfunction, those in prefrontal cortex reflect DA and NE dysfunction.

Nonstimulant medications that selectively enhance NE levels are effective for some ADHD symptoms, although less widely than stimulants [Spencer and Biederman, 2002]. Atomoxetine inhibits NE transporter and guanfacine stimulates alpha-2-adrenoreceptors, to enhance NE. In animals, suboptimal prefrontal NE results in a phenotype similar to ADHD, and NE agonists and antagonists enhance and reduce working memory function, respectively [reviewed in Brennan and Arnsten, 2008]. Further, pharmacological fMRI studies in rats showed reduction in striatal structures and increase

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in frontal cortex, relative to activation without atomoxetine [Easton et al., 2006, 2007]; there are no human fMRI studies with these medications. Thus, efficacy of NE agonists for ADHD is likely to be mediated by modulating prefrontal–striatal functional relationships.

Pathology in ADHD

Ligand-based brain imaging studies provide direct support for altered DA transmission in ADHD in prefrontal cortex, striatum, and limbic structures. Direct evidence for noradrenergic dysfunction in ADHD is currently lacking because reliable selective NE ligands are still under development. One locus of pathology in ADHD is posited to be reduced striatal DA because many (but not all) studies have found higher expression of DA transporters in the

caudate in subjects with ADHD [reviewed in Spencer et al., 2005]. Indeed, D2/D3 receptor availability and DA release were reduced in the caudate in adults with ADHD [Volkow et al., 2007]. While fMRI cannot image DA activity directly, pharmacological fMRI studies show that it is sensitive to metabolic consequences of DA release [reviewed in Vaidya, 2002]. Thus, reduced striatal activation in subjects with ADHD observed in fMRI studies may relate to reduced DA in that region. Further, that study showed that DA release was also reduced in the hippocampus and the amygdala. These regions have not been targeted by fMRI studies as yet. Direct evidence for prefrontal DA dysfunction in ADHD comes from imaging of DOPA decarboxylase activity indexing presynaptic processes. DA activity was reduced in medial and left lateral prefrontal cortex in adults [Ernst et al., 1998] but was greater in midbrain dopaminergic nuclei in adolescents [Ernst et al., 1999] with ADHD relative to controls. It is not possible to draw inferences about fMRI findings based on these studies, because how DOPA decarboxylase activity relates to fMRI signals is not known. Nevertheless, those findings point to possible developmental differences in region-specific DA activity and, furthermore, show alterations in regions comprising both mesolimbic and frontostriatal circuitry. Thus, ligand-based imaging provides strong support for altered DA transmission in the caudate, but the nature of DA or NE pathology in prefrontal cortex remains to be elucidated.

Current Models of ADHD

Models differ in putative pathological pathways and the level of elaboration of pathophysiology. In general, models accounting for human data posit dual pathways, whereas those accounting for animal data posit single pathways. As each model is detailed elsewhere, they are briefly summed here to highlight current working hypotheses. First, a dissociation has been posited between frontostriatal and mesolimbic circuits as independent sources of pathology accounting for dissociable “cool” and “hot” executive deficits [Sonuga-Barke, 2002; Castellanos et al., 2006]. Second, a computational model distinguishes between dopaminergic and noradrenergic pathophysiology in ADHD [Frank et al., 2007]. Both “hot” and “cool” executive deficits are posited to result from dopamine deficiency in frontostriatal and mesolimbic pathways,

whereas the greater response variability results from noradrenergic deficiency (high tonic but low phasic signals). Third, one single pathway account emphasizes reduced dopamine in meso-limbic circuits leading to altered reinforcement and extinction processes, as a causal route to all symptoms and deficits observed in ADHD [Sagvolden et al., 2005]. This account emphasizes learning abnormalities in ADHD, an area with few human studies. Fourth, other single pathway models focus upon regional physiology in striatal DA signaling, positing reduced tonic and increased phasic firing [Seeman and Madras, 2002] or in prefrontal DA and NE, positing deficient D1 and alpha-2-adrenoreceptor actions [Brennan and Arnsten, 2008].

In sum, while catecholaminergic pathophysiology is agreed upon by researchers, its specific nature remains to be elucidated. Current models differ from each other mainly in the level of elaboration and anatomy of emphasis. As such, putative accounts are not mutually exclusive. A primary challenge for any model is to account for phenotypic heterogeneity in ADHD. We discuss two potential physiological sources of heterogeneity below.

PHENOTYPIC HETEROGENEITY

Properties of Catecholamine Function

Two properties of catecholaminergic function may induce heterogeneity in symptom expression, response to medication, cognitive dysfunction, and functional anatomy. First, animal studies show an inverted-U relationship between level of prefrontal catecholamines and behavior [Brennan and Arnsten, 2008]. Moderate levels of DA and NE are optimal, with too much leading to distractibility and too little leading to inattentiveness. Thus, the small effect sizes for group differences on executive function observed in behavioral studies probably relate to individual variation in subjects' positions on the inverted-U function. Individual variation in catecholamine levels also determines response to MPH. Ligand-based imaging studies in ADHD found that MPH-induced increases in striatal DA were associated with symptoms of inattention in adults [Volkow et al., 2007] and attentional task performance (e.g., TOVA) in adolescents [Rosa-Neto et al., 2005]; subjects with smaller DA

changes had more inattention symptoms and poorer task performance. Thus, phenotypic expression is likely to be mediated, at least in part, by catecholamine levels.

Second, DA activity is sensitive to environmental context. Efficacy of MPH for ADHD varies by situational factors. Reduction in symptoms was greater in a classroom than playground setting [Swanson et al., 2002]. Direct evidence for the influence of environmental factors on DA function comes from two ligand-based imaging studies. In healthy adults, striatal DA response to MPH was greater in the context of motivationally salient stimuli (e.g., display of food for hungry subjects [Volkow et al., 2002]) and related positively with subjects' evaluation of task salience (e.g., rated "interest" in mathematical task [Volkow et al., 2004]). Thus, how engaging/salient the task is to subjects is likely to induce variability in prefrontal-striatal activation and its modulation by MPH in fMRI studies. In addition to endogenous factors, therefore, exogenous factors also determine catecholaminergic function.

Genetic Polymorphisms

One endogenous source of subject and functional anatomical heterogeneity in catecholaminergic function is genetic variation. Allelic variations influence phenotype expression and structural and functional anatomy by either enhancing or reducing receptor/transporter function.

Prevalence of ADHD has been associated with genetic polymorphisms for DA receptors (DRD1, DRD4, DRD5) and transporter (DAT1) and NE receptors (DBH, alpha-2-adrenoreceptor) and transporter (NET) (reviewed in [Faraone et al., 2005]), although many studies also failed to find associations. The most consistent evidence comes from DAT1 and DRD4, with greater prevalence of ADHD associated with homozygosity of the 10-repeat allele of DAT1 [see Yang et al., 2007 for meta-analysis] and the 7-repeat allele of DRD4. Homozygosity for these alleles reduces DA function, in the striatum by DAT1 and in prefrontal cortex by DRD4. The mixed findings across studies may reflect that multiple genotypes in combination, but not alone, confer vulnerability to ADHD.

DA alleles associated with ADHD affect cognitive functions dependent upon frontal-striatal, motor, and parietal regions in ADHD and control subjects. Homozygous ADHD 10-repeat DAT1

carriers had greater motor response variability and atypical visual-spatial attention [Bellgrove et al., 2005] and those for 7-repeat DRD4 had worse sustained attention [Kielsing et al., 2006] relative to heterozygotes. Homozygous 10-repeat DAT1 controls had atypical spatial attention (left-sided inattention [Bellgrove et al., 2007]), poor response inhibition and selective attention, and more hyperactive/impulsive behaviors [Cornish et al., 2005] relative to heterozygotes. Further, homozygous 7-repeat DRD4 controls had poor response inhibition [Congdon et al., 2008] and more attentional problems [Schmidt et al., 2001] relative to heterozygotes. Most importantly, these genotypes have additive effects on executive function, because homozygous carriers of both 10-repeat DAT1 and 7-repeat DRD4 alleles had the worst response inhibition [Congdon et al., 2008]. Thus, relative differences in allelic inheritance of catecholaminergic genes induce symptomatic and cognitive heterogeneity.

Genetic polymorphisms yield regional differences in brain anatomy and function across individuals. Neurotransmission affects neurotrophic factors that control structural growth and synaptic proliferation/pruning during development. Caudate but not prefrontal volume was reduced in homozygous 10-repeat DAT1 carriers [Durstun et al., 2005], whereas prefrontal cortex but not caudate was influenced by inheriting the DRD4 7-repeat allele [Shaw et al., 2007b]; right ventral prefrontal cortex and posterior parietal cortex were thinner in those subjects with ADHD. In contrast to regional selectivity in structural findings, fMRI studies suggest more pervasive differences. A preliminary fMRI study found reduced caudate and greater cerebellar activation in children with ADHD and their unaffected siblings who were 10-repeat DAT1 homozygotes relative to heterozygotes [Durstun et al., 2008]. In healthy adults, frontal activation was reduced during working memory in 10-repeat DAT1 homozygotes [Bertolino et al., 2006] and was increased in those without the 10-repeat allele (9/9 carriers [Caldu et al., 2007]). Effects of DAT1 beyond the striatum, in prefrontal cortex where expression of DA transporters is low, suggests broad effects of genetic polymorphisms on functional networks rather than single regions.

In sum, phenotypic expression is likely to be mediated by endogenous and exogenous factors that induce variability in catecholaminergic function. In

light of region-selective influence of catecholaminergic genetic polymorphisms, fMRI methods are well equipped to elucidate pathophysiological pathways for ADHD. Some promising directions for the future are discussed below.

FUTURE DIRECTIONS

An approach that combines use of pharmacological fMRI emphasizing examination of functional connectivity and careful phenotypic description that incorporates symptom and genotype measures ought to be fruitful. fMRI probes should capitalize on knowledge from healthy cognition about processes mediated by individual regions (e.g., response selection in inferior frontal cortex, evaluative processes in orbito-frontal cortex) and small circuits (e.g., orbitofrontal-ventral striatal) to manipulate variables, to test specific functional predictions in ADHD. These experiments should incorporate the following design features. First, in light of dependency of catecholamine function on environmental context, it will be insightful to manipulate contextual variables. For example, holding cognitive load constant, parametric manipulation of motivation levels (e.g., by use of incentives) or saliency (e.g., perceptual task characteristics) will be useful to elucidate heterogeneity in activation patterns. Second, treating symptom expression as quantitative continuous factors will allow for identification of regions where activation varies by levels of inattention, impulsivity, or hyperactivity. Furthermore, characteristics of DA or NE transmission can be varied by systematic manipulation of allelic variation, especially in combinations of genes to examine additive effects. Third, anatomical studies point to significant variability in developmental trajectories, and therefore, fMRI studies should control age, either restricting it to narrow ranges (e.g., 8–10 years rather than 8–12 years) or examining age differences by design. Fourth, examination of resting state connectivity by samples grouped by DA/NE alleles will provide information about functional characteristics associated with catecholaminergic tone. Preliminary studies in ADHD suggest weak connectivity between medial frontal-parietal regions [Castellanos et al., 2008]. Both regions are rich in NE and DA and differences by allelic variation would reveal baseline differences among ADHD subjects that relate to catecholaminergic function without heterogeneity induced by task factors. ■

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