Commentary

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White Matter Structure and Delay Tolerance in Attention-Deficit/Hyperactivity Disorder

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Attention-deficit/hyperactivity disorder (ADHD) is one of the most common child psychiatric disorders, characterized by age-inappropriate impulsiveness, inattention, and hyperactivity, with a prevalence of 7% worldwide. Symptoms persist into adulthood in most cases and are associated with lifelong worse academic, psychosocial, and professional outcomes. Given that inattention and poor self-control are part of the clinical definition of the disorder, ADHD, perhaps more consistently than any other psychiatric disorder, is associated with cognitive impairments, in particular in attention and inhibition domains. Thus, ADHD patients are impaired in so-called cool executive functions as measured in tasks of motor and interference inhibition, selective and sustained attention, and working memory, as well as in timing skills, such as time estimation, motor timing, and temporal foresight (1). The poor performance in these tasks has been associated in functional magnetic resonance imaging (fMRI) studies with underactivation in several domain-specific lateral fronto-striato-thalamo-parietal and frontocerebellar networks (2). However, abnormalities have also been observed in so-called hot executive functions, most commonly in tasks of temporal discounting, delay aversion, and gambling, which require reward-related decision making with the optimal choice being the option that maximizes reward but requires tolerating a temporal delay, such as waiting for a real or hypothetical delayed reward. While requiring reward-based choice behavior and therefore being mediated by hot executive medial and orbitofrontal-limbic reward processing networks, hot executive functions also contain elements of cool temporal foresight abilities mediated by lateral frontoparietal regions, such as looking into the future to understand the value of the delayed reward (1,3,4). Despite neurocognitive evidence for overlapping cool and hot neurocognitive functions involved in temporal discounting tasks (3,4), there is evidence to suggest different cognitive pathways into ADHD, with some children being more or exclusively impaired in cool executive functions, in particular in tasks of inhibitory self-control, and others having more specific problems with temporal discounting or delay aversion (5). It has been argued that both types of impairment reflect different impulsiveness problems, a more cognitive type of impulsiveness that is associated with poor self-inhibitory control versus a more affective impulsiveness type that is associated with an aversion to temporal delays. Both would represent different etiological pathways into ADHD (5).

In this issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Bessette and Stevens (6) investigated specifically whether these two neurocognitive pathway markers of ADHD based on multiple measures of inhibitory self-control and of delay aversion/temporal discounting tasks would be associated with different brain–behavior associations in ADHD compared with healthy adolescents using diffusion tensor imaging (DTI). Bessette and Stevens (6) argue that the inconsistency of case-control findings in DTI studies in ADHD could be due to cognitive heterogeneity and that different white matter structure patterns might be associated with these two different impulsivity types that are likely to represent different etiological pathways into ADHD. Therefore, rather than comparing patients and control subjects in white matter tracts directly, Bessette and Stevens (6) compared 77 adolescents with ADHD and 68 healthy adolescents in their associations between DTI measures and performance of a range of cognitive tasks that measure inhibitory impulsiveness, temporal choice behavior, and delay aversion to test for disorder-dissociated brain–behavior relationships. The more cognitive-inhibitory impulsiveness measures included commission errors on the continuous performance task, commission errors to "catch trials" in a delayed working memory task, and the stop signal reaction time in the stop task. The more affective impulsiveness measures included the degree of discounting in a delay discounting task and an experiential delay discounting task (EDT)—where subjects experienced the actual chosen delays (in seconds) rather than choosing hypothetical delays, as in the delay discounting task—and a task where waiting behavior was associated with monetary rewards (single-key impulsivity paradigm). Confirmatory factor analysis of the two hypothesized different neurocognitive pathway markers resulted in three rather than two factors: one including the cognitive inhibitory measures, another including the delay discounting and EDT, labeled "choice behavior," and a third including the EDT, single-key impulsivity paradigm, and the commission errors to catch trials in the delayed working memory task. Only the last factor, which included all the tasks containing a real delay, associated with reward in two of them (single-key impulsivity paradigm and EDT), and which the authors labeled the "delay aversion" factor, was associated with different brain–behavior relationships in healthy adolescents compared with those with ADHD. In healthy adolescents, better fractional anisotropy in white matter tracts in the bilateral corona radiata, internal capsule, inferior and superior longitudinal fasciculi, inferior fronto-occipital, and corticospinal tracts and splenium of the corpus callosum was associated with better tolerance of delayed rewards; there were negative or no associations observed in ADHD adolescents. None of the other factors were associated with differences in brain–behavior relationships between patients and control subjects. In addition, patients and control subjects did not differ in

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performance or white matter tracts in a straightforward case-control comparison in DTI.

Several of the tracts that were differentially associated with good delay tolerance in healthy compared with ADHD adolescents connect regions that play a crucial role in timing, including delay discounting, in healthy adults and adolescents, such as the internal capsule that connects the basal ganglia and thalamus with frontal, parietal, and brainstem regions, the inferior and superior longitudinal fasciculi, the fronto-occipital and corticospinal tracts that connect dorsal and inferior frontal regions with the posterior temporal, parietal, and occipital areas, or the corona radiata that connects the premotor cortex and supplementary motor area with the posterior parietal, cerebellar, and brainstem regions. The inferior frontal cortex and supplementary motor area together with their connections to striato-thalamic, parietal, and cerebellar regions are key to timing abilities (1), including delay discounting (3,4). It has been argued that impulsiveness in ADHD is closely related to abnormal timing behaviors, manifesting in poor time estimation where time is subjectively elongated, clumsy motor timing, and deficient temporal foresight, leading to poor insight into the future consequences of their behaviors and thus to impulsive choices (1,7). In fMRI, ADHD patients have abnormal activation in typical timing-mediating regions of the inferior frontal cortex, the supplementary motor area, and the striato-thalamic, parietal, and cerebellar regions during the performance of timing tasks, including temporal discounting (8). Furthermore, the findings of an abnormal brain–behavior association between several white matter tracts connecting the frontal, striato-thalamic, and posterior temporoparietal brain regions and delay aversion performance in healthy relative to ADHD adolescents in the study of Bessette and Stevens (6) resonates with a fMRI study that also observed an abnormal brain–behavior association between ADHD and healthy control subjects—despite no case-control differences in activation—between task performance and the activation of a wide range of timing-mediating regions, including the inferior frontal cortex, the supplementary motor area, and the striatal, temporoparietal, and cerebellar areas (9). Larger-sampled fMRI studies, furthermore, found reduced activation in ADHD relative to healthy adolescents in these inferior frontal, striato-thalamic, parietal, and cerebellar-occipital regions during temporal discounting (10). The involvement of visual and motor tracts in the study by Bessette and Stevens (6) likely reflects the visuo-motor nature of the tasks. Interestingly, errors in the delayed working memory task loaded negatively on the delay aversion factor in the Bessette and Stevens (6) study, suggesting that poor working memory is associated with less tolerance of delayed rewards. This is in line with the suggestion that memory systems are involved in delay discounting, given the evidence that regions involved in memory are also involved in temporal foresight and mental time travel. This has been interpreted as a dual role of memory systems for looking into the past and into the future and been linked to the importance of remembering past delays/monetary gains to guide future decisions and to enhance preference for delayed rewards (3). Some of the white matter tracts associated with delay aversion also involved limbic regions, in line with the notion that waiting for delayed rewards likely involves both 1) motivation processing regions that subjectively evaluate rewards, such as thalamus and amygdala, and are involved in "(dis)liking" of delays and 2) higher-level lateral dorsal and ventral fronto-striato-parieto-cerebellar networks that guide behavior toward future gains, overcoming the dislike of waiting through the development of delay tolerance (3,4). Interestingly, several of these white matter tracts, in particular the fronto-posterior association tracts, are among the latest to develop. The dissociated negative association with these tracts in adolescents with ADHD compared with healthy adolescents in relation to reward delay tolerance could reflect immature white matter tract development, parallel to the evidence of a maturational delay in brain structure and function development (2).

The lack of a differential association between cognitive impulsiveness and white matter tracts between adolescents with ADHD and healthy adolescents was unexpected and may reflect stronger dissociative brain–behavior associations for tolerance of delayed rewards than inhibitory behavior. The lack of case-control DTI deficits is not in line with previous work and may reflect heterogeneity of ADHD neuropathology or the fact that older ADHD patients are less impaired in brain structure than ADHD children. A more efficient way forward to test associations between cognitive subtypes of ADHD and brain structure and function measures would be to select patients who are impaired in one or the other cognitive subdomains and to test for associations between brain and behavior in these more homogenous neurocognitive subtypes.

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