The Shape of Things to Come in Attention Deficit Hyperactivity Disorder

The search for a neuroanatomic signature of attention deficit hyperactivity disorder (ADHD) has already yielded important findings. At a lobar level, there is volume loss of around 3%–4% (1), and techniques that allow a finer level of spatial resolution—such as measures of gray matter density or thickness—demonstrate marked compromise of the prefrontal cortex and interconnected striatum (2, 3). Such work is reliant on advances in analytic techniques, and as the study by Ivanov and colleagues in this issue (4) elegantly demonstrates, a potentially powerful new tool lies in the delineation of shape anomalies in key brain structures.

The study focused on the thalamus, within which different nuclei interact richly and often reciprocally with both the striatum and the cortex, forming partially segregated loops that support cognitive processes as diverse as motor control and the allocation of attentional resources. The possibility that structural anomalies of the thalamus could disrupt these circuits and lead to the cardinal symptoms of ADHD has largely been unexplored. This reflects the difficulty in reliably defining the volume of different thalamic nuclei using conventional structural MRI scans, and thus in most studies the thalamus has been treated as a unitary structure, possibly missing localized compromise of one of its composite nuclei. The study by Ivanov and colleagues rectifies this neglect by first extracting the surface contours of the thalamus from structural MRI scans of 46 youths with ADHD and 59 typically developing comparison youths. Then the degree to which each thalamic surface had to be stretched or shrunk (warped) to fit a template of the thalamus was determined. This approach allows exquisite definition of local surface changes in the ADHD group that can then be related to a reference "cytoarchitectonic" map of the underlying nuclei (which uses cellular architecture to delineate the nuclei). Surface expansions are interpreted as reflecting volume increase in underlying nuclei and surface contractions as indicative of volume loss.

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The study's most striking finding was marked volume loss in the region of the pulvinar nuclei bilaterally in the ADHD group. The pulvinar nuclei link action and vision, and the pulvinar's lateral portions, where the morphological anomalies were most prominent, support circuitry that detects salient somatosensory stimuli (5). The authors thus speculate that morphological disruption of the pulvinar could contribute to the inefficient allocation of attentional resources seen in ADHD. Somewhat distinct areas of the pulvinar were associated with symptom severity: *increased* volumes of the right pulvinar and medial-dorsal nuclei were correlated with the severity of inattention. By contrast, severity of hyperactivity was associated with *decreased* volumes in a distinct group of more lateral thalamic nuclei. Notably, these complex surface changes and associated underlying volumetric perturbations did not lead to a change in the overall volume of the thalamus in youths with ADHD relative to typically developing youths. Thus a traditional region-of-interest study examining the volume of the unitary thalamus would have missed these subtle but important diagnostic signals.

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The study complements earlier work from the same group on shape anomalies of the amygdala, a limbic structure that is interconnected with the pulvinar (6). Given the amygdala's role in the processing of affectively charged stimuli, the authors speculate that the finding of conjoint shape anomalies in the pulvinar and amygdala could represent part of the neural substrate underpinning the emotional dysregulation frequently seen in ADHD. Disturbances in the shape of striatal components of the cortico-striatal-thalamic loops have also recently been found in ADHD with prominent surface compression in the head and body of the caudate and the anterior putamen (7). It would not be surprising if linked anomalies of cortical surface morphology in ADHD were soon reported.

Of possible interest to clinicians is that pulvinar reduction in the youths with ADHD in this study was largely driven by those who were not receiving treatment with psychostimulants at the time of the scan. The youths with ADHD who were medicated had thalamic surface morphology more closely resembling that of typically developing youths and thalamic volumes that tended to be larger than those of their unmedicated counterparts. This finding adds to other demonstrations that psychostimulant treatment in ADHD is associated with more normative brain dimensions—including white matter (1) and key regions implicated in the pathogenesis of the disorder, such as the dorsolateral prefrontal cortex (8), the anterior cingulate cortex, and the cerebellar vermis (9). However, as the authors stress, these associations should not be overinterpreted. First, in this study, among the subgroup of 17 medicated patients for whom treatment duration could be determined, greater duration of treatment was associated with *smaller* volumes in regions of the right pulvinar that did not show the main effect of diagnosis—a finding running somewhat counter to the finding of pulvinar enlargement associated with psychostimulant treatment at the time of the scan. More generally, causality cannot be inferred from observational studies, and a definitive demonstration of any trophic effects of psychostimulants awaits a neuroimaging study conducted within the context of a randomized trial.

The study raises many important questions. The authors interpret the surface changes as indicative of volume loss in the underlying nuclei, which is very plausible. However, might surface changes also represent displacement of possibly volumetrically intact nuclei within the thalamus, or perhaps even result from anomalies of adjacent white matter and other structures? Second, what drives these changes? The complexity of answering this question is highlighted by the nature of the links between structural changes and symptom domains: whereas decreased local volumes accompanied hyperactivity, increased volumes accompanied inattention. Third, do these thalamic abnormalities reflect or drive structural changes in interconnected striatal, limbic, and cortical regions? Finally, how do these structural changes relate to abnormal cognitive and affective function—and which tasks are best suited to probe thalamic dysfunction?

The study exemplifies the increasing sophistication of morphological studies as they incorporate novel measures of local shape, complexity, volume, and thickness and align structural MRI with other imaging modalities, such as the delineation of white matter tracts by diffusion tensor imaging and maps of brain activation generated by functional MRI (10). In structural neuroanatomic studies of ADHD, things are indeed shaping up well.

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