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Novel Targets for ADHD Interventions: Can potential biomarkers be identified from longitudinal data?

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ADHD is a prevalent, impairing neurodevelopmental disorder. For many, but not all, individuals with ADHD, the disorder emerges in childhood and exhibits a chronic course through adolescence and adulthood. Given that many individuals show a remitting course over development, critical research, such as Michelini, Kitsune *et al.*'s (1) study reported in this issue, has focused on biological and behavioral correlates of long-term outcomes for individuals with ADHD that could elucidate mechanisms of recovery. Such research is important because of its potential to guide the development of novel interventions that will alter trajectories and confer enduring change rather than temporary symptomatic relief provided by currently available treatments.

Michelini, Kitsune *et al.*'s (1) study builds on their previous work (2) that examined predictors of ADHD persistence and remission among 279 adolescents/young adults who had been evaluated for ADHD as children. Participants completed a modified Eriksen flanker task while neurophysiological markers of conflict monitoring (N2), and unconscious (ERN) and conscious error processing (Pe) were obtained. The flanker task, a computerized measure of inhibitory control, requires participants to respond to a centrally located stimulus while ignoring interference from stimuli presented on either side (the "flankers"). In this study, participants had to indicate the directionality of a center arrow while ignoring its flanking arrows pointing in the same (low conflict condition) or opposite (high conflict condition) direction. The investigators have carried out a thoughtful, well-designed study that integrated thorough clinical assessment of ADHD symptoms and impairment with neuropsychological and neurophysiological measures in a group of adolescents and young adults who were followed from childhood. The authors report that attention-vigilance and error detection measures may distinguish ADHD Persisters from Remitters, and as possible markers of remission, they may be targets for the development of interventions.

Longitudinal studies like Michelini, Kitsune *et al.*'s (1) are essential to help us better understand life course trajectories of ADHD and correlates of better or worse outcomes. However, the complex constructs under study pose challenges to researchers. For example, how we define "persistence" and "remission" has enormous consequences for categorical

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analyses because group membership changes depending on: a) where the cut in number of symptoms is made, and b) whether impairment is taken into consideration (3). Michelini, Kitsune *et al.* (1) defined Persistence as meeting DSM-IV symptom-level criteria and the presence of significant impairment as reported by parents. Remitters could present with five or more ADHD symptoms in either the inattentive or hyperactive-impulsive domain as long as functional impairment was not reported. Notably, nearly two thirds of the Remitters (14/23) exhibited 5 symptoms in one domain (above the DSM-V cutoff for adults) indicating substantial overlap in symptom severity between Persister and Remitter groups. Medication use is another potentially thorny issue, in part because it complicates the definition of impairment. At what level of functioning should an individual be considered “impaired”? At follow-up, 47% of those who had ADHD as children were prescribed stimulant medication, with the proportion of medication use not differing across Persisters and Remitters. If an individual is taking stimulant medication and reports no impairment, does this mean they no longer meet criteria for ADHD? Or, should judgments about “impairment” take into account the treatment and other resources an individual receives (e.g., individualized education programs, testing accommodations) to help manage their disorder? Arguably, the clinician or researcher should determine a person’s level of functioning when supports are removed. Alternatively, if a person has developed compensatory behaviors to reduce the negative impact of their symptoms, it could be argued that this reflects *better* functioning despite their elevated inattention and/or hyperactivity/impulsivity, and thus they should no longer meet criteria for the disorder. Both clinically and scientifically, this is a critical question because decisions about classification (and subsequent service provision) depend on the answer. These issues provide further impetus for moving from a categorical to a dimensional approach to ADHD.

Michelini, Kitsune *et al.* (1) found a fairly high rate of persistence with 79% of individuals who had been diagnosed with ADHD as children continuing to meet DSM-IV criteria for the disorder at follow-up. Persisters performed more poorly than controls on all measures. However, Remitters differed from Persisters, but not from non-ADHD peers, on error processing indices, errors during the low conflict condition, and reaction time variability. The authors emphasize the differences in non-executive processes between Persisters and Remitters, which is contrary to the theory that development of the prefrontal cortex and associated executive functions is associated with a decline in ADHD severity (4). These findings are consistent with others who have shown non-executive functions to predict improvements in the clinical course of ADHD (5). However, the ERP analyses, which were carried out for incongruent trials, showed that Persisters’ ERN ($d=.52$, $p=.05$) and Pe ($d=.44$, $p=.05$) were attenuated compared to Remitters (1). These indicators are thought to reflect error processing and are associated with executive attention networks that are central to the regulation of cognition and affect (6). The key point is that complex networks work in concert to mediate these functions, raising questions about whether the dichotomy between executive and non-executive processes is meaningful when they are components of larger, interdependent networks. Also of note, dimensional analyses showed that for individuals who had ADHD as children, Pe, which according to the authors “represents conscious error processing to adjust response strategy,” was significantly negatively correlated with symptom and impairment severity at follow-up, even after controlling for IQ. This again

highlights the blurred boundaries between executive and non-executive functions, the continuum underlying the persister-remitter dichotomy, as well as the utility of dimensional analyses.

Studies like Michelini, Kitsune *et al.* (1) are essential because in identifying correlates of clinical course, they offer potential targets for the development of novel treatments for ADHD. Although stimulant medications continue to be the most efficacious treatment for ADHD, current pharmacological interventions do not seem to alter long-term trajectories of individuals with the disorder (7). In the non-pharmacological domain, working memory remediation has been shown to lead to better performance on working memory tests, but there is little evidence for concomitant decreases in ADHD symptoms (8). If, as Michelini, Kitsune *et al.* (1) suggest, non-executive processes and error processing distinguish persisters from remitters, developing and rigorously testing interventions that target these areas may be fruitful.

Two promising non-pharmacological interventions are mindfulness meditation and physical exercise. Mindfulness meditation involves paying attention to the present, on purpose and non-judgmentally. Treatments centered on mindfulness have been developed for a number of emotional and behavioral problems, including ADHD, with encouraging results. A recent meta-analysis of 10 published studies that delivered some form of long-term (4–13 weeks) mindfulness-based intervention to children or adults with ADHD showed that this type of treatment appeared to reduce both inattention ($d=-.66$) and hyperactive/impulsive symptoms ($d=-.53$) (9).

Research investigating the mechanism through which mindfulness affects behavior is in its infancy. However several cross-sectional and longitudinal studies show mindfulness meditation to positively affect brain structure and function (6). Long-term mindfulness practice has been associated with improved alerting, orienting and executive attention. The most consistent neuroimaging findings have shown that mindfulness practice is associated with increased activation of not only dorsolateral prefrontal cortex, but also the anterior cingulate cortex (involved in error processing) and parietal attention regions –brain regions implicated in the executive attention network (6). Future studies should integrate neuroimaging with neuropsychological and neurophysiological methods so that functional improvements can be mapped on to structural changes. This kind of multi-method approach was utilized by Michelini, Kitsune *et al.* (1) and represents an important strength of their study.

Physical activity is another intervention that shows considerable promise. As this is a fairly new interest in the ADHD literature, there are still relatively few studies that have investigated behavioral or cognitive changes following either acute or chronic exercise interventions. Most studies to date have been carried out with children and evaluate effectiveness rather than efficacy. Despite these limitations, emerging evidence suggests that chronic exercise is associated with reduced inattention and overall ADHD symptoms (10). Both acute and chronic moderate-intensity exercise have been associated with improved neuropsychological performance in several domains, including response inhibition, set shifting, sustained attention, motor skills, processing speed, and auditory attention (10).

These domains encompass both executive and non-executive functions and speak to the importance of considering neural networks involved in the regulation of behavior.

Micheline, Kitsune *et al.* (1) should be congratulated on producing the kind of research that is essential for our field. Rigorous assessment of participants repeatedly over time alongside the multi-method approach yields robust data on the course of ADHD across the lifespan, and the correlates of clinical outcomes. While the field continues to struggle with key issues such as optimal ways to impose categorical cuts on what is really a dimension, ways to account for active treatment when classifying individuals and gauging outcome, and distinguishing highly interconnected executive and non-executive processes, research such as this is critical to inspire the design of new interventions for individuals with ADHD. Ideally, such interventions will stimulate neural development and promote enduring, positive change for individuals with ADHD.

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