On the Road to Physiological Models of Brain Function in ADHD

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Persistence and symptomatic remission of attention deficit hyperactivity disorder (ADHD) into adulthood are well documented (1). An intriguing neurodevelopmental model suggested that early and enduring subcortical abnormalities account for the onset of childhood ADHD with remission reflecting the adequacy of later-developing prefrontal maturational processes (2). Guided by this model, Szekely and colleagues (3), in this issue of the *Journal*, investigated the neural substrates underlying persistence or remission of ADHD in adulthood. They employed a combination of functional MRI (fMRI) and magnetoencephalography during the same stop-signal task of motor inhibition. Importantly, nearly all (95%) of the 181 participants had been followed at the National Institute of Mental Health (NIMH) since childhood, obviating concerns regarding retrospective bias in reporting past ADHD (4).

In total, 35 adult participants with persistent ADHD (meeting current DSM-5 criteria), 47 with remitted ADHD (failing to meet full DSM-5 criteria), and 99 never-affected individuals participated. Reflecting the challenges of conducting multimodal imaging, 63 participants (35%) completed both fMRI and magnetoencephalography versions of the stop task, 85 (47%) completed only the fMRI version, and 33 (18%) completed only the magnetoencephalography version. Categorical (group-based) analyses of fMRI activations did not yield differences surviving correction for whole-brain comparisons. Fortunately, an extensive literature (e.g., see reference 5) supports specifying the inferior frontal cortex and the caudate nucleus as regions of interest for the stop task, which allows statistically more lenient analyses. History of childhood ADHD, regardless of current status, was associated with reduced caudate activity when successfully inhibiting and increased activity when failing to inhibit, relative to never-affected comparison subjects. By contrast, the group with persistent ADHD displayed reduced inferior frontal cortex activity during failed inhibition when compared with either the remitted or never-affected group, which did not differ from each other. Follow-up analysis of the decreased activation in the inferior frontal cortex revealed a significant correlation with the current number of hyperactivity/impulsivity symptoms, but not with the number of inattention symptoms.

The inclusion of magnetoencephalography with the same tracking stop task (albeit with twice as many trials) allowed a temporal dissection of the fMRI findings. Right inferior frontal cortex activity during successful inhibition, at 300 ms–350 ms after the stop signal, was increased in remitted individuals compared with those with persistent ADHD. At 500 ms–550 ms after the stop signal, theta band power in a large cerebellar cluster, a right inferior parietal cluster, and a right cuneal/posterior cingulate cluster was lowest in those with persistent ADHD, highest in never-affected comparison subjects, and intermediate in the remitted group. At 550 ms–600 ms after the stop signal, delta band power in the cerebellum and left precuneus was similarly highest in never-affected comparison subjects, lowest in those with persistent ADHD, and intermediate in remitters.

The results are consistent with the model proposed by Halperin and Schultz (2) implicating subcortical anomalies in the development of ADHD and ascribing symptomatic remission to later-occurring prefrontal maturation. The availability of magnetoencephalography data with the same task and overlapping subsets of participants further supports the involvement of the inferior frontal cortex in the process of inhibition, as well as that of cerebellar and parietal areas in later-occurring performance-monitoring processes. Locating neural processes in brain space and time is essential for articulating models of the pathophysiology of ADHD persisting into adulthood within the context of motor inhibition. As the authors note, similar approaches need to be carried out with alternative tasks. Ultimately, as they also acknowledge, developmental hypotheses can only be definitively tested using longitudinal designs (6).

Fortunately, history warrants substantial optimism that our tools will continue to improve in precision.

Of course, at the moment, conducting rigorous longitudinal examinations of brain function is far from trivial. The obverse of technology advancing rapidly, as in neuroimaging, is the difficulty of making fair comparisons over time. For example, nearly all the participants in the study by Szekely and colleagues (3) had had previous structural MRI studies at NIMH, but on a long-since decommissioned 1.5-Tesla scanner, while the current study was performed using 3-Tesla. Currently, neuroimaging data remain exquisitely sensitive to even presumably minor differences in how the data are acquired or processed. Scans of the same person on two different scanners, even the same model, are too infrequently identical. Every magnet is unique (to some extent) in its idiosyncratic inhomogeneities and quantum inscrutabilities.

Fortunately, history warrants substantial optimism that our tools will continue to improve in precision. The example of the development of electrocardiography is instructive. Electrocardiograms are now obtained rapidly and inexpensively throughout the world without clinicians having to attend to the manufacturer of the recording equipment, never mind the model or analytic software. Waller's first report of electrical activity in 1887 was obtained with a capillary mercury-filled electrometer that was photographed on a traveling plate to provide a temporal record (7, 8). Despite Waller's conclusion that the obtained signal was "certainly physiological," he was troubled by "sources of doubt" and the concern that "a definitive interpretation of the character of the variation" [of the electrometer] … may nevertheless be physically complicated by the conditions of … the human body" (7, p. 234). Happily, Einthoven observed Waller recording an electrocardiogram in 1889, and he dedicated himself to improving the capillary electrometer, being soon able to discern the five deflections of the cardiac cycle, which he labeled P, Q, R, S, and T, as they have been known since. However, it was his incorporation of advances from telegraphy, particularly the string galvanometer, that launched modern electrocardiography by 1902 (9). This rapid progress reflects the ingenuity and dedication that merited Einthoven's 1924 Nobel in Medicine or Physiology, but it also stemmed from the direct relationship between the electrocardiographic signals and cardiac physiology.

The brain yields its secrets with greater reluctance, but it is yielding. This latest contribution from the laboratory of Philip Shaw and his colleagues is not the final word on the issue, but it is a worthy illustration of the sorts of approaches that are needed. The application of multiple methods is essential, given the intrinsic limits of any single technique. At the same time, bringing diverse data types into convergence represents its own challenges, at multiple levels. For example, each method exists in its own spatial and temporal framework. The field of clinical neuroscience will soon have the opportunity to confront this challenge with the forthcoming initial data release from the Adolescent Brain Cognitive Development Study ([ABCD] https://data-archive.nimh.nih.gov/abcd). These data, obtained from nearly 10,000 9- to 10-year-old children on all three of the major MRI scanner platforms, will first challenge imagers, engineers, physicists, and statisticians to develop needed algorithms for scanner harmonization. The next task will be to optimize methods to effectively mine big brain developmental data (10). Following this path toward physiology will eventually allow us to parallel the progress of electrocardiography. After all, the first "string galvanometer was inconveniently large and immobile—it occupied 2 rooms and weighed approximately 600 pounds" (9, p. 177). Maintaining our focus on discovering physiology is the shortest path to accelerating the virtuous cycle of developing tools we need to enhance health.

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The authors report no financial relationships with commercial interests.

Accepted June 2017.

Am J Psychiatry 2017; 174:825–826; doi: 10.1176/appi.ajp.2017.17060667

REFERENCES

1. Klein RG, Mannuzza S, Olazagasti MA, et al: Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. Arch Gen Psychiatry 2012; 69:1295–1303
2. Halperin JM, Schulz KP: Revisiting the role of the prefrontal cortex in the pathophysiology of attention-deficit/hyperactivity disorder. Psychol Bull 2006; 132:560–581
3. Szekely E, Sudre GP, Sharp W, et al: Defining the neural substrate of the adult outcome of childhood ADHD: a multimodal neuroimaging study of response inhibition. Am J Psychiatry 2017; 174:867–876
4. Mannuzza S, Klein RG, Klein DF, et al: Accuracy of adult recall of childhood attention deficit hyperactivity disorder. Am J Psychiatry 2002; 159:1882–1888
5. Aron AR, Poldrack RA: The cognitive neuroscience of response inhibition: relevance for genetic research in attention-deficit/hyperactivity disorder. Biol Psychiatry 2005; 57:1285–1292
6. Kraemer HC, Yesavage JA, Taylor JL, et al: How can we learn about developmental processes from cross-sectional studies, or can we? Am J Psychiatry 2000; 157:163–171
7. Waller AD: A demonstration on man of electromotive changes accompanying the heart's beat. J Physiol 1887; 8:229–234
8. Cooper JK: Electrocardiography 100 years ago: origins, pioneers, and contributors. N Engl J Med 1986; 315:461–464
9. Rivera-Ruiz M, Cajavilca C, Varon J: Einthoven's string galvanometer: the first electrocardiograph. Tex Heart Inst J 2008; 35:174–178
10. Zhao Y, Castellanos FX: Annual research review: discovery science strategies in studies of the pathophysiology of child and adolescent psychiatric disorders—promises and limitations. J Child Psychol Psychiatry 2016; 57:421–439