

The eternal promise of EEG-based biomarkers

Getting closer?

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Several years ago, a colleague in the developmental clinic asked me to tell him what I thought about a brain mapping EEG report brought in by a parent. The report made a number of bold pronouncements about the child's brain function, such as, "Decreased current in the fusiform gyrus indicates face-processing difficulties." From my research using EEG to study the pathophysiology of developmental disabilities, I knew that making even a single conclusion about group data took years of painstaking development of cognitive experiments and obsessive analysis of the data using a variety of signal-processing techniques. The notion that automatic software could validly produce several conclusions from a few minutes' worth of spontaneous EEG data seemed far-fetched.

In this issue of *Neurology*®, Gloss et al.¹ issue a timely American Academy of Neurology (AAN) guideline regarding the role of a specific EEG technology—the theta:beta ratio (TBR)²—that is intended to aid in the diagnosis of attention-deficit/hyperactivity disorder (ADHD). This guideline follows the Food and Drug Administration's approval for marketing, in 2013, of a device that uses TBR for this purpose. In the most clinically relevant section of the guideline, the authors conclude that there is insufficient evidence currently to recommend this method as a diagnostic adjunct.

This is not the first time that the AAN has offered guidance in the decades-long and often contentious history of the use of quantitative EEG in the diagnosis of neurobehavioral disorders. Position papers^{3,4} and dissenting replies^{5,6} reflect an energetic and thoughtful dialectic. A less encouraging sign of the health of the debate is the schism by which many of those who are convinced of the utility of these techniques have formed their own professional organizations and journals. Rigorously designed experiments should yield data sufficiently compelling that all readers come to similar conclusions about the state of the field.

Good validation studies—those that offer conclusions beyond dispute—indeed are difficult to design. In many aspects, the bar is higher to validate a clinical test than to conduct the type of neurobiological

research with which we are more familiar—the comparison of 2 groups in order to say something about mechanisms underlying a diagnosis.

The key article reviewed in the guideline did a number of things very well. Although Gloss and colleagues ultimately rated the work by Snyder and colleagues^{7,8} as Class III evidence for reasons stated in the guideline, there were a number of positive points. Unlike the excesses of my colleague's "brain mapping" report, TBR was studied with a single and specific clinical aim: to determine whether a patient with ADHD symptoms is likely to have a mimicking disorder rather than ADHD itself. Additionally, Snyder and colleagues went a step beyond simple accuracy by measuring the utility of the technique. Recognizing that any EEG-based test would be used in combination with a pediatrician's clinical assessment, they calculated the degree to which TBR added additional information to that pretest assessment.

Also important is what the validation study did not claim. It did not claim to provide information about ADHD beyond the current DSM-5 diagnosis. ADHD is heterogeneous in its etiology and its symptoms, and there is a well-reasoned desire for EEG technology to tap aspects of biology that cannot be accessed by the clinical interview.⁹ The hope is that the physiology measured via EEG more directly reflects the mechanisms of the disorder, and by parsing the EEG signal carefully, it will be possible to identify subtypes (intermediate phenotypes) of ADHD that can better guide therapy in an individual patient than can any information contained within the history or physical examination. It is plausible that EEG could help fill this need. It has been a critical research tool in cognitive psychology for decades, responsible for a host of seminal discoveries, though this literature is mostly unknown to clinicians.¹⁰ Also, basic research linking the mechanisms that generate the EEG signal with the mechanisms that create cognition is beginning to coalesce into a substantial body of knowledge.¹¹ Clinically oriented basic research in this mold will continue to provide potential

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biomarkers, which must then be rigorously studied and validated.

While Research Domain Criteria and biological mechanisms may define the diagnostic approach to ADHD in the future, the field is currently limited to DSM-5 criteria. The reference standard (independent variable) in Snyder et al. was a laborious multidisciplinary evaluation using DSM-5 criteria. So if the TBR could only be shown to approximate DSM-5 criteria and not transcend them, why even bother to develop an EEG-based test?

The issue of reimbursement for procedures vs spending time with patients is a real consideration, but other factors are at play. A shortage of child psychiatrists and developmental pediatricians who focus on ADHD means that widespread ADHD treatment is often in the hands of generalists who also have to have expertise in a vast array of other disorders. Unless we invest in training far more specialist clinicians, technologies that can elevate nonspecialist expertise to approximate that of specialists can have real benefits to millions of patients.

Whether or not TBR specifically withstands the test of replication, there are many reasons to be hopeful that we are seeing a positive and dramatic shift in the field of EEG-based biomarkers. Already, computational analysis of the EEG signal is beginning to pay dividends in epilepsy and intensive care unit monitoring. A greater knowledge base of the cortical pathophysiology of behavioral disorders can and will provide grist for the biomarker mill, and we can hope that solid experimental design will prove or disprove the utility of these techniques with little controversy.

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