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Electrophysiological biomarkers of diagnosis and outcome in neurodevelopmental disorders

Shafali S. Jeste, Joel Frohlich, and Sandra K. Loo

Purpose of review

The heterogeneity in clinical presentation and outcome in neurodevelopmental disorders such as attention deficit hyperactivity disorder (ADHD) autism spectrum disorder (ASD) necessitates the identification and validation of biomarkers that can guide diagnosis, predict developmental outcomes, and monitor treatment response. Electrophysiology holds both practical and theoretical advantages as a clinical biomarker in neurodevelopmental disorders, and considerable effort has been invested in the search for electroencephalography (EEG) biomarkers in ADHD and ASD.

Recent findings

Here, we discuss the major themes in the evaluation of biomarkers and then review studies that have applied EEG to better inform diagnosis, focusing on the controversy surrounding the theta:beta ratio in ADHD; prediction of risk, highlighting recent studies of infants at high risk for ASD; and treatment monitoring, presenting new efforts in the redefinition of outcome measures in clinical trials of ASD treatment.

Summary

We conclude that insights gained from EEG studies will contribute significantly to a more mechanistic understanding of these disorders and to the development of biomarkers that can assist with diagnosis, prognosis, and intervention. There is a need, however, to utilize approaches that accommodate, rather than ignore, diagnostic heterogeneity and individual differences.

Keywords

attention deficit hyperactivity disorder, autism spectrum disorder, biomarkers, electroencephalography

INTRODUCTION

Neurodevelopmental disorders are a group of heterogeneous conditions characterized by a delay or disturbance in the acquisition of skills in a variety of developmental domains, including motor, social, language, and cognition, as defined by the *Diagnosics and Statistics Manual [1]* (DSM-5; APA 2013). Diagnoses include attention deficit hyperactivity disorder (ADHD) autism spectrum disorder (ASD), global developmental delay (GDD), and intellectual disability (ID), with major revisions made in diagnostic criteria from DSM-IV. Some common clinical features exist across this group of neurodevelopmental disorders that warrant the identification and validation of biomarkers that can guide diagnosis, predict developmental outcomes, and monitor treatment response. In this review, we will focus on the most commonly diagnosed neurodevelopmental disorders in childhood, namely ADHD and ASD, and discuss the clinical features that necessitate the search for biomarkers. We then will consider the criteria used to evaluate biomarkers

in these populations, focusing on the method of electrophysiology [electroencephalography (EEG)], and highlight recent investigations in electrophysiological biomarkers for diagnosis, prediction of diagnosis/risk status, and treatment monitoring in ADHD and ASD.

HETEROGENEITY IN PRESENTATION AND OUTCOME NECESSITATES THE SEARCH FOR QUANTIFIABLE BIOMARKERS

Both ASD and ADHD are commonly referred to as a final common pathway for multiple etiologic

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KEY POINTS

- The heterogeneity in presentation and outcome in neurodevelopmental disorders necessitates the identification and validation of biomarkers that can guide diagnosis, predict developmental outcomes, and monitor treatment response.
- From both a theoretical and practical standpoint, EEG serves as an ideal biomarker for informing diagnosis, prediction of risk and outcome in neurodevelopmental disorders.
- Although several factors may have contributed to the declining support for TBR in ADHD, the diagnostic utility of this EEG measure has not been empirically supported by recent studies.
- Given the heterogeneity apparent in ADHD and ASD, it is more likely that a multivariate biomarker can capture more variance than a single measure.
- Current and future studies in diagnostic and predictive biomarkers must move beyond group-level comparisons and focus on the stratification of individuals by relating EEG characteristics with core behaviors, such as language, social communication skills, executive function, or overall intellectual function.

variables, reflecting heterogeneity in the underlying genetic and environmental (and interactions therein) mechanisms and also in the phenotypic expression and range of symptomatology. Moreover, because these disorders are often diagnosed in early childhood, across different stages of development, there exists considerable variability in degree of change over time, both with and without intervention.

ADHD is the more prevalent neurodevelopmental disorder in children and is defined by inattention, hyperactivity, impulsivity, or a combination of these symptoms to a degree that causes functional impairment across contexts. ASD is defined by a dyad of impairments in social communication skills and the presence of repetitive patterns of behavior or restricted interests in the early developmental period. The variability in clinical presentation is rooted in severity of impairment and co-morbidities [2]. The clinical heterogeneity of these disorders presents confounds in disease stratification and prediction of outcome. For instance, it is unclear why a substantial subgroup of children with ASD (up to 30%) fails to gain spoken language despite interventions [3]. Standardized clinical measures are limited in their ability to distinguish pre-verbal from non-verbal individuals and, moreover, to capture the variability in language comprehension, reading, and overall cognitive function in this group of

children. Such an understanding would greatly inform the choice of targets in language-based interventions for individual children. As another example of the challenges rooted in heterogeneity of presentation, in ADHD, stimulants are the gold standard of treatment, yet a significant minority (approximately 30%) demonstrates a suboptimal response and/or significant adverse side-effects. Efforts to identify latent subgroups using neuropsychological measures [4], temperament dimensions [5[¶]], and resting state connectivity [6], in both ADHD and typical development, suggest that a reconceptualization of classification efforts may be needed.

CRITERIA FOR AN EFFECTIVE BIOMARKER OF DIAGNOSIS AND OUTCOME FOR NEURODEVELOPMENTAL DISORDERS

In 1998, the National Institutes of Health (NIH) Biomarkers Definitions Working Group defined a biomarker as ‘a characteristic that is objectively measured and evaluated as an indication of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention’ [7]. In neurodevelopmental disorders, the search for biomarkers has focused on measures of brain structure and function and, more specifically, those capturing cortical connectivity. These biomarkers can be divided into three primary areas, as will be expanded in following sections: diagnostic classification, risk categorization and prediction of outcome, and treatment monitoring.

Several considerations must be made in the evaluation of a brain-based biomarker in neurodevelopmental disorders (Table 1). First, the measure must have practical feasibility. Specifically, data should be collectible across multiple sites (from research settings to a doctor’s office or school) and across a heterogeneous population that ranges in age, developmental level, cognitive ability, and overall behavioral compliance with testing. Data also should be able to be collected in large populations in a timely and cost-effective manner. A biomarker should be stable and robust to state variables outside of experimental manipulation, what some may consider test-retest reliability. It should demonstrate high sensitivity and specificity to distinguish a clinical population from typical development. Furthermore, a biomarker should vary continuously in the population, relating to specific traits such as social motivation, attention, or even intellectual ability (IQ), which can then help to stratify individuals within a diagnostic category. From the standpoint of treatment monitoring, biomarkers must be sensitive to meaningful change

Table 1. Goals for and criteria used to evaluate biomarkers for neurodevelopmental disorders, from early prediction to diagnosis and treatment monitoring

	Infancy/Prodromal Period	Diagnosis	Intervention and outcome monitoring
Goals of biomarker development	(1) Predictors of diagnosis (2) Precursors to atypical behavior (3) Risk categorization	(1) Confirmation of or improved diagnosis (2) Clinical stratification (3) Establishment of treatment targets	(1) Treatment response monitoring (2) Treatment target engagement (3) Outcome prediction
Criteria to evaluate biomarkers		-Collectable across multiple sites -Collectable across heterogeneous populations -Test-retest reliability -Quantitative: varies continuously in population	
	-Relates to typical development -Sensitive to developmental change	-Relates to specific clinically relevant/core deficits -Reflects underlying neural mechanisms	-Sensitive to clinically meaningful change -Reflects mechanisms of treatment targets

over time, either because of intervention, maturation, or developmental changes. Most importantly, the biomarker must be neurobiologically meaningful, grounded in pathophysiological mechanisms of atypical development.

WHY ELECTROENCEPHALOGRAPHY?

From both a theoretical and practical standpoint, EEG serves as an ideal biomarker for characterizing neurodevelopmental disorders. EEG provides a direct measure of postsynaptic brain activity and has several orders of magnitude greater temporal resolution than functional MRI, allowing it to resolve neurophysiological oscillations and dynamics on millisecond scale. Evoked potentials are traditionally studied by averaging out noise across many trials to quantify the neural response to events or stimuli, such as face processing, whereas neural oscillations are studied by means of Fourier analysis, a method that treats signals as a linear superposition of sinusoids [8].

Compared with MRI, EEG is much more tolerant of motion artifacts, and recordings are possible in naturalistic settings, both of which facilitate the study of infants and young children [9]. Such feasibility has led to a rich understanding of EEG patterns of brain development, thereby providing a foundation for the study of atypical development. Moreover, EEG provides a method to measure the presumed mechanisms underlying neurodevelopmental disorders, such as aberrant neural connectivity and disruption of cortical excitation and inhibition balance (E/I balance), both of which are rooted in aberrations of cortical interneurons and gamma-aminobutyric acid (GABA)_A receptors

[8,10–17]. Resting-state oscillations undergo a well documented maturation in early childhood, with a decrease in slow oscillations, (theta and delta bands), increase in higher frequency activity (beta and gamma bands), and increase of interhemispheric coherence [18–20].

More refined EEG measures have more recently been introduced to measure signal properties such as complexity and information content [21]. EEG complexity depends on delicate E/I balance in neural circuits. Multiscale entropy (MSE) is a complexity metric that quantifies the unpredictability of a time series across several time scales [22]. In addition to MSE, frequency variance (FV) has been introduced as a complexity measure that examines variability in signal frequency. A recent study of preschool age children discovered a negative correlation between FV and age in resting-state EEG signals, indicating increased stability of cortical frequency states with development [23]. Functional connectivity – statistical dependencies between functional brain signals – can also be assessed using EEG recordings by a variety of methods, most commonly through the coherence of signals recorded from different electrodes. Two EEG signals are coherent if they exhibit a constant phase difference and common frequency. Hyper-synchrony between two cortical regions – driven by a loss of inhibition – might lead to elevated functional connectivity and reduced complexity of EEG signals [24,25].

DIAGNOSTIC BIOMARKERS IN ATTENTION DEFICIT HYPERACTIVITY DISORDER

Perhaps the most widely cited EEG biomarker for ADHD is the theta:beta ratio (TBR) recorded by a

single electrode at the vertex (Cz). This marker was first proposed by Lubar (1991) and was hypothesized to reflect cortical hypoarousal or slowing [26,27]. Over the following decade, several studies supportive of the link between ADHD and the TBR were published by a handful of research groups, several of which had scientific conflicts of interest. In 2006, Snyder and Hall [28] published a meta-analysis that claimed an effect size of 3.08 for the TBR in ADHD, which they suggested was predictive of sensitivity and specificity of 94%. They subsequently published an empirical study that reported 87% sensitivity, 94% specificity, and 89% overall accuracy for ADHD diagnosis that was relatively invariant according to psychiatric comorbidity, developmental level (child, adolescent), sex, and racial group [29]. These data were used in part by NEBA Health (for whom Snyder works) to apply for Food and Drug Administration approval of the TBR as a diagnostic aide, which was subsequently issued in July 2013. Although the TBR appears to be a success story for EEG biomarkers for diagnosis, controversy continues.

The controversy results from a series of recent studies by independent research groups that were not supportive of the association between the TBR and ADHD [30–36]. These negative findings were reflected in a recent meta-analysis by Arns *et al.* (2013) who concluded, ‘excessive TBR cannot be considered a reliable diagnostic measure of ADHD [37].’ In addition, there was a very strong and significant negative correlation ($r = -0.97$, $P < 0.001$) between year of publication and TBR effect size, reflecting the recent and significant decline in support for the TBR in ADHD.

To what factors can the shift be attributed? One possible factor is an increase in the TBR among control populations (potentially driven by decreased sleep duration among youth) that attenuates the TBR difference between ADHD and non-ADHD populations [37]. Another source of difference may lie in developmental factors that were uncontrolled. For example, Buyck and Wiersema (2014) reported a low diagnostic accuracy of the TBR for ADHD [area under the curve (AUC) = 0.55]; however, they obtained a much higher age classification rate (AUC = 0.97) [30]. In earlier studies, wide age ranges were typically matched but age was not used as a statistical covariate. Finally, consistent with the earlier discussion regarding ADHD heterogeneity, it is likely that there is a subgroup of individuals with ADHD with an TBR that may have been overrepresented in earlier studies because of sampling procedures. Although several factors may have contributed to the declining support for TBR in ADHD, the

diagnostic utility of this EEG measure has not been empirically supported by recent studies. Given the heterogeneity apparent in ADHD, it is more likely that a multivariate biomarker can capture greater variance than a single measure (for a more complete discussion, see Lenartowicz and Loo [38]).

DIAGNOSTIC BIOMARKERS IN AUTISM SPECTRUM DISORDER

Several studies have investigated EEG patterns that may differentiate individuals with ASD from age-matched typically developing controls, but none have attempted to validate these measures as being sensitive or specific to diagnosis. Not surprisingly, because of the wide range in ages and phenotype of the ASD group being studied, no single EEG biomarker has been identified that consistently distinguishes individuals with ASD from those without ASD. In the most comprehensive review of resting-state EEG studies in ASD, Wang *et al.* identified a possible ‘U shaped’ profile of EEG power alterations, with excess power displayed in low frequency and high frequency bands and reduced power in alpha and beta bands compared with typically developing individuals. The authors speculated that, in part, this profile results from abnormal GABAergic tone in inhibitory circuits [39]. Studies of functional connectivity have identified a general pattern of long-range under-connectivity and short-range over-connectivity in ASD, with results varying based on regions and frequency bands of interest [40–42]. Functional connectivity and coherence during cognitive and perceptual tasks have also yielded some promising findings in distinguishing ASD from typical development, with differences in connectivity patterns, particularly in interhemispheric coherence, during tasks such as face and object processing, picture naming, set-shifting [43–46].

A recent study by Eldridge *et al.* (2014) examined signal complexity through MSE in EEG recordings from an auditory oddball event-related potential (ERP) paradigm in young children ages 6–10 years old and found that MSE is a useful feature for classification of children as ASD or typically developing [47]. In an effort to understand the relationship between connectivity and complexity in ASD, Ghanbari *et al.* (2015) identified a significant difference between children with ASD and age-matched typically developing children in the relationship between connectivity and complexity using magnetoencephalography (MEG). Specifically, there were significant group differences in patterns of complexity based on brain region and frequency band. In ASD, there was an inverse relationship between

functional connectivity in the ASD group, suggesting that perhaps diminished connectivity leads to more 'unregulated and therefore complex' signals and increased entropy [48]. This study highlights the need to consider not only signal characteristics but also the relationship between variables as a diagnostic biomarker, as these relationships may shed light on underlying pathophysiological mechanisms of disease.

EEG can also inform neurophysiological mechanisms of disease in high-risk genetic variants, therefore bridging the gap from genes to behavior. For instance, duplications on chromosome 15q11-q13 ('Dup15q syndrome') confer a very high risk for global developmental delay, hypotonia, ASD, ADHD, and epilepsy [49–51]. Quite notably, a subgroup of children with Dup15q syndrome exhibit a classic EEG pattern of excessive beta (12-30 Hz) frequency activity, a feature often found in patients treated with GABAergic medications such as benzodiazepenes [52]. This signature in Dup15q syndrome likely reflects the upregulation of several GABA receptor genes located in the duplicated region. Current studies are underway to better characterize this excessive beta activity, both in mouse models and in patients, to understand the mechanism underlying this EEG pattern and to investigate whether this EEG signature relates to or predicts clinical outcomes, particularly the development of epilepsy or ASD.

Current and future studies in diagnostic biomarkers must move beyond group-level comparisons and focus on the stratification of individuals by relating EEG characteristics with core behaviors, such as language, social communication skills, executive function, or overall intellectual function. Because EEG measures such as spectral power, coherence, and complexity are continuous and relate to typical development, they hold tremendous potential for the creation of clinically meaningful subgroups within the spectra of neurodevelopmental disorders.

BIOMARKERS OF RISK PREDICTION IN AUTISM SPECTRUM DISORDER

Neurodevelopmental disorders likely result from a complex interaction of genetic susceptibility and environmental influence, and it is likely that aberrant connectivity and neural integration precede clinical evidence of developmental delay. Given that early diagnosis facilitates early intervention, which, in turn, can improve developmental outcomes, there has been tremendous interest in the identification of early predictors of atypical development. Most studies in early risk prediction have

focused on infant siblings of children with ASD, as these infants have a 20% risk of developing ASD [53]. In children who develop ASD, atypical behaviors or delayed development do not consistently emerge until the second year of life [54]. In that setting, investigations have focused on the characterization of EEG patterns that reflect neuronal connectivity in early infancy.

Several studies have demonstrated differences in high-frequency oscillations (particularly the gamma band 30-80 Hz), which reflect the binding of neural information from different networks. Elsabbagh *et al.* [55] found higher baseline and lower event-related gamma power in high-risk infants during an eye-gaze processing paradigm, whereas Tierney *et al.* reported lower gamma power at age 6 months and a flattened slope of gamma change over the first 2 years of life in high-risk infants [56]. These findings suggest a delayed maturation of cortical connections or local temporal binding, particularly in response to social stimuli. Whether they reflect a pathway specific to social communication deficits rather than overall delayed development remains to be investigated, ideally through the study of other high-risk groups, such as those with specific high-risk genetic syndromes or variants. Another study by the same group reported a distinctive and atypical pattern of hemispheric organization, based on alpha band (6-9 Hz) asymmetry, in high-risk infants regardless of ASD diagnosis. In an effort to better quantify neural integration across brain regions, Righi *et al.* [57] studied linear coherence (which represents the correlation between phase and power of two EEG signals in a frequency range) and found that infants at high risk for ASD exhibited significantly lower functional connectivity between frontal and parietal regions compared with low-risk infants. Finally, Bosl *et al.* [58] investigated non-linear complexity in high-risk infants by performing a machine learning algorithm using MSE as a feature vector and found different developmental trajectories for MSE in high and low-risk infants, with a classification accuracy of 80% based on risk status.

Notably, these studies have distinguished infants by risk status, independent of ASD diagnosis, with several studies (such as Righi *et al.*) actually performing secondary analyses in which they remove those infants who later developed ASD, to confirm that these differences truly represent biomarkers of risk status also known as endophenotypes, or heritable markers that relate to the disorder. Such an analysis, therefore, identifies associations between genetic predisposition for ASD and aberrant neural integration and connectivity. The lack of success, thus far, in identifying EEG patterns predictive of ASD diagnosis likely

stems from the relatively small sample size of children who develop ASD in these cohorts and the likelihood that a variety of genetic variants will contribute to the development of ASD in these infant siblings, each of which may result in a unique electrophysiological signature representing distinctive neural mechanisms of disease. Nevertheless, from a clinical standpoint, if electrophysiological patterns can predict overall risk for ASD, such stratification could still justify the implementation of early, developmentally appropriate interventions to enhance cognitive and behavioral outcomes regardless of the final diagnosis.

BIOMARKERS OF TREATMENT MONITORING IN AUTISM SPECTRUM DISORDER

As discussed in earlier sections, EEG studies have largely focused on disease and risk status categorization. In the only published study of EEG outcomes with intervention in ASD, Dawson *et al.* randomized toddlers (ages 18–30 months) to a standardized, well validated behavioral intervention (Early Start Denver Model: ESDM) or a community intervention for 2 years. Children who had received the ESDM intervention demonstrated patterns of face processing, electrophysiological, similar to typically developing controls. Moreover, cortical activation to faces, as defined by an alpha:theta ratio, correlated with gains in social behavior with treatment [59]. The findings suggest that the intervention, focused on social engagement, may enhance childrens' attention to and interest in social information which can then be quantified by EEG oscillatory patterns. The absence of baseline EEG assessments in the study precluded the characterization of change in oscillatory patterns with intervention. However, the study did highlight the potential utility of using neurophysiological measures of resting state and social communication function to capture specific mechanisms of change with intervention which, in turn, may elucidate the neural targets being engaged with treatment.

Recently, the National Institutes of Mental Health began an initiative called FAST-AS (Fast-Fail Trials in Autism Spectrum Disorders), which aims to spur on discovery of new medications through identification of brain targets within ASD and use of these biomarkers to test novel compounds. EEG measures were selected to be the primary dependent variables for the multisite FAST-AS trial. A multivariate EEG biomarker was developed using the following criteria: high discriminant validity between ASD and typically developing controls

and significant medication effects of the compound being tested. The EEG biomarker is now being used as an inclusion criterion (thus reducing heterogeneity in ASD subjects) for the clinical trial and will be used to monitor treatment response to a novel compound in ASD. Although results are not yet available as the trial is still ongoing, this study represents a unique, first-of-its-kind investigation in using EEG biomarkers for treatment response monitoring.

CONCLUSION

Given the broad spectrum of trajectories in both typical and atypical development, and the uncertainty that often surrounds the diagnosis of neurodevelopmental disorders, it is likely that we will need to develop multivariate markers and more complex measures that represent domains of functioning, rather than diagnostic categories, to capture variance within disorders. EEG is well poised to address this unmet need and to contribute significantly to a more mechanistic understanding of neurodevelopmental disorders. Although this area of investigation is still rapidly evolving and growing, integration of electrophysiological biomarkers with clinical measures not only informs, but also reforms, the way in which we diagnose, predict outcomes, and monitor progress with treatment in these disorders.

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Conflicts of interest

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