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Considerations in biomarker development for neurodevelopmental disorders

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Abstract

Purpose of review—Despite significant progress in recognizing the biological bases of autism spectrum disorder, diagnosis and treatment rely primarily on subjective evaluation of behavior. This review highlights the challenges unique to neurodevelopmental disorders that have limited biomarker development.

Recent findings—The field of neurodevelopmental disorders requires objective quantification of biological processes to enable designation of subgroups likely to benefit from specific treatments, index diagnostic status/risk, demonstrate engagement of targeted systems, and provide more rapid assessment of change than traditional clinical observation and caregiver report measures.

Summary—Useful biomarkers for neurodevelopmental disorders must be reliable across development, evident at the individual level, and specific to a unit of analysis, be it diagnostic status or functional process. The ultimate value of biomarkers for neurodevelopmental disorders will relate to their ease of use, cost, scalability, sensitivity, and methodological objectivity.

Keywords

Autism Spectrum Disorder; Neurodevelopmental Disorders; Biomarkers; EEG; ERP

Introduction

Since autism was first described, the field's understanding of autism as a biological disorder has evolved considerably. Early conceptualizations focused on a psychogenic etiology stemming from disruptions in parent-child relationships (1). Years later, pioneering genetic studies demonstrated the role of heritability by documenting higher concordance rates among monozygotic twins (2). This demonstration of a biological influence converged with evidence from early neuroanatomic studies demonstrating atypical brain structure in individuals with autism spectrum disorder (ASD; (3). With this recognition of biological bases of ASD, paradigms shifted, and research-based disciplines became increasingly involved in the study of ASD. Technologies advanced, permitting new assays of hemodynamic activity and less invasive, higher resolution examinations of neural structure

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Conflicts of interest

The author is an investigator on a Janssen biomarker development grant.

and function. Advocacy groups banded together to call for research support, and funding for autism research blossomed, from established private and federal sources, as well as newly created foundations, dedicated a portion of their endowment specifically to ASD. Presently, the convergence of these forces and resources has led to an expansion in autism research, with nearly 4,000 scholarly articles addressing autism published in calendar year 2014 and nearly 32,000 indexed over time in the United States National Library of Medicine at MEDLINE database; nearly 800 of these specifically reference biomarkers in ASD.

Despite this abundance of information and the numerous studies investigating biomarkers, clinical practice in ASD remains largely based on clinical judgment. The field's strongest and most reliable diagnostic tools consist of a play-based observational assessment (4) and a parent interview (5). Diagnostic criteria are behaviorally-based checklists representing a tally of symptoms across domains (6). Recent controversy regarding the publication of a new set of diagnostic criteria for ASD highlights the nascence of a biological understanding of autism (7); the alteration of a diagnostic manual has the potential to influence who does and does not have a neurodevelopmental disorder. Clinicians select treatments and issue prognoses primarily based on subjective evaluation and the results of standardized behavioral assessments. Outcome is most frequently quantified by behavioral observation or parent and teacher report. To be clear, the applications of these methods is remarkable; as an example, that clinicians can reliably quantify phenomena as abstract as social-communicative behavior is a notable clinical achievement that has significantly advanced autism research. What is salient and challenging, however, is that the nature of our methods remains essentially unchanged since Kanner (8) and Asperger (9) first wrote about autism. An increasing volume of research has yet to deliver viable, practically implementable biomarkers for ASD.

Given the immaturity of biomarker development in ASD, this review, rather than summarizing evidence for specific putative biomarkers, focuses on the nature of biomarkers and their application to ASD. I begin by operationalizing a definition of the term, biomarker, and describing the types of biomarkers most germane to clinical research in ASD. I highlight specific challenges that have contributed to the difficulties in establishing clinically useful biomarkers in autism research. Finally, I describe the potential for proximal characterization of functional biomarkers in ASD. Throughout these sections, the use of electrophysiological brain recordings is discussed as an example modality of biomarker derivation.

Biomarker definition and subtypes

A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (10). Though the term biomarker connotes biology, this functional definition allows for biomarkers in many different modalities, such as genes, brain structures, patterns of brain activity, overt behavior, and metabolites. Biomarkers can serve multiple purposes. A longstanding objective in ASD has been to develop *diagnostic biomarkers* that would provide discrete and objective indication of diagnostic status, i.e., whether a person does or does not have ASD. Given the importance of early detection and intervention in ASD outcome, a related goal has been to discover *screening biomarkers* that

would permit determination of diagnostic status or risk status prior to the emergence of behavior symptoms. In addition to diagnosis, biomarkers can be applied to aid in the development, application, or evaluation of treatments (See review (11)). *Stratification biomarkers* classify individuals into subgroups relevant to predicting or evaluating treatment. For example, a stratification biomarker for ASD might indicate a portion of children on the spectrum likely to respond to a specific treatment. *Target engagement biomarkers* provide evidence that an intervention is influencing an intended process (12). In ASD, a target engagement biomarker might reflect that a specific medication is altering neural activity in a brain region of interest. *Early efficacy biomarkers* provide a rapid indication of whether a treatment is effectively altering symptoms or processes underpinning those symptoms. For example in autism, an early efficacy biomarker might reveal changes in response to treatment within a shorter period of time than the clinical observation or caregiver report measures currently utilized in clinical trials in ASD.

Challenges to biomarker development in ASD

Age-related change

Autism is a developmental disorder. Symptoms emerge early in life and influence subsequent experience and, consequently, experience-expectant biological processes (13). It is likely that different biological systems may be at play at different points in development. For example, at any given time, the patterns of brain activity observed in individuals with ASD represent the interplay of innate neural anomalies and their developmental sequelae. Applying this insight to biomarker development, it follows that studies conducted in individuals at different developmental points may yield distinct results. To meet this challenge, it will be necessary to conduct biomarker research in the context of tightly developmentally constrained research samples or to analyze biomarkers with samples sufficiently large to permit analysis of developmental effects. To understand biomarkers across development it will also be helpful to develop biomarkers that can be applied consistently throughout the lifespan. Recognition of the role of development in the clinical phenotype of ASD suggests a complicated role for genetic biomarkers. Given environmental interactions with genotype and developmental experience, in all but a subset of cases (14), it may be difficult to extrapolate diagnostic status or developmental course based on genetic markers, suggesting the potential import of intermediary quantifications of the phenotype, such as measures of brain function (15). Direct measures of brain function represent a level of assessment that can bridge understanding of causes to clinical utility. For example, electrophysiological brain responses to human faces are understood to reflect developmental maturation (16), symptom status (17), biological factors, such as gender (18), and changes resulting from intervention (19). *Group versus individual differences.* In autism, as in most neurodevelopmental disorders, the results of research studies most commonly reflect differences in means between groups of individuals. In this way, a difference between groups typically reflects a shift in the distribution of values in a biomarker parameter. When results are reported in this fashion, it provides scant information about the relevance of a biomarker at the individual level; unless a biomarker value is true for all people with ASD, analyses of this nature provide little practicable information. Moving towards study designs that enable evaluation of effects at the individual level or in association with individual

variation on particular characteristics is a necessary advance for the translational goals of using biomarkers to provide clinically relevant information at the individual level.

Individual versus composite biomarkers

Many biomarker studies in ASD, and neurodevelopment more broadly, focus upon a particular measure as a potential biomarker. For example, a study might examine activation in a specific region of cortex association with social behavior. To expand upon the example provided above, perception of human faces might be characterized by increased activity in the fusiform gyrus, with a biomarker for ASD being hypoactivation in this area. It is possible that the centrality of a process like face perception and the importance of this brain region to this process might render this an effective biomarker. However, given the complexity of biological processes (including the potential for compensatory mechanisms in different brain regions) and the well-recognized heterogeneity of autism, more useful information may be gained through the development of more nuanced biomarkers reflecting multiple measures. For example, were one to quantify face perception using electrophysiological measures, the process could be characterized by a series of functionally distinct steps: low-level visual perception at 100 milliseconds, face structural encoding at 170 milliseconds, higher-order face decoding (e.g., emotion, identity) at 250 milliseconds, and activity in the action-perception system across this time span (20). By quantifying multiple facets of a functional process, a richer profile of individual performance is derived. Composite measures representing an individual profile of values from multiple measures within one data modality or across data modalities are likely to advance our understanding of biomarkers for complex, developmental neurodevelopmental disorders, such as ASD.

Specificity of biomarkers

Autism is an extremely heterogeneous disorder, with wide variation in both the core diagnostic features and associated characteristics, such as cognitive ability. For these reasons, the search for biomarkers of ASD, *per se*, may be unsuccessful for the majority of etiologies. As espoused by the Research Domain Criteria approach (<http://www.nimh.nih.gov/research-priorities/rdoc/>), it may be more effective to examine potential biomarkers in relation to individual variation in specific functional processes or symptom indices than in relation to diagnostic status. It is notable that many features of ASD are shared by other disorders. For example repetitive and restricted behaviors are features of obsessive compulsive disorder, and disrupted social cognition is evident in schizophrenia spectrum disorders (SZS). When one considers that most treatments are contingent upon variation in specific function and dysfunction rather than diagnostic status, it suggests that the most attainable and most directly implementable biomarkers may index characteristics related to specific functional domains rather than diagnostic status. To take again the example of electrophysiological brain response to human faces, atypical neural response is observed in both ASD (21-23) and SZS (24-26) but is not universal in either population (27-35). Rather than corresponding to diagnostic boundaries, variability in neural response to faces reflects dimensional deficits across disorders such as social competence (33, 34), distress (36), empathy (37), emotional sensitivity (38), global functioning (39), and social engagement (25, 29, 40).

A path forward

In developing biomarkers for ASD, the potential translational benefit will be, to an extent, contingent upon the nature of technologies employed. Key goals in the field of autism research include detecting atypical development earlier in life, empirically defining subgroups, measuring treatment outcomes, specifying mechanisms to target during treatment, and predicting treatment response. To realize these key translational goals, it will be necessary to embrace methods that are economical, scalable, sensitive, and objective. Electrophysiological methods offer many of these benefits (20).

Applicability

Electrophysiological methods are relatively easy to use and therefore applicable across a large functional (e.g., developmental or intellectual disability) and developmental range (e.g., infancy). Most electrophysiological techniques only require a participant to tolerate sensors on skin. Movement artifact for electrophysiological recordings are trial-specific can be removed from data or corrected to preserve the integrity of a recording.

Cost and scalability

Electrophysiological methods are highly cost effective means of measuring biological processes. In this way, cost of use does not application to the same extent as other biological assays. Additionally, electrophysiological recording facilities are widely available in existing health care system, enabling efficient large-scale implantation with extant infrastructure. Low cost of psychophysiological methods and widespread availability suggest the potential for realistic applications of biomarker discoveries to clinical applications.

Sensitivity

Electrophysiological recordings are likely to provide more sensitive measurement of processes relevant to biomarker discovery than behavioral methods. Electrophysiological recordings may index processes that have not yet emerged in will behavior and those that may never be evident in behavior. Because the behaviors upon which an ASD diagnosis is based do not emerge until the second year after birth, such methods may elucidate atypical processes prior to the over display of atypical behavior.

Objectivity

Electrophysiological measures enable a high level of methodological rigor in ascertainment of biomarker parameters compared to behavioral methods. Identical recording facilities and experimental paradigms will offer consistent data collection in multiple locations, without the need for development and maintenance of clinician reliability. This represents a key advantage in the potential for application of biomarkers in diverse clinical settings and for the conduct of multi-site clinical trials.

Conclusion

Great progress has been made in recognizing the biological basis of autism spectrum disorder; however, research has delivered few practically implementable biomarkers thus far. Specific needs within the field of ASD research are objective quantifications of biological processes to (a) enable designation of subgroups likely to benefit from a particular treatment, (b) index diagnostic status or risk, (c) demonstrate engagement of specific biological systems, and (d) provide more rapid assessment of change than traditional measures based on clinical observation and caregiver report. The nature of autism as a developmental disorder characterized by great heterogeneity complicates biomarker discovery efforts. Successful strategies must describe biomarkers that are reliable across development, evident at the individual level, and specific to a unit of analysis, be it diagnostic status or functional process; to achieve these objectives may require composite markers spanning multiple measures within one data collection modality or integrating modalities of data collection. The ultimate value of biomarkers for ASD will relate to their ease of use, cost, scalability, sensitivity, and realistic objectivity.

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Key points

- Despite significant progress in recognizing and understanding the biological bases of autism spectrum disorder, diagnosis and treatment rely primarily on subjective evaluation of behavior.
- Biomarkers with significant translational value have not yet been developed for neurodevelopmental disorders.
- Given their wide applicability, low cost, high accessibility, acute sensitivity, and objectivity in measurement, electrophysiological recording methods hold great promise for derivation of biomarkers for neurodevelopmental disorders.