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Psychophysiological biomarkers: Working around behavioral response limitations.

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Limitations in participants' repertoire of reliable behavioral responses, due to immaturity or intellectual and developmental disabilities, frequently present a challenge for evaluating cognitive skills or documenting intervention effects. Few direct, standardized behavioral measures are optimized for obtaining information directly from very young or atypically developing individuals. Thus, informant reports or behavioral observations are often the only source of information about the subject's abilities. While highly valuable, these data are indirect and may be affected by respondent bias.

Recent advances in the accessibility of noninvasive, low-cost measures of physiological processes, such as eye movements, skin conductance, and electrical brain activity, have led to increased interest in the identification and use of direct and objective biomarkers. Such measures could index sensory, cognitive, and affective processes, while placing minimal, if any, demands on voluntary, overt behaviors. As a result, the field of developmental neuropsychology and psychophysiology has seen a substantial increase in the number of published studies reporting diagnostic and/or developmental group differences on various physiological metrics.

However, for a physiological response to become a useful biomarker, in addition to being accessible and affordable, it also needs to index a process, mechanism, or characteristic relevant to the diagnosis or phenotypic categorization, and to be quantifiable and interpretable at the individual level, sensitive to change, and predictive of outcomes (McPartland, 2016; Ewen & Beniczky, 2017). The four papers in this special issue demonstrate several prospective biomarkers at different stages of identification and validation in infants, children, and adults.

Foss-Feig et al. capitalized on the millisecond-level temporal resolution of the event-related potentials (ERPs) to evaluate the role of rapid auditory processing (auditory gap detection task) in sensory and language symptoms of school-age children with autism spectrum disorder (ASD). The authors not only reported group differences between children with ASD and typical peers, but also identified the canonical auditory P2 response as an informative marker of sensory processing in general and of clinical features of ASD in

particular, as suggested by correlations with both parent reports and direct assessments of sensory, language, and social functions. The known cortical sources and functional interpretation of the auditory P2 help offer new insights into neural processes associated with ASD. Moreover, the authors identify a specific characteristic – ERP response during rapid auditory temporal processing – that could be used to classify the otherwise heterogeneous population of persons with ASD into distinct subgroups for the purpose of better phenotypic categorization and future treatment. Finally, because ERP response to behaviorally undetected gaps corresponded to clinical symptomatology, this metric shows good promise for use in populations where overt behavioral responses are unattainable.

A study by Chorna et al. represents the next step in establishing auditory ERPs in response to speech as effective biomarkers of language abilities. Previously published reports in infants and children with typical and atypical development have documented that auditory ERPs are sensitive to maturational differences and predictive of future performance on standardized behavioral measures of cognition and language. The current study in preterm infants selected a subset of known ERP markers of speech sound differentiation and demonstrated their sensitivity to change following a two-week intervention (action-contingent exposure to mother's voice). The findings extend support for the emerging idea that auditory ERPs can be used as a discriminative and responsive biomarker of speech and language processing. They have particular implications for researchers and clinicians working with preverbal or minimally verbal individuals, for whom few effective language assessment options currently exist.

Shifting from the central to peripheral nervous system measures, Zengin-Bolatkale et al. demonstrate that measures of skin conductance, a physiological response indexing sympathetic nervous system arousal, can help uncover predictive markers of risk for persistent stuttering in preschool children. When children initially present for stuttering-related concerns, it is difficult for clinicians to know who will recover on their own versus who will need treatment to improve speech fluency. Using a longitudinal study design, Zengin-Bolatkale et al. document that children who remain stuttering at one year follow-up evidenced heightened sympathetic arousal during a stressful speaking task at baseline. Furthermore, task-related changes in skin conductance are interpreted to reflect emotional reactivity, thus identifying it as a particular process associated with the increased risk for stuttering.

Finally, the study by Key et al. demonstrates feasibility of using eye tracking measures during free visual exploration as markers of hyperphagia in children and adults with Prader-Willi syndrome (PWS). Currently, caregiver reports are the main source of data on food-related interests and behavior in PWS. With several treatments targeting hyperphagia being developed, there is a great need for additional objective measures to predict and evaluate outcomes. Gaze data recorded during a 2.5-minute sequence of food and non-food images revealed that more severe hyperphagia is associated with increased attention to food presented among other high-interest items. Reported test-retest reliability values for the eye tracking measures strengthen the suggestion that gaze characteristics may be a promising direct, objective, and stable biomarker that could be obtained repeatedly, in subjects of

diverse age and ability levels. Therefore, this measure could serve as an outcome measure to examine change in food-related interests in future treatment studies.

In the current research climate, the need for effective biomarkers of cognitive, perceptual, and emotional processes that could be used for diagnostic and functional assessments or for predicting and evaluating treatment outcomes is high. The goal of this set of papers is to provide examples to inspire researchers and clinicians to expand their use of physiological measures and to look beyond the identification of group differences when considering such tools as possible biomarkers in their population of interest. Establishing psychometric properties (e.g., test-retest reliability and sensitivity to change) and evaluating prospective psychophysiological biomarkers against available “gold standard” measures are important steps toward making them interpretable at the single-subject level and transitioning promising leads from research labs to practical implementation in treatment studies and clinical practice.

References

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