Translational Mechanistic Biomarkers for the 21st Century

Daniel C. Javitt, M.D., Ph.D.

The alpha rhythm of the EEG was first described by Hans Berger in 1929 (1) and represented the first evidence that scalp-recorded electrical activity could provide information on underlying brain activity. A key feature of the occipital alpha rhythm, which is generated primarily in the visual cortex, is that it is "blocked" by photic stimulation as reflected in a temporary suppression of ongoing alpha activity. By 1957, the first papers describing impaired alpha responsiveness to photic stimulation in schizophrenia had been published, including descriptions of differential impairments among schizophrenia subtypes (2).

Thus, the study by Parker et al. (3), in this issue of the *Journal*, builds on a venerable tradition of neurophysiological investigation in schizophrenia. The P300 component of the auditory event-related potential, which is the main biomarker used by Parker et al., was first described by Sutton et al. in 1965 (4), followed shortly thereafter by studies documenting P3 impairments in schizophrenia (5). Since then, numerous other neurophysiological responses have been investigated across the psychotic disorders continuum, including 1) auditory steady-state response and mismatch negativity that index impaired early auditory processing; 2) visual P1, N1, and N2m to magnocellular-biased stimuli that index impaired early visual processing; and 3) frontal theta/N2 potentials that index impaired cognitive control (6).

The study by Parker et al. addresses the question of whether such measures are ready to move from the "bench" to the "bedside" and answers with a resounding "Yes." First, the authors show that neurophysiological paradigms, such as the auditory oddball paradigm, can feasibly be deployed across multiple sites with high cross-site reliability. Second, they demonstrate replicability across studies, with correlation strengths (r) >0.9 between measures obtained in this study and those obtained in a prior collaborative study by this network called the Bipolar-Schizophrenia Network for Intermediate Phenotypes 1 (B-SNIP1) study. The study-to-study consistency is thus impressive and rivals the cross-study reliability of EEG features typically used for assessment of neurological disorders such as interictal spikes in epilepsy (7) or EEG slowing in dementia (8).

This study is also noteworthy because the analyses go beyond simple "time-domain" event-related potential approaches to also investigate event-related oscillatory activity. In the standard event-related potential approach, responses are averaged across stimulus presentations and collapsed across spectral frequencies, which has the effect of discarding information inherent in trial-to-trial response variability, as well as information present discretely within individual frequency ranges. Furthermore, in this study, the event-related oscillatory approach is applied to responses to both deviant and standard stimuli in the oddball paradigm, providing even greater sensitivity to abnormal local circuit-level neural dysfunction in schizophrenia.

In the oddball paradigm, individuals listen to a series of repetitive standard tones and must detect an infrequent "oddball" stimulus, sometimes by button press but in this case by counting. A tacit assumption of many studies focusing on event-related potential responses in the oddball paradigm is that the sensory responses to the standard are intact, and only the additional activity related to detection of the deviant stimulus is impaired. Over the past decades, however, deficits in early auditory processing have become increasingly documented in schizophrenia and are best detected using spectral or "neuro-oscillatory" approaches. Inclusion of event-related oscillatory measures, therefore, greatly increases the sensitivity of the analyses for between-group classification.

The study by Parker et al. addresses the question of whether [neurophysiological] measures are ready to move from the "bench" to the "bedside" and answers with a resounding "Yes."

For example, while the typical P3 study analyzes only two measures—amplitude and latency—Parker et al. identified 26 measures of interest. This led to multivariate predictors that significantly segregated between nonpsychotic compared with psychotic bipolar disorder patients, as well as between the different patient groups and healthy control subjects. There is thus no doubt that multivariate approaches such as these are required to capture the complexity of information processing dysfunction observed across psychotic disorders.

In the Parker et al. study, responses were assessed using narrow-band filtering of the average EEG for each participant, yielding the spectral component of the average response. Of note, even further information can be extracted when spectral analyses are applied to responses to each individual stimulus within the oddball paradigm, rather

than just to the average response across stimuli. The additional spectral measures include 1) intertrial coherence, also termed phase-locking, which assesses the degree to which stimuli synchronize ongoing brain rhythms, and 2) single-trial total or "induced" power, which assesses the degree to which stimuli increase excitatory drive into the cortex (6).

For example, when individuals attend to a sequence of auditory stimuli, as in the oddball paradigm, their brain rhythms typically align ("entrain") to the presentation rate of the stimuli. Because stimuli are typically presented at a rate of ~1 stimulus/second, the entrainment is reflected as an increase in intertrial coherence within the delta (0.5–4 Hz) frequency band. Delta entrainment allows the brain to "rest" in-between stimuli and then focus its processing resources specifically to when the next stimulus is expected, a process termed "active sensing." In schizophrenia, this process breaks down, leading to the inefficient processing that gives rise to P3 deficits (9). While this process is captured somewhat by the metrics developed by Parker et al., additional single-trial analyses of the B-SNIP data sets might provide even further mechanistic insights into mechanisms underlying impaired auditory sensory responsiveness across the psychotic disorders continuum.

Some challenges also remain in moving neurophysiological measures such as P3 to standard clinical practice. First, neurophysiological research has been driven in part by the "endophenotype" concept (10), as referenced by Parker et al. However, the heritability of P3 has been estimated only at ~0.4–0.5 (11), which is not much different from the heritability of psychotic symptoms as a whole. Similar heritability estimates have been obtained for resting-state oscillatory measures (12). There is also a considerable size mismatch between current genetic studies, which may include upwards of 100,000 subjects, compared with the sample size achievable even in the largest event-related potential consortia. Therefore, whether or not neurophysiological measures will prove useful as endophenotypes remains an open question.

Second, as in the present study, neurophysiological measures are often graded across different patient groups rather than being multimodally distributed. Thus, they support dimensional nosologies, rather than the type of categorical nosologies typically required in clinical medicine. With the exception of tone matching, which appears to be bimodally distributed in schizophrenia and thus may index physiologically distinct subgroups (13), most biomarkers produce overlapping distributions across populations similar to that shown in Figure 4 of the Parker et al. study. P3 deficits may also be observed in other disorders, such as major depression or dementia. This nonspecificity may further limit the diagnostic utility of P3 when applied to "real world" clinical populations. Future studies will be needed to see whether the multivariate approach can lead to further differentiation across disorders.

An alternative formulation for the use of neurophysiological measures is to consider them more specifically as mechanistic translational biomarkers within the context of the 21st Century Cures Act. This act, which was passed in 2016, seeks to use biomarkers to aid in development of new treatment approaches through its Biomarker Qualification Program (BQP). Biomarkers are categorized into specific contexts of use, including identification of susceptibility/risk, diagnosis, effect monitoring, prognostic forecasting, response prediction, or pharmacodynamic assessment of target engagement (14).

For example, traditionally defined P3 has recently been shown by the North American Prodrome Longitudinal Study (NAPLS) to significantly predict transition to schizophrenia among clinical high-risk individuals, albeit with relatively small effect size (15). A potential test of the multivariate approach proposed by Parker et al. would be to apply it to the NAPLS data set and evaluate the degree to which inclusion of their additional variates leads to increased sensitivity in predicting conversion. Alternatively, as with mismatch negativity (16), P3 may prove useful for establishing target engagement within early-stage drug development. In general, adopting the BQP terminology would assist in communicating the proposed context of use for neurophysiological biomarkers as they are developed.

One of the greatest challenges facing the field of neurophysiology in schizophrenia is that we have too many measures that are abnormal, rather than too few. For example, the alpha "blocking" that was first described in the 1950s is now more commonly termed "event-related desynchronization" and has been shown to strongly distinguish between individuals with schizophrenia, who show marked hypo-responsiveness to the stimuli, and adults with autism spectrum disorder, who show equally marked hyper-responsiveness (17). Other measures such as auditory steady-state response and mismatch negativity have similarly been replicated over multiple studies. However, much like the field of neuropsychology prior to the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative, multiple parametric variations of each paradigm are in use across different laboratories and consortia, limiting comparability across studies.

Large consortia, such as the Consortium on the Genetics of Schizophrenia, B-SNIP, and NAPLS, have now demonstrated the consistency and cross-site scalability of neurophysiological biomarkers. The critical challenge now is how to best embed these into translational and mechanistic research frameworks and harness them for the development of improved nosologies and new treatment approaches.

AUTHOR AND ARTICLE INFORMATION

Division of Experimental Therapeutics, Columbia University Medical Center, N.Y.

Send correspondence to Dr. Javitt (dcj2113@cumc.columbia.edu).

Supported in part by U.S. Public Health Service grant R01 MH49334.

Dr. Javitt has served as a consultant to Autifony, Boehringer Ingelheim, Biogen, and SK Life Sciences; he holds intellectual property rights for use of *N*-methyl-D-aspartate modulators in the treatment of neuropsychiatric

disorders, for parcel-guided transcranial magnetic stimulation treatment of depression, and for EEG-based diagnosis of neuropsychiatric disorders; and he holds equity in Amino Acid Solutions, Inc., Glytech, and NeuroRx.

Accepted August 16, 2021.

Am J Psychiatry 2021; 178:893–895; doi: 10.1176/appi.ajp.2021.21080812

REFERENCES

1. Berger H: Über das Elektrenkephalogramm des Menschen (on the EEG in humans). Arch Psychiatr Nervenkr 1929; 87:527
2. Blum RH: Alpha-rhythm responsiveness in normal, schizophrenic, and brain-damaged persons. Science 1957; 126:749–750
3. Parker DA, Trotti RL, McDowell JE, et al: Auditory oddball responses across the schizophrenia-bipolar spectrum and their relationship to cognitive and clinical features. Am J Psychiatry 2021; 178:952–964
4. Sutton S, Braren M, Zubin J, et al: Evoked-potential correlates of stimulus uncertainty. Science 1965; 150:1187–1188
5. Roth WT, Cannon EH: Some features of the auditory evoked response in schizophrenics. Arch Gen Psychiatry 1972; 27:466–471
6. Javitt DC, Siegel SJ, Spencer KM, et al: A roadmap for development of neuro-oscillations as translational biomarkers for treatment development in neuropsychopharmacology. Neuropsychopharmacology 2020; 45:1411–1422
7. Jing J, Herlopian A, Karakis I, et al: Interrater reliability of experts in identifying interictal epileptiform discharges in electroencephalograms. JAMA Neurol 2020; 77:49–57
8. Meghdadi AH, Stevanović Karić M, McConnell M, et al: Resting state EEG biomarkers of cognitive decline associated with Alzheimer's disease and mild cognitive impairment. PLoS One 2021; 16:e0244180
9. Lakatos P, Schroeder CE, Leitman DI, et al: Predictive suppression of cortical excitability and its deficit in schizophrenia. J Neurosci 2013; 33:11692–11702
10. Gottesman II, Gould TD: The endophenotype concept in psychiatry: etymology and strategic intentions. Am J Psychiatry 2003; 160:636–645
11. Malone SM, Vaidyanathan U, Basu S, et al: Heritability and molecular-genetic basis of the P3 event-related brain potential: a genome-wide association study. Psychophysiology 2014; 51:1246–1258
12. Narayanan B, O'Neil K, Berwise C, et al: Resting state electroencephalogram oscillatory abnormalities in schizophrenia and psychotic bipolar patients and their relatives from the Bipolar and Schizophrenia Network on Intermediate Phenotypes Study. Biol Psychiatry 2013; 76:456–465
13. Dondé C, Martínez A, Kantrowitz JT, et al: Bimodal distribution of tone-matching deficits indicates discrete pathophysiological entities within the syndrome of schizophrenia. Transl Psychiatry 2019; 9:221
14. U.S. Food and Drug Administration; National Institutes of Health; Group F-NBW: BEST (Biomarkers, EndpointS, and other Tools) Resource. https://www.ncbi.nlm.nih.gov/books/NBK326791. Silver Spring, Md., U.S. Food and Drug Administration; Bethesda, Md., National Institutes of Health, 2016
15. Hamilton HK, Roach BJ, Bachman PM, et al: Association between P300 responses to auditory oddball stimuli and clinical outcomes in the psychosis risk syndrome. JAMA Psychiatry 2019; 76:1187–1197
16. Sehatpour P, Javitt DC, DeBaun HM, et al: Mismatch negativity as an index of target engagement for excitation/inhibition-based treatment development: a double-blind placebo-controlled, single-dose cross-over study of the serotonin type-3 receptor antagonist CVN058. Neuropsychopharmacol 2021;
17. Martínez A, Tobe R, Dias EC, et al: Differential patterns of visual sensory alteration underlying face emotion recognition impairment and motion perception deficits in schizophrenia and autism spectrum disorder. Biol Psychiatry 2019; 86:557–567