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Authors

Light, Gregory A

Makeig, Scott

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Commentary

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Electroencephalographic Biomarkers of Psychosis: Present and Future

Gregory A. Light and Scott Makeig

> "Psychiatry is a young, still developing science that must, against sharp opposition, gradually achieve the position it deserves according to its scientific and practical importance. There is no doubt that it will achieve this position—for it has at its disposal the same weapons which have served the other branches of medicine so well: clinical observation, the microscope and experimentation" (1).

The extent to which schizophrenia (SZ) and psychotic bipolar disorder (BD) represent distinct illnesses has been the focus of debate since Kraepelin and Blueler's early descriptions of dementia praecox and manic depressive insanity. Their hope, expressed more than a century ago, was that the tools of neuroscience at the time ("clinical observation, the microscope and experimentation") would lead to improved understanding and treatments of these devastating disorders. In the past century, spectacular advances have occurred at the intersections of neuroscience, psychopharmacology, and genomics. However, few, if any, laboratory tests to inform diagnoses, guide treatments, and monitor response to interventions have graduated from laboratories to clinics. Clinicians still must rely on behavioral observation and careful interview techniques to make inferences about patients' inner experiences and deductions about the impacted neural systems. Although we have refined indirect clinical assessments for diagnosis and treatment, these methods have evolved relatively little since the late 19th century.

In this issue of *Biological Psychiatry*, Ethridge *et al.* (2) from the Bipolar-Schizophrenia Network on Intermediate Phenotypes (B-SNIP) provide a sophisticated characterization of response to auditory deviance in a heterogeneous sample of 940 patients with SZ, patients with BD, and first-degree family members tested at five geographically distributed sites. Such large and diverse participant cohorts provide substantial confidence in the robustness and generalizability of neurophysiologic findings of familial risk as a prelude to genetic analyses. The authors apply a novel approach to examining evoked electroencephalography (EEG) responses to deviant auditory ("oddball") stimuli interleaved in a train of standard tones. Although most endophenotype studies assess only a single diagnostic group, the B-SNIP group uncovered strong evidence of both shared and unique deficits in sensory and cognitive processes across psychotic disorders. In particular, some of the biomarkers of familial risk (N100, P3b) were more specific to SZ, whereas another response abnormality (P2) was specific to BD, and another (N2) was common to both psychoses. This landmark B-SNIP study by Ethridge *et al.* begins to address some long-standing limitations of traditional EEG analysis. Their results support the increasingly tangible possibility of integrating neurophysiologic biomarkers into 21st century diagnostics and therapeutics and add to accumulating evidence that understanding and treatment of varying psychotic states of individual patients may be improved in the near future using low-cost, EEG measures sensitive to the underlying neurobiology of SZ and BD.

EEG Sources and EEG Scalp Channels

Well-established biophysics of brain volume conduction dictate that currents recorded at scalp channels do not flow directly upward from underlying cortex. Rather, nearly every scalp electrode sums potentials from nearly every cortical source area. The difficulty in deriving accurate estimates of the brain sources of recorded scalp channel potentials is the primary reason that EEG has been denigrated as being a low-resolution brain imaging modality despite its superior time resolution and other desirable qualities. However, most clinical studies focus on a single frontocentral electrode channel at which both peak amplitudes and patient deficits tend to be largest—even when scalp-channel information is available from multiple sensors.

To attempt to use more of this now readily available EEG information, Ethridge *et al.* employ principal component analysis (PCA) to distill objectively averaged event-related potential responses into distinct elements with forthcoming genomic analyses of PCA–derived EEG endophenotypes. PCA capitalizes on spatial relationships across sensors, reducing both noise and redundant scalp-channel information to a few variables that capture as much of the trial-averaged response variance as possible.

Toward More Robust EEG Biomarkers

In our view, the measurement advance of Ethridge *et al.* represents a first step toward extracting more information about cortical function available in EEG. Future studies of this and other rich psychiatric EEG datasets may wish to capitalize on information about cortical source-level response dynamics available via decomposition of the unaveraged multichannel EEG signals into spatiotemporally and functionally distinct source signals. As is well known, raw EEG data include and may even be dominated by nonphysiologic noise (e.g., line noise, electrode movement artifacts) plus potentials contributed by nonbrain physiological processes (e.g., muscle activity, eye blinks and saccades). Dealing with nonbrain artifacts can be particularly difficult in clinical samples. Brain-generated contributions to EEG signals predominantly sum far-field potentials arising from locally coherent cortical field activities within small cortical areas that function as effective EEG sources.

SEE COMPANION ARTICLE ON PAGE 127

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We have shown that application of independent component analysis to unaveraged EEG data allows spatiotemporal separation of components of individual noise, nonbrain artifacts, and cortical brain sources (3). Identifying effective sources of distinct information within the whole EEG study allows for precise identification and quantification of activities in the several cortical areas supporting auditory and cognitive processing. These more direct measures of distinct contributions of cortical areas can exhibit improved sensitivity to group and individual illness-related genetic and clinical characteristics than scalp channel measures that sum all source contributions. Although the relative novelty, complexity, and computational demands of independent component analysis have limited its rate of adoption in EEG studies of clinical populations (4,5), we have recently demonstrated that auditory deviance response measures, applied to cortical source activities derived from independent component analysis decomposition, can offer more detailed characterization of SZ group and individual deficits than single-channel measures, accounting for substantial portions of variance in multiple measures of clinical, cognitive, and psychosocial functioning. Source-resolved EEG measures also show promise for use in psychiatric diagnosis (5–7) and in genomic analysis (8,9).

EEG Biomarkers for Treatment Selection

A strategy for "translating" findings from psychiatric neuroscience to inform treatments in real-world settings involves rational use of evidence about individual subjects obtained from biomarkers to select appropriate treatments (6,8). Given the abundance of evidence of auditory system dysfunction in chronic psychotic illness (e.g., auditory hallucinations, impaired auditory attention and working memory, verbal learning and memory), interventions based on tuning the fidelity and accuracy of auditory information processing may dramatically improve cognition in SZ (10). There is emerging evidence that evoked responses to auditory oddball stimuli can yield EEG biomarkers with substantial theoretical and empirical links to both the mechanisms targeted by auditory training and the resulting improvements in cognition and psychosocial functioning. To this end, we recently found that the auditory mismatch negativity and later peak features of responses to unattended auditory oddball stimuli predict response to initial exposure to auditory training and are sensitive and early indices of sensory "engagement." We can envision a future in which EEG information in conjunction with other demographic, clinical, and genetic predictors may be used both to improve the identification of individuals at clinical risk for developing psychosis and to inform assignment of interventions that are most likely to provide therapeutic benefits (6,8,11).

EEG Biomarkers for Treatment Monitoring

In addition to the relative absence of predictive biomarkers in clinical practice, few, if any, laboratory tests are available for monitoring responses to treatments for psychotic illness. Such biomarkers could be useful for determining when a given patient has reached the point of diminishing returns or stopped responding to a treatment altogether, prompting changes to the treatment regimen. Possibly, EEG-based biomarkers may also contribute to this unmet need critical to development of next-generation, precise, personalized, and even preemptive interventions, potentially including highly individualized, source-resolved EEG feedback training or stimulation studies, or both.

Using EEG Biomarkers in Clinical Care

Although it appears that electrophysiologic data, noninvasively recorded from the scalp, has tremendous promise for yielding "actionable" biomarkers of individual psychiatric status (8), much work is required to ensure their effective application in clinical settings. Given the low base rate of psychosis in the general population and the current movement toward implementing screening procedures in schools and clinics, obstacles to potential employment of EEG biomarkers (e.g., false-positive findings) are certain to arise. Beyond the substantial validation required for large-scale deployment, instrumentation will need to be simplified to allow administration by nonspecialists in real-world community treatment centers. To this end, the Consortium on the Genetics of Schizophrenia recently demonstrated that neural responses to deviant auditory oddball stimuli can be reliably measured in settings without extensive technician training or expertise in EEG assessment and analysis (11). Such ready "scalability" should also be a development goal for studies using future, more sensitive, source-resolved EEG biomarkers.

In summary, the results reported by Ethridge *et al.* (2) add to accumulating evidence that relatively low-cost functional EEG biomarkers may guide 21st century assessments of and treatments for psychoses. Since many translational EEG biomarkers are sensitive to pharmacologic, behavioral, and psychosocial interventions, they exhibit promise for predicting and monitoring response to treatments.

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Article Information

From Veterans Integrated Service Network-22 Mental Illness, Research, Education and Clinical Center (GAL), U.S. Department of Veterans Affairs VA San Diego Healthcare System, San Diego; and Department of Psychiatry (GAL) and Swartz Center for Computational Neuroscience (SM), Institute for Neural Computation, University of California, San Diego, La Jolla, California.

Address correspondence to Gregory A. Light, Ph.D., Department of Psychiatry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0804; E-mail: glight@ucsd.edu.

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