EEG Biomarkers of Psychosis, Present and Future

Gregory A. Light [1,2] & Scott Makeig [3]

[1] VISN-22 Mental Illness, Research, Education and Clinical Center (MIRECC), VA San Diego Healthcare System

[2] Department of Psychiatry, University of California San Diego, La Jolla, CA

[3] Swartz Center for Computational Neuroscience, Institute for Neural Computation, University of California San Diego, La Jolla, CA

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> *"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."* [Kraepelin E. *Psychiatry: A Textbook for Students and Physicians*. Vol 1. Canton, OH: Science History Publications; 1899]

The extent to which schizophrenia (SZ) and psychotic bipolar disorder (BD) represent distinct illnesses has been the focus of great debate since Kraepelin and Blueler's early descriptions of dementia praecox and manic depressive insanity. Their hope, over 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. Yet few if any laboratory tests to inform diagnoses, guide treatments, and monitor response to interventions have graduated from laboratories to clinics. Clinicians must still rely on behavioral observation and careful interview techniques to make inferences about patients' inner experiences and thereby secondary deductions about the impacted neural systems. While we have refined our indirect clinical assessments for diagnosis and treatment, these methods have nevertheless evolved relatively little since the late 19th century.

In this issue, Ethridge and colleagues 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 SZ, 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 the findings of neurophysiological representations of familial risk for psychosis as a prelude to forthcoming genetic analyses. The authors apply a novel approach to examining evoked EEG responses to deviant auditory ('oddball') stimuli interleaved in a train of standard tones. Whereas most studies of endophenotypes 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 measured biomarkers of familial risk in their study (N100, P3b) were more specific to SZ, whereas another response abnormality (P2) was specific to BD and yet another (N2) was common to both psychoses. This landmark B-SNIP study of Ethridge *et al.* begins to address some longstanding limitations of traditional EEG analysis. Their results support the increasingly tangible possibility of integrating neurophysiological biomarkers into 21st century diagnostics and therapeutics and add to accumulating evidence that in the near future, understanding and treatment of the varying psychotic states of individual patients may be improved using neurally direct and low-cost source-resolved EEG measures of brain function that are sensitive to the underlying neurobiology of SZ and BP.

EEG sources / EEG scalp channels. Well-established biophysics of brain volume conduction dictate that currents recorded at scalp channels do not all flow directly upwards from underlying cortex. Rather, nearly every scalp electrode sums potentials from nearly every cortical source area (1). 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 at best a low-resolution brain imaging modality despite its superior time resolution and other desirable qualities (2). Yet, the majority of clinical studies focus on a single frontocentral electrode channel at which both peak amplitudes as well as patient deficits tend to be largest -- even when scalp-channel information is available from up to 256 scalp sensors.

To attempt to use more of this now readily available EEG information, Ethridge *et al.* employ principal component analysis (PCA) to objectively distill *averaged* event-related potential (ERP)

responses into distinct elements with forthcoming genomic analyses of the PCA-derived EEG endophenotypes. PCA capitalizes on spatial relationships across the scalp sensors, reducing both noise and the redundant scalp-channel information to a few variables that capture as much of the overall trial-averaged response variance as possible.

Towards more robust EEG biomarkers. In our view, the measurement advance of Ethridge et al. represents a first step towards extracting more of the information about cortical function available in EEG data. Future studies of this and/or other rich psychiatric EEG datasets may wish to capitalize on a still richer cache of information about cortical source-level response dynamics available via decomposition of the *un-averaged* multichannel EEG signals into spatiotemporally and functionally distinct source signals. As is well known, raw EEG data includes and may even be dominated by non-physiological noise (line noise, electrode movement artifacts, etc.) plus potentials contributed by non-brain physiological processes (scalp and neck muscle activity, eye blinks and saccades, etc.). Dealing with non-brain 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*.

We have shown that application of independent component analysis (ICA) to *un-averaged* EEG data allows spatiotemporal separation of individual noise, non-brain (artifact), and cortical brain sources (3-5). Further, identifying effective sources of distinct *information* within the whole EEG data allows more precise identification and quantification of activities in the several cortical areas supporting auditory and cognitive processing. These more direct measures of the distinct contributions of cortical areas can exhibit improved sensitivity to group and individual subject illness-related genetic and clinical characteristics than scalp channel measures that sum all source contributions. While the relative novelty, complexity, and computational demands of ICA analysis have limited its rate of adoption in EEG studies of clinical populations (6, 7), we have recently demonstrated that standard auditory deviance response measures, applied to cortical source activities derived from the scalp channel data by ICA 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 (7-9) and in genomic analysis (10, 11).

EEG biomarkers for treatment selection. A strategy for “translating” findings from psychiatric neuroscience to inform treatments in real-world settings is to rationally use evidence about individual subjects obtained from biomarkers to select appropriate treatments (8, 10). 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 (12). 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 as to resulting improvements in cognition and psychosocial functioning.

To this end, recently we have found that the auditory mismatch negativity (MMN) and later peak features of responses to unattended auditory oddball stimuli predict response to initial exposure to auditory training and are therefore sensitive and early indices of sensory 'engagement' (13). Thus, we can envision a future in which EEG information used in conjunction with other demographic, clinical, and genetic predictors may be used to both improve the identification of individuals at clinical risk for developing psychosis and inform assignment to interventions that are most likely to provide therapeutic benefits (8, 10).

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 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 and/or stimulation studies.

Using EEG biomarkers in clinical care. While it appears that electrophysiological data, noninvasively recorded from the scalp, has tremendous promise for yielding "actionable" biomarkers of individual psychiatric status (10), much work will be required to ensure their effective application in clinical settings. Given the low base rate of psychosis in the general population, and the current movement towards implementing screening procedures into schools and clinics, obstacles to potential employment of EEG biomarkers including false positives, etc., are certain to arise. Beyond the substantial degree of validation that will be required to prompt large-scale deployment, the required instrumentation will need to be simplified to allow administration by non-specialists in real-world community treatment centers. To this end, the Consortium on the Genetics of Schizophrenia (COGS) 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 (14, 15). Such ready "scalability" should also be a development goal for studies using future, more sensitive, source-resolved EEG biomarkers.

In sum, the results reported by Ethridge et al. add to accumulating evidence that relatively low-cost functional EEG biomarkers identified through more adequate processing of multichannel EEG data may guide 21st century assessments of and treatments for psychoses, given their sensitivity to identifying convergent and divergent patterns of neural responses (as in the national B-SNIP and COGS studies), their sensitivity to behavioral treatments, and their possible resulting uses to select, predict, and monitor treatment responses.

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