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In search of biomarkers in psychiatry: EEG-based measures of brain function

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Abstract

Current clinical parameters used for diagnosis and phenotypic definitions of psychopathology are both highly variable and subjective. Intensive research efforts for specific and sensitive biological markers, or biomarkers, for psychopathology as objective alternatives to the current paradigm are ongoing. While biomarker research in psychiatry has focused largely on functional neuroimaging methods for identifying the neural functions that associate with psychopathology**,** scalp electroencephalography (EEG) has been viewed, historically, as offering little specific brain source information, as scalp appearance is only loosely correlated to its brain source dynamics.

However, ongoing advances in signal processing of EEG data can now deliver functional EEG brain-imaging with distinctly improved spatial, as well as fine temporal, resolution. One computational approach proving particularly useful for EEG cortical brain imaging is independent component analysis (ICA). ICA decomposition can be used to identify distinct cortical source activities that are sensitive and specific to the pathophysiology of psychiatric disorders.

Given its practical research advantages, relatively low cost, and ease of use, EEG-imaging is now both feasible and attractive, in particular for studies involving the large samples required by genetically informative designs to characterize causal pathways to psychopathology. The completely non-invasive nature of EEG data acquisition, coupled with ongoing advances in dry, wireless, and wearable EEG technology, makes EEG-imaging increasingly attractive and appropriate for psychiatric research, including the study of developmentally young samples. Applied to large, genetically and developmentally informative samples, EEG imaging can advance the search for robust diagnostic biomarkers and phenotypes in psychiatry.

Review

Since its modern inception, psychiatry has relied on diagnostic tools that are restricted to the evaluation of behavioral and clinical phenotypes. Diagnoses are based on description of symptoms, mental status examinations, and on clinical behavioral observations in line with diagnostic categories listed in the Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) (1) or the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (2). While these tools have enabled important and necessary decisions in relation to diagnosis, the inherently heterogeneous symptom presentation of most, if not all, psychiatric disorders has led to somewhat arbitrary cut-offs for disorder and subtype classifications.

Recent major advances in understanding of the genetic, neurobiological, and developmental underpinnings of psychopathology have indicated further heterogeneity in the etiology and pathophysiology of disorders that are clinically described as homogeneous constructs. Against this background of complexity, there is an intensive search for specific and sensitive biological markers, or biomarkers, which might be used in place of the highly variable and subjective clinical parameters currently used in clinical diagnosis, and as phenotypes for etiological and pathophysiological investigations.

For at least 200 years biological phenomena have been observed to be associated with psychiatric illness. This has led to numerous attempts to identify reliable diagnostic tests based on these phenomena (3). To date, however, reliable and objective diagnostic tests for psychiatry remain elusive. Non-invasive biomarker research in psychiatry has focused largely on neuroimaging as a tool for identifying neural functions that are meaningfully associated with psychopathology (4). The number and power of the tools available for examining brain functions that contribute to the understanding of the brain circuitry in psychopathology increased greatly during the 1990s with the development of functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). fMRI in particular has been advantageous for biomarker identification as its inverse modeling algorithms non-invasively allow researchers and clinicians to model and interpret the hemodynamic signal with high spatial resolution in the brain. Without these mathematical innovations, MR and fMRI recording would not be widely used today. These methods supplemented and greatly expanded findings from the earliest established functional brain imaging modality, electroencephalography (EEG).

EEG is the measurement of the ongoing electrical activity of the brain recorded non-invasively from electrodes on the scalp. In contrast with other brain imaging methods, EEG has excellent temporal resolution, though as traditionally interpreted it has limited spatial resolution. Recently, however, EEG has attracted increased interest for development of biomarkers for psychiatric diagnosis and phenotype definition. The reasons for this resurgence in interest are threefold.

First, ongoing advances in signal processing and visualization of EEG activity greatly improve the spatial resolution of EEG imaging. Such advances take advantage of the ability of EEG measures to both spatially and temporally characterize fast-changing events in the brain that are likely to be important to the understanding of the etiology and pathophysiology of psychiatric disorders. Second, the relatively low cost of EEG data collection means it is accessible for studies on the large number of samples now known to be required for identifying reliable and informative biomarkers, in particular for psychiatric genetic research. Third, EEG is the most non-invasive and portable of all the neuroimaging methods. Practical advantages of EEG data collection include the possibility of including participants who cannot be included in MRI studies, such as those with metal in the body. The portability of EEG is now being exploited through development of dry, wireless, wearable, high-density EEG systems (5) that make the routine use of EEG imaging in most recording locations feasible. Specifically, the lightweight EEG sensors and the lack of strict head movement constraints imposed by modern EEG recording and analysis methods allow accessible testing of developmentally young samples, a desirable approach for studies seeking to enable earlier detection of disorders.

Traditionally the fluctuating voltage patterns of EEG data are analyzed on an electrode-by-electrode basis in one of two ways. The most commonly used method averages data across many segments that are time-locked to events of interest, for example a task stimulus, to give an event-related potential (ERP) for each scalp channel. Typically, ERP features, such as amplitude or latency, are analyzed and reported only at the electrode channel at which the feature is maximally expressed. While the ERP approach is useful, only a small percentage of the total recorded EEG signal is reflected in the ERP average. Alternatively, the ongoing EEG channel signals may be processed using spectral analysis, across a time period of interest, to identify the mean or relative power measures for one or more EEG frequency bands of interest (usually in the range 1 Hz to 70 Hz), whether or not the activity is time-locked to identified experimental events. The latter method is sometimes referred to as quantitative EEG, or qEEG, measurement.

These methods for modeling EEG data have proven useful in the identification of functional brain activity measuring differences associated with psychiatric disorders. For example, one of the most robust findings in the cognitive neuroscience of psychiatry is that reduced amplitude of the P3 (or P300, a positively inflected ERP peak that occur around 300 milliseconds after a task target stimulus) is associated with numerous psychiatric and behavioral disorders including alcohol abuse (6-30) and schizophrenia (31-56). Another ERP peak that has been reliably associated with schizophrenia is the P50 (57), which in addition to the P300 shows excellent test-retest reliability (58-60). Similarly, ERP components related to cognitive control and response inhibition have shown consistent association with attention deficit hyperactivity disorder (ADHD) (61-70) and also show strong test-retest reliability (60, 71-73). The psychometric properties of EEG and ERP measures are equivalent to other functional neuroimaging measures, including fMRI and PET (74-79).

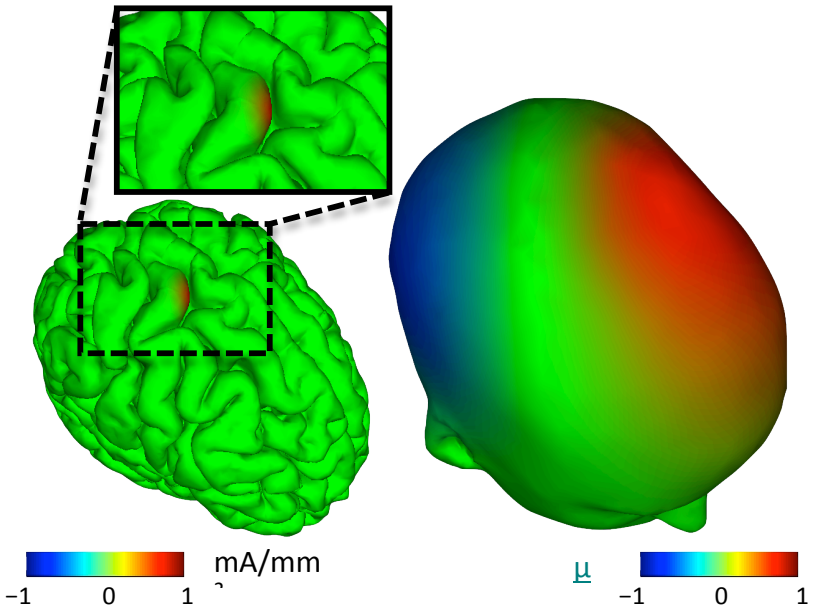

Figure 1. A simulated cortical source and its scalp EEG projection. *Simulation of coherent local field activity across a single cm²-scale cortical location (left, red), and its electrical scalp projection (right, blue & green). This illustrates the broad 'point-spread' of EEG source activity, which prevents the interpretation of scalp EEG channel signals as indexing activity only in directly underlying brain areas. Each effective EEG source projects to nearly the whole scalp – excepting only a thin (here, green) line parallel to the cortical source area. Units: (left) current source density in milliamps per square millimeter; (right) scalp potential in microvolts. Derivation of electrical head models is described in Akalin Acar et al. (2009).*

Both ERP and quantitative EEG analysis methods identify functionally meaningful measures by reducing the high complexity and dimensionality of EEG data, typically recorded at hundreds to thousands of samples per second with tens to hundreds of scalp channels, to a few summary measures at most. For example, an EEG dataset may contain 64 scalp channels of data recorded for many minutes at 500 samples per

second, while a typical report may concern a few ERP peak features extracted at one scalp channel from the relatively small portion of these data immediately following a set of targeted experimental events. This approach attempts to reduce the complexity of the recorded EEG to that of the recorded behavior (typically less than one behavioral response per second) by averaging across epochs time-locked to sets of events assumed to elicit similar brain function and comparing at most a few resulting channel ERP features to behavioral differences across groups, conditions, and/or treatments.

While such an approach can identify coherent ERP features with signal-to-noise ratio adequate for stably comparing group, task, and/or treatment conditions, doing so also means there is a great reduction in the amount of information about brain function that is extracted from the data. Furthermore, measures of scalp electrical voltage are difficult to interpret directly in terms of underlying brain processes and functions. This is largely because, as illustrated in Figure 1, EEG data collected from any point on the scalp may include activity from multiple processes occurring within a large cortical volume due to volume conduction through cerebrospinal fluid, the skull, and the scalp. This can create significant uncertainty regarding the spatial origins of nearly any EEG signal recorded at any point on the scalp. In contrast, fMRI achieves good spatial source resolution, which makes it relatively well-suited to the localization of metabolic changes correlated with brain function. As a consequence, fMRI has emerged as the method of choice for many investigations of brain function within psychiatry. However, recent major advances in computer hardware and signal processing are greatly increasing the amount of spatially and temporally precise information about brain function that can be extracted from EEG data (Table 1).

Table 1: Comparison of resolution, cost, and invasiveness of brain imaging methods

	Scalp EEG	**Source EEG**	**fMRI**	**PET**
Spatial Resolution	20-30 mm	5-10 mm	1-5 mm	2 mm
Temporal Resolution	1-4 msec	1-4 msec	0.8-1 sec	0.2-0.3 se
Cost*	$45	$45	$650	$1900
Invasiveness	Non-invasive	Non-invasive	Non-invasive	Invasive

*per participant

Application of Independent Component Analysis (ICA) to EEG

As scalp-recorded EEG data are mixtures of activity from a variety of unknown brain as well as non-brain sources (eye movements, scalp muscle activity, electrical line noise, electrocardiographic activity, etc.), separation of the signal contributions of each these sources to the scalp data can be viewed as a blind source separation problem. An oft-used analogy is the cocktail party problem. In a recording of a cocktail party, made from as many microphones as participants, each microphone ('cocktail party noise') channel signal will sum the voices of all the participants with relative strengths that vary according to their distance and spatial arrangement. Using a few, relatively weak statistical assumptions it is possible to use Independent Component Analysis (ICA) to "invert" the linear mixing process thereby extracting the individual voice signals from the recorded mixtures. In the EEG context, the effective source signals (akin to cocktail party 'voices') are spatially coherent local field potential signals, emerging within the vast complexity of cortical electrical dynamics, that project to the scalp by simple volume conduction and are linearly mixed at the recording electrodes, with each other and with potentials conducted from non-brain sources (eyes, muscles, heart, etc.), to form the recorded EEG signals.

Independent component analysis (ICA) algorithms can invert this linear mixing process; essentially they learn, from the data itself, spatial filters that separate the EEG data into a sum of component processes with maximally distinct or independent time courses (80). With correct application, ICA methods can be used to separately identify these independent component processes without relying on *a priori* knowledge of their individual properties or locations. Many independent component (IC) source processes project to the scalp in a *dipolar* spatial pattern compatible with the projection of field activity from a single cortical location (81). A dipolar pattern is one that matches the projection pattern of a single, tiny, oriented battery within the brain. The best-fitting tiny battery position and orientation together define *the equivalent dipole* as an approximate source location. The spatial locations of both the equivalent dipoles, and under favorable circumstances, the actual source locations for independent component processes with dipolar projections can be estimated using an electrical head model, optimally one built from an individual participant magnetic resonance head image though a best-fit standard template head model provides a small margin of localization error (82).

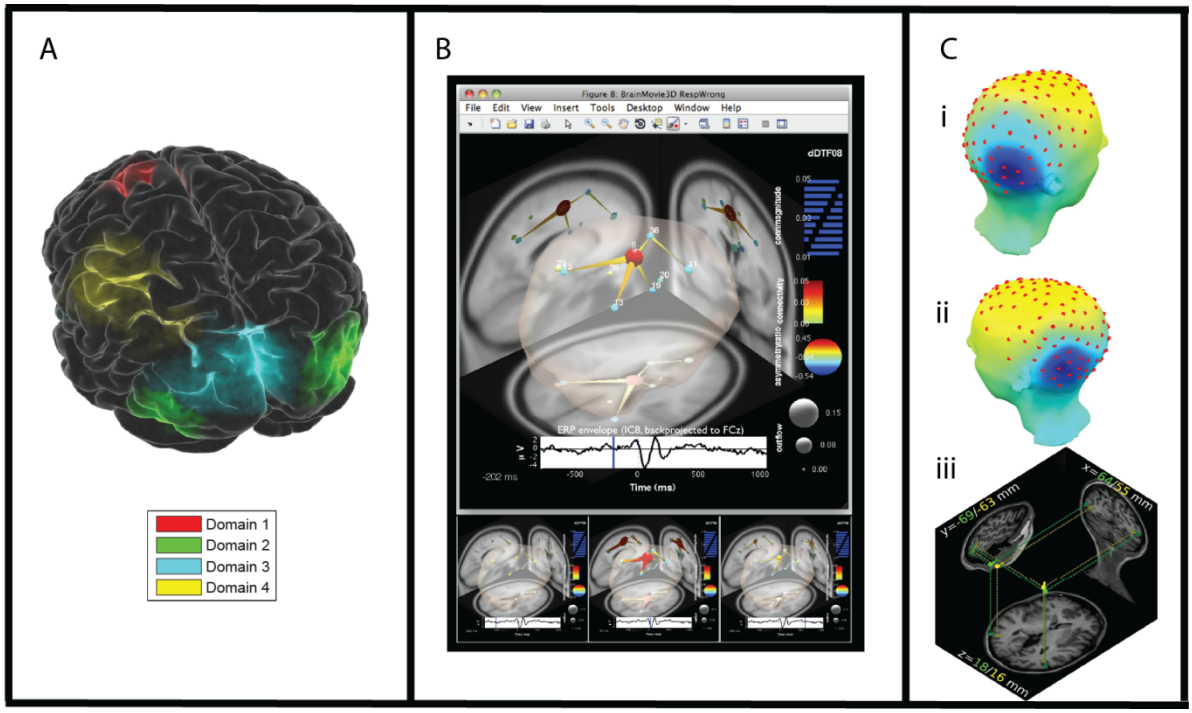

Figure 2. Examples of EEG source imaging

A. ***Source decomposition of EEG data;*** *Five functional source domains containing similar independent component processes across subjects, projected (in color) onto a cortical surface template from the Montreal Neurological Institute. Color intensities of the cortical surface voxels indicate the density of equivalent source dipoles in underlying cortex. Measure Projection Analysis processing and visualization tools are described in Bidgely-Shamlo et al. (2013).*

B. ***EEG-based brain connectivity analysis and visualization;*** *Several frames from an interactive BrainMovie3D animation showing an event-related transient causal relationship in the (4-7 Hz) theta band between four otherwise independent sources (at 200 ms (top) and at −520, 40, and 600 ms (bottom) latencies relative to button presses in error). This gives a cortical network interpretation of the classic "error-related negativity" (ERN) phenomenon observed during error recognition. Source Information Flow Toolbox (SIFT) processing and visualization tools are described in Delorme et al. (2012).*

C. ***Coherent local field activity within a single cortical patch*** *forms an effective brain EEG source that projects to the entire scalp. i) and ii) scalp projections (colors: green is 0, yellow positive, blue negative). iii) Location of the equivalent current dipole in the subject MRI-based head model. The Neuroelectromagnetic Forward Head Modeling Toolbox (NFT) is described in Akalin Acar and Makeig (2009).*

Methods and software for imaging source dynamics of cortical activity from high-density scalp recordings are steadily evolving (Figure 2; 81, 83, 84, 85) and are now freely available as open source software (81, 86-88). Methods are being further developed for identifying spatial consistency in the sources identified using ICA across multiple participants (85, 89). Such advances are essential for comparison of sources across the large numbers of participants required for genetic studies of psychiatric disorders.

During the last 15 years, it has been established that ICA can separate high-density EEG data into as many as dozens of brain source processes whose origins in the cortex can be identified, in favorable cases, with cm or better accuracy (90-95). ICA decomposition of EEG data into separate source activities identifies component processes that are not only temporally near independent but also functionally independent in the sense that they exhibit more distinct patterns of response to a range of experimental events than do the raw channel recordings which must represent mixtures of different sources. Moreover, by separating the brain source processes from non-brain source contributions to recorded EEG data (from eyes, scalp muscles, heart, line noise, etc.), ICA decomposition further increases the signal-to-noise ratio of brain component process measures relative to scalp channel measures. The functional independence of IC sources suggests they are more sensitive and specific than scalp channel measures to the pathophysiology of psychiatric disorders; a premise that is supported by results of ICA-based source imaging in studies of brain function in depression (96) and schizophrenia (97).

While the use of such advanced EEG methods within psychiatry research and practice is currently limited, the field of cognitive neuroscience can provide guidance for future work. The decomposition of EEG into its independent sources has improved understanding of a wide variety of functions in the general population, including face processing (98-100), cognitive control (101, 102) and mirror neuron activity (103). Of particular interest to investigations of psychopathology that would benefit from improved understanding (and objective measures) of emotion, ICA-based analysis can identify brain sources that correspond to distinct suggested emotions (104). Such an approach has the potential to provide objective markers and phenotypes of the degree of affective and emotional abnormality in psychiatric disorders such as schizophrenia and depression.

The advantages of these new EEG source imaging methods bring EEG to the forefront of functional neuroimaging, and thus biomarker and phenotype definition, in psychiatry. The relatively low cost of EEG recording permits data collection in the large sample numbers required for dissecting the potentially multiple causal pathways that

contribute to the development of psychopathology. Studies to date indicate that there is likely to be much overlap in the etiology and pathophysiology underlying psychiatric disorders, (see e.g. 105) but we need greater understanding of the nature and extent of this overlap in relation to neural circuits and cognitive systems. A further question is the degree to which there is heterogeneity within disorders at the levels of genetic and environmental risk factors and brain systems: it is possible that each individual has a unique combination of risk factors. Large samples will enable improved understanding and better stratification of the brain functions that underlie disorder phenotypes and their proposed subtypes.

Data collection in large twin and family samples indicate that estimates of the role of genetic factors in EEG measures parallel those found in twin and family studies of behavior and and brain structure and surpass those for fMRI (106-111) with a meta-analysis of twin studies of EEG alpha frequency power indicating a meta-heritability estimate of 80% (112). Twin and family studies can of course go beyond simply estimating the genetic and environmental contribution to single measures and examine whether the relationship between brain marker and disorder can be explained by shared genetic (or environmental) variance. Guided by the huge corpus of literature on the association of various EEG measures with psychopathology, many studies have indicated that EEG/ERP variables share genetic or environmental variance with psychiatric disorders (57, 58, 62, 65, 113-119). An initial study of cognitive control in ADHD indicates that ICA-derived source measures of frontal-midline theta may share more genetic variance with the disorder than traditional scalp-based measures (120). While further studies are necessary, it is possible that the improved signal-to-noise ratio of source imaging measures in EEG provides a better representation of the underlying frontal-midline cortical theta activity (as also demonstrated by Onton et al. 2005; 121) and therefore also should improve the sensitivity of the twin design to detect genetic effects on brain function measures and their overlap with the disorder.

Through improved biomarker and phenotype definition in large genetically-informative designs, it will be possible to improve understanding of the etiology and pathophysiology of psychiatric disorders. A common goal for the application of the genetic biomarker, or endophenotype, strategy has been to facilitate the identification of risk factors for psychiatric disorders. Alternative strategies for the application of these biomarkers and endophenotypes have been recently proposed however, so that they also aim to improve characterization of how risk variants are related to neurobiological and neurophysiological phenotypes that underlie psychiatric disorders (122). Such understanding will in turn improve the functional characterization of specific genetic

and environmental risk factors and characterize the extent to which these brain-based markers or phenotypes index disorder risk, and thus may guide prevention strategies.

Research into the role of brain function in the development of psychiatric disorders has a strong focus on the identification of at-risk children and the use of longitudinal designs. The non-invasive nature of EEG recording allows data collection in infants and children who may not be amenable to other neuroimaging approaches due to the noise and close confines of scanners (fMRI, PET), the need for injections of radioactive tracer elements (PET), and also the need for imaged subjects to keep their head still throughout data collection in non-EEG brain imaging. If a biomarker is present throughout development, even before the onset of the disorder, it could be used to detect vulnerability for the disorder in young children. Such an approach is exemplified by a number of infant studies where the children are deemed at risk of developing psychiatric and neurodevelopmental disorders by virtue of having a family member (usually an older sibling) with the disorder. The aim of these studies is to identify EEG, and other, biomarkers that predict the development of neurodevelopmental and psychiatric disorders; in particular autism spectrum disorders (123-140). A predictive relationship between the biomarker and the disorder could guide early, and potentially individualized, intervention programs that may greatly improve prognosis.

In combination with genetically sensitive designs, analysis of longitudinal data can describe the degree to which a brain function measure is mediating causal effects on behavior (141). Such an approach is demonstrated by the Minnesota Twin Family Study (142), which aims to investigate the role of EEG-indexed brain function in both continuity and change in externalizing psychopathology. The use of genetically informative designs allows the investigation of whether neural function mediates genetic or environmental influences on continuity or change in symptomatology. Further, it can identify whether alterations in brain function are markers of vulnerability to psychopathology, or a consequence of psychopathological behavior. For example, longitudinal studies of the association between the P3 ERP peak activity and alcoholism indicate that the P3 peak amplitude indexes a genetic vulnerability to alcohol abuse, rather than altered neural function produced by increased alcohol consumption (143, 144). This contributes to the characterization of biological pathways between risk factors (genetic or environmental), brain function, and behavior.

The current increasing application of EEG imaging to the understanding of the etiology and pathophysiology of psychiatric disorders is buoyed by recent advances in computational modeling that can vastly improve the spatial and temporal characterization of cortical circuits and systems involved in cognitive performance and behavior planning, execution, and evaluation. One goal for future development is to

move beyond DSM diagnoses in psychiatry to classify disorders that are based on identifiable neural circuits (4, 145). A recent initiative by the US National Institute of Mental Health (NIMH) aims to close the gap in understanding between the symptoms and causes of psychopathology. Uncertainties about phenotype definition in psychiatry may have impeded the discovery of risk factors for the development of disorders. One of the practical goals for this effort, called Research Domain Criteria (RDoc), is to encourage studies to use dimensional measures of psychopathology, including indicators of functional brain disruption, rather than DSM diagnoses.

Biomarkers, or endophenotypes, are an alternative strategy to more directly assay the effects of disorder risk variants and thus accelerate identification. A motivation for the biomarker approach is the heterogeneity of DSM disorders. As illustrated by the original rationale for the RDoC initiative, patients with the same ostensible diagnosis may actually only share one or two symptoms in common and therefore the biological roots may differ substantially (145). Psychiatric disorders are likely to involve multiple brain systems and patients may differ in the extent to which processing in these systems is affected. With this in mind, the RDoC approach doesn't map neatly on to current DSM diagnoses. Five broad domains in mental function are described by the initiative measured at multiple levels of function with further links to specific neural circuits (146, 147). The five candidate domains of RDoc are Negative and Positive Valence Systems, Cognitive Systems, Systems for Social Processes and Arousal and Regulatory Processes. These domains and circuits transcend DSM diagnoses to attain further connection between biological abnormalities and symptoms (145, 147). In large genetically and developmentally informative samples, applications of new approaches to EEG analysis and imaging will advance the search for robust neural system biomarkers in psychiatry.

Psychiatric disorders also possibly have heterogeneity at the genetic level. Current genetic approaches indicate that psychiatric illness risk may be associated with large numbers of genes, each variant of extremely small effect. Alternatively, genetic contributions to psychopathology could be related to rare variants, with the average variant having a larger effect. In either case, heterogeneity can dilute the effect size of gene association studies. The development of biomarkers could be described as a virtuous cycle in psychiatric research. The more refined and improved the definition and stratification of psychiatric disorders, the better the foundation for research that will in turn further ameliorate disorder definition and stratification. Application of biomarkers to research can aid both discovery of specific risk factors for psychiatric disorder, and functional characterization of the roles of those risk factors in disorder development. Functional neuroimaging measures identified as causal mechanisms in psychopathology could aid prediction of clinical outcomes.

Large collaborative studies that utilize preexisting EEG and genetic data could reach sample sizes of many thousands in number (65, 106, 148-150). Given larger sample sizes and the increasing understanding of neurobiological pathways, partly enabled by the use of EEG source-imaging methods, genetic approaches, such as genome-wide association (GWA) and genome-wide complex trait analysis (GCTA), will further clarify etiological genetic variants associated with risk for psychopathology (151, 152). While sample sizes of several thousand are required to identify individual genes (which is possible with EEG), further more focused studies could aim to evaluate the mediating role of EEG measures of brain function in psychopathology. Such an approach may provide an evidential foundation for targeted analysis using more expensive and invasive imaging measures, including multimodal imaging combining EEG and fMRI, for example (153). Future large collaborative research studies become even more feasible with the development of portable and wireless dry-sensor EEG systems. Such systems combined with sufficient wireless computing and communication infrastructure mean that data collection is possible in –home, or in-clinic. In short, the age of EEG imaging in psychiatry is far from over but rather may be, in many senses, just beginning.

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