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A Review of Recent Literature Employing Electroencephalographic Techniques to Study the Pathophysiology, Phenomenology, and Treatment Response of Schizophrenia

Gary Marcel Hasey · Michael Kiang

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Abstract Clinical experience and research findings suggest that schizophrenia is a disorder comprised of multiple genetic and neurophysiological subtypes with differential response to treatment. Electroencephalography (EEG) is a non-invasive, inexpensive and useful tool for investigating the neurobiology of schizophrenia and its subtypes. EEG studies elucidate the neurophysiological mechanisms potentially underlying clinical symptomatology. In this review article recent advances in applying EEG to study pathophysiology, phenomenology, and treatment response in schizophrenia are discussed. Investigative strategies employed include: analyzing quantitative EEG (QEEG) spectral power during the resting state and cognitive tasks; applying machine learning methods to identify QEEG indicators of diagnosis and treatment response; and using the event-related brain potential (ERP) technique to characterize the neurocognitive processes underlying clinical symptoms. Studies attempting to validate potential EEG biomarkers of schizophrenia and its symptoms, which could be useful in assessing familial risk and treatment response, are also reviewed.

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G. M. Hasey (✉) · M. Kiang
Department of Psychiatry and Behavioural Neurosciences, Faculty of Health Sciences, St Joseph's Healthcare Hamilton, McMaster University, 100 West 5th Street, Hamilton, Ontario, Canada L8N 3K7
e-mail: ghasey@sympatico.ca

M. Kiang
e-mail: kiang@mcmaster.ca

G. M. Hasey
Department of Electrical and Computer Engineering, School Of Biomedical Engineering, St Joseph's Healthcare Hamilton, McMaster University, 100 West 5th Street, Hamilton, Ontario, Canada L8N 3K7

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Introduction

Antipsychotic medications have revolutionized the treatment of schizophrenia. Although science played less of a role than serendipity in the introduction of these drugs [1, 2], better understanding of the pathophysiology of schizophrenia is key to developing more effective treatments. This is a challenging task as schizophrenia is probably not a single disease but a heterogeneous syndrome with many different biological subtypes [3, 4], each showing preferential response to different treatments [5].

The search for relevant biomarkers of schizophrenia and its subtypes has been biochemical, genetic and technological. Technologies employed include electroencephalography (EEG), computerized tomography (CT), magnetic resonance imaging (MRI), magnetoencephalography (MEG), positron emission tomography (PET) and near-infrared spectroscopy. Among these technologies EEG and MEG are the only ones that measure brain electrical activity directly as postsynaptic ionic flow in cortical pyramidal neurons [6]. EEG and MEG also have the significant advantage of greater temporal resolution, i.e., changes in neuronal activity occurring over a few milliseconds can be detected [7], versus a scale of several seconds for functional MRI. EEG has the advantages of much lower cost, greater accessibility, no radiation exposure, and no need to confine the subject in the very small space of a scanner bore.

However, EEG suffers from disadvantages of poor spatial resolution, because of dispersion or "smearing" of the electrical signal by the cerebrospinal fluid, skull and scalp; and limited capacity to detect electrical activity at subcortical sites [8]. First introduced by Berger in 1924, EEG has undergone many technological and analytic advances, most importantly the conversion from analogue to digital recording. Digital technology [9] has made quantitative EEG (QEEG) possible permitting spectral analysis, coherence studies, topographical mapping, evoked potentials and dipole analysis/source localization. More recently mathematical signal processing techniques, such as machine learning (ML), have allowed researchers to extract information from the EEG signal that can be useful in diagnostic classification [10••], treatment response prediction [11••] or determination of an antipsychotic drug's site of action [12••].

In this review we discuss reports published during the past two years that used EEG to study schizophrenia. The review is divided into sections focusing on resting EEG, studies of EEG during cognitive task performance, studies using machine learning analysis, and studies using EEG event-related brain potentials (ERPs) to probe more dynamic brain responses.

Resting-State Studies

While subtle neuropathological findings in schizophrenia may be highlighted during performance of specific tasks, potentially important abnormalities may also be detected during the quiet resting state [13–15, 16•].

Cognitive processes such as logical reasoning and working memory are known to be disturbed in schizophrenia. Nikulin et al. [16•] point out that longer-term temporal interactions, i.e., occurring over tens of seconds, may be necessary to examine these phenomena. This group studied long-range temporal correlations (LRTC) over 5 to 50 seconds in 18 patients with schizophrenia, three with schizoaffective disorder and 28 matched healthy control participants (HCPs) during the resting state. Postulating reduced connectivity and therefore increased "randomness" they expected LRTC to be decreased in patients. LRTC in both the alpha and beta range were lower across most EEG leads in patients compared with controls suggesting increased variability or more "random-like" neuronal activity. While the authors speculated that this may be associated with thought disorder they did not report correlations with measures of psychopathology. Unexpectedly, they observed greater temporal cross-correlation between changes in alpha and beta oscillations in patients compared with HCPs.

It has been suggested that some EEG abnormalities may represent an endophenotype [17] for schizophrenia. Studying resting EEG in 128 schizophrenia patients, 80 unaffected relatives and 110 HCPs, Hong et al. [18••] observed increased gamma (40-85 Hz) power in patients, but not in relatives, compared with HCPs. In contrast increased midline theta-alpha (5-11 Hz) power was seen in both patients and relatives compared with controls. The authors hypothesized that the latter finding may be "an elementary abnormal rhythm marking aspects of the genetic liability for schizophrenia." They speculate that excess theta may result from altered GABAergic activity in the hippocampus, where theta rhythms may originate. Although the patients were not drug-free when tested, medication-induced effects on theta oscillations are unlikely as increased theta activity was also seen in the unmedicated relatives.

As some QEEG oscillations are temporally related to intermittent symptoms of schizophrenia examination of such oscillations may offer some insights into the neurophysiological nature of these symptoms. Koutsoukos et al. [19••] studied QEEG activity before and during auditory verbal hallucinations (AVH) in eight patients with treatment-resistant schizophrenia. They observed increased phase coupling of theta and gamma frequencies in left frontotemporal regions 1.5 to 2 seconds prior to AVHs. They speculate a gating phenomenon whereby theta oscillations "drive or modulate gamma amplitude" during AVH production.

Ray and Ram [20•] examined coherence and power spectrum in 60 persons with schizophrenia divided into those with formal thought disorder (FTD+) or those without (FTD-) and 30 matched HCPs. Mean spectral power and high frequency (beta1, beta2, gamma1, gamma2) *intra*hemispheric coherence was greatest in FTD-, lowest in FTD+and intermediate in controls. In contrast, *inter*hemispheric coherence was greatest in FTD+, lowest in FTD- and intermediate in controls. As EEG synchronization may reflect functional connectivity between different brain regions, the authors speculate that FTD may result from disturbed intra- and inter-hemispheric connectivity.

Cognitive Performance Studies

The previously discussed resting theta power increase in patients compared with HCPs reported by Hong et al. [18••] was also noted by Hanslmayr et al. [21•] when QEEG was measured in 26 persons with schizophrenia and 26 HCPs. Here resting analyses were augmented by measurements made during a computerized visual attention task (counting moving geometrical objects with unexpected appearances of a monkey-like shape). HCPs showed pronounced theta power increases in Brodmatnn areas 6, 9, 46, 7, 22 during the task but patients did not. Although, overall, the patients were much less likely to notice the monkey than controls, those patients who did also showed theta increases comparable to controls, suggesting that theta modulation is required to cognitively process visual information. The authors speculate that

elevated resting theta activity and failure to modulate theta during a challenging cognitive task may be markers of treatment response. Indeed Surmeli et al. [22•] used elevated theta activity as a target for an operant conditioning treatment using QEEG-based neurofeedback (NF), reporting 82 % improvement in PANSS scores over a mean of 58.5 one-hour NF sessions in 48 drug–free schizophrenia participants.

The inability of patients with schizophrenia to modulate electrophysiological activity in response to a cognitive task has also been demonstrated elsewhere. Carlino et al. [23•] examined integration of neuronal networks in 17 schizophrenia patients and 17 matched HCPs. They calculated the correlation dimension (D2) of the EEG signal, defining D2 as the "number of independent variables necessary to describe the behavior of a dynamic system." The authors cite studies showing that, in healthy persons, D2 is greatest during performance of divergent tasks requiring creative solutions, intermediate during more concrete convergent tasks, and lowest during mental relaxation. Carlino et al. recorded QEEG in their participants during relaxation, and counting either forward or backward. As expected D2 was increased during the cognitive tasks compared with rest in HCPs. Although they showed higher global D2 than controls at rest, the patients could not increase D2 further during the counting tasks. The investigators hypothesize that this inability to modulate neuronal networking may underlay impaired information processing in schizophrenia, particularly if manifest as an inability to distinguish internal from external stimuli.

Disturbed executive functioning is an important symptom of schizophrenia. Wolwer et al. [24•] examined electrophysiological correlates of executive functioning in 12 patients with first-episode schizophrenia, and 12 matched HCPs. They measured cortical electrical current density during the Trail-Making Test-B task and employed low-resolution electromagnetic brain tomography (LORETA), a statistical technique that imposes anatomical constraints on mathematical methods to calculate the potential deeper source of a scalp-recorded EEG signal. Using eye-tracking technology the authors could determine whether a subject was "planning" or "monitoring" performance at any given time. During planning all participants showed increased current density in the dorsolateral prefrontal cortex, cingulate gyrus and inferior parietal cortex. Although the patients made more planning eye movements, their prefrontal current density increase was significantly smaller compared with controls, and task performance was also lower. Better task performance correlated with higher current density. These data suggest that poorer executive functioning and planning in schizophrenia might result from inability to activate prefrontal regions required for task planning and execution.

Both sleep and executive functioning are disturbed by schizophrenia [25]. Ramakrishnan et al. [26] examined previous night's sleep architecture in 20 schizophrenia patients who were then asked to perform the Trail-Making-B and Tower of London Tasks. Increased slow-wave sleep and a greater number of K-complexes (large surface-negative complexes followed by a positive wave occurring predominantly during stage 2 sleep) were correlated with better executive functioning.

Another core symptom of schizophrenia is impairment of social and emotional cognition, including facial affect perception, attribution of others' mental states, and empathy [27]. Simulation theory hypothesizes that empathy arises from experiencing others' sensory or motor experiences as though they were one's own [28]. McCormick et al. examined this phenomenon in 16 schizophrenia participants and 16 HCPs by studying the "mirror neuron" system via measurement of the Mu rhythm (8-13 Hz) in leads over sensorimotor cortex [29••]. Mu rhythm in healthy individuals is suppressed when the subject performs a motor task or observes another performing a motor task. Unexpectedly, actively psychotic patients showed greater Mu suppression after actual and observed hand movements than did HCPs and non-psychotic patients. Left-hemisphere Mu suppression correlated with psychotic symptoms. The authors suggest that this may contribute to misattribution of socially relevant stimuli. It is also possible that this enhanced sensitivity to others' actions could lead to difficulty distinguishing one's own actions and feelings from those of others'.

Machine Learning Methods

Advances in signal processing are now available that allow the researcher to search systematically through very large data sets, e.g., the EEG, to discover information relevant to some classification task, e.g., separating schizophrenic from healthy subjects, and treatment responders from non-responders. Also known as "data mining," the basic steps of ML include: i) collecting training data: e.g., EEG data, from a sample of subjects for whom the relevant class is already known; ii) feature extraction: extracting a large number of variables or features from this EEG training set; iii) feature processing: calculating coherences, power, power ratios etc. using feature data; iv) feature selection: identifying a small subset of features which can be used to classify subjects; v) classifier construction: applying this reduced feature set in a multidimensional matrix to separate subjects by class; vi) testing the classifier to estimate its accuracy.

Commonly during the initial phases ML algorithms are developed and tested in the same subjects because only limited amounts of training and test data are available at the outset. When this approach is used special statistical approaches such as nested cross-validation must be employed to minimize the possibility of "over-fitting," i.e.,

overestimating the predictive accuracy of the resulting model.

Khodayari et al. [10••] developed ML algorithms capable of correctly classifying 85 % of subjects by diagnosis in a study using resting QEEG data from 40 schizophrenia patients, 91 healthy participants, 64 with major depressive disorder and 12 with bipolar depression. The same group developed other ML algorithms capable of predicting response to clozapine with over 85 % accuracy [11••]. To do so they used data from a single pre-clozapine resting EEG collected from 23 participants with treatment–resistant schizophrenia. Since the algorithm performed equally well in an independent sample of 14 additional test participants whose data were not used for training purposes, over-fitting was not a major factor. The predictive features selected by the ML algorithms were mainly coherences between left temporal leads and left frontal and parietal leads in the 6 to 13 Hz range.

This group [12••] further explored the relationship between EEG and clozapine treatment by combining ML with brain source localization methods to examine auditory oddball P300 responses in 66 healthy volunteers and 47 schizophrenia patients. Patients were studied before and after treatment. Several source generators of P300 which changed after clozapine treatment (though only in responders) were identified. At baseline these same features, mainly in central and right temporal regions, differentiated patients from healthy volunteers with 84 % accuracy. These pilot data suggest that ML analysis of EEG may be an extremely useful tool in the management of schizophrenia.

ERP Studies

The ERP technique provides cognitive neuroscientists with a useful window on information processing in the brain. In this technique, continuous EEG is recorded via an array of electrodes at the scalp while the participant performs a cognitive task suitable for addressing the given research question. In such a task, stimuli are presented over many trials and the participant may be required to make a response. For a particular class of stimulus or response (i.e., a cognitive "event"), EEG segments or "epochs" lasting a given amount of time before and after the event are averaged over all instances ("trials") of this event. This procedure serves to eliminate brain activity that is unrelated to the event and hence theoretically averages to zero, given a large enough number of trials. Thus, in the resulting average ERP, voltage changes over time are a continuous, millisecond-level record of synchronous activity of neocortical pyramidal neurons related to the cognitive event. In studies of normal individuals, ERPs are most informative when used to compare differences in cognitive processing between experimental conditions in which a given factor is systematically varied. Comparing ERPs between conditions may then shed light on the time course and factors affecting cognitive brain activity in the experimental paradigm in question.

Many ERP studies of schizophrenia can be classified into three broad categories. The first category includes studies that compare patients' ERPs with those of healthy individuals to refine our understanding of how patients' cognitive processing is abnormal. In the second, researchers aim to clarify whether an ERP component previously shown to be abnormal in schizophrenia is an endophenotype, or trait marker of genetic liability for the disorder [17], which would make it useful in population studies aiming to identify genetic determinants of schizophrenia. In the third type of study, ERP abnormalities known to improve with treatment of the illness are used as objective biomarkers of therapeutic response in trials of novel candidate drugs. Below we will review recent highlights in each of these categories.

Using ERPs to Characterize Abnormal Cognition

Leonard et al. [30•] used an ERP index of visual working memory (WM) load, the contralateral delay activity (CDA), to investigate whether WM deficits in schizophrenia are qualitatively similar to the state seen at the low end of the continuum of healthy individuals; or whether these deficits reflect distinct pathology. The CDA is normally observed during the retention period of a visual WM task. Its amplitude has been found to increase with the number of objects to be remembered, and reaches an asymptote when this number reaches the individual's WM capacity; it is thus thought to reflect the amount of resources allocated to maintaining items in WM [31, 32]. Leonard et al. [30•] found that in schizophrenia patients, CDA was larger than normal when one object was to be remembered, but smaller than normal when arrays of three or five objects were to be remembered, even when the patients were matched to controls of similar behavioral WM capacity. There was no evidence of faster decline of CDA amplitude over time in the patients, which would have suggested faster decay of WM representations. The authors interpreted the results to suggest that schizophrenia patients tend to hyperfocus, devoting more than normal attentional resources to a single item, but having difficulty distributing attention broadly over multiple items. This latter abnormality would negatively impact behavioral performance when there is a larger number of items to remember. This conclusion was also supported by the finding that schizophrenia patients with large CDA amplitudes at a memory load of one object were more likely to exhibit *reduced* behavioral performance at a memory load of five versus three objects.

Another ERP component observed to be abnormal in schizophrenia is the lateralized readiness potential (LRP), an ERP index of motor response preparation. It manifests

as a gradually increasing voltage negativity beginning around 500 ms to one second prior to a prepared movement, over the motor cortex contralateral to the movement [33, 34]. To isolate this activity, the LRP is derived by taking the ERP at sites contralateral to the movement, and subtracting the ERP measured at corresponding sites on the ipsilateral side. Previously, Luck et al. [35] found the LRP to be smaller (less negative) than normal in schizophrenia, suggesting deficient motor preparation. Participants were required to press a button with one hand in response to rare stimuli and with the other hand to frequent ones. No deficits were found in patients in the amplitude of another ERP response, the P300, elicited by rare versus frequent attended stimuli, suggesting that the LRP reduction was not due to difficulties in perceiving or categorizing stimuli.

Building on this work, Kappenman et al. [36] aimed to distinguish whether LRP amplitude deficits reflect impaired activation of the correct response, and/or failure to suppress activity associated with the incorrect response. To this end, they compared LRPs in schizophrenia patients and controls in a flankers task. On each trial, participants viewed a target that was either a left- or right-pointing triangle; with flankers, one above and one below the target, that were both either left- or right-pointing triangles, or squares. Participants had to press either a left or a right button with the corresponding hand, to indicate which direction the target was pointing. Thus, flankers were pointed either in the same direction as the target (low-conflict condition), in the opposite direction (high-conflict condition), or neither (neutral). The authors hypothesized that, if schizophrenia patients fail to suppress activity associated with the incorrect response, then they would exhibit a smaller LRP in the high-conflict condition, in which such activity would presumably be greater. However, the LRP was equally reduced in patients in the low- and high-conflict conditions, suggesting that patients' LRP deficits are due to failure to activate the correct response.

The N400 is a negative-going ERP waveform occurring around 400 ms after any potentially meaningful stimulus, such as a word or a picture. Normally, its amplitude is made smaller (less negative) by factors that activate or prime the corresponding concept, including relatedness to preceding context [37–40]. Numerous N400 studies have found evidence that this priming of related items is reduced in schizophrenia. These studies reported larger than normal N400s to targets that were related to preceding primes, and/or smaller than normal N400 relatedness priming effects, in schizophrenia [41–46]. Some studies have found that these abnormalities are correlated with psychotic symptoms (delusions and hallucinations) [47–49]. These results raise the possibility that impaired use of context to activate related items may contribute to delusions, perhaps by causing patients to perceive contextually-related stimuli as incongruent, in turn precipitating a delusional explanation for this aberrant experience. In contrast, a few other schizophrenia N400 studies have found *increased* priming of related targets [42, 50, 51]. However, this abnormality appears specific to the combination of weakly related targets, short prime-target time intervals of <300 ms, and patients with disorganized speech [41, 42] – suggesting that hyperpriming of weakly related concepts may underlie this symptom. On balance, however, N400 studies of schizophrenia patients provide evidence of a general reduction in priming of related concepts, at least at time intervals of approximately 300 ms or greater.

In a recent study, Kiang et al. [52] aimed to distinguish whether this reduction is due to: (a) lower-level deficits in maintaining the prime stimulus in working memory; or (b) impaired functional connections between meaningful concepts in long-term semantic memory. They hypothesized that if (a) is true, then schizophrenia patients would show less than normal reduction in N400 amplitude for stimuli that are identical to a preceding prime (*N400 repetition priming*). Instead, patients exhibited normal N400 repetition priming, along with the expected deficits in N400 priming of related targets, consistent with a primary abnormality of functional connections within semantic memory.

Validating ERP Endophenotypes of Schizophrenia

Along with the P300, the auditory mismatch negativity (MMN) is a putative endophenotype of schizophrenia [53]. MMN is a relative ERP negativity seen as early as 50 ms after rare ("deviant") versus frequent ("standard") stimuli, even when the participant is not actively attending to the stimuli [54], and its amplitude is reduced in schizophrenia [55, 56•]. For auditory stimuli, MMN appears to be most consistently reduced for duration deviants, compared to frequency or intensity deviants [57]. Consistent with criteria for an endophenotype, MMN is heritable [58, 59], MMN deficits in schizophrenia patients are state-independent [60], and such deficits are also found in unaffected relatives [61]. A number of recent studies have contributed to further validation of MMN as a schizophrenia endophenotype, by establishing that it is already reduced in the earliest stages of the illness, and in persons with attenuated symptoms below the threshold for a diagnosis of schizophrenia [62–64]. In addition, Kaur et al. [65] showed that MMN amplitudes in bipolar-spectrum disorders lie on a continuum between those seen in schizophrenia and normal populations, supporting the validity of a shared diathesis model of psychotic and bipolar disorders that overlaps traditional diagnostic categories.

Another ERP component which may potentially be useful as a schizophrenia endophenotype is the event-related negativity (ERN). This is a negative ERP waveform that peaks approximately 50 ms after a person makes an erroneous

response on a choice response task [66], observed even when the individual is not consciously aware of having made an error [67]. It is smaller than normal in schizophrenia [68–70, 71•], and this deficit is associated with poorer real-world functioning [71•]. Consistent with endophenotypic status, the ERN is heritable [72], and is reduced in early stages of the illness and diagnostically subthreshold cases [73], as well as in schizophrenia patients' unaffected siblings [74•]. Taken together, these findings support the need for further research to test the validity of the ERN as an endophenotype of schizophrenia.

Using ERP Biomarkers of Schizophrenia in Clinical Trials

A major current priority in schizophrenia research is the identification and validation of biomarkers, including ERP indices associated with particular symptoms of the disorder [75–77]. Identification of such biomarkers could improve our understanding of neurophysiological abnormalities underlying these symptoms. Such biomarkers could also aid in drug development by serving as: (a) targets for screening of putative agents for therapeutic effects; (b) earlier markers of therapeutic response than symptom assessments; and (c) identifiers of patient subpopulations that exhibit the corresponding abnormality and are thus most likely to benefit from a particular treatment [75, 77]. One instance of a putative schizophrenia biomarker is P50 suppression [78]. P50 is an early (around 50 ms) ERP response to auditory stimuli. When two stimuli (e.g., two identical clicks) are heard in quick succession, the P50 elicited by the second stimulus is normally smaller than that elicited by the first stimulus, and the percentage reduction is termed the P50 suppression index. This P50 suppression is decreased in schizophrenia, and this abnormality is associated with cognitive impairment [79]. Recently, Zhang et al. showed that a novel $\alpha 7$ nicotinic acetylcholine receptor agonist, tropisetron, normalized P50 suppression deficits at the same time as it improved cognition [80]. This result suggests that P50 suppression deficits hold promise as a biomarker for future trials of cholinergic agents for treatment of cognitive deficits in schizophrenia.

Conclusion

The recent studies which we have reviewed confirm the utility of EEG as a neuroinvestigative tool for schizophrenia research. Renewed interest in "resting state" measures, sophisticated ERP paradigms and new mathematical techniques such as ML have yielded potentially important information regarding neuropathology, neurophysiology and cognition in schizophrenia. New biomarkers with potential diagnostic and therapeutic relevance have been identified. Discovery of such biomarkers is particularly important given the current absence of objective means to confirm diagnosis and determine optimal treatment for schizophrenia and other psychiatric disorders. EEG offers a direct measure of neuronal activity and very high temporal resolution, coupled with low cost, relative portability and accessibility, and is therefore not only a useful research tool but, pending confirmation of some of the biomarker studies described above, a potentially excellent choice for everyday deployment in community clinics.

Compliance with Ethics Guidelines

Conflict of Interest Gary Marcel Hasey is an unpaid board member of Digital Medical Experts, has patent applications dealing with machine learning analysis of EEG to establish diagnosis and determine treatment response of mental illnesses; and owns stock shares in Digital Medical Experts.

Michael Kiang declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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