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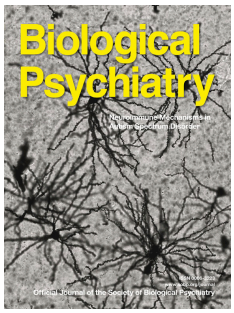


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Running Title: ERP Biomarkers of Psychosis Risk

# Electroencephalography and Event-Related Potential Biomarkers in Individuals at Clinical High Risk for Psychosis

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**Abstract**

Clinical outcomes vary among youth at clinical high-risk for psychosis (CHR-P), with approximately 20% progressing to full-blown psychosis over 2-3 years and 30% achieving remission. Recent research efforts have focused on identifying biomarkers that precede psychosis onset and enhance the accuracy of clinical outcome prediction in CHR-P individuals, with the ultimate goal of developing staged treatment approaches based on the individual's level of risk. Identifying such biomarkers may also facilitate progress toward understanding pathogenic mechanisms underlying psychosis onset, which may support the development of mechanistically-informed early interventions for psychosis. In recent years, EEG-based event-related potential (ERP) measures with established sensitivity to schizophrenia have gained traction in the study of CHR-P and its clinical outcomes. In this review, we describe the evidence for ERP abnormalities in CHR-P and discuss how they inform our understanding of information processing deficits as vulnerability markers for emerging psychosis and as indicators of future outcomes. Among the measures studied, P300 and mismatch negativity are notable because deficits predict conversion to psychosis and/or CHR-P remission. However, the accuracy with which these and other measures predict outcomes in CHR-P has been obscured in the prior literature by the tendency to only report group-level differences, underscoring the need for inclusion of individual predictive accuracy metrics in future studies. Nevertheless, both P300 and mismatch negativity show promise as electrophysiological markers of risk for psychosis, as target engagement measures for clinical trials, and as potential translational bridges between human studies and animal models focused on novel drug development for early psychosis.

Longer duration of untreated psychosis in schizophrenia is associated with poorer treatment response and increased likelihood of decline in cognitive, occupational, and/or social functioning. These observations have motivated research efforts to improve early detection of psychosis and identify individuals with putatively prodromal symptoms who are at increased risk for a psychotic disorder, with the ultimate goal of developing early interventions that yield improved clinical outcomes, including the possibility of psychosis prevention. Success of early intervention and prevention approaches ultimately depends on accurate assessment of psychosis risk. Over the last several decades, clinical diagnostic criteria have been developed and validated that prospectively identify individuals with putatively prodromal symptoms, also referred to as the "clinical high-risk for psychosis" (CHR-P) state, "at-risk mental state," or "psychosis risk syndrome" (1). These criteria generally include the presence of attenuated positive symptoms, brief intermittent psychosis symptoms, and/or recent functional deterioration within the context of genetic risk for psychosis.

Although the validity of CHR-P criteria for predicting future psychosis transition has been repeatedly demonstrated (2), clinical outcomes vary substantially among CHR-P individuals. Approximately 15-29% of CHR-P individuals progress to full psychosis over 2-3 years (2-4), whereas 30% achieve symptom remission and are presumably no longer at risk (4). While algorithms predicting these outcomes using clinical and cognitive data have been developed and validated (5,6), they are not yet sufficiently accurate to support major treatment decisions such as whether antipsychotic medication should be initiated. Accordingly, recent research efforts have focused on identifying biomarkers that precede psychosis onset and improve the accuracy of predictions about future clinical outcomes. Identification of such biomarkers may also elucidate pathogenic mechanisms underlying psychosis onset, which in turn may guide the development of more mechanistically-informed interventions.

Electroencephalography (EEG)-based measures, and event-related potentials (ERP) in particular, have several characteristics that make them suitable as biomarkers of psychosis risk. ERPs are scalp-recorded voltage fluctuations in the EEG time-locked to stimuli or responses that become evident after averaging over repeated trials. Typically originating from post-synaptic potentials in cortical pyramidal neurons, ERPs result from ion flow across the cell membrane in response to neurotransmitters binding with receptors on the post-synaptic cell. When post-synaptic potentials across similarly oriented neurons occur simultaneously, the field potentials summate and resulting voltage is detected on the scalp. ERPs have high temporal resolution, with sensitivity to transient changes in neural activity over tens or hundreds of milliseconds, allowing for tracking of information processing from early sensory and perceptual stages to later higher-order cognitive processes. Accordingly, ERPs are well-positioned to detect the physiological consequences of abnormalities in neurotransmission that characterize schizophrenia.

Another advantage of ERPs as potential biomarkers is that several ERP components can be recorded during tasks requiring minimal attention, thereby avoiding the pitfalls of measuring brain activity during complex tasks psychiatric patients may struggle to perform due to cognitive/motivational deficits. Furthermore, with respect to preclinical studies, human ERPs are directly translatable to non-human electrophysiology; animal models of ERP paradigms are sensitive to pharmacological and genetic manipulations relevant to psychosis. For these reasons, ERPs have gained traction in the study of schizophrenia and CHR-P individuals as markers of illness progression and as measures of target engagement for drug development studies.

Several ERP components reliably shown to be deficient in schizophrenia have been the focus of ERP studies aimed at developing risk biomarkers in CHR-P. Here, we review the available evidence for ERP abnormalities in CHR-P individuals and how these abnormalities

inform our understanding of information processing deficits as vulnerability markers for emerging psychosis. Details of studies are provided in the Supplement.

*Sensory/perceptual components*

N100 is a negative component that peaks approximately 100ms after stimulus onset for auditory stimuli and 150ms for visual stimuli. N100 amplitude is sensitive to stimulus physical features (e.g., intensity, duration, rise time). In studies of psychiatric disorders, N100 is often measured in oddball target detection paradigms in response to infrequent deviant sounds relative to frequent standard sounds, although it can be elicited in the absence of explicit task demands. Regardless of the paradigm, N100 amplitude is reduced among medicated and unmedicated schizophrenia patients (7) and their first-degree relatives (8,9). N100 is followed by P200, a positive-going potential peaking 200ms post-stimulus. While they often covary, P200 and N100 can be distinguished experimentally, topographically, and functionally, so are unlikely to reflect a single neural process. Like N100, P200 reductions have been reported in schizophrenia (10,11).

Several studies have examined auditory N100 amplitude among CHR-P individuals. Three studies have demonstrated reductions relative to healthy controls (HCs) (12-14), although another reported no group differences (15). All three studies demonstrating N100 reductions relative to HC reported no differences from schizophrenia patients. N100 amplitude deficits were also associated with increased severity of symptoms in a combined sample of healthy, CHR-P, and psychotic children (16).

Few studies have examined early visual components in CHR-P. These studies generally suggest that early visual ERPs, including visual N100 (17) and P100 (18), are intact in CHR-P individuals, although one study suggested that motion-induced N2m amplitude and its associated delta frequency oscillatory response is reduced in CHR-P and may predict psychosis conversion (18).

*N100 suppression during self-generated vocalization*. Auditory N100 has been used as a readout of the auditory cortical response to self-generated speech sounds during vocalization (19). Normally, the cortical response to self-generated sounds is suppressed relative to when the sounds are passively heard during playback of speech recordings, which has been attributed to an efference copy/corollary discharge mechanism that prepares sensory brain regions to recognize stimuli produced by our own actions. Numerous studies have shown deficient N100 suppression during self-generated speech in schizophrenia patients (9,20-22) and their first-degree relatives (9). Recent studies have shown deficient N100 suppression during vocalization in CHR-P relative to HCs that correlated with unusual thought content severity (22,23).

*Sensory gating.* P50, which peaks at the scalp vertex approximately 50ms post-stimulus, is elicited during a sensory gating paradigm in response to pairs of auditory stimuli separated by a 500ms interstimulus interval. Normally, P50 is larger after the first stimulus (S1) than the second stimulus (S2). The S1 response is thought to reflect the capacity to register an initial auditory stimulus, while the relatively suppressed S2 response reflects gating-out of irrelevant sensory information in order to protect processing of S1 (24). Using paired stimulus paradigms, deficits in sensory gating (i.e., deficient suppression of the response to S2 relative to S1; S2:S1 ratio or S1-S2 difference) have been shown in schizophrenia patients for P50 (25-27), and less commonly, for N100 and P200 (28-30) in which this suppression effect is also evident. Family studies suggest these abnormalities are heritable (31,32).

Three studies have documented deficient P50 or N100 suppression in CHR-P relative to HC (29,33,34), reporting medium to large effect sizes. Another study found no reductions in P50 or N100 suppression (35), while another reported that P50 and N100 suppression were associated with clinical severity across a combined sample of healthy, CHR-P, and schizophrenia participants (36).

Two studies followed CHR-P individuals longitudinally to examine whether sensory gating impairments are associated with future transition to psychosis. Van Tricht and colleagues (37) reported that baseline N100 suppression difference scores, but not P50 or P200 metrics, differentiated future converters from nonconverters (Cohen's d=0.62). While N100 suppression deficits contributed modestly to psychosis prediction, they did not predict time-to-conversion among CHR-P individuals. Others found that P50 and N100 suppression do not differentiate converters from nonconverters, although N100 suppression difference scores were reduced among converters relative to HCs, with nonconverters falling intermediately between them (29).

*Mismatch Negativity*

Mismatch negativity (MMN) occurs 100-250ms after stimulus onset and is maximal over frontocentral electrodes. It is elicited by discriminable deviant sounds occurring during a series of repeated "standard" sounds (38). MMN reflects automatic feature analysis in the auditory cortex, referred to as auditory sensory "echoic" memory because of its reliance on representations of what has been "standard" in the recent processing stream in order to detect deviance (38,39). MMN also reflects short-term synaptic plasticity and predictive coding, with MMN signaling a prediction error when a deviant stimulus violates the expectancy that a standard stimulus will recur, which builds over presentations of successive standards (40). MMN is considered preattentive and is elicited automatically when individuals are instructed to engage in an unrelated task (38). Indeed, MMN is largely unaffected by top-down information processing (38), allowing examination of auditory processing dysfunction in schizophrenia without the confounding influence of attentional and motivational deficits (41).

Deficient MMN has been well-documented in schizophrenia (42,43). Some inconsistencies in prior literature may be due to the specific deviant stimulus eliciting the MMN (e.g., duration, frequency, intensity). There is some evidence that duration-deviant MMN (dMMN) may be more sensitive to schizophrenia than frequency-deviant MMN (fMMN; 42,44),

particularly among first-episode patients (45), although some studies have not found this effect (44,46).

Evidence of reduced amplitudes in CHR-P suggests that MMN is compromised prior to psychosis onset (36,47-58) (ds=0.28-0.88) although some studies have failed to find such evidence (59-63) (ds=0.0-0.32). In studies that also examined schizophrenia patients, MMN amplitudes in CHR-P individuals were either intermediate between HCs and schizophrenia patients (50,58,60) or similar to those of patients (36,47,52). As in the schizophrenia literature, the extent of the MMN reduction in CHR-P may depend on the eliciting stimulus. The majority of CHR-P studies examined dMMN (36,47-53,55-58), but some reported greater reductions in dMMN than fMMN (53,55,60,64), similar to first-episode schizophrenia (45), while others have reported no differences between deviant types (47,48). One study also reported MMN deficits among CHR-P individuals using a duration+frequency double-deviant stimulus (47), a finding replicated by the North American Prodrome Longitudinal Study (NAPLS; 65).

Several studies have also shown baseline MMN amplitude reductions in future converters relative to nonconverters, reporting generally large effect sizes (47,51,62,64). There are also a couple reports with non-significant effects, or effects in the opposite direction than expected, based on a small number of converters (49,59). Some suggest the conversion effect may be specific to dMMN (64), while others found reduced baseline MMN in CHR-P converters across deviant types (47).

Importantly, there is evidence that smaller baseline MMN predicts shorter time-to-conversion among CHR-P individuals, particularly when using duration+frequency double-deviant MMN amplitudes as the predictor (47,65). Moreover, Kim and colleagues (66) recently showed that dMMN distinguishes future CHR-P remitters from nonremitters (d=0.72). Nonremitters had reduced amplitudes at baseline relative to remitters and HCs and MMN predicted later functional recovery (66).

*Repetition Positivity.* Recent predictive coding models led to the discovery of the "repetition positivity" (RP), a component elicited by standards that increases with successive standard repetitions, consistent with strengthening of the standard's memory trace and associated prediction that it will recur (67). While schizophrenia literature is still small and mixed (68,69), a recent NAPLS analysis of the RP showed deficient amplitudes in CHR-P individuals, both for earliest appearing standards and more prominently for late appearing standards within local sequences of repeating standards following each deviant (65). This deficit was worse in CHR-P individuals who transitioned to psychosis, and greater deficits were predictive of shorter time-to-conversion.

*P300*

P300 is a positive voltage deflection in the stimulus-locked ERP that occurs 300ms post-stimulus, elicited during an oddball target detection task by behaviorally relevant infrequent salient stimuli interspersed among frequent standard stimuli (70). P300 amplitude is thought to reflect controlled attentional resource allocation (70,71), contextual updating of working memory (72), and stimulus salience processing (73). There are two subcomponents of P300 that depend on specific task conditions: P3b is elicited by infrequent target stimuli subjects must respond to (e.g., press a button, count), whereas P3a is elicited by infrequent non-target novel distractor stimuli requiring no response (70). P3b reflects effortful top-down attentional allocation and is maximal over parietal electrodes, while P3a reflects automatic, bottom-up orienting of attention, has a frontocentral scalp maximum, and peaks 25-50ms earlier than P3b (70).

Both target P3b and novelty P3a amplitudes are reduced in schizophrenia, particularly when elicited by auditory stimuli (25,74,75). Amplitude reductions are also evident in patients' first-degree relatives, consistent with P300 amplitude reduction reflecting genetic risk for schizophrenia (76,77). Some studies have shown that P300 amplitude also fluctuates with clinical state (78,79) and that abnormalities worsen with longer illness duration (80,81).

CHR-P studies of P300 have consistently demonstrated deficient P3b amplitudes to auditory (12,15,82-90) and to a lesser extent, visual (17,83), target oddball stimuli (ds=0.49-1.6). In some studies, the magnitude of deficits in CHR-P individuals and schizophrenia patients has been similar (12,17,83). One study examining change in P300 over time failed to find further decline in P3b amplitude after psychosis onset among converters (91). Fewer studies have examined P3a among CHR-P individuals, but evidence exists for reduced auditory (12,49,50,61,63,82,83) and visual (83,92) amplitudes in response to novel or unattended deviant stimuli (ds=0.29-0.76) (but see (59)).

P300 has also been examined among longitudinally-tracked CHR-P individuals. Seversl studies suggest auditory target P3b is associated with future psychosis onset, differentiating converters from nonconverters (82,83,88,91), reporting medium to large effect sizes. There is also one report of deficient visual target P3b amplitudes among converters relative to nonconverters (83). Both auditory (82,83,88) and visual (83) target P3b deficits predict shorter time to psychosis onset. Moreover, the NAPLS consortium recently reported that relatively normal auditory target P3b was associated with future CHR-P remission (82). Although Kim et al. (93) found no baseline target P3b amplitude differences between remitters and nonremitters, target P3b amplitudes predicted improvement in negative and general psychopathology symptoms.

Studies examining whether novelty P3a is associated with psychosis conversion have yielded mixed results. While one group reported that auditory novelty P3a amplitudes predicted both conversion and remission (94), others have not found novelty P3a to differentiate converters from nonconverters (59,82,83) or predict time to psychosis onset when elicited by auditory (82,83) or visual (83) stimuli.

*Other Higher-Order Cognitive ERPs*

Few studies have examined other higher-order cognitive ERPs in CHR-P. The amplitude of the error-related negativity (ERN), which is a response-locked ERP elicited by commission

errors during choice response, is reduced in schizophrenia (95). The only study that examined ERN in CHR-P reported amplitude reductions (96). One CHR-P study has examined the late positive potential (LPP), which reflects emotional reactivity and is typically greater for both pleasant and unpleasant relative to neutral stimuli (97). While schizophrenia patients have generally shown an intact hedonic response and similar LPP amplitudes to HCs (98,99), one study found attenuated LPP to pleasant and unpleasant stimuli in CHR-P individuals (100).

*Neural Oscillations*

Schizophrenia has been linked to abnormalities in neural oscillations and their synchrony. Resting-state EEG spectral abnormalities in schizophrenia have been reported, including increased delta and theta and decreased alpha power (101,102). CHR-P studies have also identified resting spectral abnormalities that predict psychosis conversion, including increased theta and delta power, either alone (103) or in combination with symptom severity (104,105), and decreased alpha peak frequency (103) (but see (106)).

Schizophrenia is also associated with abnormalities in gamma-band (30-80Hz) oscillations, which have been implicated in sensory registration, cross-modal sensory integration, and higher-order cognitive functions (107). Event-related gamma oscillations are typically quantified by transforming the time-voltage domain EEG signal into the time-frequency domain, yielding measures including total power, evoked power, and phase-locking factor (PLF) or intertrial phase coherence (108,109).

Schizophrenia patients have deficits in both power (110,111) and PLF (109-111) of the early auditory gamma-band response, an obligatory gamma burst evident 50-100ms following an auditory stimulus. Such deficits have been linked to abnormalities in parvalbumin expressing GABAergic interneurons and NMDARs in schizophrenia (112). In addition, gamma oscillations are often measured using the gamma auditory steady-state response (ASSR), an EEG response entrained to click trains (often 500ms or longer) presented at a 40Hz driving

frequency. Gamma ASSR power and PLF deficits are the most replicated gamma oscillation abnormalities in schizophrenia (113).

Despite numerous gamma oscillation studies in schizophrenia, few studies have examined gamma oscillations in CHR-P. Tada and colleagues (114) found reduced late-latency gamma ASSR total power and PLF in CHR-P relative to HC that were comparable to deficits in schizophrenia. In contrast, others (63) found normal 40Hz gamma ASSR evoked power and PLF in CHR-P. Finally, Perez and colleagues (115) examined early auditory gamma-band responses to standard tones presented during an oddball task in CHR-P. CHR-P individuals demonstrated reduced gamma evoked power similar to schizophrenia patients and marginally reduced PLF. There were no differences between converters and nonconverters.

Alpha-band (8-12Hz) oscillations coordinate synchronous activity between distributed cortical regions via thalamo-cortical tracts (116) and are prominent during cortical idling. Alpha power is suppressed during effortful cognitive tasks requiring attention, response inhibition, and/or other top-down control functions (107), a phenomenon known as alpha event-related desynchronization (ERD; 117). Thus, alpha-ERD is posited to reflect release from cortical inhibition and engagement of cortical networks during cognitive task performance (116). Oddball tasks show decreases in alpha power during processing of target stimuli (118). Both schizophrenia patients (119) and CHR-P individuals (120-122) demonstrate reduced alpha-ERD to target tones relative to HCs. Recent NAPLS analyses demonstrated that CHR-P converters exhibited reduced alpha-ERD relative to nonconverters and HCs, and that decreased alpha-ERD predicted a shorter time-to-conversion (122).

## Discussion

This review highlights emerging evidence that several EEG/ERP biomarkers known to be abnormal in schizophrenia are also abnormal in individuals meeting CHR-P criteria, consistent with these abnormalities preceding the onset of full-blown psychosis. Importantly,

P300 (82,83,88,91,94) and MMN (47,51,64,65) have been shown to predict conversion to psychosis in several independent studies. While not yet replicated, studies have shown other ERP deficits to predict conversion, including N100 sensory gating (37), RP memory trace effects (65), and alpha-ERD (122). Other established EEG/ERP abnormalities in schizophrenia, including baseline elevations (123,124) and stimulus-driven reductions in gamma oscillations (113), as well as deficient sensory and higher-order cognitive ERPs, remain understudied in CHR-P individuals.

*Predictive accuracy*

The accuracy with which EEG/ERP measures predict outcomes in CHR-P has been obscured by a focus on testing differences between groups in prior studies. This underscores the need for future studies to include individual predictive accuracy metrics (e.g., area under the curve, sensitivity/specificity, positive/negative predictive value). Receiver operating characteristic (ROC) curves demonstrate sensitivity and specificity tradeoffs as a test's discrimination threshold is systematically varied. The area under the ROC curve (AUC) summarizes a test's accuracy for classifying individuals as belonging to one of two groups across all possible discrimination thresholds and reflects the percentage of randomly drawn pairs of individuals, one from each group, that a test correctly classifies. Of note, it is possible to transform effect size measures like Cohen's d to AUC (125). However, the accuracy of this estimate depends on the assumptions that the test is normally distributed within each group and that variances are equal between groups (125). Since violations of these assumptions can change the estimated AUC relative to the AUC calculated directly from the data, direct calculation of the AUC is preferable. Furthermore, it is important to recognize that in the sample used to develop a binary classifier, the AUC tends to be inflated due to overfitting; shrinkage of a classifer's predictive accuracy is expected when implemented in an independent cross-validation sample (126), underscoring the importance of cross-validation to realistically assess a classifier's performance. Finally, it should be noted that while the AUC metric treats all

classification errors as equally serious, the value of false-positive and false-negative errors will vary depending on the purpose for which the test is being used (127). For example, false positive predictions of future conversion are less tolerable when deciding who should receive antipsychotic medication (i.e., emphasis on specificity) than when deciding who should receive a treatment with more benign side effects (i.e., emphasis on sensitivity). Over the range of EEG/ERP measures being examined, we will likely find evidence of sensitivity and specificity trade-offs that will prove relevant for the specific clinical decision being considered.

*Utility of EEG/ERP biomarkers*

Although most prior CHR-P studies that tracked clinical outcomes focused on whether EEG/ERP abnormalities predict conversion, a few studies have shown that having relatively normal MMN (66) and P300 (82,94) amplitudes at CHR-P diagnosis predicted future remission. Clinically, treatment planning can potentially benefit from both predictive relationships: those at greatest risk for conversion based on biomarker status may benefit from the most aggressive multimodal interventions, whereas those most likely to remit based on biomarker status may simply require clinical monitoring with minimal intervention. Indeed, one of the potential roles for EEG/ERP markers is to help build staged treatment approaches stratified based on an individual's level of risk. The fact that EEG is relatively inexpensive to acquire, particularly compared with other biomarker domains such as MRI, and the possibility that "turn-key" EEG systems could feasibly be placed in clinical settings as part of a multimodal assessment of individuals presenting with attenuated psychotic symptoms, contribute to ongoing interest in EEG/ERP research aimed at further development and refinement of predictive biomarkers. Moreover, future clinical trials aimed at testing novel medications will benefit from biomarkers that can be used to enrich the CHR-P sample for psychosis risk and/or screen out individuals most likely to remit. EEG/ERP measures reviewed here show some potential to serve in this role, along with other clinical (5), biological (128), and genetic (129) measures.

To date, the EEG/ERP measures showing the most promise for predicting CHR-P outcomes have yielded moderate effect sizes, suggesting they are unlikely to be clinically useful as standalone prognostic tests. However, prior studies have relied on traditional EEG/ERP methods and measures. The potential for alternative preprocessing and measurement approaches to yield EEG/ERP measures with improved predictive accuracy remains largely unexplored; focusing on individual prediction accuracy, rather than group-level statistical significance, can motivate efforts to develop and evaluate such alternative approaches. In addition, it may be that EEG/ERP predictors of outcome work well for only a sub-group of CHR-P individuals. Future studies should examine variables that may moderate the relationship between EEG/ERP predictors and outcomes, allowing identification of subgroups for whom predictive accuracy is sufficiently strengthened to justify their use. Finally, the potential for EEG/ERP measures to contribute to multivariate algorithms incorporating other biomarker and clinical measures for predicting clinical outcomes remains largely unexplored and warrants greater attention.

EEG/ERP biomarkers sensitive to CHR-P and its clinical outcomes can also provide insight into neuropsychological and neurobiological mechanisms underlying CHR-P symptoms and psychosis onset. Psychologically, both MMN and P300 are elicited by improbable deviant stimuli in streams of standard stimuli and both show greater amplitudes when the deviant stimulus is preceded by longer trains of standard stimuli (67,130), consistent with predictive coding models that posit repetition-driven strengthening of the expectation that a standard will recur along with a larger prediction error signal (amplitude) when the expectation is violated. However, the preattentive nature of MMN and the dependence of P300 on top-down attention, coupled with their distinct latencies and scalp topographies, suggest underlying mechanistic differences between them despite similar dependence on stimulus probabilities and contextually-derived stimulus expectancies. For example, neuroanatomically, MMN generators

have been localized to auditory (layer 1; 131) and frontal cortex (132,133), while target P300 has been localized to temporo-parietal junction (134,135), with amplitude deficits potentially implicating compromise of these regions in those at greatest risk. Moreover, MMN generation has been mapped to the theta frequency band in human (136) and animal (131,137) studies, while alterations in delta oscillations are associated with P300 deficits observed in schizophrenia (138), suggesting that distinct neural circuits may be involved in the generation of these ERPs.

Inferences about the neurochemical moderators of EEG/ERP measures come mainly from pharmacological challenge studies. While these studies are limited by the fact that drugs seldom interact with only one neuroreceptor type and produce downstream effects on other neurotransmitter systems, it is noteworthy that NMDAR antagonists have been shown in animal (131,139) and human (140) studies to reduce MMN, while human studies have similarly shown NMDAR antagonists to reduce target P300 (141). Thus, MMN and P300 deficits in CHR-P converters are consistent with hypothesized NMDAR hypofunction as an underlying pathophysiological mechanism in schizophrenia (142,143). Unlike MMN, which seems to show relatively specific mediation by NMDAR neurotransmission, P300 has also been linked to noradrenergic (144), dopaminergic (70), and GABAergic systems (145), as well as serotonin 5-HT2A (146), cholinergic muscarinic (147) and cannabinoid receptors (148,149).

A further advantage of EEG/ERP biomarkers for elucidating neurobiological mechanisms underlying psychosis risk is that many of them, including MMN, P3a, sensory gating of P50 and N100, and resting and stimulus-evoked gamma oscillations, can be recorded in animal models, including rodents (139) and non-human primates (150). The translational bridges afforded by EEG/ERP measures distinguish them from many other biomarker domains, particularly MRI, and motivate ongoing research to refine these measures and establish homologies with similar measures in animals.

**Conclusions**

Among the EEG/ERP measures studied, P300 and MMN are particularly notable because deficits predict clinical outcomes, including conversion and/or remission. Therefore, P300 and MMN show the greatest promise as electrophysiological markers of risk for psychosis, as target engagement measures for pharmacological studies targeting receptors known to moderate their amplitudes, and as potential translational bridges between human studies and animal models focused on drug development for early psychosis.

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## Disclosures

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