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# Forecasting Psychosis by Event-Related Potentials—Systematic Review and Specific Meta-Analysis

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## ABSTRACT

**BACKGROUND:** Prediction and prevention of psychosis have become major research topics. Clinical approaches warrant objective biological parameters to enhance validity in prediction of psychosis onset. In this regard, event-related potentials (ERPs) have been identified as promising tools for improving psychosis prediction.

**METHODS:** Herein, the focus is on sensory gating, mismatch negativity (MMN) and P300, thereby discussing which parameters allow for a timely and valid detection of future converters to psychosis. In a first step, we systematically reviewed the studies that resulted from a search of the MEDLINE database. In a second step, we performed a meta-analysis of those investigations reporting transitions that statistically compared ERPs in converting versus nonconverting subjects.

**RESULTS:** Sensory gating, MMN, and P300 have been demonstrated to be impaired in subjects clinically at risk of developing a psychotic disorder. In the meta-analysis, duration MMN achieved the highest effect size measures.

**CONCLUSIONS:** In summary, MMN studies have produced the most convincing results until now, including independent replication of the predictive validity. However, a synopsis of the literature revealed a relative paucity of ERP studies addressing the psychosis risk state. Considering the high clinical relevance of valid psychosis prediction, future research should question for the most informative paradigms and should allow for meta-analytic evaluation with regard to specificity and sensitivity of the most appropriate parameters.

*Keywords:* Meta-analysis, Mismatch negativity (MMN), P300, Prediction, Prodrome, Psychosis, Sensory gating

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Disturbances of neurophysiological processes have repeatedly been observed in patients with psychotic disorders, particularly schizophrenia (1). Concomitant with the growing clinical interest in prevention (2,3), the neurophysiological underpinnings of subclinical and prodromal states have gained increasing attention. Particularly, alterations of information processing in the presychotic stages might serve as markers of illness development and thus allow for a timely identification of persons subsequently converting to psychosis (4–7).

Clinical studies demonstrated that the prospective identification of a specific prodrome is limited by the probabilistic character of clinical criteria (2,4). Although high-risk studies evinced that prediction of psychosis employing psychopathological variables is possible (8), the inherent uncertainty of psychosis prediction called for a paradigm shift (9). Since the majority of subjects displaying prepsychotic symptoms do not develop psychosis in the foreseeable future (8), the respective clinical state has to be considered a risk syndrome, possibly leading to various outcomes, rather than a prodrome mandatorily leading to psychosis (2). However, since psychosis is considered the worst outcome of the at-risk syndrome and since prevention represents the most promising strategy to overcome the still unfavorable prognosis of overt psychosis (3), the limitations of clinical psychosis prediction warrant objective parameters to enhance the timely identification of future converters to psychosis (10–15).

The search for biological markers that predict psychosis thereby faces its main challenge: to elucidate which biological parameters validly discriminate between future converters and nonconverters. These parameters presumably represent correlates of the crucial pathophysiological processes leading to psychosis. Furthermore, such markers would allow for a quantification of risk not only in terms of magnitude but also in terms of time to event, i.e., transition (11,15).

It has long been hypothesized that subtle disturbances of information processing contribute to psychosis, particularly in the early stages of the disorder, and neurophysiological studies lend further support on this hypothesis. Event-related potentials (ERPs) uniquely provide the opportunity to investigate these neurophysiological alterations.

In the present article, we aim to explore which ERPs represent the most promising candidates for a neurophysiological identification of the psychosis prodrome. We first give a systematic overview on ERPs in the psychosis risk state representing the candidate measures for prediction. Then, the candidate measures for which comparisons between future converters and nonconverters have been published



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are validated by meta-analysis. Finally, most recent investigations already providing predictive models are highlighted.

## Methods and Paradigms in Cognitive Neurophysiology

Disturbances in the sensory domain are particularly well documented in the auditory system in schizophrenia (16,17) (see Supplement 1 for overview). Much attention has been dedicated to the neuronal integrity of auditory processing, which is mirrored by ERPs appearing within 350 milliseconds after stimulus presentation, i.e., P50, N100, mismatch negativity (MMN), and P300 (16–18). Potentials pointing to the earliest stages of auditory processing (P50, N100) are assumed to represent the integrity of sensory gating in that the respective amplitude in response to the second of paired clicks is decreased in healthy subjects (19). Later components (MMN, P300) contribute to sensory context updating, reflected by increased amplitudes in response to rare tones (19). In contrast to P50, N100, and MMN, which reflect preattentive functions and hence warrant no active cooperation of the subject, P300 paradigms involve the participant's attention to deviant stimuli (19). All of the aforementioned components have repeatedly been demonstrated to be altered in schizophrenia (16,17).

### P50/N100

With regard to sensory gating, schizophrenia subjects display a diminished difference between P50 and N100 waves elicited by the first click (S1) compared with the respective ERP in response to a second click (S2) presented within 500 milliseconds (16,18). Usually analyzed gating parameters are the difference measure (S1 − S2), the ratio (S2/S1), and the suppression index [(1 − S2/S1) × 100], respectively. Some evidence suggests that the reliability of the N100 ratio is superior to that of the corresponding P50 measure (18), but it has been suggested that this finding is due to a different signal-to-noise ratio (19). Impaired sensory gating is thought to reflect the subject's diminished ability to screen out irrelevant sensory information.

### MMN

With regard to MMN in schizophrenia, amplitude reductions have been demonstrated in each of the paradigm conditions, i.e., duration deviants and frequency deviants, respectively (17). MMN waveforms represent the mathematical difference between potentials in response to standard stimuli compared with those in response to randomly presented deviants and reflect first, the ability to discriminate stimuli, and second, the pertinent echoic memory processes (20). Duration and frequency MMN are thought to relate to different neuronal generators and are hence conceptualized as independent components (21). Some studies suggest that the frequency MMN might only be disturbed in later stages of illness, i.e., about 2 years after psychosis onset (22).

### P300

Regarding the P300, which regularly displays a larger amplitude in response to infrequent but attended deviants in a series of standard tones, two subcomponents can be identified, the P3a with an amplitude maximum at frontal leads and the following P3b with maximum amplitudes at parietal electrode sites (23). The P3a subcomponent is thought to reflect automatic processing of novelty, whereas the P3b corresponds to memory updating (23).

## METHODS AND MATERIALS

We carried out a search of the MEDLINE database. We used the following Medical Subject Heading categories: [P50 OR N100 OR sensory gating OR mismatch negativity (MMN) OR P300] AND [ultra high risk OR prodrome OR at risk mental state (ARMS) OR clinical high risk (CHR)] AND [psychosis OR schizophrenia]. Studies were included if current at-risk criteria [cognitive-perceptive/cognitive disturbances, ultra-high risk (21–24) were employed in the respective studies. If more than one paper was published on the same study sample, only the main findings are listed in detail in tables; additional findings are summarized in the text. In a first step, study results were analyzed irrespective of the report of transitions in the respective high-risk samples. The second step of our analysis only included those studies reporting transitions that statistically compared ERPs in converting subjects with nonconverting subjects.

For the second step, a meta-analysis (method: generic inverse variance; effect measure: standardized mean difference, 95% confidence intervals) was performed for the respective ERP measures. P300 and the combined duration-frequency MMN were excluded, since yet only one study, respectively, presented extractable data regarding each of these parameters. Chi-square test was used for heterogeneity (fixed-effects model). For sensitivity analysis, studies were removed from the meta-analysis procedure in systematic iterations. Re-analyzing the data with different statistical methods (mean difference and/or random-effects model) had no considerable effect on the results. Statistical analyses employed the Review Manager (RevMan) 5.2.7 (The Cochrane Collaboration, London, United Kingdom).

## RESULTS

### Neurophysiological Parameters in the Psychosis Risk State

**Sensory Gating.** Six studies were identified that investigated P50 and N100 gating in the at-risk state (Table 1). Of these, four reported significant gating alterations in subjects at risk with regard to P50 ratio, suppression, and N100 difference, respectively, compared with healthy control subjects (18,25–27).

One study suggested that P50 suppression alterations might be rather confined to at-risk subjects with a family history of schizophrenia (26). Myles-Worsley *et al.* (26) demonstrated, in turn, that P50 ratio deficits may be more pronounced in at-risk subjects with affected first-degree relatives but that the gating alterations can be observed independent of family history of psychosis (25). However, the generalizability of the latter study might be limited, since it was conducted in an isolated population from Micronesia.