Prediction of Psychosis by Mismatch Negativity

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Background: To develop risk-adapted prevention of psychosis, an accurate estimation of the individual risk of psychosis at a given time is needed. Inclusion of biological parameters into multilevel prediction models is thought to improve predictive accuracy of models on the basis of clinical variables. To this aim, mismatch negativity (MMN) was investigated in a sample clinically at high risk, comparing individuals with and without subsequent conversion to psychosis.

Methods: At baseline, an auditory oddball paradigm was used in 62 subjects meeting criteria of a late risk at-state who remained antipsychotic-naive throughout the study. Median follow-up period was 32 months (minimum of 24 months in nonconverters, $n = 37$). Repeated-measures analysis of covariance was employed to analyze the MMN recorded at frontocentral electrodes; additional comparisons with healthy controls (HC, $n = 67$) and first-episode schizophrenia patients (FES, $n = 33$) were performed. Predictive value was evaluated by a Cox regression model.

Results: Compared with nonconverters, duration MMN in converters ($n = 25$) showed significantly reduced amplitudes across the six frontocentral electrodes; the same applied in comparison with HC, but not FES, whereas the duration MMN in in nonconverters was comparable to HC and larger than in FES. A prognostic score was calculated based on a Cox regression model and stratified into two risk classes, which showed significantly different survival curves.

Conclusions: Our findings demonstrate the duration MMN is significantly reduced in at-risk subjects converting to first-episode psychosis compared with nonconverters and may contribute not only to the prediction of conversion but also to a more individualized risk estimation and thus risk-adapted prevention.

Key Words: At-risk mental state, EEG, late initial prodromal state, mismatch negativity, prediction, schizophrenia

Prediction has become a main aim of psychosis research, and current symptomatic at-risk criteria, including ultra-high risk (UHR) criteria and particularly attenuated psychotic symptoms, have repeatedly been shown to delineate a significantly increased risk of psychosis in help-seeking samples across various conceptualizations and operationalizations (1–6). However, results of early detection studies have also consistently demonstrated a need for further enhancement of an individual risk evaluation, which is a prerequisite to the aim of developing risk-adapted preventive measures (6–8). Several prediction models based on clinical or demographic variables have already been suggested to increase specificity, predominately at the costs of an unfavorable drop in sensitivity (9). Although first methodological steps have been taken to overcome this problem (6), parameters beyond clinical and demographic variables will also have to be considered to significantly improve individual risk assessment. In line with this, recent longitudinal studies have already provided the first indication that neurocognitive (10) as well as biological parameters derived from structural or functional brain imaging may indeed contribute to such a stratification of risk (11–13).

With regard to electrophysiologic and magnetoencephalographic parameters, few studies examined at-risk stages (14–19), although many components of event-related potentials have been shown to be reduced in schizophrenia (20), such as sensory gating (P50), target and novelty processing (P300 family), and change detection (mismatch negativity, MMN). Further, disturbances in sensory information processing have been proposed as an important pathophysiological mechanism underlying the development of psychosis, particularly schizophrenia (21), and have even been discussed as potential endophenotypes (20). Surrogate markers of theses disturbances therefore appear as promising candidates for a further characterization of at-risk states; this might be particularly true for MMN, which was repeatedly and reliably shown to be reduced in schizophrenia (22,23).

MMN is defined as a preattentional change detection response, which is elicited whenever a certain stimulus deviates in any dimension from a preceding sequence of standards; it is conceptualized as a correlate of the integrity of the sensory network (24). Research addressing auditory processing has often employed an oddball paradigm that uses randomly assigned duration or frequency deviants in a series of standard tones to elicit the MMN (24–26). It was proposed that primary and secondary auditory as well as, potentially, frontal cortices were involved in the generation of the MMN response (21,27,28). An involvement of the glutamate/*N*-methyl-D-aspartate (glu/NMDA) system in the generation of the MMN has been suggested (29), and several (30,31), although not all (32), studies supported this finding.

A reduction of the MMN, in particular, in response to duration deviants (dMMN), appears to be specific to schizophrenia (20,33,34). Furthermore, MMN deficits were correlated with functional deficits in schizophrenia patients (35), and MMN deficits as well as their relationship to poor functional status were stable in later stages of the illness, that is, in chronic schizophrenia (36). MMN

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studies on unaffected first-degree relatives of patients with schizophrenia have had inconsistent results (37–40), and thus it is as yet unclear whether an MMN deficit reflects liability for psychosis. A first cross-sectional study on the MMN in subjects at risk for psychosis according to the basic symptom criterion of cognitive disturbances (16), reported that this group already exhibited a slight, although nonsignificant, reduction of the MMN amplitude, which, on average, was intermediate between healthy control and neuroleptic-free inpatients with schizophrenia but showed a large within-group variance (16). However, this study did not examine whether a more pronounced reduction was actually related to a subsequent conversion to psychosis.

This longitudinal study therefore aimed to investigate whether at-risk subjects with subsequent conversion to psychosis have already shown reduced MMN amplitudes at baseline compared with at-risk subjects who did not convert to psychosis within the follow-up period. In addition, the contribution of MMN to an individualized prediction of psychosis was evaluated.

Methods and Materials

Subjects

The study was approved by the local ethics committee. Written informed consent was obtained after complete description of the study to the subjects.

Subjects were recruited as part of the prospective early detection and intervention studies of the German Research Network on Schizophrenia (GNRS) (41,42) and had to fulfill the criteria for a late at-risk state of psychosis (8), that is, presence of attenuated positive symptoms (APS) and/or brief limited intermittent positive symptoms (BLIPS) within the 3 months preceding the study. An APS risk state was defined by the presence of at least one of the following symptoms appearing several times per week for a period of at least 1 week: 1) ideas of reference, 2) odd beliefs or magical thinking, 3) unusual perceptual experiences, 4) odd thinking and speech, or 5) suspiciousness or paranoid ideation. BLIPS comprised the presence of 1) hallucinations, 2) delusions, 3) formal thought disorder, or 4) gross disorganized or catatonic behavior, spontaneously resolving within less than 1 week. Both APS and BLIPS were assessed with the "Early Recognition Inventory based on the retrospective assessment of the onset of schizophrenia" (ERIraos) (43).

Further inclusion criteria were 1) age between 18 and 40 years, 2) MMN baseline recording at the time of first contact with the Cologne early detection service, 3) no antipsychotic medication for at least 6 months before and at baseline as well as throughout follow-up or until conversion, and 4) in case of nonconversion, follow-up period of at least 24 months.

General exclusion criteria were 1) lifetime DSM-IV (44) diagnosis of schizophrenia, schizophreniform, schizoaffective, delusional disorder, or bipolar disorder; 2) lifetime DSM-IV diagnosis of brief psychotic episode with a duration of more than 1 week; 3) DSM-IV diagnosis of delirium, dementia, amnestic and other cognitive disorders, mental retardation, mental disorders due to a general medical condition or mental disturbances due to psychotropic substances; 4) DSM-IV diagnosis of alcohol or drugs abuse/dependency within the past 3 months before the study; in case of drug abuse, to be rated as "at-risk" symptoms, onset of the respective symptoms had to precede abusive drug consumption and/or symptoms had to persist during a drug-free period of at least 12 (hallucinogens, amphetamines) and 4 weeks (cannabis), respectively; 5) continuous treatment with high-potency antipsychotics for more than 1 week at any time in life and any treatment with antipsychotics within 3 months before study entry; and 6) diagnosis of epilepsy and/or history of head injury or other neurological disorders.

Conversion to psychosis was assessed with the respective sections of the German version of the Structured Clinical Interview for DSM-IV (45); using the anchor point method (46), the onset of psychosis was dated for the month in which the onset of the first positive symptom persisting for more than 1 week was reported.

Sixty-two at-risk subjects fulfilled the intake criteria: 25 converted to psychosis (AR-C), on average within 7.04 $\pm$ 7.0 months (range 1–24 months); 23 (92%) were diagnosed with schizophrenia, one with schizophreniform disorder, and one with delusional disorder. Of the 37 at-risk subjects who did not convert (AR-NC) within the time period of 24 months, 23 (62%) showed a remission of at-risk symptoms, and 14 (38%) still reported them. Finally, of the nonconverters, 11 subjects received diagnoses of nonpsychotic psychiatric disorders (DSM-IV): 5 fulfilled the criteria for an anxiety disorder, 1 comorbid with a somatoform disorder, 5 fulfilled the criteria for an affective disorder, 1 had comorbid anxiety disorder, and 1 fulfilled the criteria for a somatoform disorder and substance abuse.

Converters and nonconverters were comparable with regard to age and the level of education (Table 1). Not showing any difference in group distribution, 24 subjects were smokers, 10 of the converters and 14 of the nonconverters [$\chi^2(1) = .140$, $p = .708$]. Further, MMN amplitudes did not significantly differ between smokers and nonsmokers for duration MMN [$F(1,52) = .226$, $p = .636$] or frequency of MMN [$F(1,36) = .00$, $p = .992$] (47). At baseline, one patient had received venlafaxine, one fluoxetine, one an unspecified antidepressant drug, and three lorazepam.

Additional explorative analyses were performed to compare the findings in at-risk subjects to healthy control subjects (HC) and

Table 1. Demographic Characteristics

	Study Sample			Comparison Samples			
	Whole Sample	AR-NC	AR-C	Statistics F(*df*)/p^a χ^2(*df*)/p^b	HC	FES	Statistics F(*df*)/p^c χ^2(*df*)/p^d
Age (years) [mean (SD)]	24.8 (6.0)	25.4 (6.0)	24.4 (6.1)	.75(1)/.39[a]	25.8 (4.0)	26.0 (6.5)	4.67(3)/.19[c]
Gender (male/female)	41/21	23/14	18/7	.64(1)/.42[b]	35/32	26/7	7.37(3)/< .10[d]
Handedness (right/left)	58/4	34/3	24/1	.45(1)/.50[b]	63/4	27/5	.34(3)/0.32[d]
School education (years), mean (SD)	12.1 (1.4)	12.0 (1.5)	12.3 (1.2)	.46(1)/.50[a]	12.5 (1.1)	11.5 (1.8)	9.71(3)/< .05[c]

AR-C, at-risk— conversion; AR-NC, at-risk—no conversion; FES, first-episode schizophrenia subjects; HC, healthy controls.
[a]AR-NC vs. AR-C, analysis of variance.
[b]AR-NC vs. AR-C, chi-square test.
[c]Study sample vs. comparison groups, analysis of variance.
[d]Study sample vs. comparison groups, chi-square test.