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Original article

Mismatch negativity: Alterations in adults from the general population who report subclinical psychotic symptoms

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ABSTRACT

Background: Deficits of mismatch negativity (MMN) in schizophrenia and individuals at risk for psychosis have been replicated many times. Several studies have also demonstrated the occurrence of subclinical psychotic symptoms within the general population. However, none has yet investigated MMN in individuals from the general population who report subclinical psychotic symptoms.
Methods: The MMN to duration-, frequency-, and intensity deviants was recorded in 217 nonclinical individuals classified into a control group ($n = 72$) and three subclinical groups: paranoid ($n = 44$), psychotic ($n = 51$), and mixed paranoid-psychotic ($n = 50$). Amplitudes of MMN at frontocentral electrodes were referenced to average. Based on a three-source model of MMN generation, we conducted an MMN source analysis and compared the amplitudes of surface electrodes and sources among groups.
Results: We found no significant differences in MMN amplitudes of surface electrodes. However, significant differences in MMN generation among the four groups were revealed at the frontal source for duration-deviant stimuli ($P = 0.01$). We also detected a trend-level difference ($P = 0.05$) in MMN activity among those groups for frequency deviants at the frontal source.
Conclusions: Individuals from the general population who report psychotic symptoms are a heterogeneous group. However, alterations exist in their frontal MMN activity. This increased activity might be an indicator of more sensitive perception regarding changes in the environment for individuals with subclinical psychotic symptoms.

1. Introduction

There is growing evidence for a continuum of psychosis from subclinical psychotic symptoms (SPS) without the need for treatment up to manifest schizophrenia [1,2]. Whereas schizophrenia is considered a comparatively rare disease (lifetime prevalence 0.4–0.7%), SPS are very common in the general population [3–6]. A systematic review by Linscott and van Os [1] reported a median prevalence rate for SPS of 7.2%. However, because SPS are often temporary and not well pronounced, only a small proportion of persons with such symptoms actually develop a clinically relevant and diagnosable psychotic disorder [7]. Two symptom dimensions can be distinguished within the SPS. The schizophrenia nuclear symptoms (SNS) which include psychotic symptoms such as hearing voices and the schizotypal signs (STS) consisting of paranoid ideations [4].

In contrast to subjects in a clinical high-risk state of psychosis [8], the sole presence of psychotic experiences are not in themselves associated with a need for clinical care [9]. Nevertheless, van Os et al. [10] recognized the predictive value of SPS for the potential onset of psychotic diseases. Although the annual rate of conversion (0.56%) of individuals with SPS to a clinical relevant psychotic disorder is relatively low, the rate is still 3.5 times higher than for individuals without SPS [11].

The pathophysiological mechanisms underlying the development of manifest schizophrenia have been widely studied. Biological markers and their predictive power are of particular interest to psychosis researchers [12]. In patients with schizophrenia, one useful approach is to investigate alterations of sensory

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processing in recordings of auditory event-related potentials [13]. Significantly smaller amplitudes of mismatch negativity (MMN) in schizophrenia have been an important finding frequently replicated in electrophysiological studies of auditory processing [14,15]. Currently, there is evidence from several studies for the potential usefulness of MMN in psychosis prediction. However, up to date standardized and validated paradigms for clinical use are missing [16,17].

MMN is defined as a preattentive component of auditory-evoked potentials [15] that is elicited when a sequence of frequent, repetitive stimuli is interrupted by an unexpected deviant stimuli that differ in at least one physical stimulus dimension [18]. In recent years, MMN is considered to be a correlate of an underlying predictive coding process [19,20]. The predictive coding theory hypothesizes a hierarchical neural architecture where each level provides predictions about the state of the level below. Discrepancy between prediction and actual input from the lower level value lead to a prediction error [21].

Previous research has suggested that MMN deficits could be specific to schizophrenia [22,23], in particular, reduced duration MMN (dMMN) [24]. For example, dMMN and intensity MMN (iMMN) deficits are possibly more prominent in the early stage of schizophrenia, whereas a reduction of frequency MMN (fMMN) occurs mainly at later stages of the illness [25,26]. However, a recent study has shown that MMN deficits are not dependent upon the type of deviant stimulus that might be presented [27].

It is possible that MMN deficits, especially dMMN amplitude, are strongly associated with poor functioning in schizophrenia patients [28]. However, investigations with unaffected first-degree relatives have revealed inconsistent findings [29–32]. Thus, diminished MMN amplitude might be linked to current functional impairment in schizophrenia but not to a genetic liability [33].

A recent review by Todd et al. in 2013 [34] compiled some evidence for altered MMN in clinical groups of persons at high risk for psychosis, even though previous data concerning the prediction of transition to psychosis were not sufficiently supportive. However, since impaired MMN in schizophrenia patients was first reported by Shelley et al. in 1991 [35], MMN deficits have been observed in persons with bipolar disorder [36,37], depressive disorder [38], and panic disorder [39]. In summary, the results of impaired MMN in persons with other types of illness are less distinct and serious compared to those seen in schizophrenia patients.

The generators of MMN have been identified bilateral temporal in the primary and secondary auditory cortices [15]. Moreover, there are contributions from frontal regions to MMN like the inferior frontal gyrus and the anterior cingulate cortex [40,41]. A recent study found reduced MMN source activation in schizophrenia patients mainly constrained to medial frontal brain areas. The authors conclude that initial auditory sensory discrimination is not disturbed in schizophrenia. However, the impairments in medial frontal regions cascade forward and produce widespread cortical networks dysfunction [42].

Assuming a psychosis continuum, the aim of our study was to investigate whether nonclinical adults in the general population who report SPS also show MMN alterations. To our knowledge, there is only one study which investigated MMN in non-psychotic individuals with auditory verbal hallucinations. Compared to a control group, no significant differences regarding MMN amplitudes and latencies were found [43].

Given a continuum from SPS to manifest schizophrenia [44], we hypothesized that individuals with SPS had impaired MMN when compared with persons in the control group. We also addressed the question of whether specific SPS subtypes–classified according to symptoms of paranoia and psychoticism–are associated with alterations of the frontal and temporal sources of MMN.

2. Methods and materials

2.1. Study design and sampling

This study was part of the ZInEP (www.zinep.ch) Epidemiology Survey [45], which comprised four components: telephone screening, semi-structured face-to-face interviews supplemented by self-report questionnaires, neuro-sociophysiological laboratory examinations, and longitudinal survey. Our criteria for selecting participants followed those of the Zurich Study [46,47], with the goal of generating a representative sample of 20- to 41-year-old Swiss residents comparable in age and gender to the assessment setting of the Zurich cohort study. Psychopathology was screened by the SCL-27 [48], a shortened version of the SCL-90-R [49]. The SCL-27 comprises the six subscales: depressive, dysthymic, vegetative, agoraphobic, sociophobic and symptoms of mistrust. The number of items per subscale varies between four and six. Additionally, similar to the SCL-90-R a global severity index (GSI) is available. The correlation between SCL-27-GSI and SCL-90-R-GSI index was reported as high as $r = 0.95$ [48].

Following the face-to-face interviews and stratification according to Symptom Checklist (SCL)-27 [48] status, age, and sex, we chose persons with psychotic symptoms and control-group participants for laboratory examinations at the ZInEP Center for Neurophysiology and Sociophysiology. This produced a study sample of 227 individuals, from which three individuals were excluded due to incomplete EEG recordings and another seven because of too many blink artifacts ($< 75\%$ of suitable trials). Ultimately, our analyses were based on 217 participants who provided all required data from the questionnaires and the neuropsychological testing.

The ZInEP Epidemiology Survey was approved by the Ethics Committee of the canton of Zurich (KEK) and complied with the Declaration of Helsinki. All participants gave their written informed consent after receiving a detailed description of the study.

2.2. Sample

The sample consisted of 122 females (56.2%) and 95 males (43.8%), with a mean age of 30.41 years (SD = 6.6). Approximately half of all participants (57.9%) held a higher educational degree (vs. basic education); 72.6% were single, 23.7% married, and 3.7% divorced; 78% had no children; and 89.6% were right-handed. All participants spent one day at the ZInEP Center for Neurophysiology and Sociophysiology where they underwent five different modules of examinations [45].

2.3. Measures

Handedness (dichotomized: right- and left-handed) was assessed by the Edinburgh Handedness Inventory [50], the most widely applied questionnaire in this field [51]. Bilateral-handed participants were excluded from further analysis. Cronbach's α and Raykov's factor p for the 10-item inventory were measured at 0.95 [52]. Details are presented in Table 1. Educational status was dichotomized into high school diploma/technical college/university degree vs. lower level, i.e., basic education.

The SPS were evaluated along the scales of STS and SNS. These two scales were derived from the SCL-90-R symptom dimensions "paranoid ideation" (maintained to STS) and "psychoticism" (maintained to SNS), representing marked symptom dimensions of subclinical psychosis [3,4,53]. Both had been validated in earlier studies [3,4,53] and were part of the screening interview for the ZInEP Epidemiology Survey. The SNS include four items: delusions of control, auditory hallucinations, thought-broadcasting and thought-intrusion. The STS include eight items e.g.: blame others