



## 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.

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## 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](http://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  $\alpha$  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

**Table 1**  
Demographic and clinical characteristics of the study sample.

	Total sample		Affected				Group comparisons	
	N = 217	CON (N = 72)	GA (N = 145)	PAR (N = 44)	PSY (N = 51)	PAR-PSY (N = 50)	GA vs. CON (P-value)	Across all subsamples (overall P-value)
Gender	122 (55.22)	41 (56.94)	81 (55.86)	28 (63.64)	27 (52.94)	26 (52.00)	0.88	0.66
Female N (%)								
Age (years ± SD)	30.41 ± 6.58	31.17 ± 6.51	30.03 ± 6.60	29.48 ± 6.70	30.26 ± 6.31	30.28 ± 6.90	0.23	0.60
Education (high versus low) N (%)	125 (57.87)	49 (69.01)	76 (52.41)	21 (47.73)	32 (62.75)	23 (46.00)	<b>0.02</b>	<b>0.03<sup>a</sup></b>
Handedness (right/left in %)	89.64/10.36	85.71/14.29	91.54/8.46	94.87/5.13	86.05/13.95	93.75/6.25	0.21	0.30
SCL-27 (mean ± SD) depression	2.07 ± .76	1.63 ± .55	2.29 ± .76	2.34 ± .72	2.00 ± .60	2.55 ± .85	< <b>0.001</b>	< <b>0.001<sup>b</sup></b>
SCL-27 (mean ± SD), dysthymia	2.36 ± .84	1.92 ± .73	2.57 ± .82	2.48 ± .74	2.44 ± .79	2.80 ± .87	< <b>0.001</b>	< <b>0.001<sup>c</sup></b>
SCL-27 (mean ± SD), social phobia	2.19 ± .89	1.58 ± .59	2.50 ± .85	2.63 ± .82	2.01 ± .64	2.90 ± .84	< <b>0.001</b>	< <b>0.001<sup>d</sup></b>
SCL-27 (mean ± SD), agoraphobia	1.54 ± .72	1.21 ± .38	1.70 ± .79	1.76 ± .89	1.37 ± .36	1.98 ± .88	< <b>0.001</b>	< <b>0.001<sup>e</sup></b>

CON: control group; GA: general-affected group; PAR: paranoid group; PSY: psychotic group; PAR-PSY: paranoid-psychotic group; significant results are printed in bold. mean ± S.D. given where applicable. Pairwise post-hoc comparisons (Bonferroni):

<sup>a</sup> PAR, PAR-PSY < CON.

<sup>b</sup> PAR, PSY, PAR-PSY > CON; PAR-PSY > PSY.

<sup>c</sup> PAR, PSY, PAR-PSY > CON.

<sup>d</sup> PAR, PSY, PAR-PSY > CON; PAR, PAR-PSY > PSY.

<sup>e</sup> PAR, PAR-PSY > CON, PSY.

for your troubles, most people cannot be trusted, feeling watched by others and having ideas that other do not share [4]. A median split (1.25 for SNS and 2.25 for STS) was used to divide the study participants into high- and low-scores of SPS. High-scorers formed the general affected (GA) group, which was then divided into three SPS subgroups:

- paranoid group (PAR = high-scores on the STS and low-scores on the SNS);
- psychotic group (PSY = high-scores on the SNS and low-scores on the STS);
- paranoid-psychotic group (PAR-PSY = high-scores above the median on both STS and SNS scales).

The control group (CON = below the median scores per the SNS and STS scales) consisted of the low-scorers.

#### 2.4. Recording

The BrainAmp amplifier and Brain Vision Recorder software (Brain Products GmbH, Munich, Germany) were used to record electroencephalogram (EEG) data. A 32-channel EEG was produced by carefully positioning a nylon cap (BrainCap MR 32 standard; EASYCAP, Herrsching-Breitbrunn, Germany) that attached silver/silver-chloride electrodes to the scalp in accordance with the international 10/20 system, for which the FCz electrode served as the recording reference. One EOG electrode was placed below the right eye and ground was placed at AFz. The sampling rate was 500 Hz. A band-pass filter of 0.1 to 100.0 Hz (12 dB/octave rolloff each) was used to collect the data. Impedances of the scalp electrodes were kept below 10kΩ. Using headphones with Presentation software (Neurobehavioral Systems, Inc., San Pablo, CA, USA), we presented 2400 acoustic stimuli binaurally in pseudo-randomized order. During the recording, each participant was seated in a comfortable chair, advised to relax, and asked to watch

a silent “Mr. Bean” film presented on a monitor screen at eye level to distract attention away from the source of the stimuli [26]. The acoustic stimuli included 1896 standard (1000 Hz, 100 ms, 80 dB; 79% of all stimuli presented), 168 duration-deviant (1000 Hz, 50 ms, 80 dB; 7% of total stimuli), 168 frequency-deviant (1200 Hz, 100 ms, 80 dB; 7% of total stimuli), and 168 intensity-deviant tones (1000 Hz, 100 ms, 70 dB; 7% of total stimuli) which were presented in a pseudo-random order without recurring pattern in one continuous block. The stimulus onset asynchrony was 500 ms and there were at least two standard stimuli between each deviant. During the 20-min EEG session, the participant was closely observed by well-trained professionals.

#### 2.5. Data preprocessing and analysis

The continuous EEG files obtained for each participant were first loaded manually into Brain Electrical Source Analysis (BESA) software (version 5.3; MEGIS Gräfelfing, Germany). The recorded EEGs were re-referenced to an average reference. Before beginning the averaging procedure, we digitally filtered the EEG data offline with a low cut-off of 1 Hz (12 dB/octave each) and a high cut-off of 20 Hz (12 dB/octave each) [26]. Afterwards, the individual EEG files were visually examined and divided into 500-ms epochs that included a 100-ms prestimulus baseline interval. If one of the two EOG channels (horizontal/vertical) detected eye movement, the associated EEG epoch was rejected. Trials with amplitudes exceeding 100 μV were also discarded. Only participants providing at least 75% accepted trials were included in the study. The remaining trials (95.4% for CON, 94.3% for PAR, 93.3% for PSY, and 92.5% for PAR-PSY) were averaged individually for each participant and each condition (duration-, frequency-, or intensity-deviant).

The second step in our analysis involved calculating individual standard and MMN average waveforms for each participant and each condition. MMN waveforms were calculated by subtracting the standard waveform from the particular deviant (duration, frequency, or intensity) waveform. The MMN waveforms associated with six

frontocentral surface electrodes – Fz, F3, F4, Cz, C3, and C4 – were used to assess the peak MMN amplitude and latency [24,26]. Latency windows were selected on the basis of butterfly plots from the average waveforms of the whole group. Peak amplitude was determined within a latency window of 150 to 250 ms poststimulus for the duration deviant, 115 to 225 ms for the frequency deviant, and 170 to 240 ms poststimulus for the intensity deviant. Our four groups were analyzed individually for each of the three conditions. Grand average files were calculated separately for each group and condition.

## 2.6. Source analysis

For the Dipole Source Analysis procedure, we used the BESA spatiotemporal source analysis tool in accordance with BESA tutorial by Hoehstetter et al. [54] and the work from Berg and Scherg [55]. A spherical head model was utilized with three regional sources (RS) in individual orientations. This construct of three orthogonal dipoles is suitable for modeling activity from the differently oriented gyral surfaces of a brain region [54] whereas tight changes in location generate smaller effects on the EEG scalp topography than do orientation differences. Two symmetrical sources were defined for the temporal lobe, based on knowledge that MMN is generated bilaterally in the primary auditory cortices [26]. The third source was located in the frontal cortex, in accordance with reports of the contribution made by the right frontal cortex in generating MMN [56,57]. Here, we used MRI image CLARA (“Classical LORETA Analysis Recursively Applied”), an iterative application of the LORETA (Low-resolution electromagnetic tomography) algorithm, in which the source space is implicitly reduced in each iteration. The MMN source activity was determined for each participant and deviant condition by using the source model described above. Finally, we acquired offline statistics from the individual source waveforms and their adjusted orientations to evaluate potential differences among the four study groups and three deviant conditions.

## 2.7. Statistical analysis

Descriptive statistics for demographic and clinical characteristics were provided for the entire sample, SPS-subsamples

(PAR, PSY, PAR-PSY), GA and CON (Table 1). Chi-square statistics were used to compare categorical variables between groups while a one-way analysis of variance (ANOVA) was conducted to compare the distributions of continuous variables across groups. Pairwise group comparisons were performed using multinomial logistic regressions with changing reference categories for categorical data and Bonferroni post-hoc comparisons for continuous data. Similarly, distributions of MMN waveform conditions (duration, frequency, intensity)–i.e., six surface electrodes (Fz, F3, F4, Cz, C3, C4) and the three RS (left temporal, right temporal, frontal)–were compared across groups via one-way ANOVAs (Table 2). Finally, multivariate logistic regression models were developed to estimate the association of MMN and group assignment. All models were adjusted for sex, age, education level, and psychopathology. The SPS subsamples or GA were each compared against CON as the reference group. Odds ratios (OR) were calculated with 95% CI (Table 3). Because of significantly higher dMMN at the frontal and the left temporal source in PSY versus CON, we post-hoc tested whether PSY differed from the other groups as well. Therefore, multivariate logistic regression models were calculated for dMMN with PSY serving as the reference group (Table 4).

All statistical analyses were performed using STATA software (version 12/SE) for Mac (StataCorp LP, TX, USA).

## 3. Results

### 3.1. Sociodemographic and clinical characteristics

Both GA and SPS subsamples differed significantly from those of CON in their sociodemographic characteristics of education and psychopathology (Table 1). Accordingly, pairwise post-hoc comparisons (Bonferroni) against CON revealed lower educational levels in PAR and PAR-PSY. Furthermore, all subgroups had almost always higher psychopathology scores than CON. Individuals in the PSY group had lower scores for depression, social phobia, and agoraphobia than individuals from the PAR-PSY group and lower depression and social phobia scores than individuals from the PAR group.

**Table 2**  
MMN peak amplitudes ( $\mu\text{V}$ ) and source activity (nAm).

		Affected					Group comparisons	
		Syndrome-specific subsamples					GA vs. CON	Across all subsamples
		CON	GA	PAR	PSY	PAR-PSY		
Surface electr.		Mean ( $\mu\text{V}$ ) $\pm$ SD					P-value	overall P-value
Fz	Duration	-1.16 $\pm$ .48	-1.07 $\pm$ .42	-1.06 $\pm$ .46	-1.05 $\pm$ .51	-1.09 $\pm$ .54	0.21	0.63
Cz		-.94 $\pm$ .42	-.93 $\pm$ .44	-.91 $\pm$ .42	-.98 $\pm$ .54	-.88 $\pm$ .32	0.76	0.67
Fz	Frequency	-1.28 $\pm$ .57	-1.28 $\pm$ .63	-1.21 $\pm$ .45	-1.23 $\pm$ .60	-1.40 $\pm$ .77	0.98	0.42
Cz		-.95 $\pm$ .48	-.97 $\pm$ .50	-.91 $\pm$ .40	-.99 $\pm$ .52	-1.00 $\pm$ .55	0.80	0.79
Fz	Intensity	-1.19 $\pm$ .70	-1.08 $\pm$ .58	-.97 $\pm$ .50	-1.01 $\pm$ .48	-1.16 $\pm$ .71	0.25	0.32
Cz		-1.05 $\pm$ .57	-.99 $\pm$ .55	-.93 $\pm$ .43	-1.05 $\pm$ .56	-1.00 $\pm$ .62	0.47	0.65
Source		Mean (nAm) $\pm$ SD					P-value	overall P-value
Left temporal	Duration	14.93 $\pm$ 7.91	14.25 $\pm$ 6.88	14.34 $\pm$ 6.71	15.00 $\pm$ 7.48	13.39 $\pm$ 6.42	0.52	0.64
Right temporal		15.02 $\pm$ 6.94	15.62 $\pm$ 7.27	14.91 $\pm$ 6.42	16.58 $\pm$ 7.92	15.26 $\pm$ 7.31	0.56	0.62
Frontal		15.33 $\pm$ 12.79	17.62 $\pm$ 14.58	15.45 $\pm$ 10.82	22.43 $\pm$ 17.18	14.62 $\pm$ 13.53	0.26	<b>0.01</b> <sup>a</sup>
Left temporal	Frequency	13.50 $\pm$ 5.62	13.03 $\pm$ 6.40	12.76 $\pm$ 5.76	13.09 $\pm$ 6.85	13.21 $\pm$ 6.58	0.60	0.94
Right temporal		11.74 $\pm$ 5.19	11.37 $\pm$ 5.00	10.80 $\pm$ 4.36	11.82 $\pm$ 4.94	11.41 $\pm$ 5.62	0.61	0.75
Frontal		19.25 $\pm$ 10.92	20.93 $\pm$ 12.90	16.93 $\pm$ 10.03	22.48 $\pm$ 13.77	22.88 $\pm$ 13.66	0.34	0.05
Left temporal	Intensity	15.01 $\pm$ 7.83	13.47 $\pm$ 7.20	13.75 $\pm$ 6.94	13.56 $\pm$ 6.56	13.12 $\pm$ 8.13	0.15	0.53
Right temporal		14.62 $\pm$ 7.24	13.72 $\pm$ 6.24	14.08 $\pm$ 5.94	14.03 $\pm$ 5.75	13.08 $\pm$ 7.01	0.34	0.66
Frontal		14.19 $\pm$ 10.41	14.61 $\pm$ 10.31	15.92 $\pm$ 11.03	14.72 $\pm$ 10.68	13.34 $\pm$ 9.29	0.78	0.67

CON: control group; GA: general-affected group; PAR: paranoid group; PSY: psychotic group; PAR-PSY: paranoid-psychotic group; Surface electr.: Surface electrode.

<sup>a</sup> Pairwise post-hoc comparisons (Bonferroni): PSY > CON and PSY > PAR-PSY ( $P < 0.05$ ); PSY > PAR ( $P < 0.1$ )

**Table 3**  
Results of multinomial logistic regression analysis.

	Source	PAR	PSY	PAR-PSY	GA versus CON
		Versus CON OR (95%CI) <sup>a</sup>	OR (95%CI) <sup>a</sup>	OR (95%CI) <sup>a</sup>	OR (95%CI) <sup>a</sup>
Model 1 <sup>b</sup> - Duration	Left temporal	.68 (.35–1.33)	<b>.49 (.27–.88)</b>	.52 (.25–1.08)	<b>.56 (.34–.95)</b>
	Right temporal	.90 (.50–1.61)	1.33 (.79–2.23)	1.05 (.56–1.95)	1.11 (.71–1.74)
	Frontal	1.35 (.71–2.57)	<b>2.76 (1.57–4.84)</b>	1.49 (.75–2.94)	<b>2.15 (1.28–3.59)</b>
Model 2 <sup>c</sup> - Frequency	Left temporal	.84 (.47–1.52)	.77 (.47–1.26)	1.04 (.58–1.84)	.82 (.53–1.28)
	Right temporal	.84 (.46–1.53)	1.02 (.62–1.66)	.77 (.42–1.41)	.95 (.60–1.48)
	Frontal	.81 (.44–1.49)	1.44 (.93–2.23)	1.71 (1.00–2.94)	1.35 (.90–2.03)
Model 3 <sup>d</sup> - Intensity	Left temporal	.90 (.48–1.70)	.84 (.49–1.47)	1.06 (.54–2.06)	.89 (.54–1.46)
	Right temporal	.91 (.49–1.68)	1.08 (.64–1.82)	.88 (.46–1.70)	1.00 (.62–1.61)
	Frontal	.92 (.55–1.56)	.99 (.64–1.54)	.69 (.39–1.21)	.93 (.62–1.41)

CON: control group; PAR: paranoid group; PSY: psychotic group; PAR-PSY: paranoid-psychotic group; GA: general-affected group; OR: odds ratio; 95%CI: 95% confidence interval; significant OR are printed in bold.

<sup>a</sup> Adjusted for sex, age, education, SCL-27 depression, SCL-27 dysthymia, SCL-27 agoraphobia, SCL-27 social phobia.

<sup>b</sup> Significant covariates in model 1 for: - PAR (vs. CON): education(-), SCL-27 depression(+), SCL-27 social phobia(+); - PSY (vs. CON): sex(-), SCL-27 social phobia(+); - PAR-PSY (vs. CON): sex(-), education(-), SCL-27 depression(+), SCL-27 social phobia(+).

<sup>c</sup> Significant covariates in model 2 for: - PAR (vs. CON): education(-), SCL-27 depression(+), SCL-27 social phobia(+); - PAR-PSY (vs. CON): sex(-), education(-), SCL-27 depression(+), SCL-27 agoraphobia(+), SCL-27 social phobia(+).

<sup>d</sup> Significant covariates in model 3 for: - PAR (vs. CON): education(-), SCL-27 depression(+), SCL-27 social phobia(+); - PAR-PSY (vs. CON): sex(-), education(-), SCL-27 depression(+), SCL-27 agoraphobia(+), SCL-27 social phobia(+).

### 3.2. MMN mean amplitude values

Mean peak amplitudes and standard deviations (SD) of MMN at Fz and Cz are presented in Table 2 (values of the other frontocentral electrodes are presented in the supplement Table S1), and grand averages of the surface electrodes F3, Fz and F4 are displayed in Fig. 1. No significant group differences in MMN amplitudes for any deviant condition were found at the six frontocentral electrodes. We also found no significant correlation between symptom measures and MMN amplitudes.

### 3.3. MMN source activity

The three regional sources were located as follows: RS1, left superior temporal lobe; RS2, right superior temporal lobe; and RS3, anterior cingulate gyrus (Fig. 2). As entered into the Talairach space, these three sources were based on the left and right transverse temporal gyri (primary auditory cortices, Brodmann 41) and the anterior cingulate area (Brodmann 24). Table 2 presents the mean peak amplitudes and SD of MMN waveforms for deviant conditions at the three sources. The ANOVAs revealed a significant group difference at the frontal source for the duration-deviant stimuli

( $P = 0.01$ ) and a trend-level difference for the frequency-deviant MMN ( $P = 0.05$ ). Intensity-deviant MMN activities at the three sources indicated no significant group differences.

Table 3 shows the results from multinomial regression models for estimating group membership probability (GA and SPS subsamples versus CON) according to source (left temporal, right temporal, or frontal) and condition (duration, frequency, or intensity). All models were adjusted for sex, age, education level, and psychopathology. These data demonstrated that GA and PSY, in particular, were more likely than CON to have higher dMMN (Table 3: model 1) as measured at the frontal source. Higher dMMN at the left temporal source was independently and negatively associated with PAR or PSY. Higher frontal-measured fMMN (Table 3: model 2) more likely occurred in PAR-PSY while iMMN (Table 3: Model 3) was not specifically linked to group membership. Based on these findings, we selected dMMN for additional post-hoc analysis according to source (Table 4: CON, PAR, PAR-PSY vs. PSY). In this analysis CON was more likely than PSY to have higher dMMN measured at the left temporal source. The higher dMMN at the frontal source was negatively associated with CON, PAR, and PAR-PSY.

## 4. Discussion

Our primary study objective was to examine whether nonclinical individuals who report SPS present any variance in their generation of MMN which in turn is associated with scales of mental health and psychosis symptoms used in daily clinical routine. Overall, our study groups differed significantly on all reviewed psychopathological measures. Whereas MMN surface amplitudes did not reach statistical significance across groups, the source analysis revealed findings of particular interest. Thus, we concluded that significant group differences in MMN generation exist at the frontal source for duration-deviant stimuli ( $P = 0.01$ ) and also uncovered a trend ( $P = 0.05$ ) for frequency-deviant sounds.

Some researchers have suggested that dMMN is a sensitive marker in the prediction and early course of psychosis [22], whereas impairments of frequency deviants apparently happen

**Table 4**  
Results of supplemental analysis.

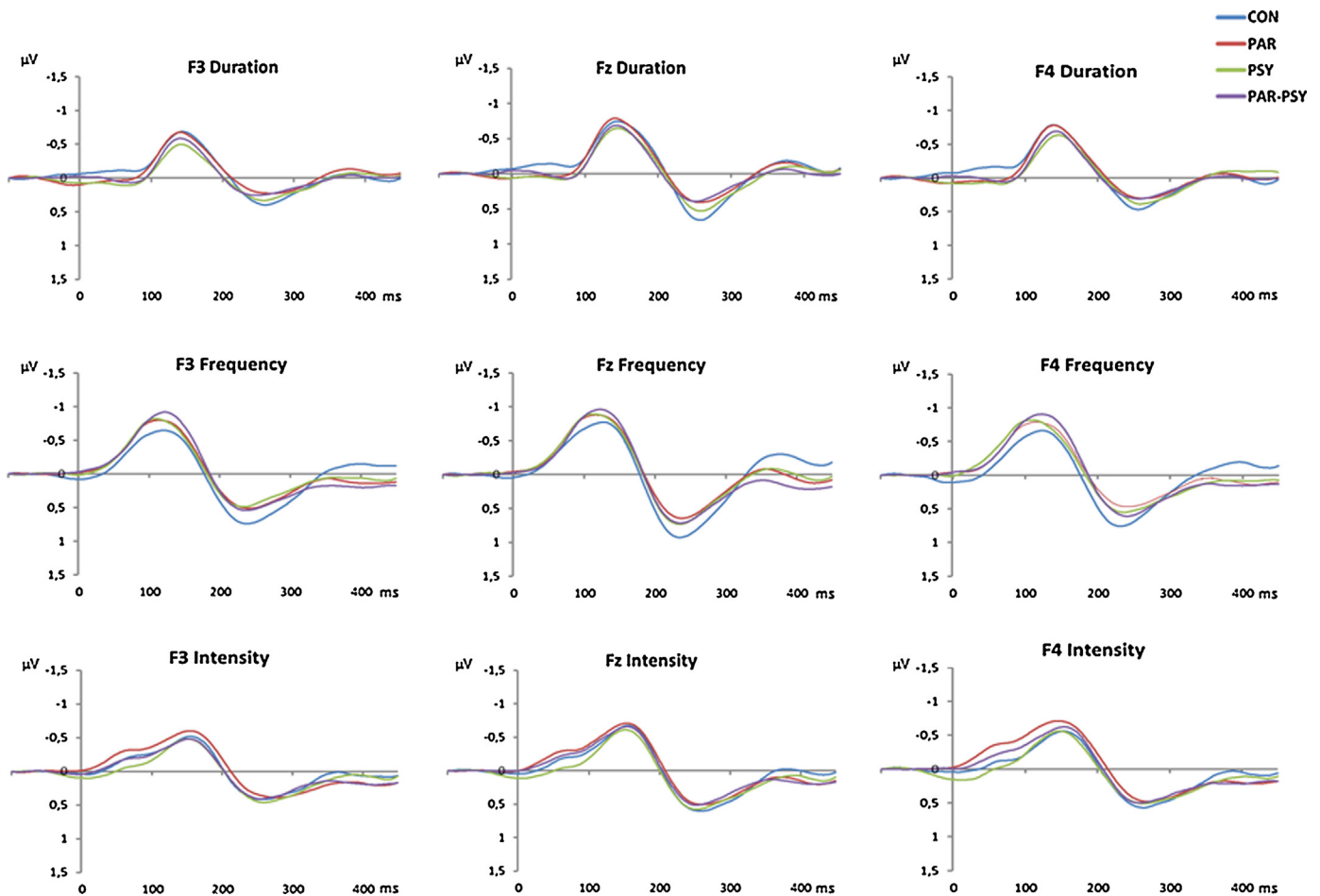
	CON	PAR	PAR-PSY
	Versus PSY OR (95%CI)	OR (95%CI)	OR (95%CI)
Duration			
Left temporal source	<b>2.05 (1.13–3.71)</b>	1.39 (.71–2.71)	1.07 (.53–2.17)
Right temporal source	.75 (.45–1.27)	.68 (.38–1.21)	.79 (.43–1.45)
Frontal source	<b>.36 (.21 – .64)</b>	<b>.49 (.28–.87)</b>	<b>.54 (.30–.98)</b>

CON: control group; PAR: paranoid group; PSY: psychotic group; PAR-PSY: paranoid-psychotic group; OR: odds ratio; 95%CI: 95% confidence interval; significant OR are printed in bold. All model were adjusted for sex, age, education, SCL-27 depression, SCL-27 dysthymia, SCL-27 agoraphobia and SCL-27 social phobia. Significant covariates for:

CON (vs. PSY): sex(+).

PAR (vs. PSY): education(-), SCL-27 dysthymia(-), SCL-27 social phobia(+).

PAR-PSY (vs. PSY): education(-), SCL-27 social phobia(+).



**Fig. 1.** Grand average MMN surface waveforms for duration deviants in microvolts at F3, Fz and F4. CON = control group; PAR = paranoid group; PSY = psychotic group; PAR-PSY = paranoid-psychotic group.

later in illness progression. Similarly, Todd et al. [25] have reported that dMMN and iMMN deficits occur predominantly in the early stages of schizophrenia, based on observations that fMMN impairment becomes more significant as the course of illness unfolds. The early disturbance of dMMN may be due to the complex processing of time dependent discriminations. This processing requires many brain areas (e.g., prefrontal cortex and inferior parietal lobe) which have been previously implicated in the pathogenesis of schizophrenia [58].

In contrast, Hay et al. [27] have reported no difference between types of deviants. Nevertheless, current evidence is more consistent for impaired MMN in duration deviants for both individuals at-risk for psychosis and those who manifest schizophrenia [15].

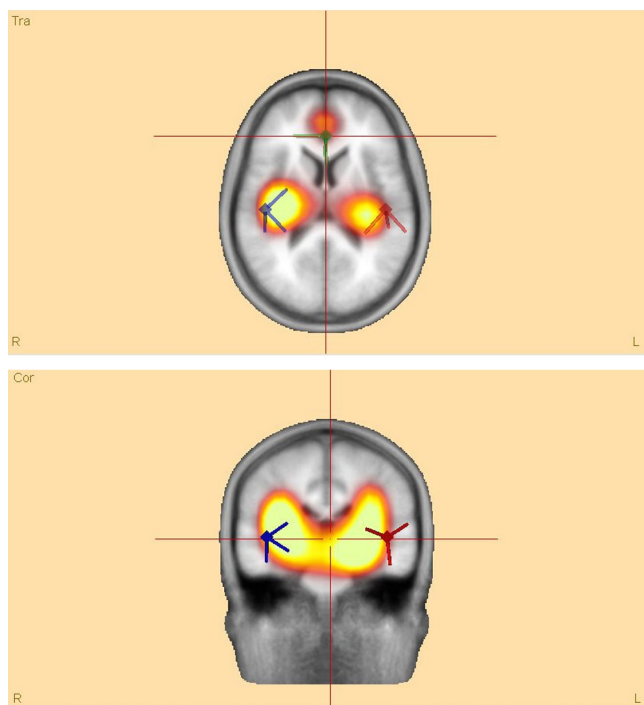
Our findings demonstrate that a high symptom load of SPS in healthy persons is linked to alterations in the development of MMN. These data reveal a clear difference in MMN generation at the frontal source between CON and PSY for duration deviants as well as a trend-level difference between CON and PAR-PSY for the frequency-deviant stimuli. In summary, PSY shows increased dMMN at the frontal source when compared with our other study groups.

Some researchers have reported impaired MMN amplitudes selectively at frontocentral electrodes in schizophrenic patients. They suggested that even if the temporal MMN component is relatively intact, the frontal contribution to MMN is selectively impaired in schizophrenia [59,60]. Only a few studies found larger MMN amplitudes in schizophrenic patients compared to healthy controls [61,62]. Kirino and Inoue divided their sample of unmedicated schizophrenic patients in subjects with greater

and subjects with smaller MMN amplitudes. In comparison, the subjects with larger MMN amplitudes had a shorter duration of illness and an earlier age of onset [63]. However, the majority of studies found diminished MMN amplitudes in both manifest schizophrenic patients and subjects at risk for developing a psychotic disorder [7,16,64]. Thus, our finding of a greater frontal MMN source activity in subjects reporting SPS is contrary to previous findings in schizophrenia and subjects at risk. However, the results are only partially comparable, since most published studies are based on the results of surface electrodes. In our study, we found only changes at frontal source and not at surface electrodes.

Activity at the frontal source is assumed to reflect the involuntary switching of attention to the detected mismatch in the auditory environment [65,66]. The occurrence of increased MMN activity at frontal brain areas in persons reporting SPS might be an indicator of a more sensitive perception regarding changes in the environment. In contrast to manifest schizophrenia, those individuals do utilize an intact, powerful auditory cortex change-detection mechanism, as reflected by the lack of alterations in both temporal MMN sources. The increased activity in the frontal source could mean that subliminal changes in the environment are given special significance. But it is also possible that this increased activity reflects a protective or compensatory mechanism that prevents the presentation of overt psychosis despite the presence of SPS.

The failure to identify any statistically significant difference in MMN surface amplitudes across our study groups might have occurred because the duration-deviant stimuli applied in our study



**Fig. 2.** The three regional source model of MMN and distributed source analysis CLARA (screenshot from BESA software). Talairach coordinates: left temporal source ( $-52.3, -15, 10.1$ ), right temporal source ( $53, -19, 10.2$ ) and frontal source ( $2.3, 14, 31.4$ ).

were shorter (50 ms) than the standard tone (100 ms). We followed the guidelines stipulated by Duncan et al. [26], who recommended that MMN duration deviants should usually be shorter than standard tones. However, recent investigations have shown that duration-increment MMN is significantly diminished for persons in an at-risk mental state for psychosis [67–69]. Atkinson et al. [67] have found that duration-decrement deviants had less effect in subjects at-risk mental state for psychosis while other studies have shown no significance effect on MMN for duration-decrement deviants in such study groups [24,70]. Todd et al. [34] have reported that evidence is accumulating for duration-increment deviants that are more sensitive to the at-risk mental state when compared with other deviant models.

The investigation presented here had several methodological limitations. First, educational levels varied widely for our four subsamples, although that was still accounted for in multivariate analyses. Second, unlike in many neurophysiological evaluations, not all participating individuals were right-handed. To our knowledge, however, an influence of handedness on MMN amplitudes has not yet been reviewed. Unlike most MMN studies no nose reference was used which may limit the comparability to other findings.

This study was designed to investigate adult individuals within the general population. Therefore, the probability of discovering evident and relevant impairments of MMN amplitudes and potential associations with clinical scales was obviously lower than what we might have expected if we had focused entirely on manifest schizophrenic patients with full-blown psychotic symptoms.

## 5. Conclusion

Our results contribute new aspects to improve the current understanding as our data are not confounded by other potential

components, e.g., medication or other treatments. In summary, we were able to demonstrate that alterations of MMN exist within members of the general population who report SPS. Individuals with overall SPS (GA) and, especially, persons with elevated schizophrenia nuclear symptoms (PSY) are more likely to have greater frontal source activity elicited by dMMN. Follow-up studies would be desirable to determine whether alterations in dMMN are state or trait markers of SPS.

## Disclosure of interest

The authors declare that they have no competing interest.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eurpsy.2016.01.001>.

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