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Reduced magnetic mismatch negativity: a shared deficit in psychosis and related risk

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Abstract

Background. Abnormal auditory processing of deviant stimuli, as reflected by mismatch negativity (MMN), is often reported in schizophrenia (SCZ). At present, it is still under debate whether this dysfunctional response is specific to the full-blown SCZ diagnosis or rather a marker of psychosis in general. The present study tested MMN in patients with SCZ, bipolar disorder (BD), first episode of psychosis (FEP), and in people at clinical high risk for psychosis (CHR).

Methods. Source-based MEG activity evoked during a passive auditory oddball task was recorded from 135 patients grouped according to diagnosis (SCZ, BD, FEP, and CHR) and 135 healthy controls also divided into four subgroups, age- and gender-matched with diagnostic subgroups. The magnetic MMN (mMMN) was analyzed as event-related field (ERF), Theta power, and Theta inter-trial phase coherence (ITPC).

Results. The clinical group as a whole showed reduced mMMN ERF amplitude, Theta power, and Theta ITPC, without any statistically significant interaction between diagnosis and mMMN reductions. The mMMN subgroup contrasts showed lower ERF amplitude in all the diagnostic subgroups. In the analysis of Theta frequency, SCZ showed significant power and ITPC reductions, while only indications of diminished ITPC were observed in CHR, but no significant decreases characterized BD and FEP.

Conclusions. Significant mMMN alterations in people experiencing psychosis, also for diagnoses other than SCZ, suggest that this neurophysiological response may be a feature shared across psychotic disorders. Additionally, reduced Theta ITPC may be associated with risk for psychosis.

Introduction

Mismatch negativity (MMN) is a pre-attentive event-related potential (ERP) that measures the brain cortical response to occasional deviant stimuli in an otherwise repetitive series of standard stimuli (Näätänen, Paavilainen, Rinne, & Alho, 2007). Specifically, it refers to an early negative deflection in the waveform obtained by subtracting activity evoked by deviant stimuli from activity elicited by standard stimuli. The most accredited MMN hypothesis interprets this brain potential as a prediction error signal: a brain response to sensory information that deviates from prior beliefs (Friston, 2005; Garrido, Kilner, Stephan, & Friston, 2009). Accordingly, there is consensus on defining MMN as an index of brain adaptability to environmental changes (Fitzgerald & Todd, 2020).

Functional imaging studies have shown that the auditory MMN originates in the bilateral auditory cortices with later involvement of frontal regions (Garrido et al., 2009). MMN reflects amplitude enhancement and increased phase synchronization of Theta (4–8 Hz) oscillations associated with processing deviant stimuli (Fuentemilla, Marco-Pallares, Munte, & Grau, 2008). Theta oscillations originate from the interplay between pyramidal neurons and GABAergic interneurons (Javitt, Lee, Kantrowitz, & Martinez, 2018).

MMN, particularly when elicited by tone-duration increment, is attenuated in schizophrenia (SCZ), as first shown by Shelley and collaborators (Shelley et al., 1991). Many studies have

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reported blunted MMN amplitude in SCZ, making it one of the most robust and replicable findings in this disorder (Javitt et al., 2018; Kim, Blumberger, & Daskalakis, 2020; Light et al., 2020). Abnormal MMN amplitude in SCZ has been proposed to reflect a deficit in short- and long-range connectivity across auditory regions in detecting deviant stimuli (Koshiyama et al., 2020). Sparser findings show that MMN alterations are also present in other populations of patients with psychotic symptoms (Erickson, Ruffle, & Gold, 2016), like in bipolar disorder (BD) (Raggi, Lanza, & Ferri, 2021) and in first-episode psychosis (FEP) (Haigh, Coffman, & Salisbury, 2017), and in subjects at clinical high risk for psychosis (CHR) (Bodatsch, Brockhaus-Dumke, Klosterkotter, & Ruhrmann, 2015; Tada et al., 2019). A recent study with more than 500 CHR participants reported only limited evidence of significant MMN reduction in this population, whereas the MMN deficit was associated with future conversion and earlier onset of full-blown psychosis (Hamilton et al., 2022). Hence, the debate is still open about whether MMN alterations are peculiar to SCZ (Baldeweg & Hirsch, 2015; Erickson et al., 2016; Umbricht et al., 2003) or are instead shared by patients with a history of psychosis. In such a scenario, MMN might be informative on disease onset (Hamilton et al., 2022; Naatanen, Shiga, Asano, & Yabe, 2015; Nagai et al., 2013), progress (Fujioka et al., 2020; Perez et al., 2014; Shaikh et al., 2012), or resilience (Hamilton, Roach, & Mathalon, 2021) in people at clinical risk of psychosis.

Current knowledge of MMN activity derives primarily from electroencephalography (EEG) studies focused on ERPs. An ERP results from increased amplitude and/or enhanced synchronization of specific frequencies (Makeig, Debener, Onton, & Delorme, 2004). Hence, ERP amplitude analyses might miss subtle abnormalities in brain dynamics at the spectral frequency level. For instance, Grent-'t-Jong and collaborators (Grent-'t-Jong et al., 2020) showed that FEP and CHR differ in Gamma frequency evoked by dynamic visual stimuli, with both showing reduced phase synchronization, but only the first having also lower amplitude than controls. These results show that, compared to ERP amplitude analyses, the spectral frequency level might offer a more accurate characterization of the functional deficit affecting different clinical populations.

Low-density EEG experiments suffer from limited spatial resolution. Magnetoencephalography (MEG) offers a superior spatial resolution due to the robustness of magnetic activity to tissue-boundary field distortions. However, EEG can register the activity of brain regions independently of their orientation (Hunold, Funke, Eichardt, Stenroos, & Haueisen, 2016) while MEG might miss some deep and radial brain areas (Baillet, 2017; Hillebrand & Barnes, 2002). Nevertheless, MEG preferential sensitivity to signals in the brain sulci walls makes this method suitable for accurate source localization of the auditory MMN activity at both the sensor and the source levels. Evidence of this is that, in EEG recording, MMN for auditory stimuli is generally registered over medial frontocentral electrodes, whereas bilateral temporal sensors are the primary recording locations of the magnetic MMN (mMMN) in MEG signal. Hence, compared to previous EEG studies, source-based time-frequency analysis of MEG activity associated with deviant tone exposure in people who have psychosis or are at risk for psychosis might provide insight into the activity of the auditory cortex to characterize the relationship between MMN anomalies and psychosis.

MEG has been already employed to study various psychiatric disorders, moving neurophysiological research closer to brain generators (Uhlhaas et al., 2017). The majority of MEG studies tested abnormal mMMN amplitudes in SCZ (for a review, see Rojas, 2019), but few experiments investigated reduced mMMN in BD (Shimano et al., 2014; Takei et al., 2010) and CHR (Shin et al., 2009), reporting results that were consistent with those in the EEG literature. Only one study investigated both SCZ and BD, finding that BD patients had an mMMN amplitude intermediate between SCZ and controls (Braeutigam, Dima, Frangou, & James, 2018). However, to date, no MEG study has considered mMMN as a neurophysiological deficit of psychosis, considering different diagnostic profiles within the same experimental protocol.

The present experiment studied together four different clinical subgroups: patients with schizophrenia (P-SCZ), bipolar disorder with psychotic features (P-BD), first episode of psychosis (P-FEP), and people at clinical high risk for psychosis (P-CHR). Subthreshold psychosis symptoms characterize this latter condition (e.g. cognitive disturbances, attenuated psychotic symptoms, or brief and limited intermitted psychosis syndrome). CHR individuals have greater risk of developing psychosis than the general population (Millan et al., 2016). We aimed to test whether reduced mMMN is an attribute of psychosis or risk beyond categorical diagnosis. Similar mMMN reductions across these diagnoses would suggest that psychosis is linked to the abnormal adaptation of the sensory system to external changes. Moreover, identifying mMMN deficits in CHR would inform whether this neurophysiological response might be a risk index.

To this end, we employed source-based mMMN analyses of event-related fields (ERF), including Theta power activity and Theta inter-trial phase coherence (ITPC), in the four subgroups of patients and in four subgroups of neurotypical control participants matched for age and gender with patients (NC-SCZ, NC-BD, NC-FEP, and NC-CHR). CHR and FEP are generally younger than SCZ and BD. Therefore, this design accounts for potential demographic differences between the subgroups and offers an extended perspective that clarifies the potential inferences – for instance, a significant result for different patients *v.* controls contrasts cannot arise because of biased sampling of healthy controls in a single group. If reduced mMMN is an unspecific factor of psychosis, we expect a significant effect of Group, with patients showing smaller mMMN than controls, without a significant interaction between Group (P and NC) and Diagnostic Subgroup (SCZ, BD, FEP, and CHR) – which, instead, would point to a deviation of groups with respect to this index. Additionally, we assessed whether, in line with the observation of reduced phase synchrony but preserved power in CHR during a visual change detection task (Grent-'t-Jong et al., 2020), Theta ITPC is a more reliable index of psychosis, particularly in CHR, than Theta power. Finally, we tested the effect of psychopharmacological treatment on the mMMN outcomes.

Material and methods

Participants

We recruited 328 people, but the data of 15 participants were not analyzed because of excessive movement or strong external noise during the recording. The remaining 313 participants included 177 healthy people without any history of psychological or neurological disorders and 136 patients: 48 SCZ, 28 BD, 20 FEP, and 40 CHR. One patient with BD was not included in the study because she did not present psychotic symptoms. Hence, the final sample of the four patient subgroups was 48 P-SCZ, 27 P-BD, 20 P-FEP, and 40 P-CHR, for a total of 135 cases. The four independent

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Table 1. Demographic and clinical characteristics of participants in the eight groups

	P-SCZ ($N = 48$)	NC-SCZ ($N = 48$)		P-BD ($N = 27$)	NC-BD ($N = 27$)	
Sex (m/f)	31/17	21/27	N.S.	17/10	15/12	N.S.
Age, years	33 ± 1.6	31 ± 0.9	N.S.	31 ± 1.6	28 ± 1.5	N.S.
Socioeconomic status[a]	37.0 ± 3.0	40.5 ± 2.4	N.S.	31.9 ± 3.1	42.4 ± 3.9	*
IQ[b]	108.1 ± 1.4	115.8 ± 0.7	***	111.2 ± 1.3	115.6 ± 0.7	***
PANSS[c]						
Positive	17.9 ± 1.3			12.8 ± 1.7		
Negative	21.0 ± 1.1			15.2 ± 1.5		
General	39.5 ± 1.8			31.3 ± 2.5		
Total	77.8 ± 3.5			59.2 ± 5.0		
	P-FEP ($N = 20$)	NC-FEP ($N = 20$)		P-CHR ($N = 40$)	NC-CHR ($N = 40$)	
Sex (m/f)	10/10	11/9	N.S.	21/19	17/21	N.S.
Age, years	22 ± 0.5	23 ± 0.5	N.S.	20 ± 0.8	22 ± 0.4	N.S.
Socioeconomic status	36.1 ± 3.2	44.4 ± 4.0	N.S.	33.1 ± 2.6	35.8 ± 2.4	N.S.
IQ	107.4 ± 1.9	117.1 ± 0.5	***	110.5 ± 1.2	114.5 ± 0.5	**
PANSS						
Positive	11.7 ± 1.7			11.6 ± 0.7		
Negative	16.9 ± 2.1			15.9 ± 1.4		
General	29.0 ± 3.0			30.7 ± 1.5		
Total	57.6 ± 6.3			58.2 ± 2.9		

N.S., not significant; $p > 0.5$; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
[a]Hollingshead index (N): P-SCZ = 42, NC-SCZ = 43, P-BD = 27, NC-BD = 24. P-FEP = 14, NC-FEP = 19, P-CHR = 34, NC-CHR = 37.
[b]Test di Intelligenza Breve [Brief Intelligence Test] (N): P-SCZ = 41, NC-SCZ = 43, P-BD = 26, NC-BD = 25, P-FEP = 15; NC-FEP = 19, P-CHR = 36, NC-CHR = 38.
[c]PANSS (N): P-SCZ = 44, P-BD = 20, P-FEP = 8, P-CHR = 31.

neurotypical control subgroups were defined by selecting controls that best matched age and gender for each patient (48 NC-SCZ, 27 NC-BD, 20 NC-FEP, and 40 NC-CHR).

Based on Structured Clinical Interview for DSM-IV assessment (First, Spitzer, Gibbon, & Williams, 1996), participants in P-SCZ had a diagnosis of schizophrenia or schizoaffective disorder, while participants in P-BD had a diagnosis of Type I bipolar disorder with psychotic symptoms. Participants in P-FEP were people who had experienced a first psychotic episode within the last 12 months. The risk for psychosis in P-CHR was assessed with the Italian version of the Comprehensive Assessment of At Risk Mental States (CAARMS; Yung et al., 2005). The severity of symptoms related to psychosis was valuated with the Italian version of the Positive And Negative Symptoms Scale (PANSS; Kay, Fiszbein, & Opler, 1987). Table 1 reports demographic data of participants in the different groups, along with PANSS scores for the four diagnostic subgroups.

Forty-seven out of 48 P-SCZ, 20 out of 27 P-BD, 15 out of 20 P-FEP, and 8 out of 40 P-CHR had been receiving psychopharmacological treatment to mitigate psychiatric symptoms (see Table 2) and were studied after one month of stable treatment.

The ethics committee of the University Hospital of Bari approved the MEG protocol of the present study, and all the participants gave their informed consent for the recording of both clinical and MEG data.

Procedure

The auditory task employed to elicit mMMN was a passive oddball task with duration deviant stimuli (Michie et al., 2000). A sequence of 667 pure tones (1000 Hz, 80 dB) was presented to both ears through ear tubes while participants watched a silent Tom & Jerry video. Stimuli were either 50 ms long (standard) or 100 ms long (deviant). The standard:deviant ratio was 11:1. Deviant and standard stimuli were pseudo-randomly intermixed, with the constraint that the first deviant stimulus appeared after fifteen standard stimuli, and at least one standard stimulus was interposed between two deviant stimuli. The inter-stimulus interval was 500 ms. Participants were instructed to ignore the auditory signals and focus on the cartoon instead, so they could accurately answer questions about the movie after the experiment. Indeed, after the MEG session, each participant had to answer one question regarding a scene in the cartoon. All participants included in the study answered correctly to the question.

MEG data recording and processing

The MEG signal was recorded with Elekta Neuromag® TRIUX (Elekta Neuromag Oy, Helsinki, Finland). The recording sample rate was 1000 Hz. Offline, the MEG signal was first processed with Elekta MaxFilter™ software (Elekta Neuromag Oy, Helsinki, Finland) to remove external noise with temporal Signal-Space Separation (Taulu & Simola, 2006) and correct for head-movements according to five Head-Position Identifiers. Afterwards, the signal was processed with the MATLAB-based toolbox Brainstorm (Tadel, Baillet, Mosher, Pantazis, & Leahy, 2011), following the standard group analysis processing pipeline (Tadel et al., 2019). Signal was first filtered from the standard Europe's electricity grid frequency and high frequencies (notch

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Table 2. Types of pharmacological treatment received by patients in the four groups

	P-SCZ[a] ($N = 48$)	P-BD[a] ($N = 27$)	P-FEP ($N = 20$)	P-CHR ($N = 40$)	
Antipsychotics (oral and/or long-acting injections)	44 (92%)	15 (56%)	14 (70%)	5 (13%)	***
Mood stabilizers (Valproate, Lithium, Lamotrigine)	21 (44%)	15 (56%)	3 (15%)	2 (5%)	***
Antidepressants	7 (15%)	6 (22%)	2 (10%)	5 (13%)	N.S.
Benzodiazepines	22 (46%)	3 (11%)	2 (10%)	1 (3%)	***

N.S., not significant; $p > 0.5$; * = $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
[a]Medications not recorded for 1 P-SCZ and 1 P-BD.

filter: 50 Hz; low-pass filter: 60 Hz). Artifacts associated with eye movements and heartbeat were identified and corrected by using ICA trained on all the sensors (number of independent components: 20), whereas residual artifacts were afterwards detected and rejected automatically (reference activity 0–60 s, 1 s time-windows; conservative detection with a sensitivity parameter of 5). The signal was then segmented into epochs that started 500 ms before stimulus onset and lasted for 1100 ms to account for edge artifacts in time-frequency analysis.

For the computation of the inverse source model, when necessary, the head position was manually adjusted to fit in the MEG helmet, and the individual head model was constructed as overlapping spheres with 15 002 vertices. A noise covariance matrix of empty room recording was used. After linear scaling, the sensor-based signal was converted into source-based signal with standard Low Resolution Brain Electromagnetic Tomography (sLORETA, Pascual-Marqui, 2002) of constrained vertices reconstructing a template MRI brain model (ICBM152). All the analyses focused on vertices corresponding to the right (29 vertices) and left (40 vertices) parcellations of the Destriuex atlas (Destrieux, Fischl, Dale, & Halgren, 2010), mapping the transverse temporal sulcus, the superior temporal gyrus, and the transverse temporal gyrus. These areas cover the locations of the primary and secondary auditory cortex (Shapleske, Rossell, Woodruff, & David, 1999), the regions where the auditory MMN originates (Garrido et al., 2009).

The analysis considered only the standard stimulus that preceded each deviant stimulus to obtain an equal number of standard and deviant stimuli. Segments with artifacts were not included in any analysis. In ERF analysis, source-based signal was normalized to z-scores according to the 200 ms pre-stimulus interval, converted to absolute values, and spatially smoothed before averaging. In time-frequency analyses, the signal was down-sampled to 200 Hz and processed with a set of complex Morlet wavelets (Cohen, 2014). The complex sine waves ranged from 4 Hz to 60 Hz, logarithmically spaced in twenty steps, whereas the Gaussian taper increased from 4 to 10 cycles as a function of frequency. Time-frequency power was computed as the mean power of the absolute value of the complex-value functions, converted to decibel (dB) to obtain signal changes relative to baseline (from −200 to −40 ms). ITPC was the mean angle of the complex-value functions. All the time-frequency analyses were performed vertex-wise before averaging the results across vertices to account for the effect of the sign in the MEG signal.

Each analysis focused on the mMMN, obtained by subtracting deviant from standard stimuli across the two bilateral regions of interest. The mMMN values were computed as the maximum peak amplitude (Luck & Gaspelin, 2017) in time windows selected according to the points when the grand-average mMMN-wave reached half of its maximum amplitude. The time window used for mMMN ERF amplitude analyses was 150–225 ms, while 100–300 ms was the time window in time-frequency analyses. Different time windows had to be selected because of the decrement in temporal precision resulting from time-frequency decomposition. Power and ITPC analyses considered only Theta-band activity between 4 and 9 Hz.

The distributions of ERF mMMN peak amplitude values of P and NC were analyzed to detect outliers. Four control participants (2 NC-CHR, 1 NC-BD, and 1 NC-FEP) and three patients (1 P-BD, 1 P-FEP, and 1 P-CHR) had mMMN peak ERF amplitudes larger than 1.5 inter-quartile difference, so their data were excluded from all the analyses (see additional online Supplemental Material).

To test the hypothesis that mMMN alterations are found in the continuum of the psychosis spectrum across different diagnoses, we computed omnibus ANCOVAs that considered Group (P *v.* NC) and Diagnostic Subgroup (SCZ, BD, FEP, *v.* CHR) as between-participants factors, and participants' age as a covariate. Power analysis performed with G*Power (Faul, Erdfelder, Lang, & Buchner, 2007) indicated that, with 263 participants divided into 8 groups, the two-factors ANCOVA had a power of 0.80 to detect a medium effect ($f = 0.25$), like the MMN difference between patients and controls (Erickson et al., 2016), with an α level of 0.05. See additional online Supplemental Material for analyses of Laterality (right *v.* left) and Condition (standard *v.* deviant).

To discount the possibility that a single subgroup drove main effects of the ANCOVAs and because testing subgroup differences was part of our hypothesis, we additionally performed pre-planned two-tailed two-sample t tests. This procedure tested the hypothesis of lower mMMN for each contrast of patients against the respective controls. Results from patients with SCZ served to replicate prior evidence, whereas results from the other groups tested subgroup-specific hypotheses to establish a statistical benchmark for future mMMN studies. Here, α levels were corrected for multiple comparisons with the Holm-Bonferroni method.

To assess whether significant group differences were not driven by medications intake in patients, we investigated the effect of antipsychotics (treated patients, $N = 77$, and not-treated patients, $N = 55$), benzodiazepines ($N = 28$ and $N = 104$), and mood stabilizers ($N = 40$ and $N = 92$). The three mMMN parameters were the dependent factors of ANCOVAs that had medications as three independent factors and age as a covariate, in models that considered only the main effects of the three types of psychopharmacological treatment on the mMMN but no interactions.

Results

Event-related field (ERF)

Analysis of mMMN ERF peak amplitudes across the four subgroups (see Fig. 1) revealed that the main effect of Group was

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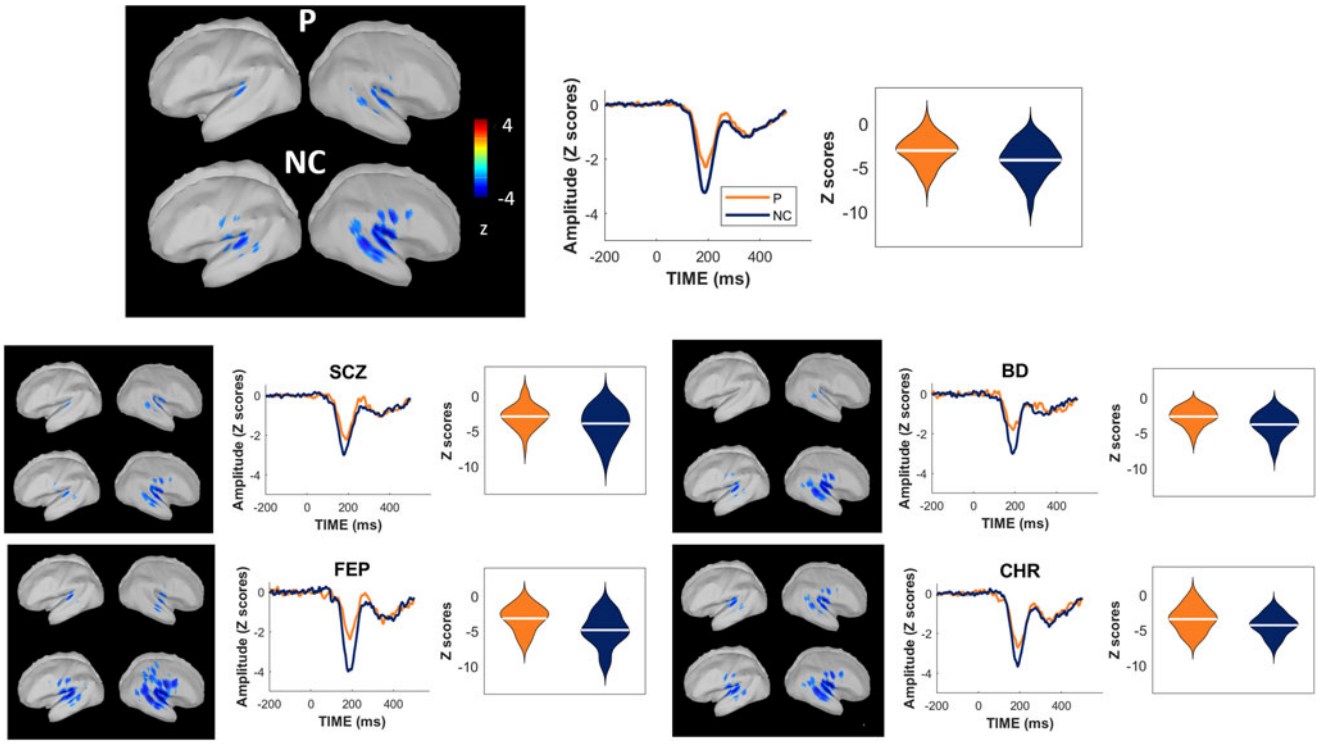

Fig. 1. Brain figures: depiction of brain activity (standard minus deviant) evoked over the left and the right hemisphere at 190 ms. Line-plots: grand-average mMMN ERF activity over time. Violin-plots: distributions of individual mMMN ERF peak amplitude values extracted from the selected time-window, with mean mMMN ERF peak amplitude depicted as a white line. The upper panel reports data of the transdiagnostic analysis, while the lower panel shows data for the four diagnostic subgroups.

significant, $F(1,254) = 25.06$, $p < 0.001$, $\eta^2_p = 0.090$, but the main effect of Diagnostic Subgroup and the interaction between Group and Diagnostic Subgroup were not significant, $Fs < 1$. The covariate factor Age was also significant, $F(1,254) = 8.80$, $p = 0.003$, $\eta^2_p = 0.033$. This significant effect of Age indicated that as age increases the mMMN ERF peak amplitude is significantly less negative, $r = 0.22$, $p < 0.001$. Along with the reliable evidence of smaller mMMN in patients with psychosis (P) than controls (NC), the non-significant interaction between Group and Diagnostic Subgroup reflects that mMMN ERF peak amplitude reductions are not strongly associated with the diagnostic subgroup.

We conducted pre-planned *t* tests to establish the significance of the mMMN ERF amplitude reduction for each diagnosis (see Fig. 1). The reduction was significant, with medium to large effect sizes, for all the diagnostic subgroups: SCZ (P-SCZ *v.* NC-SCZ), $t(94) = 2.48$, $p = 0.015$, $d = 0.51$, BD (P-BD *v.* NC-BD), $t(50) = 2.76$, $p = 0.008$, $d = 0.77$, FEP (P-FEP *v.* NC-FEP), $t(36) = 2.50$, $p = 0.017$, $d = 0.81$, and CHR (P-CHR *v.* NC-CHR), $t(75) = 2.36$, $p = 0.021$, $d = 0.54$.

The analysis of Medications on mMMN ERF peak amplitude did not show any significant effect, $ps > 0.359$.

Theta power

The analysis of Theta power (see Fig. 2) showed that the main effect of Group was significant, $F(1,254) = 13.91$, $p < 0.001$, $\eta^2_p = 0.051$, but the main effect of Diagnostic Subgroup and the interaction between Group and Diagnostic Subgroup were both not significant, $Fs < 1.16$, $ps > 0.321$. The effect of Age was not significant, $F(1,254) < 1$. These results indicated that patients had lower mMMN-related Theta power than controls.

The following tests performed to assess the statistical significance of Theta power effects in each diagnostic subgroup (see Fig. 2) revealed that the power reduction was significant only for SCZ, $t(94) = 3.35$, $p = 0.001$, $d = 0.68$, but not significant for BD, $t(50) = 1.87$, $p = 0.068$, $d = 0.52$, FEP, $t(36) = 1.55$, $p = 0.131$, $d = 0.50$, and CHR, $t(75) = 0.83$, $p = 0.408$, $d = 0.19$.

The analysis of Medications on Theta power did not show any significant effect, $ps > 0.146$.

Theta inter-trial phase coherence (ITPC)

The analysis of Theta ITPC (see Fig. 3) showed that the main effect of Group was significant, $F(1,254) = 18.80$, $p < 0.001$, $\eta^2_p = 0.069$, but the main effect of Diagnostic Subgroup and the interaction between Group and Diagnostic Subgroup were both non-significant $Fs < 1$. The effect of Age was short of significance, $F(1,252) = 3.36$, $p = 0.068$, $\eta^2_p = 0.013$. These results indicated that patients had lower mMMN-related Theta synchronization across diagnoses.

Diagnosis-based ITPC analyses showed that Theta ITPC (see Fig. 3) was significantly reduced in SCZ, $t(94) = 3.20$, $p = 0.002$, $d = 0.65$. The concurrent indication of a significant effect for CHR, $t(75) = 2.32$, $p = 0.023$, $d = 0.53$, did not survive correction for multiple comparisons. The reduction was not significant in the other two contrasts: BD, $t(50) = 1.72$, $p = 0.093$, $d = 0.48$, and FEP, $t(36) = 1.95$, $p = 0.060$, $d = 0.63$.

The analysis of Medications on Theta ITPC did not show any significant effect, $ps > 0.261$.

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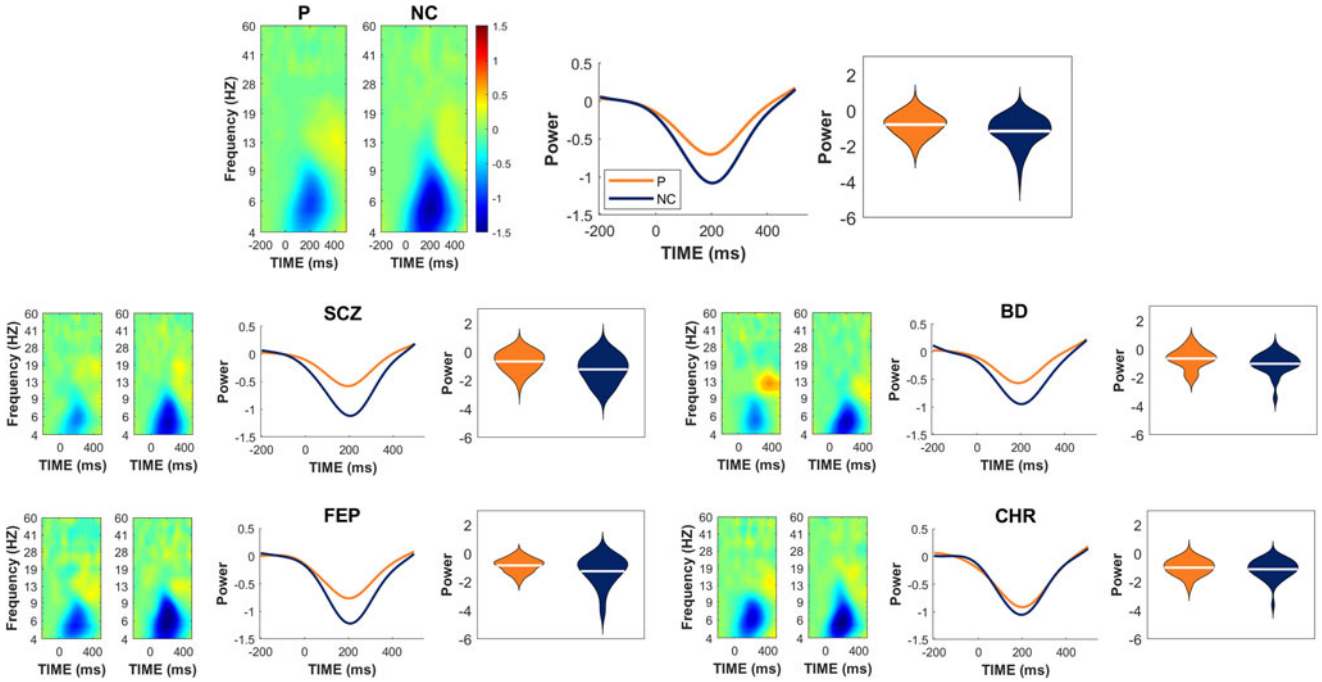

Fig. 2. Filled contour plots: depiction of mMMN (standard minus deviant) time-frequency power for frequencies between 4 and 60 Hz over time. Line-plots: grand-average mMMN Theta power over time. Violin-plots: distributions of individual mMMN Theta power values extracted from the selected time-window, with mean mMMN Theta power depicted as a white line. The upper panel reports data of the transdiagnostic analysis, while the lower panel shows data for the four diagnostic subgroups.

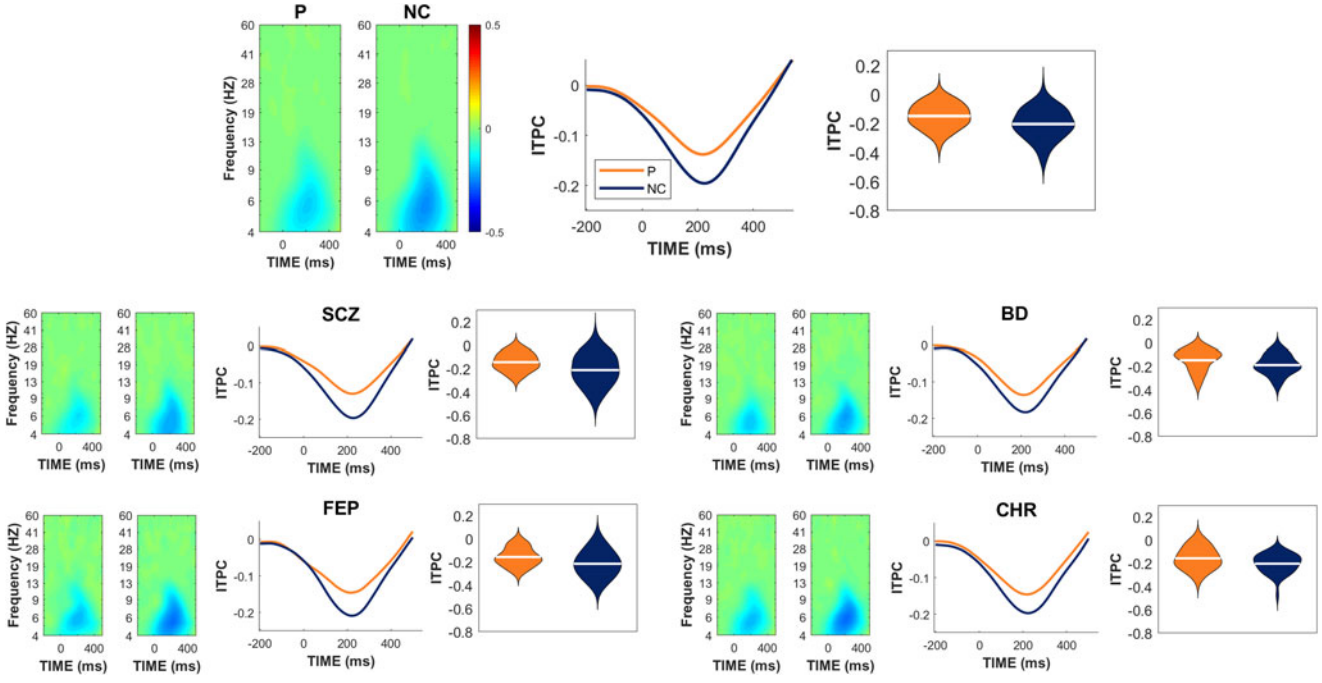

Fig. 3. Filled contour plots: depiction of mMMN (standard minus deviant) time-frequency ITPC for frequencies between 4 and 60 Hz over time. Line-plots: grand-average mMMN Theta ITPC over time. Violin-plots: distributions of individual mMMN Theta ITPC values extracted from the selected time-window, with mean mMMN Theta ITPC depicted as a white line. The upper panel reports data of the transdiagnostic analysis, while the lower panel shows data for the four diagnostic subgroups.

Discussion

The present experiment investigated the auditory mMMN, a pre-attentive neurophysiological index reflecting brain adaptability to deviant stimuli (Näätänen et al., 2007), in SCZ, BD, FEP, and CHR. The study aimed to test the validity of this neurophysiological response as an index of psychosis and as a marker of

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risk for psychosis. To this end, MEG was employed to enhance source localization and restrict the analysis to the bilateral auditory cortices. Within this area of interest, we compared mMMN indices (ERF amplitude, Theta power, and Theta ITPC) in people with psychosis or at risk *v.* controls, first by considering psychosis as a transdiagnostic factor, then with a focus on each diagnostic category.

The presentation of a deviant auditory stimulus evoked an enhancement of the ERF activity (namely mMMN) over bilateral temporal sensors, with the source of activity centered in the superior temporal gyri around the primary and secondary auditory cortex locations. People with psychosis had overall reduced mMMN peak amplitude, Theta power, and Theta ITPC, and this effect seemed to apply to psychosis without a strong association to the diagnostic profile and medication. Pre-planned follow-up assessments of the significance of the mMMN reduction in each diagnostic subgroup showed significant, medium to large, effect sizes in ERF peak amplitude in each subgroup contrast, with a concurrent reduction of Theta power and Theta ITPC in SCZ and an indication of reduced Theta ITPC in CHR. Despite the evidence of mMMN reductions also in BD and FEP in both types of spectral analyses, the contrasts were not significant. However, the non-significant interactions in the analyses that considered the four subgroups within the same statistic suggest that this apparent difference across individual contrasts might be linked to chance or statistical power.

A recent meta-analysis of EEG studies suggests that MMN alterations are present also in BD, FEP, and CHR (Erickson et al., 2016), but this study is the first testing these populations within the same MEG experiment. The results supply additional evidence that mMMN reductions are not specific to SCZ but they affect all clinical conditions characterized by psychosis. Significant mMMN reductions were also observed in subjects at risk for psychosis. CHR is a premorbid profile of psychosis but only about 1 in 6 CHR suffer a worsening of the psychotic symptoms and receive a diagnosis of SCZ within five years (Lang et al., 2022). Presently, the lack of clinical follow-ups in the CHR population impedes determining the progression trajectory of our participants. A longitudinal study is required to establish whether the present effect was driven by those who will transition to SCZ or another chronic psychotic disorder (Fujioka et al., 2020; Hamilton et al., 2022; Perez et al., 2014; Shaikh et al., 2012). However, the observation of significant mMMN reduction in CHR, among whom only few are expected to progress to full-blown psychosis, suggests that MMN might be a potential neurobiological marker in people with a greater risk for psychosis, irrespective of clinical course.

The indication of reduced phase synchronization in CHR aligns with recent MEG outcomes that showed reduced phase synchronization in Gamma frequency evoked by dynamic visual stimuli (Grent-'t-Jong et al., 2020). Hence, phase analysis might be more sensitive than power analysis in detecting functional deficits before the formulations of a diagnosis based on symptoms. However, power and ITPC seem to be differently involved by the physical aspect of the deviant stimuli, with frequency-deviant stimuli increasing Theta power and duration-deviant stimuli enhancing Theta ITPC (Lee et al., 2017). Hence, in the present experiment, reduced ITPC in CHR might reflect the property of the deviant stimulus rather than a general functional deficit. Importantly, since most of the CHR were not medicated, the indications of reduced mMMN in this subgroup suggest that altered mMMN in psychosis or in people at risk for psychosis is not exclusively dependent on the effects of medications.

The observation of reduced mMMN in people with full-blown psychosis and in people with sub-threshold psychotic symptoms is consistent with the model put forward by Thomas and collaborators (Thomas et al., 2017), in which an abnormal early auditory information processing is upstream in the cascade of processes that escalate to severe and persistent positive and negative symptoms and a decline of cognitive functions (see also Koshiyama et al., 2021). Hence, mMMN might be an important marker of psychosis, offering a neurophysiological index for early detection of people at risk. Since phase synchronization seems to be the basis of coordinated interaction between brain areas (Varela, Lachaux, Rodriguez, & Martinerie, 2001), diminished phase synchronization might reflect altered brain functional integration, or 'dysconnection', as a core feature of psychosis (Friston, Brown, Siemerkus, & Stephan, 2016). However, the present MEG recording failed to detect the frontal component of the mMMN, where the right and left auditory activities converge. Hence, these data could not test the relevance of long-range functional connectivity. A simultaneous EEG/MEG recording might compensate for the MEG low sensitivity to radial and deep activity (Hunold et al., 2016), enabling a precise identification of all the brain sources contributing to the mMMN.

By including three groups of patients with a history of full-blown psychotic symptoms and a group of people with subthreshold psychosis, the present results indicate that mMMN reductions do not exclusively affect SCZ but also other clinical and subclinical psychiatric profiles characterized by psychosis. A recent meta-analysis of MMN studies in patients with major depressive disorder reported significant MMN reductions for duration deviant stimuli in these patients as well (Tseng, Nouchi, & Cheng, 2021). Hence, our findings do not specifically ascribe mMMN deficits to psychosis among psychiatric conditions; however, we show that, within the psychotic spectrum, mMMN reduction is not exclusive of SCZ and is already present in recent-onset and in potential prodromic stages of chronic psychotic diagnoses.

One limitation of the present study was the difficulty in matching patients and controls according to IQ and socio-economic status. However, supplementary analyses indicated that mMMN amplitude does not correlate with these factors (see online Supplemental Material). Interestingly, the mMMN amplitude correlated with participants' age, with ERF peak amplitude declining over age (Cheng, Hsu, & Lin, 2013; Kiang, Braff, Sprock, & Light, 2009; Tsolaki, Kosmidou, Hadjileontiadis, Kompatsiaris, & Tsolaki, 2015) in a clinical population as well. Matching controls and patients for age and gender within each diagnostic subgroup was therefore a strength of the present design in which we investigated younger adults (CHR and FEP) and older adults (BD and SCZ) within the same experiment.

In conclusion, our findings suggest that mMMN – a neurophysiological pre-attentive index of brain adaptability to stimulus changes – could become a target for research aimed at studying the neurophysiological underpinnings of full-blown or subthreshold psychosis. Moreover, analyses of phase synchronization may be informative in detecting a psychosis condition also at a prodromal phase of illness.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S003329172200321X.

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Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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