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Mismatch Negativity reduction in the left cortical regions in first-episode psychosis and in individuals at ultra high-risk for psychosis

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ABSTRACT

Mismatch Negativity (MMN), an electrophysiological component that represents sensory memory processing, has been proposed as a potential vulnerability marker for psychosis. Some studies have reported a more evident MMN amplitude reduction in the left cortical regions in patients with schizophrenia. Little is known about this asymmetric pattern in patients in their first episode of psychosis (FEP) and individuals at ultra-high risk for psychosis (UHR). The aim of this study was to explore the scalp distribution of MMN in 20 FEP patients, 20 UHR subjects and 23 healthy controls. Both clinical groups were antipsychotic naïve. MMN was obtained during a passive auditory paradigm with duration deviant tones and analyzed from 15 frontocentral electrodes. There was a significant group effect in MMN amplitude ($F = 3.4$, $p = 0.04$), showing a decrement in both FEP and UHR compared to controls (FEP mean difference (MD) $= -0.48$, $p = 0.02$; UHR MD $= -0.44$, $p = 0.04$), and this amplitude decrement was more evident in the left middle regions for both clinical groups ($p < 0.01$). In conclusion, we found a clear amplitude reduction of duration MMN in FEP patients and UHR individuals, especially in the left cortical regions. The observed pattern in both clinical samples supports the notion that MMN could be a vulnerability marker for psychosis. We propose to continue the study of this MMN laterality effect in future longitudinal studies.

1. Introduction

Schizophrenia is one of the psychiatric disorders for which the search of vulnerability markers has become especially relevant in recent years (Ruhrmann et al., 2012). The aim of this research has been to facilitate early diagnosis and treatment, consequently improving quality of life in this clinical population (Yung et al., 1998).

One of the most studied potential vulnerability markers for psychosis is Mismatch Negativity (MMN), an event related potential (ERP) that represents the automatic ability to detect deviations in the auditory context. MMN constitutes the most sensitive, and probably the unique measure for the neurophysiological correlates of sensory memory (Näätänen et al., 2007). The selection of MMN as a potential vulnerability marker was derived from wide evidence showing a MMN amplitude reduction in chronic schizophrenia and first-episode psychosis (FEP) patients (Shelley et al., 1991; Salisbury et al., 2002; Light and Braff, 2005; Umbricht et al., 2006; Todd et al., 2008). Additionally, certain deviant related features have been associated with clinical and functional aspects of the disease: while frequency deviant MMN abnormalities are associated with illness chronicity, duration deviant MMN changes are observed even in the early stages of the disease (Umbricht et al., 2003).

In the last decade, several studies have reported a decrement of MMN amplitude in individuals identified as being at ultra high-risk for psychosis (UHR) (Brockhaus-Dumke et al., 2005; Bodatsch et al., 2010; Atkinson et al., 2012; Jahshan et al., 2012; Shaikh et al., 2012). UHR corresponds to a prepsychotic or 'prodromal' phase in which subthreshold psychotic symptoms and cognitive decline are observed (Yung and McGorry, 1996). Moreover, Bodatsch et al. (2010), Shaikh et al. (2012) and Perez et al. (2013) reported that those UHR individuals who later made the transition to psychosis displayed smaller MMN amplitudes than those who did not. However, there are still some MMN features that have not been explored in this clinical population. Specifically, to our knowledge, there are no reports of the scalp distribution of MMN in UHR subjects. MMN amplitude reduction in

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schizophrenia patients shows an asymmetric pattern corresponding to lower amplitudes in the left cortical regions (Javitt et al., 1993; Hirayasu et al., 1998; Kreitschmann-Andermahr et al., 1999; Pekkonen et al., 2002; Youn et al., 2003). Therefore, our aim was to explore the scalp distribution of MMN in antipsychotic naïve FEP patients and UHR subjects.

2. Materials and methods

2.1. Participants

Twenty patients in their first non-affective psychosis episode, assessed by the Structured Clinical Interview for DSM-IV (First et al., 1997) and 20 participants identified as UHR using the Structured Interview for Prodromal Syndromes (SIPS) (Miller et al., 2003) were recruited from the inpatient psychiatric service, the emergency department, and the Adolescent Program of Neuropsychiatric and Imaging Study (PIENSA) of the National Institute of Neurology and Neurosurgery (INNN) of Mexico. Both groups were antipsychotic naïve. General exclusion criteria were: presence of any concomitant medical or neurological illness, current substance abuse or history of substance dependence (excluding nicotine), comorbidity of any other axis I disorders or psychomotor agitation. FEP patients were deemed eligible if they had less than two years of psychotic symptoms. Twenty three right-handed similar in age and gender healthy controls were recruited from schools and by Internet social network advertisements. Additional exclusion criteria for the healthy control group were having a history of psychiatric illness and positive familiar history for schizophrenia. All participants were screened for drugs of abuse (e.g., cannabis, cocaine, heroin, opioids and benzodiazepines) at the time of study inclusion.

The study was approved by the Ethics and Scientific Committees of the INNN and subjects signed an informed consent if they agreed to voluntarily participate in the study. Written consent from both parents and assent for subjects younger than 18 years of age (the age of consent in Mexico) was obtained from all subjects prior to participation. All the procedures of the study were in accordance with the Declaration of Helsinki.

2.2. Experimental paradigm

MMN was obtained with a passive auditory paradigm using the STIM 2 software (Neuroscan Inc., Charlotte, North Carolina). Frequent tones (100 ms/1000 Hz) mixed with deviant tones (250 ms/1000 Hz) were presented in an established order (9 frequent, 1 deviant), with an interstimulus interval of 300 ms, according to Umbricht et al. (2003). A total of 1517 tones (1365 frequents, 152 deviants) were presented in a single block. During the 10 minute recording session, reading material was given to the participants.

2.3. Electrophysiological recording

A 0.5 to 30 Hz digital monopolar EEG was continuously recorded with SCAN 4.3.1 software (Neuroscan Inc., Charlotte, North Carolina) with a sampling rate of 1000 Hz, using a NuAmps digital amplifier (Neuroscan Inc., Charlotte, North Carolina) and with the tip of the nose as reference. We used 19 tin electrodes (10–20 International System (Jasper, 1958)) attached to an elastic cap (ElectroCap Inc., Eaton, Ohio). Blinks and ocular activity were reduced from the EEG using an algorithm of SCAN 4.3.1 Edit software based on the recording of two electrodes on the external and superior orbital canthus of the right eye. EEG segments showing ± 50 μV artifacts in any electrode were excluded from the analyses. After an additional off-line filter with a bandwidth of 1–30 Hz, EEG epochs of 400 ms were generated with a pre-stimulus interval of 100 ms. Baseline correction and linear detrend were applied to all epochs. Averaged potentials were obtained separately for frequent and deviant tones with the same number of epochs (100) for each electrode in all participants. To obtain MMN, the grand average of the electrical response to the frequent tones was subtracted from the grand average of the corresponding response to deviant tones for each participant.

2.4. Data and statistical analysis

MMN was defined as the most negative wave between 150 and 300 ms after stimuli onset. Mean amplitudes in the 50 ms surrounding the identified peaks in Fz were obtained for all electrodes. Latencies were calculated from the onset of the tones to the MMN peak in the Fz electrode.

Analysis of variance (ANOVA) was used to compare MMN latencies as well as demographic characteristics among control, FEP and UHR groups. Nominal variables were analyzed using χ^2 tests.

To compare MMN amplitudes between groups, repeated-measures ANOVA (RMA) was applied. Two within-subject factors for electrodes were included: laterality (5 levels: left (F7, T3, T5), left-middle (F3, C3, P3), middle (Fz, Cz, Pz), right-middle (F4, C4, P4) and right (F8, T4, T6)) and frontality (3 levels: anterior (F7, F3, Fz, F4, F8), central (T3, C3, Cz, C4, T4) and posterior (T5, P3, Pz, P4, T6)). The group (UHR, FEP and controls) was the between-subject factor. The Greenhouse-Geisser correction was applied to all the RMA analyses. Post hoc comparisons were made using the Least Significant Difference test.

In order to explore the symmetry pattern of MMN in our samples, Spearman rank correlations were performed using the amplitude in each group across homologue sites. Finally, additional Spearman rank correlations were done between all MMN amplitudes and general scores of symptomatology (SIPS scale for the UHR group and Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) for the FEP group) and functional status (Global Assessment Functioning (GAF)) in both clinical groups. Statistical significance was set at $p < 0.05$ for all analyses. Statistical analyses were performed using SPSS v16.0 software (SPSS, Chicago, Illinois).

3. Results

3.1. Demographic data

Table 1 shows the sample demographic data. The DSM-IV diagnoses of the patients with FEP included in the study were as follows: brief psychotic disorder ($n = 6$), schizophreniform disorder ($n = 5$), and schizophrenia ($n = 9$). No differences were found in years of school education, gender and civil status among groups. However, UHR subjects were younger than FEP patients ($F_{(2,62)} = 4.5$, $p = 0.015$, mean difference (MD) $= -4.64$, $p = 0.04$) and both clinical samples reported a significant lower percentage of employment relative to the control group ($\chi^2 = 17.8$, $df = 6$, $p = 0.007$).

3.2. MMN results

The RMA analysis showed a higher MMN amplitude in middle regions for all groups (lateral effect: $F_{(2.2,\ 133.5)} = 95.6$, $p < 0.001$, Fig. 1). Although MMN amplitudes were higher in anterior regions for all groups (frontal effect: $F_{(1.2,\ 73.2)} = 54.4$, $p < 0.001$), both clinical groups showed a clear anterior reduction compared to posterior regions (group × frontality effect: $F_{(2.4,\ 73.2)} = 5.6$, $p = 0.003$).

The overall group effect was significant ($F_{(2,\ 60)} = 3.4$, $p = 0.04$). Post hoc analysis showed lower amplitudes in both clinical groups compared to the control group (FEP MD $= -0.48$, $p = 0.02$; UHR MD $= -0.44$, $p = 0.04$). No differences between FEP and UHR groups were found (MD $= 0.04$, $p = 0.85$, Table 2).

The group × laterality effect showed that MMN amplitude reductions were more evident in the left, left-middle and middle regions for both clinical groups, especially for the UHR group. In the right-middle

Table 1
Sample demographic data.

	Mean (SD)			p
	UHR	FEP	Control	
Age, mean (SD)	20.8 (5.3)	26.1 (7.2)	22 (4.9)	0.01[a]
Years of education, mean (SD)	11.7 (2.5)	12.3 (6.8)	13.7 (3.1)	0.33[a]
Gender (male/female)	13/7	13/7	10/13	0.80[b]
Civil status (single/married)	19/1	18/2	23/0	0.31[b]
Occupation (student/employee/student & employee/no occupation)	10/4/1/5	3/7/0/10	15/5/2/1	0.01[b]
PANSS positive symptoms		22.9 (5.4)		
PANSS negative symptoms		15.6 (5.3)		
PANSS general symptoms		44.8 (10.5)		
SIPS positive symptoms	11.1 (4.4)			
SIPS negative symptoms	15.6 (5.4)			
SIPS disorganization symptoms	8.1 (2.9)			
SIPS general symptoms	7.3 (3.3)			
GAF	59.8 (11.2)	36.2 (19.9)		<0.001[c]

UHR: Ultra high-risk group; FEP: First episode psychosis group.
[a] ANOVA.
[b] Chi square.
[c] T-test.

regions this effect was only evident for the FEP group. No significant differences were observed for the right regions across groups (Table 2, Fig. 2).

The Spearman correlation analysis showed a clear symmetry of MMN amplitudes in the control group, but this was not the case for both clinical groups, in which non-significant correlations were found between inferior frontal (F7–F8) and anterior temporal (T3–T4) regions (Table 3). No significant correlations were found between GAF and clinical scores and MMN amplitudes in either group.

4. Discussion

This study analyzed the scalp distribution of the well-known duration MMN decrease in FEP patients and UHR for psychosis subjects. The main finding was significantly lower MMN amplitudes in the left but not right regions in both clinical groups. Our results are consistent with previous reports that have shown a stronger left-than-right MMN amplitude effect in schizophrenia patients. Some of these reports have associated this lateralized effect with the left anatomical abnormalities reported in this population (Javitt et al., 1993; Hirayasu et al., 1998; Kreitschmann-Andermahr et al., 1999; Pekkonen et al., 2002; Youn et al., 2003). Nevertheless, this lateralization effect has not been a consistent finding (Salisbury et al., 2002; Umbricht et al., 2003, 2006).

In this study, UHR subjects showed a similar pattern of MMN amplitude reduction compared to FEP patients. To our knowledge, this is the first report demonstrating that both clinical populations share lower left-than-right MMN amplitudes. Other studies that reported the consistent MMN reduction in FEP and UHR with wide arrays or only midline frontocentral electrodes have not described this asymmetric pattern (Brockhaus-Dumke et al., 2005; Bodatsch et al., 2010; Atkinson et al., 2012; Shaikh et al., 2012; Perez et al., 2013). These studies have described that this significant reduction is deeper in frontal regions, which agree with our results. From our perspective, the similar

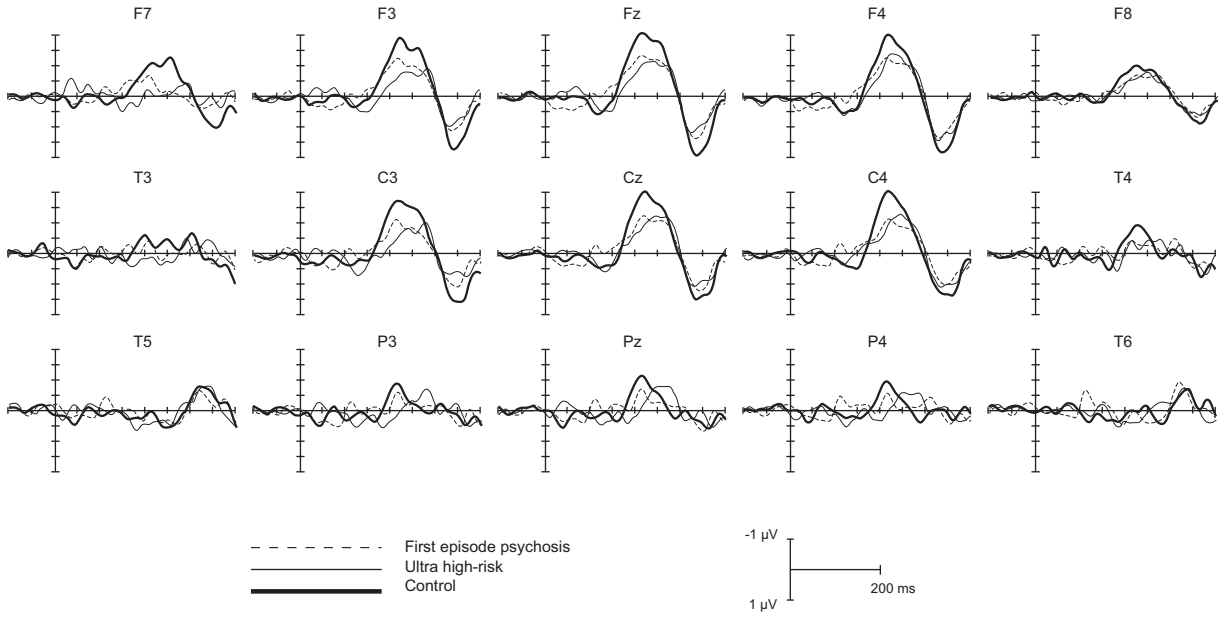

Fig. 1. Grand averages of MMN from the three groups in the 15 analyzed electrodes.

Table 2
Differences in MMN amplitudes between groups for each frontal and lateral factor levels.

Factor/level	Control group compared to	Mean difference	p
Frontal factor			
Anterior	UHR	−0.79	<0.001
	FEP	−0.80	<0.001
Central	UHR	−0.57	0.02
	FEP	−0.58	0.02
Posterior	UHR	0.05	0.8
	FEP	−0.06	0.8
Lateral factor			
Left	UHR	−0.52	0.03
	FEP	−0.39	0.09
Left-middle	UHR	−0.66	<0.01
	FEP	−0.63	<0.01
Middle	UHR	−0.52	0.04
	FEP	−0.63	0.02
Right-middle	UHR	−0.41	0.1
	FEP	−0.58	0.02
Right	UHR	−0.8	0.7
	FEP	−0.16	0.5

UHR: Ultra high-risk group; FEP: First episode psychosis group.

MMN profile in terms of scalp distribution between FEP and UHR supports the well-established proposal of this ERP as a reliable vulnerability marker for psychosis.

Since MMN seems to be generated in the primary auditory and frontal cortex (Näätänen et al., 2012) our findings may be consistent with studies reporting the left temporal lobe structural abnormalities in FEP and chronic schizophrenia (Hirayasu et al., 1998; Youn et al., 2003). Moreover, it has been reported that these structural abnormalities are associated with MMN amplitude reduction in patients with schizophrenia (Salisbury et al., 2007; Rasser et al., 2011). It must be noted that those results correspond to MMN amplitude reductions for frequency deviants of recently diagnosed and chronic medicated patients. To our knowledge, there are no reports showing such associations in antipsychotic naïve FEP patients and UHR subjects for duration deviant MMN amplitudes.

MMN amplitude reductions for duration deviants may indicate a deficit in the integration of the temporal features of the stimulus,

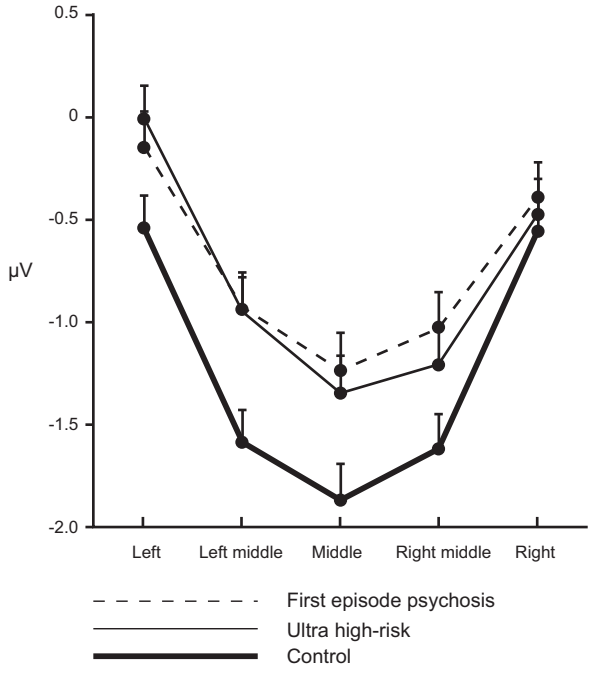

Fig. 2. Means and standard errors of MMN amplitudes in each laterality factor from the three groups.

Table 3
Correlation analysis of MMN amplitudes between homologue areas for the three groups.

Channel pair	Control r value	UHR r value	FEP r value
F3–F4	0.89**	0.78**	0.66*
C3–C4	0.80**	0.89**	0.75**
P3–P4	0.89**	0.82**	0.93**
F7–F8	0.68**	−0.05	0.17
T3–T4	0.55*	0.26	0.46
T5–T6	0.74**	0.85**	0.82**

UHR: Ultra high-risk group; FEP: First episode psychosis group.
* $p < 0.01$.
** $p < 0.001$.

which has already been described by Michie (2001) as one of the possible initial perceptual disturbances in psychosis. Since the left temporal lobe seems to be preferentially engaged in the analysis of the timing and sequential properties of the auditory context (Zatorre and Belin, 2001; Zatorre et al., 2002), the early neuroanatomical abnormalities in this area reported in psychosis may affect this process. Nevertheless, it must be considered that our experimental task consisted of a fixed sequence of stimuli with highly predictable deviance occurrence. The left temporal lobe is also specialized in the identification of stable changes in auditory sequences, so our results regarding asymmetry of MMN could reflect a particular deficit in psychotic patients and UHR subjects when the task demands preferentially left processing for auditory stimuli. The asymmetric pattern for MMN that we report here should be compared to others obtained during tasks in which the deviant stimuli are randomized or unpredictable, since this would require a higher active participation from the right hemisphere, which is widely known for novelty detection sensitivity (Martin, 1999; Mulert et al., 2004; Ribolsi et al., 2009).

Other studies have reported asymmetry in the amplitude decrement of other ERPs such as P3a (Mondragón-Maya et al., 2013) and P3b (Salisbury et al., 1998; Salisbury et al., 1999; Frommann et al., 2008) in FEP and UHR individuals. In the case of the P3a, this asymmetry effect seems to continue along the illness progression (Cortiñas et al., 2008). Moreover, in the case of P3b, its amplitude reduction has been associated to corresponding asymmetric neuroanatomical abnormalities in schizophrenia (Ford, 1999; Ribolsi et al., 2009). The left temporal lobe structural changes have been consistently reported from different imaging studies (Kasai et al., 2003; Zhou et al., 2003; Kawasaki et al., 2008) and such abnormalities correspond to specific structures like the left Heschl gyrus (Kasai et al., 2003), which is known to be linked to MMN generation (Näätänen and Kähkönen, 2009).

No significant associations were found between GAF scores and MMN in both clinical groups. In the case of UHR, our results coincide with other reports (Shin et al., 2009; Jahshan et al., 2012). Nevertheless, significant associations have been reported between MMN amplitudes and GAF scores in patients with chronic schizophrenia (Light and Braff, 2005; Jahshan et al., 2012). The fact that our FEP group did not show such association raises the need for future studies to explore the moment along the illness course at which both measures become linked, as this could be informative in terms of both neurocognitive and psychosocial functioning decrease. Additionally, future cross-sectional and longitudinal studies in larger samples are needed to address the heterogeneity of functional outcomes in the UHR population (Addington et al., 2011), prediction of conversion to full-blown psychosis (Cannon et al., 2008; Ruhrmann et al., 2010; de la Fuente-Sandoval et al., 2013), and the effect of psychotropic medication on this population.

The small sample size of this study represents a limitation. Nevertheless, it must be noted that the careful recruitment of the participants and their antipsychotic naïve condition make this a unique population. Since this is a cross-sectional study, a follow-up is needed for the clinical samples in order not only to know the

MMN prediction capacity for psychosis as other studies have done (Bodatsch et al., 2010; Shaikh et al., 2012; Perez et al., 2013) but also to assess the scalp topographic pattern of this ERP before and after psychosis onset, as well as under treatment response. This would provide insight into the electrophysiological changes during the illness progression. Additionally, these changes could be linked to the connectivity and gray matter reduction previously described for UHR and FEP (Ribolsi et al., 2009).

In conclusion, we found a clear amplitude reduction of duration MMN in antipsychotic naïve FEP patients and UHR individuals. Such decrements were more pronounced in the left cortical regions of both clinical samples, which support the notion that MMN is a promising vulnerability marker for psychosis.

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Contributors

Rodolfo Solís-Vivanco ran the experiment with all participants, designed the analyses and wrote the manuscript since the first draft.

Alejandra Mondragón-Maya ran the experiment with all participants and wrote the manuscript since the first draft.

Pablo León-Ortiz interviewed and identified the clinical groups and recruited all the participants.

Yaneth Rodríguez-Agudelo supervised the study and reviewed the manuscript along its progress.

Kristin S. Cadenhead provided general methodological advice and proof-read the manuscript.

Camilo de la Fuente-Sandoval interviewed and identified the clinical sample, provided general methodological advice and reviewed the manuscript along its progress.

All authors contributed to and have approved the final manuscript.

Conflict of interest

C de la Fuente-Sandoval has received grant support from Instituto de Ciencia y Tecnologia del Distrito Federal, and Janssen (Johnson & Johnson) and has served as a consultant or speaker for Carnot Laboratories, Eli Lilly, Janssen and AstraZeneca. The rest of the authors have no conflicts of interest to disclose.

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