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Reduced P3a amplitudes in antipsychotic naïve first-episode psychosis patients and individuals at clinical high-risk for psychosis

Alejandra Mondragón-Maya [a], Rodolfo Solís-Vivanco [a,*], Pablo León-Ortiz [b], Yaneth Rodríguez-Agudelo [a], Guillermina Yáñez-Téllez [c], Jorge Bernal-Hernández [c], Kristin S. Cadenhead [d], Camilo de la Fuente-Sandoval [b,e]

[a] Neuropsychology Department, Instituto Nacional de Neurología y Neurocirugía, Insurgentes Sur 3877, La Fama, Tlalpan, 14269, Mexico City, Mexico
[b] Laboratory of Experimental Psychiatry, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico
[c] Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Av. de los Barrios 1, Los Reyes Iztacala, Tlalnepantla, Mexico
[d] Department of Psychiatry, University of California San Diego, La Jolla, USA and San Diego Veterans Affairs Medical Center, 9500 Gilman Drive, La Jolla, CA 92093-0603, USA
[e] Neuropsychiatry Department, Instituto Nacional de Neurología y Neurocirugía, Mexico City, Mexico

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ABSTRACT

Event related potentials (ERP) associated with early sensory information processing have been proposed as possible vulnerability markers for psychosis. Compared to other ERPs reported in schizophrenia research, like Mismatch Negativity (MMN), little is known about P3a, an ERP related to novelty detection. The aim of this study was to analyze the MMN-P3a complex in 20 antipsychotic naïve first-episode psychosis patients (FEP), 23 antipsychotic naïve individuals at clinical high-risk for psychosis (CHR) and 24 healthy controls. The MMN-P3a amplitudes and latencies were obtained during a passive auditory mismatch frequency deviant ERP paradigm and analyzed in frontal and central scalp regions. There were no significant differences in MMN amplitude between groups. There was a significant group difference in P3a due to reduced amplitude ($F_{[2,64]} = 3.7$, $p = 0.03$) in both CHR and FEP groups (Mean difference (MD) = 0.39, $p = 0.04$ and MD = 0.49, $p = 0.02$, respectively) compared to the control group and this effect was most prominent on the right side (Group × laterality effect: MD = 0.57, $p < 0.01$ and MD = 0.58, $p < 0.01$, respectively). No significant differences were observed for MMN or P3a latencies between groups. Although a P3a decrement in chronic schizophrenia and FEP has been previously reported, our results suggest that this novelty detection impairment is present even in pre-psychosis stages in antipsychotic naïve subjects. This study supports the evidence that P3a could represent a neurophysiological vulnerability marker for the development of psychosis.

1. Introduction

Schizophrenia is a disabling chronic mental illness. A 'prodromal phase' characterized by subthreshold psychotic symptoms and a decline in everyday functioning (Fusar-Poli et al., 2010; Yung and McGorry, 1996), usually precedes the onset of psychosis and is often accompanied by neurocognitive deficits (Seidman et al., 2010) that are predictive of later psychotic illness (Lencz et al., 2006; Niendam et al., 2007; Riecher-Rössler et al., 2009; Sorensen et al., 2006). Individuals who meet criteria for the putative prodrome of psychosis are referred to be at ultra high risk, at-risk or as 'clinical high-risk for psychosis' (CHR). In the past 15 years, great efforts have been made to identify individuals at-risk for developing schizophrenia and understand the mechanism by which psychosis develops because early intervention could improve functional outcome and quality of life (Schimmelmann et al., 2008; Singh et al., 2012; Yung et al., 1998, 2004).

The observed clinical and neurocognitive deficits of patients in the early stages of psychosis may arise in part due to dysfunction in the coordination of neural activity at the earliest stages of sensory and cognitive information processing (Green and Nuechterlein, 1999). Event Related Potential (ERP) paradigms in response to sensory, motor or cognitive processes have been widely used to

Abbreviations: ANOVA, Analysis of Variance; CHR, Clinical high-risk for psychosis; ERP, Event related potentials; FEP, First-episode psychosis patients; INNN, National Institute of Neurology and Neurosurgery of Mexico; MMN, Mismatch Negativity; PANSS, Positive and Negative Syndrome Scale; SD, Standard Deviation; SE, Standard Error.

* Corresponding author. Neuropsychology Department, Instituto Nacional de Neurología y Neurocirugía, Insurgentes Sur 3877, La Fama, Tlalpan, 14269, Mexico City, Mexico. Tel./fax: +52 55 5528 7878.
E-mail address: rodolfoso@hotmail.com (R. Solís-Vivanco).

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study early information processing abnormalities in brain disorders such as schizophrenia (Luck, 2005). Mismatch Negativity (MMN) is related to the detection of deviant or infrequent stimuli found in a specific and stable acoustic context (Duncan et al., 2009; Näätänen et al., 2007). Deviant stimuli elicit an MMN that peaks 100–200 ms after the onset of the deviant stimuli. Deficits in MMN generation using a variety of stimulation parameters (e.g., oddball stimuli that differ in frequency or duration) are a robust finding in chronic schizophrenia (Javitt et al., 2000; Light and Braff, 2005; Shelley et al., 1991) but the literature on MMN in the early stages of the disease is mixed, with some studies identifying abnormalities (Devrim-Ucok et al., 2008; Hermens et al., 2010; Umbricht et al., 2006) and others failing to detect any significant decrements in either duration or frequency MMN in patients with a psychotic illness duration of less than three years (Salisbury et al., 2002; Valkonen-Korhonen et al., 2003). Recent studies of CHR individuals using a passive auditory oddball paradigm with a duration deviant stimulus have reported decrements of MMN relative to controls (Atkinson et al., 2012; Bodatsch et al., 2010; Bramon et al., 2008; Brockhaus-Dumke et al., 2005; Frommann et al., 2008; Jahshan et al., 2012; Özgürdal et al., 2008; Shaikh et al., 2012; Van der Stelt et al., 2005; Van Tricht et al., 2010). While authors such as Todd et al. (2008) and Salisbury et al. (2002) have suggested that MMN abnormalities to frequency deviants may occur later in the course of illness.

Another ERP related to novelty detection is P3a, which is defined as a positive peak that appears 250–350 ms after the occurrence of unexpected stimuli (Polich, 2007). This electrophysiological component represents the involuntary orientation of attention towards an infrequent stimulus that reaches maximum amplitude at frontal areas of the scalp (Friedman et al., 2001). Deficits in P3a amplitude have been identified in chronic and antipsychotic naïve first- episode psychosis patients (FEP) and now in CHR subjects. Atkinson et al. (2012) and Jahshan et al. (2012) reported MMN and P3a amplitude reductions using a passive auditory duration deviant paradigm in CHR subjects and FEP patients while Valkonen-Korhonen et al. (2003) found P3a amplitude reductions but not MMN changes in a group of never medicated FEP patients in a frequency deviant paradigm. Although MMN to frequency deviants has been assessed in CHR subjects (Brockhaus-Dumke et al., 2005), the P3a component has not been evaluated in this population.

In addition, although MMN appears to be insensitive to antipsychotic medication in schizophrenia (Korostenskaja et al., 2005; Umbricht et al., 1998, 1999), both dopaminergic agents and antipsychotic administration have effects on P3a (Garcia-Garcia et al., 2011; Kähkönen et al., 2002; Marco-Pallarés et al., 2010; Solís-Vivanco et al., 2011; Takeshita and Ogura, 1994), highlighting the importance of studying the P3a in an antipsychotic naïve sample. The aim of this study was to analyze MMN and P3a in FEP patients and individuals at CHR, both naïve to antipsychotic medication, using a passive auditory frequency deviant paradigm.

2. Materials and methods

2.1. Participants

The study was approved by the Ethics and Scientific Committees of the National Institute of Neurology and Neurosurgery of Mexico (INNN) and subjects were included following successful completion of an informed consent procedure. Participants less than 18 years age (the age of consent in Mexico) volunteered for the study and their parents or legal guardians signed the written consent.

Twenty patients during their first non-affective psychotic episode and 23 participants identified as clinical high-risk for schizophrenia were recruited from the inpatient psychiatric service, first psychotic episode clinic, and the Adolescent Program of Neuropsychiatric and Imaging Study (PIENSA) of the INNN. All subjects were asked for demographic data and interviewed using the structured clinical interview for DSM-IV (First et al., 1997) and the CHR group met Structured Interview for Prodromal Syndromes (SIPS) criteria (Miller et al., 2003) for study entry. Patients were excluded if they had the following: any concomitant medical or neurological illness, current substance abuse or history of substance dependence (excluding nicotine), comorbidity of any other axis I disorders, were considered to be at high risk for suicide, or showed psychomotor agitation. Both groups were antipsychotic naïve and no other medication, besides the ones that the participants were taking at the time of inclusion, was allowed before the electrophysiological recording. There was no wash-out period for current medications. Twenty-four right-handed similar in age and gender healthy controls were also recruited from schools and by internet advertisements. The healthy control participants were assessed in the same manner as the patients and any subject with a history of psychiatric illness or positive familiar history for schizophrenia was excluded. All participants were screened for drugs of abuse (e.g., cannabis, cocaine, heroin, opioids and benzodiazepines) at inclusion.

2.2. Passive auditory frequency deviant paradigm

MMN and P3a were obtained using a passive auditory paradigm using the STIM 2 software (Neuroscan Inc., Charlotte, North Carolina). Frequent tones (100 ms/1000 Hz) mixed with deviant tones (100 ms/1500 Hz) were presented with a fixed order throughout the recording (9 frequent, 1 deviant), with an interstimulus interval of 300 ms. Stimulation was presented in a single block which contained a total of 1517 tones (1365 frequents, 152 deviants). During the stimulation period, reading material was given to the participants. The recording session lasted approximately 10 min.

2.3. EEG recording and ERPs

The digital EEG was continuously recorded from 19 tin electrodes (10-20 International System (Jasper, 1958)) attached to an elastic cap (ElectroCap Inc., Eaton, Ohio) and using the tip of the nose as reference. We used SCAN 4.3.1 software (Neuroscan Inc., Charlotte, North Carolina), with a bandwidth of 0.5–30 Hz and a sampling rate of 1000 Hz, using a NuAmps digital monopolar amplifier (Neuroscan Inc., Charlotte, North Carolina). Eye movements were recorded with two electrodes in the external and superior orbital canthus of the right eye. Ocular activity was reduced from the EEG recordings using an algorithm of SCAN 4.3.1 Edit software. Electrodes impedance was kept below 5 kΩ. 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, which were detrended and baseline corrected. Averaged potentials were obtained separately for frequent and deviant tones with 100 sweeps each for all participants. To obtain MMN and P3a, the grand average of electrical response to the frequent tones was subtracted from the grand average of the corresponding response to deviant tones for each subject.

2.4. Data and statistical analysis

After visual inspection of the grand average difference waves, MMN was defined as the most negative wave between 100 and 200 ms., and P3a was defined as the largest positive wave between 250 and 350 ms. Mean voltage amplitudes in the 50 ms surrounding the identified peaks in Fz were calculated in all electrodes. Latencies

were obtained from the onset of the tones to the highest MMN and P3a peak in the Fz electrode using the SCAN Edit software.

The results are presented in means and standard deviations (±SD). Statistical analyses were performed using SPSS v16.0 software (SPSS, Chicago, Illinois). Latencies of MMN and P3a, demographic and clinical characteristics of the sample were compared between controls, FEP and CHR groups with analysis of variance (ANOVA), with the exception of nominal variables, which were analyzed using χ^2 tests.

Independent repeated-measures ANOVA (RMA) was used to analyze MMN and P3a amplitudes, with two within-subject factors for electrodes F3, Fz, F4, C3, Cz and C4: laterality (3 levels: left, middle and right) and frontality (2 levels: frontal and central). The group (CHR, 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. Statistical significance was set at $p < 0.05$.

Spearman correlations were used to assess the relation between clinical and electrophysiological data. The statistical threshold was established with $p \leq 0.05$ in order to control for multiple comparisons; $p = 0.05/4$ for clinical scales in CHR group (SIPS positive, negative, disorganization, general) and $p = 0.05/3$ for clinical scales in FEP (PANSS positive, negative and general).

3. Results

3.1. Demographic and clinical characteristics

Differences between groups were found for age and occupation. *Post hoc* analysis revealed that FEP patients were significantly older than CHR individuals (26.1 ± 7.2 vs. 20.1 ± 5.4 years, respectively, $F_{[2,66]} = 5.06$, $p < 0.01$), with no significant differences between control participants and both clinical groups. Nevertheless, since age was significantly different between groups, we included it as a covariate in the variance analyses. Regarding occupation, 50% of the FEP patients reported no academic or labor activities, vs. 22% of the CHR and 4% of the control group ($\chi^2 = 18.03$, $p < 0.01$). No statistical differences were found between groups for gender, education and marital status (see Table 1). Two of the CHR subjects were taking a selective serotonin reuptake inhibitor (SSRI) at the time of the study (1 Fluoxetine, 1 Sertraline) and none of the participants in the three groups were taking benzodiazepines, mood stabilizers or anticonvulsants at the time of recording. DSM-IV diagnoses of the FEP group were as follows: schizophrenia ($n = 9$), schizophreniform disorder ($n = 5$) and brief psychotic disorder ($n = 6$). Table 2.

3.2. MMN and P3a

No significant differences were observed for the ERPs to the frequent tones between groups (supplementary material). Grand MMN and P3a averages in the three groups are shown in Fig. 1. MMN showed a homogeneous distribution over the analyzed electrodes (laterality: $F_{[1.7,\ 107.1]} = 0.79$, $p = 0.43$; frontality: $F_{[1,63]} = 1.33$, $p = 0.25$). After adjusting for the significant effect of age ($F_{[1,63]} = 4.2$, $p = 0.04$), there were no significant differences for MMN amplitude between groups ($p > 0.05$). There was no effect of age or significant differences between groups on MMN latency.

There was no significant effect of age on P3a amplitude ($F_{[1,63]} = 0.23$, $p = 0.63$) or latency ($F_{[1,63]} = 0.88$, $p = 0.35$), so it was excluded from subsequent analyses. There was a main effect of group for the mean amplitude of P3a ($F_{[2,64]} = 3.7$, $p = 0.03$). *Post hoc* analysis revealed that this effect was due to a lower amplitude in both the FEP and the CHR groups compared to the control group (Mean difference (MD) = 0.49, $p = 0.015$ and MD = 0.39, $p = 0.04$, respectively). P3a showed a frontal distribution in the three groups ($F_{[1,64]} = 5.88$, $p = 0.02$); an interaction between laterality × group was observed ($F_{[3,109]} = 2.8$, $p = 0.04$). *Post hoc* analysis indicated significant higher amplitudes of P3a in central regions in the control group compared to the FEP group (MD = 0.4, $p = 0.03$) and a trend compared to the CHR group (MD = 0.49, $p = 0.06$), as well as significant higher amplitudes in right regions in the control group compared to both the FEP and CHR groups (MD = 0.57, $p < 0.01$ and MD = 0.58, $p < 0.01$, respectively). These results did not change when CHR subjects that were taking an SSRI were excluded from the analysis (data not shown). Although there were no significant differences between groups in the left regions, the control group showed a trend for higher P3a amplitudes compared to the FEP group (MD = 0.39, $p = 0.06$, Fig. 2). There were no significant differences between groups with respect to P3a latencies ($F_{[2,66]} = 1.88$, $p = 0.16$). No significant correlations between any clinical measure in the CHR or FEP groups and MMN and P3a measures were observed (i.e., all rs < 0.4, $p > 0.08$).

Table 1
Demographic and clinical characteristics of the sample.

	FEP	CHR	Controls	*p* value
Age (±SD) years	26.1 (7.2)	20.1 (5.4)	22.6 (5.8)	<0.01[a]
Gender (male/female)	13/7	16/7	14/10	0.72[b]
Education (±SD) years	12.3 (6.8)	11.2 (2.8)	13.6 (2.8)	0.18[a]
Marital status (single/married)	18/2	22/1	24/0	0.28[b]
Occupation, N (%) (Student/ Employee/Student & employee/ No occupation)	3/7/0/10	12/5/1/5	15/6/2/1	<0.01[b]
Use of SSRIs	0/20	2/23	0/24	0.02[c]
PANSS Positive Symptoms	22.90 (5.4)			
PANSS Negative Symptoms	22.50 (5.3)			
PANSS General Symptoms	44.80 (10.5)			
SIPS Positive Symptoms		10.48 (4.5)		
SIPS Negative Symptoms		15.09 (5.4)		
SIPS Disorganization Symptoms		7.70 (3.2)		
SIPS General Symptoms		7.17 (3.2)		

FEP, First-episode psychosis group; CHR, Clinical High-Risk for Psychosis group; SD, Standard deviation; SSRIs, Selective Serotonin Reuptake Inhibitor.
[a] ANOVA.
[b] χ^2test.
[c] *p* value corresponding to the group effect on P3a amplitude when CHR participants under SSRIs treatment are excluded from the RMA analysis.

4. Discussion

The present study analyzed MMN and P3a in antipsychotic naïve individuals at clinical high risk for schizophrenia and first-episode psychosis patients in a passive auditory oddball paradigm using a frequency deviant stimulus. Our main finding was a significant P3a amplitude reduction in both clinical groups compared to healthy controls.

Table 2
Descriptive data for MMN and P3a of Fz and Cz channels for the three groups.

		FEP	CHR	Controls	F (DF)	*p* value
MMN, Mean (SD)						
Amplitude (μV)	Fz	−1.50 (1.08)	−1.96 (1.3)	−1.70 (1.2)	1.14 (2,64)	0.33
	Cz	−1.24 (0.97)	−1.63 (1.3)	−1.42 (1.5)		
Latency (ms)	Fz	125.3 (15.9)	144.91 (43.6)	132.13 (22.01)	2.37 (2,64)	0.10
P3a, Mean (SD)						
Amplitude (μV)	Fz	0.57 (0.82)	0.74 (0.7)	1.06 (0.76)	3.70 (2,64)	0.03
	Cz	0.77 (0.73)	0.79 (0.7)	1.27 (0.85)		
Latency (ms)	Fz	243.25 (35.5)	233.04 (28.9)	249.7 (24.7)	1.88 (2,64)	0.16

FEP, First-episode psychosis group; CHR, Clinical High-Risk for Psychosis group; DF, Degrees of freedom; SD, Standard deviation.

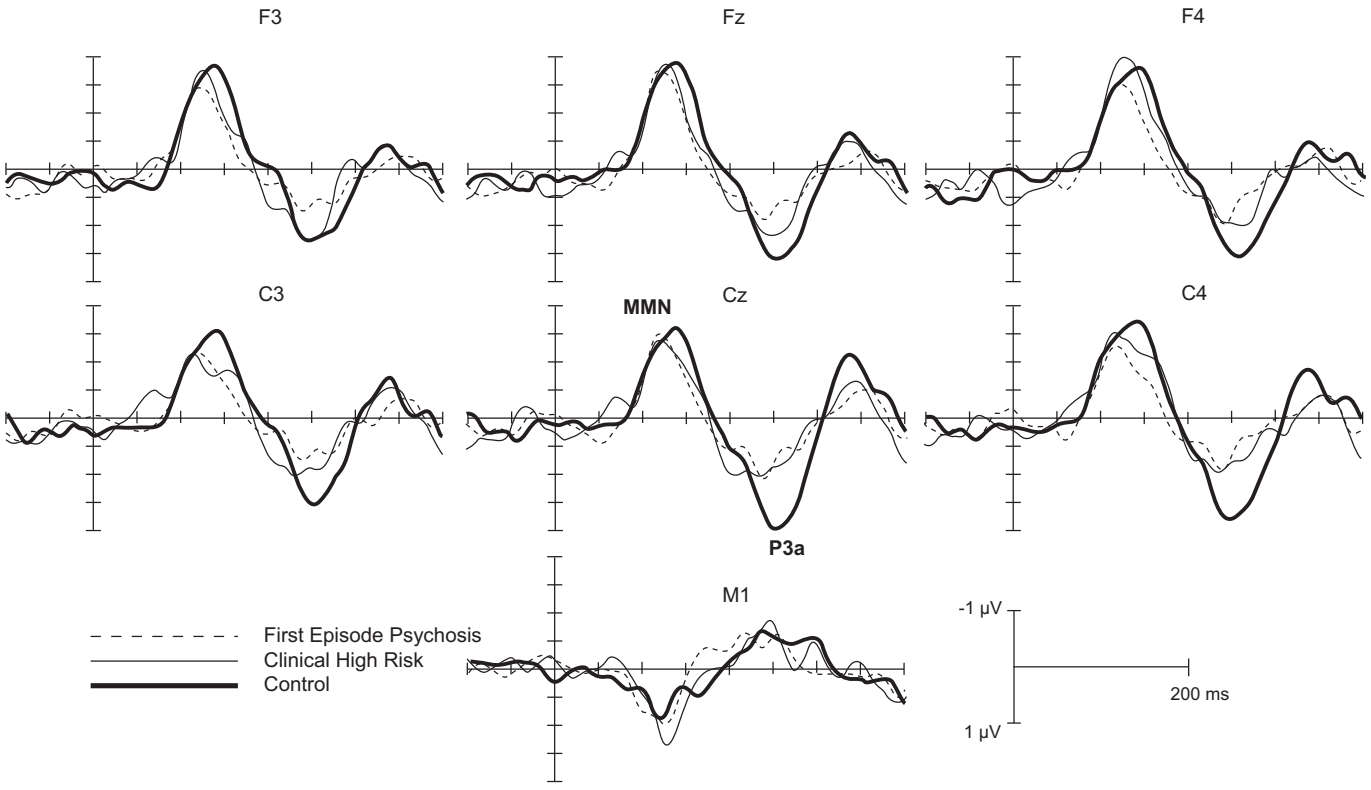

Fig. 1. MMN and P3a grand averages in the three groups.

MMN has shown promising results as a possible vulnerability marker for schizophrenia (Atkinson et al., 2012; Bodatsch et al., 2010; Brockhaus-Dumke et al., 2005; Jahshan et al., 2012; Shaikh et al., 2012). However, it must be noted that this ERP has been sensitive to CHR participants and FEP patients only when the auditory disparity is triggered by a change in the stimuli duration, rather than another stimulus feature (i.e., frequency) (Mitchie, 2001; Todd et al., 2008; Umbricht and Krljes, 2005). Since MMN in this study was obtained using a passive auditory frequency deviant, our results are consistent with previous reports where the same deviant modality was used (Todd et al., 2008; Valkonen-Korhonen et al., 2003). Nevertheless, decreased amplitude of frequency MMN has been observed in chronic schizophrenia patients (Salisbury et al., 2002). Consequently, it would be relevant to continue analyzing MMN in different deviant modalities in longitudinal designs to identify those illness stages in which different afferents from the auditory and frontal cortex responsible for the difference waveforms obtained, fail to produce the mismatch detection process. It is also important to consider that we used a fixed pattern for the presentation of the deviant stimuli, and this could have had an effect in the MMN amplitude of the groups (Todd et al., 2010).

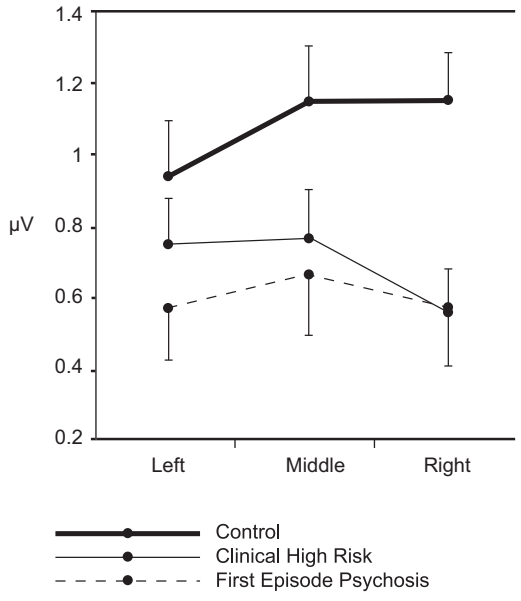

Fig. 2. Mean ± SEM amplitudes for P3a in left (F3, C3), middle (Fz, Cz) and right (F4, C4) scalp regions in the three groups.

A recent study by Kaur et al. (2012) studied MMN and P3a in FEP patients that were divided according their symptomatology: FEP affective-spectrum (bipolar disorder with psychotic features and major depressive disorder with psychotic features) and FEP schizophrenia spectrum (schizophrenia, schizoaffective disorder, and schizophreniform disorder). These authors found significant correlations between MMN amplitudes and psychiatric symptomatology for the whole patient group. Although we did not find any significant correlations between any clinical measure in the FEP group and MMN and P3a measures, these discrepancies could be related to the fact that our sample did not include affective psychosis.

To our knowledge, this is the first study where P3a is reported in antipsychotic naïve individuals at CHR in a passive frequency deviant MMN paradigm. Since it has been demonstrated that dopamine and antipsychotic administration have effects on P3a generation (Garcia–Garcia et al., 2011; Kähkönen et al., 2002; Marco-Pallarés et al., 2010; Solís-Vivanco et al., 2011; Takeshita and Ogura, 1994), the study of antipsychotic naïve subjects is clearly important.

Since clinical and experimental data have revealed that P3a represents the involuntary shift of attention to potentially relevant stimuli (McCarthy et al., 1997; Polich, 2007), it is assumed that schizophrenia patients show an impairment in the automatic attentional shift. This could represent a general increased distractibility in attentional tasks, as it has been confirmed by Cortiñas et al. (2008). Since we obtained the P3a in a passive auditory mismatch detection paradigm, the relation between the observed impairment of novelty detection in this sample and the presumed increased distractibility (i.e., larger reaction times or error rate) at a behavioral level remains unknown. It would be relevant to assess the P3a characteristics in these clinical groups using "active" attention tasks with unpredictable deviant stimuli widely reported in involuntary attention research (Escera et al., 2000; Schröger et al., 2000). The functional and cognitive implication of P3a amplitude decrement in CHR and FEP patients should be studied further. The difficulty to shift the attentional set automatically could strongly influence the neuropsychological dysfunction reported in schizophrenia (i.e., executive function) (Bozikas et al., 2005; Freedman and Brown, 2011; Luck and Gold, 2008). Supporting this assumption, Valkonen-Korhonen et al. (2003) have proposed that sensory information processing deficits in schizophrenia become more evident in later stages, where novelty detection and attention dependent mechanisms are involved. According to these authors and Sato et al. (2002), these deficits could be related to an impaired functioning of frontal attentional mechanisms.

It has been proposed that the neurophysiological generators of P3a correspond to prefrontal cortex, hippocampus and striatum (Alho et al., 1994; Escera and Corral, 2007). Consistent with the above, a recent meta-analysis reported that individuals identified at CHR, showed decrement in gray matter of the right superior temporal gyrus, left medial frontal gyrus, right middle frontal gyrus, bilateral hippocampus regions and bilateral anterior cingulate (Fusar-Poli et al., 2011a, 2011b; Wood et al., 2008). Moreover, individuals who progressed to a full-blown psychotic disorder, showed volume reduction in the right inferior frontal gyrus and the right superior temporal gyrus (Fusar-Poli et al., 2011a). In our study, the P3a amplitude decrement was greater on the right in both clinical groups. This result was previously reported by Cortiñas et al. (2008) in chronic medicated patients. To our knowledge, there are no previous reports about this lateralization effect of P3a in individuals at CHR. The decrement in P3a in the right regions could be an important finding since it has been reported that the novelty detection is mainly processed in the right frontal lobe (Deouell and Knight, 2009; Stevens et al., 2005). Thus, P3a amplitude decrement could be due to the major neural loss at right frontal regions observed in CHR subjects. Nevertheless, it would be imperative to carry out studies in which brain structural data (such as grey matter volume (Pantelis et al., 2003) and cortical thickness (Jung et al., 2011)), and P3a characteristics could be associated in individuals at risk for psychosis.

Limitations of this study need to be considered. First, the relatively small sample we assessed. All of the participants in the current study were naïve to antipsychotic treatment, which makes this small sample quite valuable. Second, we did not include cognitive evaluations or structural MRI analyses: we therefore could not address the possibility of an effect of cognition or gray matter loss associated with P3a amplitude reduction. Third, we do not know the proportion of those individuals at CHR that will develop psychosis, since the present study is a cross-sectional one. Longitudinal studies have found that between 19% and 40% of individuals at CHR develop a primary psychotic illness within 1–2.5 years of follow-up (Cannon et al., 2008; de la Fuente-Sandoval et al., in press; Ruhrmann et al., 2010; Yung et al., 2003). Due to the heterogeneity of clinical outcomes in the CHR population (Addington et al., 2011), further longitudinal studies are needed to determine the true difference in MMN and P3a of those subjects that will convert to psychosis. Longitudinal assessment is essential to identify information processing and cognitive features of those individuals who will develop psychosis in the future. The results reported by Atkinson et al. (2012) revealed that those individuals who later developed psychosis, displayed smaller P3a amplitudes than those who did not convert.

In conclusion, we found a decrement of P3a amplitude, but not frequency deviant MMN, in subjects at CHR and at an FEP that were naïve to antipsychotic treatment. This amplitude decrement is more evident at right scalp regions in both clinical samples. Our results support the evidence that P3a could represent a neurophysiological vulnerability marker for psychosis. It's imperative to continue exploring P3a sensitivity and reliability for the early identification of individuals at risk for schizophrenia.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2012.12.017.

Conflict of interest

C de la Fuente-Sandoval has received grant support from CONACyT, ICyTDF and Janssen (Johnson & Johnson), and has served as consultant and/or speaker for IMS Health, Carnot Laboratories, Eli Lilly and Janssen. The rest of the authors declare no conflict of interest.

Contributors

A Mondragón-Maya conducted the study, ran the experiment with all participants and wrote the manuscript since the first draft.

R Solís-Vivanco ran the experiment with all the participants, undertook the statistical analyses and wrote the manuscript since the first draft.

P León-Ortíz interviewed and identified the clinical sample, recluted all the participants and reviewed the manuscript along its progress.

Y Rodríguez-Agudelo supervised the protocol and reviewed the manuscript along its progress.

G Yáñez-Téllez supervised the protocol and reviewed the manuscript along its progress.

J Bernal-Hernández supervised the experimental design and reviewed the manuscript along its progress.

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

C 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.

Role of funding source

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UC-MEXUS, CONACyT, PUIS and SNI had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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