Auditory mismatch negativity, P300, and disability among first-episode schizophrenia patients without auditory hallucinations

Nagy Fawzy[a], Osama Gado[a], Ahmed M. Abdalla[a], Wailed M. Ibrahim[b]

[a]Department of Psychiatry, [b]Department of Audiology Unit, ENT, Zagazig University, Zagazig, Egypt

Correspondence to Nagy Fawzy, PhD, Department of Psychiatry, Zagazig University, Zagazig, Sharkia, Egypt
Tel: +20552386386; fax: 0552386386;
e-mail: nagyfawzy2007@yahoo.com

Received 04 January 2015
Accepted 03 April 2015

Egyptian Journal of Psychiatry
2015, 36:112–117

Objectives

The aim of this study was to determine the functional deficits, including the inter-related domains of attention, memory, and information processing, among first-episode schizophrenia patients without auditory hallucinations. Such deficits could be evaluated objectively utilizing measurements of auditory-evoked potentials.

Patients and methods

The study sample consisted of two groups: group I included 58 first-episode schizophrenia patients without auditory hallucinations recruited from the psychiatric outpatient's clinics of Zagazig University Hospitals and group II included 53 participants selected randomly from Zagazig University Hospitals' visitors. Patients were subjected to a semistructured psychiatric interview using DSM-IV criteria for diagnosis, and auditory mismatch negativity (MMN) and P300 were assessed in schizophrenia patients before and after treatment. The degree of disability was assessed and its correlation with auditory processing function was determined.

Results

Our study showed no statistically significant difference as regards MMN measures with any observable effect of atypical antipsychotics; the P300 component showed delayed latency and smaller amplitude before treatment and markedly enhanced after treatment, and there was statistically significant correlation between the degree of disability and MMN, as well as P300 measures, before and after treatment.

Conclusion

The current study concluded that the attention-dependent processes reflected in P300 measures are already defective during the early stage of schizophrenia and could be improved with the use of an atypical antipsychotic medication.

Keywords:
auditory mismatch negativity, disability, P300, schizophrenia

Egypt J Psychiatr 36:112–117

1110-1105

Introduction

Schizophrenia is a complex illness that is characterized by significant impairment of social, psychological, and cognitive functioning (Adler *et al.*, 2004). Poor executive functions, together with defective attention and echoic memory, are the main cognitive deficits encountered in schizophrenic patients (Ehrenreich *et al.*, 2007; Ranganath *et al.*, 2008). These deficits are mostly subtle and are often detected with specific neurophysiological tests. Among these tests are the measurements of auditory mismatch negativity (MMN) and P300. Schizophrenic patients mostly have a deficit in auditory sensory processing as reflected by the reduction in MMN and P300 amplitudes (Kircher *et al.*, 2004; Arnfred, 2006; Salisbury *et al.*, 1998). Many authors have reported that these deficits appear to be unmodulated with the utilization of the typical antipsychotic medication (Light *et al.*, 2000). Nowadays, with the introduction of atypical antipsychotics into the mainstream treatment of schizophrenia, it is important to fully explore its neurobiological and clinical effects in such patients. This work was designed to assess the inter-related domains of auditory sensory processing, memory, and attention in schizophrenic patients before and following the use of an atypical antipsychotic medication. The auditory MMN can occur in response to deviance in pitch, intensity, or duration. The auditory MMN is a frontocentral negative potential with sources in the primary and nonprimary auditory cortex and a typical latency of 150–250 ms after the onset of the deviant stimulus. Sources could also include one from the right opercular part of the inferior frontal gyrus. The amplitude and latency of the MMN is related to how different the deviant stimulus is from the standard. Large deviances elicit MMN at earlier latencies. For very large deviances, the MMN can even overlap the N100 (Campbell *et al.*, 2007). Auditory event-related potentials are averaged neural responses that are time locked to some specified auditory event (Stapells, 2004). Such an event could be a physical stimulus, a change in a train of stimuli, a missing stimulus, or a stimulus that has been designated to be a target one. These potentials could be divided into two major categories: Sensory-evoked potentials and processing-contingent potentials (PCPs) (Steinschneider *et al.*, 1992).

 DOI: 10.4103/1110-1105.158120

Sensory-evoked potentials represent the obligatory sensory processing stage, which depend upon the presence of auditory stimuli, and are sensitive to changes in the physical characteristics of the stimuli (Martin *et al.*,2006). In contrast, PCPs are associated with further processing of the sensory stimuli beyond the obligatory stage (Martin *et al.*, 2006). These potentials are associated with active, attention-dependent, perceptual, or cognitive processes and with automatic processing that is not under volitional control (Stapells, 2004). MMN and P300 are the two main components of PCPs. Both refer to the ability to compare a deviant stimulus from a previously stored set of identical stimuli. Odatsch *et al.* (2011) found that MMN durations were reduced in a group of schizophrenia patients who later went on to have psychotic episodes, suggesting that MMN durations may predict future psychosis. MMN is an automatic preattentive response that is thought to reflect the short-term memory and is independent of higher-level cognitive processes (Kircher *et al.*, 2004). However, P3b component of the P300 response cannot be elicited without selective activation of the attention-triggering mechanisms; thus, it reflects the conscious perception of the stimulus change (Stapells, 2004).

Patients and methods

This study was carried out in the psychiatry outpatient clinics of Zagazig University Hospitals between April 2013 and June 2014. The study sample consisted of 58 patients with the diagnosis of first-episode schizophrenia, who were recruited from the psychiatric outpatient clinic of Zagazig University Hospitals, and 53 healthy volunteers as a control group recruited from Zagazig University Hospitals' visitors. Inclusion criteria were as follows: patients fulfilling the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. criteria for schizophrenia in the patient group, age between 16 and 40 years, both sexes, and individuals from all educational and socioeconomic classes. The exclusion criteria were as follows: patients with other psychiatric or physical disorders, auditory hallucinations, mental retardation, substance dependence, history of documented learning disability, metabolic disorders, patients previously treated with antipsychotic medication, and those with hearing loss. All participants provided written informed consent before the start of the study. Approval was obtained from the Institutional Review Board (IRB) and the Department of Psychiatry, Zagazig University.

Detection of schizophrenia and other psychotic disorders was based on the semistructured psychiatric interview with resultant DSM-IV-TR diagnosis (American Psychiatric Association, 2000) Disability was measured with the help of the WHO Disability Assessment Schedule, version 2.0 (WHO/DAS II). It is a 36-item semistructured interview that measures the self-reported difficulty of functioning in six major domains, which are considered to be important in most cultures.

Equipment

A two-channel audiometer Orbiter model 922 connected to a sound-treated booth.

A middle ear analyzer Interacoustic model AT 235h.

Auditory evoked potential system, Intelligent hearing systems model Smart EP, version 2.39.

Measurements of auditory evoked potentials: For every patient, both MMN and P300 were measured twice, at two different sessions, just before and 3 months after treatment. The following procedure was used:

(1) *Stimulus parameters*: The stimuli were presented binaurally within an odd-ball paradigm, with the frequent stimulus (the phoneme ba for MMN and 1 KHz tone burst for P300) occurring in 80% and the rare stimulus (the phoneme da and 1.5 KHz tone burst) occurring in 20% of the total number of presentations. The stimuli were presented at a rate of 1/s with an intensity of 75 dB nHL.
(2) *Recording parameters*: A two-channel recording was used with the common electrode on FPz, the two active electrodes on Cz and Pz, and the two reference electrodes on M1 and M2.
(3) *Technique*: Only for P300 measurement, the patients were instructed to be mentally attentive and to count the number of the rare stimuli. A total of 100 sweeps were presented with averaging of the rare and frequent sweeps on separate traces.
(4) *Data analysis*: On comparing the frequent and rare waveforms, MMN and P300 responses were identified, with subsequent measurement of their latencies and amplitudes.

Statistical plane

χ^2-Test analysis was utilized to compare the sociodemographic characteristics of the study group with that of the control group. Thereafter, the analysis of variance (ANOVA) test was used to detect the differences between the two groups before and after treatment as regards the latency and amplitude of MMN and P300. On the basis of the ANOVA test results, post-hoc comparisons were conducted to determine which groups differ from each other. For such propose, Tukey's studentized range test was used. Such a test yields a value that is called the honestly significant difference (HSD) value.

Statistical analyses

The statistical differences between the mean of the tested groups were compared with the HSD value. If the HSD value was above the statistical differences, the differences were considered to be statistically significant. Significance levels were set at *P* value of 0.05 or less.

$$\text{HSD} = q\sqrt{\frac{\text{MS within}}{n}},$$

where q is a table value that corresponds to the group number and the degree of freedom at *P* value of 0.05 or less; n is number of tested values; MS is mean square that is obtained from the already computed ANOVA.

Finally, Pearson's correlation test (*R*-value) was used to correlate the degree of disability with the measures of both MMN and P300 before and after treatment.

Results

The present study reported the sociodemographics and characteristics of the study group and the control group (Table 1). For every patient, MMN and P300 components were measured twice, just before and 3 months after the use of medication. The results were compared with that of the control group. As regards the speech elicited MMN, no statistically significant difference was observed between the three measurements without any observed effect of medication (Table 2). In contrast, the mean latencies and amplitudes of the tonal P300 component are presented in Table 3. Patients showed delayed latencies and smaller amplitudes before medication compared with those of the control group. Such difference is proved to be statistically significant (Table 3). Following treatment, patients still had delayed latencies and smaller amplitudes; however, a statistically significant improvement was observed on comparing the measures before and after treatment

Table 1 Sociodemographic characteristics of the study group and the control group

Variables	Patients (*n* = 58)	Controls (*n* = 53)	Test statistics	
			F	*P*
Age (mean ± SD)	29.1 ± 9.05	25.5 ± 5.9	1.12	0.27
Sex [*n* (%)]			χ^2	*P*
Male	32 (55)	28 (53)	0.27	0.60
Female	26 (45)	25 (47)		
Marital status [*n* (%)]				
Single	18 (69)	19 (36)	0.004	0.99
Married	40 (31)	34 (64)		
Residence [*n* (%)]				
Rural	39 (67)	37 (70)	1.04	0.32
Urban	19 (33)	16 (30)		
Education [*n* (%)]				
Low	26 (45)	20 (38)	0.05	0.93
High	32 (55)	33 (62)		
Employment [*n* (%)]				
Employed	33 (57)	18 (34)	2.98	0.19
Unemployed	25 (43)	35 (66)		
Home atmosphere [*n* (%)]				
Bad	31 (53)	18 (34)	2.19	0.87
Good	27 (47)	35 (66)		

Table 2 Comparison between mismatch negativity measures in the control group and the study group before and after treatment

Variables	Measure	MMN latency (ms)	MMN amplitude (uυ)
Control group	X_1	202	4.13
	SD1	± 13.5	0.82
Study group before treatment	X_2	197	3.78
	SD2	± 8.07	0.62
Study group after treatment	X_3	200	3.87
	SD3	± 12.3	0.55
ANOVA	MS	132.9	0.45
	F	2.21	2.7
	P	0.115	0.07
HSD		6.35	0.37

ANOVA, analysis of variance; HSD, honestly significant difference; MMN, mismatch negativity; MS, mean square

(Table 3). Such improvement with treatment was also noticed for the degree of disability as measured with WHO/DAS II (Table 4). Furthermore, the amplitude of the P300 component showed a significant negative correlation with the degree of disability, denoting smaller amplitudes with higher degrees of disability. Such finding was observed with and without treatment (Table 5).

Discussion

Cognitive impairment is a common feature in schizophrenic patients, which is thought to reflect the neurophysiological and neurochemical changes in the auditory cortex. The functional state of the neural substrate of auditory information processing for those patients could be objectively probed with measurement of auditory cortical event-related potentials (Korostenskaja and Kahkonen, 2007). For such purpose, an odd-ball paradigm is used to elicit MMN and P300 responses to phoneme and tonal deviants, respectively. Such stimuli could reflect the preattentive and attention-dependent information processing at various levels of difficulty. Patients having effects of previous antipsychotic medications as well as patients with negative symptoms were excluded in order to allow maximum psychological stability during testing. Moreover, patients with predominantly negative symptoms mostly have a more pronounced cognitive impairment (Mubarak *et al.*, 1999). Measurements were carried out just before and 3 months after utilization of risperidone treatment, which is thought to modulate the neurochemical changes in those patients. For speech-elicited MMN, no statistically significant difference could be detected between patients and healthy controls (Table 2). Utilizing different types of physically deviant tones, Salisbury *et al.* (2002) and Magnoac *et al.* (2008) reported similar results. They concluded that the reduction in MMN is usually present in patients with chronic schizophrenia but not with first onset cases. Furthermore, Umbricht and Krljes (2005), on summarizing the results on MMN changes from about 40 published studies, concluded a strong association between a deficient MMN generation and chronic schizophrenia. Recently, Fisher *et al.* (2008) and Todd *et al.* (2008) showed specific MMN changes only with the use of duration and intensity deviants.

Table 3 Comparison between P300 measures in the control group and the study group before and after treatment

Variables	Measure	P300 latency (ms)	P300 amplitude (uυ)
Control group	X_1	357	15.0
	SD1	49.3	2.51
Study group before treatment	X_2	556	7.47
	SD2	25.3	1.25
Study group after treatment	X_3	357	15.5
	SD3	46	2.05
ANOVA	MS	692.4	5.66
	F	12.05	65.9
	P	<0.001	<0.001
HSD		14.51	1.36

ANOVA, analysis of variance; HSD, honestly significant difference; MS, mean square.

Table 4 Degree of disability among schizophrenic patients based on the WHO/DAS II score before and after treatment

Degree of disability	Before treatment		After treatment	
	n (%)	*X* score	*n* (%)	*X* score
None	0	–	18 (31)	12.9
Mild	0	–	3 (5)	28.5
Moderate	26 (45)	48.2	23 (39)	48
Severe	17 (29)	66.6	9 (20)	66
Extreme	15 (26)	88.2	3 (5)	90.5
Total	58 (100)	64.1	58 (100)	43.3

Statistically significant improvement of disability after treatment ($P > 0.001$).

Table 5 Correlation between the degree of disability and mismatch negativity, as well as P300 measures, before and after treatment

Disability	MMN		P300	
	Latency	Amplitude	Latency	Amplitude
Before treatment	0.53	−0.58	0.56	−0.72*
After treatment	0.52	−0.47	0.41	−0.78*

MMN, mismatch negativity; *Statistically significant according to *R*-value.

In the current study, phoneme deviants were utilized aiming to detect a different observation among first episode cases. The rationale came from reviewing the study of Korostenskaja *et al.* (2003), who concluded that the sensitivity of MMN in schizophrenic patients could be improved with other measurement parameters such as the slope of the ascending MMN wave or the MMN area. However, it seems that MMN deficits in schizophrenic patients are progressive and mostly not manifested at the illness onset. In contrast with MMN results, a statistically significant difference was detected in P300 response between schizophrenic patients and healthy controls (Table 3). P300 studies with unmedicated schizophrenic patients are quite rare (Korostenskaja and Kahkonen, 2007). Jeon and Polich (2003) and Salisbury *et al.* (1998) observed deficient P300 latency and amplitude, respectively, at initial hospitalization of those patients. Such observation could indicate that the attention-dependent processes reflected in P300 component are already slowed down during the early stages of schizophrenia. This speculation is supported by Mathalonab *et al.* (2000), who concluded that reduced P300 amplitude may be used as a marker of an early onset variant of schizophrenia. Such amplitude reduction is also associated with an increase in the degree of disability (Table 5). Iwanami *et al.* (1999) reported a similar finding and concluded that P300 amplitude could be used as an index for disability of daily life in schizophrenia. Following treatment, both P300 latency and amplitude were significantly enhanced; however, it was still outside the normal values. It is likely that the alleviation of negative symptoms with treatment is responsible for such improvement.

Umbricht *et al.* (1999) and Iwanami *et al.* (2001) obtained similar results after 6–9 and 4 weeks of treatment, respectively, utilizing doses between 4 and 6 mg/day. Contrary to these results, Korostenskaja and Kahkonen (2007) showed no changes in P300 parameters with treatment. Their patients were treated only for 2 weeks at a dose of 2.5 ± 1 mg/day. Actually, it seems that, the effect of treatment on active attention as measured by P300 is dose and time dependent. Furthermore, the amplitude of the P300 component showed a significant negative correlation with the degree of disability, denoting smaller amplitudes with higher degrees of disability. The attention-dependent processes reflected in P300 measures are already defective during the early stage of schizophrenia and could be improved with the use of an atypical antipsychotic medication.

Conclusion

The current study concluded that the attention-dependent processes reflected in P300 measures are already defective during the early stage of schizophrenia and could be improved with the use of an atypical antipsychotic medication.

Recommendations

We recommend performing auditory MMN and P300 for schizophrenia patients as a method for the diagnosis and efficacy of treatment. Further studies are required to show the difference between chronic and first-episode schizophrenia.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

Adler LE, Olincy A, Cawjhra E, *et al.* (2004). Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. Am J Psychiatry 161:1822–1828.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 2000.

Arnfred SM (2006). Exploration of auditory P50 gating in schizophrenia by way of difference waves. Behav Brain Funct 2:6.

Campbell T, Winkler I, Kujala T (2007). N1 and the mismatch negativity are spatiotemporally distinct ERP components: disruption of immediate memory by auditory distraction can be related to N1. Psychophysiology 44:530–540.

Ehrenreich H, Hinze-Selch D, Stawicki S, Aust C, Knolle-Veentjer S, Wilms S, *et al.* (2007). Improvement of cognitive functions in chronic schizophrenic patients by recombinant human erythropoietin. Mol Psychiatry 12:206–220.

Fisher DJ, Labelle A, Knott VJ (2008). The right profile: mismatch negativity in schizophrenia with and without auditory hallucinations as measured by a multi-feature paradigm. Clin Neurophysiol 119:909–921.

Iwanami A, Yamashina M, Kazamatsuri H, Kamijima K (1999). P300 and disability of daily life in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 23:423–430 .

Iwanami A, Okajamay M, Isono H, *et al.* (2001). Effect of respridone on event – related potentials in schizophrenic patients. Pharmacopsychiatry 43:73–79.

Jeon YW, Polich J (2003). Meta-analysis of P300 and schizophrenia: patients, paradigms, and practical implications. Psychophysiology 40:684–701.

Kircher TTJ, Rap A, Grodd W, *et al.* (2004). Mismatch negativity response in schizophrenia; a combined fMRI and whole-head EMG study. Am J Psychiatry 161:294–304.

Korostenskaja M, Kahkonen S (2007). Neurochemical regulation of auditory information processing studies with EEG/MEG: application to schizophrenia [MD Thesis]. Finland: Cognitive Brain Research Unit, Department of Psychology, Helsinki University.

Korostenskaja M, Dapsys K, Maciulis V, Ruksenas O (2003). Evaluation of new MMN parameters in schizophrenia. Acta Neurobiol Exp (Wars) 63:383–388.

Light GA, Geyer MA, Clementz BA, Cadenhead KS, Braff DL (2000). Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications. Am J Psychiatry 157:767–771.

Magnoac E, Yeapabc S, Thakoreac JH Garavanabc H, *et al.* (2008). Are auditory-evoked frequency and duration mismatch negativity deficits endophenotypic for schizophrenia? High-density electrical mapping in clinically unaffected first-degree relatives and first-episode and chronic schizophrenia Biol Psychiatry 64:385–391.

Martin BA, Kelly L, Stapells DR (2006). Principles and applications of cortical auditory evoked potential. In: Burkard RF, Eggermont JJ, Marvel D, (editors) *Auditory evoked potential: basic principles and clinical applications*. Baltimore, USA: Lippincott Williams & Wilkins; 482–507.

Mathalon DH, Ford JM, Rosenbloom M, Pfefferbaum A (2000). P300 reduction and prolongation with illness duration in schizophrenia. Biol Psychiatry 47:413–427.

Mubarak A, El Dod A, Gad S (1999). Neurological and cognitive deficits in schizophrenic patients. German J Psychiatry 2:22–33.

Odatsch M, Ruhrmann S, Wagner M, *et al.* (2011). Prediction of psychosis by mismatch negativity. Biol Psychiatry 69:959–966.

Ranganath C, Minzenberg MJ, Ragland JD (2008). The cognitive neuroscience of memory function and dysfunction in schizophrenia. Biol Psychiatry 64:18–25.

Salisbury DF, Shenton ME, Sherwood AR, Fischer IA, Yurgelun-Todd DA, Tohen M, McCarley RW (1998). First-episode schizophrenic psychosis differs from first-episode affective psychosis and controls in P300 amplitude over left temporal lobe. Arch Gen Psychiatry 55:173–180.

Salisbury DF, Shenton ME, Griggs CB, *et al.* (2002). Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. Arch Gen Psychiatry 59:686–694.

Stapells DR (2004). Cortical event-related potentials to auditory stimuli. In: J Katz, (editor) *Handbook of clinical audiology*. Baltimore, USA: Lippincott Williams & Wilkins; 378–406.

Steinschneider M, Tenke CE, Schroeder CE, Javitt DC, Simpson GV, Arezzo JC, Vaughan HG Jr (1992). Cellular generators of the cortical auditory evoked potential initial component. Electroencephalogr Clin Neurophysiol 84:196–200.

Todd J, Michie PT, Schall U, *et al.* (2008). Deviant matters: duration, frequency, and intensity deviants reveal different patterns of mismatch negativity reduction in early and late schizophrenia. Biol Psychiatry 63:58–64.

Umbricht D, Krljes S (2005). Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res 76:1–23.

Umbricht D, Javitt D, Novak G, Bates J, Pollack S, Lieberman J, Kane J (1999). Effects of risperidone on auditory event-related potentials in schizophrenia. Int J Neuropsychopharmacol 2:299–304.