Auditory Processing - Contingent Potentials and disability in Schizophrenic Patients Treated with Atypical Antipsychotic Medication

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ABSTRACT

Background: Schizophrenia is conceptualized as a neuro-developmental disease with multiple functional deficits including the interrelated domain of attention, memory and information processing. Such deficits could be evaluated objectively utilizing measurements of auditory evoked potentials. **Subjects and methods:** For such purpose auditory mismatch negativity (MMN) and P300 were assessed in 38 first-episode schizophrenic patients just before and after risperidone treatment. The study assessed the degree of disability and its correlation with auditory processing. **Results:** On comparing the measured values with that of the normal control subjects, no statistically significant difference was detected as regards MMN measures with any observable effect of atypical antipsychotic. On the other hand, P300 component showed delayed latency and smaller amplitude for the unmedicated patients that were markedly enhanced after atypical antipsychotic treatment; also there is statistically significant correlation between the degree of disability and MMN as well as P300 measures before and after treatment. **Conclusion:** These results indicated that the attention-dependent processes reflected in P300 measures are already defective in the early stage of schizophrenia and could be improved with the use of atypical antipsychotic medication.

Key words: Schizophrenia, Auditory Processing, Contingent Potentials, Atypical antipsychotic.

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INTRODUCTION

Auditory event-related potentials (ERPs) are averaged neural responses that are time locked to some specified auditory event [1]. Such 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 (SEPs) and Processing-contingent potentials (PCPs)[2]. SEPs represent the obligatory sensory processing stage that depend upon the presence of auditory stimuli, and are sensitive to changes in the physical characteristics of the stimuli (3). On the other hand, the PCPs are associated with further processing of the sensory stimuli beyond the obligatory stage[3]. These potentials are associated with active, attention-dependent, perceptual or cognitive processes and with automatic processing that is not under volitional control[1]. Mismatch negativity (MMN) and P300 are the two main components of the PCPs. Both refer to the ability to compare a deviant stimulus from a previously stored set of identical stimuli. MMN is an automatic pre-attentive response that is thought to reflect

the short-term memory and is independent of higher-level cognitive processes[4]. While, 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[1].

Schizophrenia is a complex illness that is characterized by significant impairment of social, psychological and cognitive functioning[5]. Poor executive functions together with defective attention and echoic memory are the main cognitive deficits encountered in schizophrenic patients[6-7]. These deficits are mostly subtle and are often detected with specific neurophysiological tests. Among these tests are the measurements of auditory MMN and P300. Schizophrenic patients mostly have a deficit in auditory sensory processing as reflected by the reduction of MMN and P300 amplitudes[4, 8-9]. Many authors reported that these deficits appear to be unmodulated with the utilization of the typical antipsychotic medication[10]. Nowadays, with the introduction of the atypical antipsychotics into the mainstream treatment of schizophrenia, it is important to fully explore its neurobiological and clinical effects among those patients. Second-generation antipsychotic agents were found to be inconsistently more effective than first-generation agents in alleviating negative, cognitive, and depressive symptoms and had a lower liability to cause tardive dyskinesia[11]. This work is designed to assess the interrelated domains of auditory sensory processing, memory and attention in schizophrenic patients prior to and following the use of atypical antipsychotic medication.

SUBJECTS AND METHODS

Study Group: According to the semi-structured psychiatric interview using the DSM-IV criterion, 38 patients with diagnosis of first-episode schizophrenia were recruited from the psychiatric outpatient clinic of Zagazig University Hospitals. To be included in the study, patients should have predominantly negative symptoms with an age between 20 and 45 years with no limitation as regards social or occupational classes, and were in good physical health. Participants excluded if there is a history of mood, personality or schizo-affective disorder, documented learning disability or developmental disorder, mental retardation, history of substance abuse, dementia as well as any chronic illness and those with hearing loss. All participants provided written informed consent before testing.

Control Group: Thirty-two normal healthy subjects were selected from the visitors as well as the nurses and workers of the audiology unit, Zagazig University Hospitals. They match the study group as regards the inclusive and exclusive criteria without any history of psychiatric disorder among them and their family.

This study has been done between August 2008 and April 2009 and all participants gave a written consent.

Psychiatric assessment:

1- Collection of brief socio-demographic data and assessment of the mental state.

2- Treatment*:* Risperidone, as one of the atypical antipsychotics, was given for each patient by a dose ranging between 2-4mg/day regularly for 3 months.

3- Measurement of disability: It was measured with the help of the world health organization disability assessment schedule version 2.0 (WHO/ DAS II). It is a 36 items semi-structured interview that measures the

self-reported difficulty of functioning in six major domains which are considered to be important in most cultures.

Equipment: 2-channel audiometer Orbiter model 922 connected to sound-treated booth. Middle ear analyzer inter-acoustic 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 the use of risperidone and 3 months after. For such purpose, 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 1.5KHz tone burst) occurring in 20 % of the total number of presentations. The stimuli were presented at a rate of 1/sec. by 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 while 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: by comparing the frequent and rare waveforms, MMN as well as P300 responses were identified with subsequent measurement of their latencies and amplitudes.

Statistical Analyses:

Chi–square analysis was utilized to compare the socio–demographic characteristics of the study with that of the control group. Then, 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. According to 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 test yields a value that is called the honestly significant difference (HSD) value. The statistical differences between the mean of the tested groups were compared to this value. If it was above it, the differences were considered to be statistically significant. Significance levels were set at $P \leq 0.05$.

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

q = a table value that corresponds to the groups number and the degree of freedom at $P \leq 0.05$.
n = number of tested values.
MS = (mean square) that is obtained from the already computed ANOVA.
Finally, Pearson's correlation test was used to correlate the degree of disability with the measures of both MMN and P300 before and after treatment.

RESULTS

Among patients who were selected to participate in the study, 18 males and 20 females were able to complete the whole test battery. The results of the remaining 14 patients were omitted. Thus, data from 32 normal control subjects and 38 patients with

first-episode schizophrenia were analyzed. On comparing the socio-demographic characteristics, both study and control groups tend to be equivalent (table 1).

For every patient, MMN and P300 components were measured twice, just before and 3 months after the utilization of the atypical antipsychotic 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 3 measurements without any observed effect of Risperidone (table 2).

Table (1): Socio - demographic characteristics of the study versus the control group.

Variables		Study group (N=38)		Control group (N=32)		Chi - square Analysis	
		N	%	N	%	x^2 (df=1)	P
Sex	Males	26	68.4	20	62.5	0.27	0.60
	Females	12	31.6	12	37.5		
Residence	Urban	13	34.2	10	31.2	0.07	0.74
	Rural	25	65.8	22	68.8		
Education	Low	16	42.1	13	40.6	0.02	0.90
	High	22	57.9	19	59.4		
Marital state	Married	24	63.1	20	62.5	0.003	0.95
	Unmarried	14	36.9	12	37.5		
Home atmosphere	Good	17	44.7	20	62.5	2.19	0.87
	Bad	21	55.3	12	37.5		
Special habits	Positive	22	57.9	12	37.5	2.89	0.09
	Negative	16	42.1	20	62.5		

Table (2): Comparison between MMN measures in the control group and the study group before and after treatment.

Group	Measure	MMN latency (ms.)	MMN amplitude (uv.)
Control group	X1	202	4.13
	SD1	13.5	0.82
Study group before ttt	X2	197	3.78
	SD2	8.07	0.62
Study group after ttt	X3	200	3.87
	SD3	12.3	0.55
ANOVA	MS	132.9	0.45
	F	2.21	2.7
	P.value	>0.05	>0.05
HSD		6.35	0.37

MS = mean square HSD = honestly significant difference

On the other hand, the mean latencies and amplitudes of the tonal P300 component are presented in (table 3). Unmedicated patients showed delayed latencies and smaller amplitudes when compared with those of the control group. Such difference is proved to be statistically significant (table 3).

Following Risperidone treatment, patients still have delayed latencies and smaller amplitudes; however, a statistically

significant improvement was observed on comparing the measures before and after treatment (table 3). Such improvement with treatment was also noticed for the degree of disability as measured with WHO/DAS II (table 4).

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

Group	Measure	P300 latency (ms.)	P300 amplitude (uv.)
Control group	X1	327	12.0
	SD1	29.3	2.31
Study group before ttt	X2	356	7.47
	SD2	23.3	1.23
Study group after ttt	X3	337	11.5
	SD3	26	2.03
ANOVA	MS	692.4	3.66
	F	12.05	63.9
	P.value	< 0.001	< 0.001
HSD		14.51	1.06

MS = mean square HSD = honestly significant difference

Table (4): Degree of disability among schizophrenic patients before & after treatment

Degree of Disability	Before ttt		After ttt	
	No. (%)	X Score	No. (%)	X Score
None	0.0	0.0	12 (31.6)	12.9
Mild	0.0	0.0	2 (5.3)	28.5
Moderate	17 (44.7)	48.2	15 (39.4)	48.0
Severe	11 (28.9)	66.6	7 (18.4)	66.0
Extreme	10 (26.4)	88.2	2 (5.3)	90.5
Total	38 (100)	64.1	38 (100)	43.3

This table showed statistically significant improvement of disability after treatment (p >0.001*)*

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 Risperidone treatment (table 5).

Table (5): Correlation between the degree of disability and MMN as well as P300 measures before and after treatment

Disability	MMN		P300	
	Latency	Amplitude	Latency	Amplitude
Before ttt	0.41	- 0.37	0.36	- 0.69*
After ttt	0.32	- 0.27	0.29	- 0.58*

** Statistically significant according to r- value*

DISCUSSION

Cognitive impairment is a common feature in schizophrenic patients that 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[12]. 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 were selected to avoid the effect of any other previous forms of antipsychotic medications as well as these patients with negative symptoms to allow the maximum psychological stability during testing. Moreover, patients with predominantly negative symptoms mostly have a more

pronounced cognitive impairment[13]. Measurements were done just before and 3 months after utilization of Risperidone treatment that is thought to modulate the neurochemical changes in those patients.

For the speech-elicited MMN, no statistically significant difference could be detected between patients and healthy control group. Utilizing different types of physically deviant tones detected similar results and concluded that the reduction of MMN is usually present in patients with chronic schizophrenia but not with first onset cases[14-15]. Furthermore, a review summarizing the results on MMN changes from about 40 published studies, concluded a strong association between a deficient MMN generation and chronic schizophrenia[16]. Recently, specific MMN changes wer detected only with the use of duration and intensity deviants[17-18]. In the current study, phoneme deviants were utilized aiming to detect a different observation among first episode cases. Inaddition, 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[19]. However, it seems that MMN deficits in schizophrenic patients are progressive and mostly not manifested at the illness onset.

By contrast with MMN results, a statistically significant difference was detected in P300 response between the schizophrenic patients and the healthy control group. Although P300 studies with unmedicated schizophrenic patients are quite rare[12]. Also deficient P300 latency and amplitude respectively at initial hospitalization of those patients was seen[9,19]. Such observation could indicate that the attention-dependent processes reflected in P300 component are already slowed down in the early stages of schizophrenia. This speculation is supported by Mathalonab et al. who concluded that reduced P300 amplitude may be used as a marker of an early onset variant of schizophrenia[20]. Such amplitude reduction is also associated with an increase in the degree of disability. A similar conclusion was reported that P300 amplitude could be used as an index for disability of daily life in schizophrenia[21]. Following Risperidone 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. Similar results were obtained after 6-9 and 4 weeks of treatment respectively utilizing doses between 4-6mg/day[22-23]. Contrary to these results, No changes in P300 parameters with Risperidone treatment was detected[12]. Their patients were treated only for 2 weeks by a dose of 2.5±1mg/day. Actually, it seems that the effect of Risperidone 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. Such finding was observed with and without Risperidone treatment.

Disability mean scores in the current study showed statistically significant improvement after treatment, as disability in schizophrenic patients has been reported to be related to negative syndrome cognitive symptoms[24]. A number of researchers have reported the role of long term hospitalisation in causing disability[25],

as many patients in the study had been hospitalized for different periods in the past, so it has a role in causing disability, every person with a schizophrenic disorder should be provided with the combination of optimal dose antipsychotics, to enhance work and social goals and reducing residual symptoms, and assertive home-based management[26].

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