Schizophrenia Research 108 (2009) 151–157

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Neuroleptic effects on P50 sensory gating in patients with first-episode never-medicated schizophrenia

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ARTICLE INFO

Article history:
Received 27 August 2008
Received in revised form 13 November 2008
Accepted 15 November 2008
Available online 23 December 2008

Keywords:
Sensory gating
P50
First-episode schizophrenia

ABSTRACT

Sensory gating deficit, as reflected by P50 suppression, has been demonstrated in schizophrenia. Despite extensive evidence of the irreversible effects of typical neuroleptics on this deficit, recent studies of atypical neuroleptics have produced inconsistent findings on the reversibility of P50 suppression in schizophrenia. As the majority of these studies were limited by either their cross-sectional design or the recruitment of patients on multiple medications, the current study was designed to examine the effects of different neuroleptic medications on the P50 sensory gating index in patients with first-episode, never-medicated schizophrenia. P50-evoked potential recordings were obtained from 62 normal controls when they entered the study and from 65 patients with first-episode, never-medicated schizophrenia at baseline and after six weeks of different neuroleptic treatments (sulpiride [n=24], risperidone [n=24] and clozapine [n=17]). The first-episode, never-medicated schizophrenia patients had impaired sensory gating relative to the normal controls (mean=94.19% [SD=61.31%] versus mean=41.22% [SD=33.82%]). The test amplitude S2 was significantly higher in the schizophrenia patients than in the normal controls. The conditioning amplitude S1 and the positive symptom scores were related to the P50 gating ratios in schizophrenia at baseline. There was no change in P50 sensory gating (P>0.10) and a significant improvement in the clinical ratings (P>0.10) after six-week neuroleptic treatment for schizophrenia. P50 sensory gating was not significant for the patients who received sulpiride, risperidone or clozapine at baseline (F=1.074, df=2, 62, P=0.348) or at endpoint (F=0.441, df=2, 62, p=0.646). Our findings indicate that there is P50 sensory gating impairment in first-episode, never-medicated schizophrenia and that treatment with typical and atypical antipsychotics has no significant impact on such gating in this illness.

1. Introduction

The inhibitory properties of the central nervous system have long been examined using conditioning-testing paradigms, under which the amount of attenuation in the neural response to the second of two identical stimuli indexes the strength of the inhibitory pathway. This paradigm has been adapted in psychophysiological research as a test of "sensory gating," and it has provided basic support for theories that postulate that individuals with schizophrenia demonstrate less effective regulation over the influx of sensory information to the brain (Adler et al., 1982; Braff et al., 1995). More specifically, the decrement in the amplitude of the P50 event-related potential (ERP) evoked by the second S2 relative to the first S1 of two auditory "clicks," which is commonly expressed

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doi:10.1016/j.schres.2008.11.016

as the suppression ratio S2/S1, is smaller in schizophrenia and is thought to reflect weak inhibition or the gating of the repeated stimulus (Freedman et al., 1987).

This deficient P50 suppression in schizophrenia patients has been confirmed repeatedly and is, according to two meta-analytic studies, one of the strongest and most reliable findings in the schizophrenia literature (Heinrichs, 2004; Bramon et al., 2004). It has prompted further studies to clarify the clinical and neural substrates of the earlier findings. Poor P50 suppression also occurs among the non-psychotic family members of patients with schizophrenia, which indicates that these deficits are not sufficient to produce the syndrome of schizophrenia, but may reflect an intermediate phenotypic marker (Adler et al., 1999; Freedman et al., 2000; Myles-Worsley, 2002). In this context, a linkage between P50 gating and the α_7 nicotinic receptor has been reported (Freedman et al., 1997).

The effects of medication on P50 suppression were initially studied to assess the dopaminergic involvement in deficient P50 suppression among schizophrenia patients. This initial study compared unmedicated patients with those taking typical antipsychotics and with normal subjects. P50 suppression was lower in the schizophrenia patients than it was in the normal subjects, and, in addition, there were no significant differences in this suppression between the medicated and unmedicated patients (Freedman et al., 1983). Myles-Worsley (2002) also found that patients who had been free of typical antipsychotic medication for at least 10 weeks were just as likely to exhibit the P50 sensory gating deficit as were patients who were receiving therapeutic doses of these medications. Furthermore, in the medicated patient group, the P50 sensory gating ratio was uncorrelated with the medication dose (Myles-Worsley, 2002). A recent study failed to find any relationship between a conventional antipsychotic dose and the P50 ratio (Louchart-de la Chapelle et al., 2005). These results suggest that impaired P50 sensory gating occurs independently of the effects of typical antipsychotics in a variety of patients at different stages of the illness.

Typical neuroleptic treatment fails to ameliorate this deficit. However, recent studies of atypical antipsychotic medications suggest that they do have an effect on P50 gating. Clozapine treatment improved P50 gating in the patients who responded to it, although this gating had been abnormal during previous treatment with typical neuroleptics (Nagamoto et al., 1996). Clozapine's amelioration of the P50 auditory gating deficit was stable in a subsequent follow-up over a 5- to 27-month period of observation (Nagamoto et al., 1999). In a cross-sectional study, Becker et al. (2004) compared patients treated with clozapine and those treated with conventional antipsychotics and found that the former had significantly lower sensory gating ratios than did the latter. Significantly reduced sensory gating ratios have been found in patients treated with clozapine, risperidone and olanzapine compared with those treated with conventional antipsychotics (Light et al., 2000). Adopting a double-blind, placebo-controlled trial design, Arango et al. (2003) found no significant differential effects in sensory gating ratios between inpatients with schizophrenia who received haloperidol and olanzapine. A recent meta-regression analysis of the relationship between medication and P50 ratios, which reviewed study reports from January 1994 to August 2003, found no significant effect of antipsychotics on the P50 sensory gating ratio, but the researchers did not divide these antipsychotics into typical and atypical medicines (Bramon et al., 2004).

Atypical medications differ from one another in their occupancy of various catecholaminergic and serotonergic receptors at therapeutic doses (Kinon and Lieberman, 1996; Kasper et al., 1999), and there are significant differences in their effects on behavioral outcome measures such as negative symptoms, cognitive dysfunction and mood stabilization (Ichikawa and Meltzer, 1999). A post hoc division of subjects treated with atypical antipsychotics by Light et al. (2000) suggested that the improvement appeared to be mainly based on the effects of clozapine and, to a lesser degree, olanzapine, as the subjects who received risperidone continued to have sensory gating in the range seen in patients who received typical neuroleptics (Light et al., 2000). By adopting a Bonferroni adjustment for pair-wise comparisons, it was found that the patients treated with clozapine had significantly better sensory gating ratios than did those who received any other atypical medication. Sixty-two percent of the patients treated with clozapine had P50 ratios within the normal range, compared with 24% of the patients who received risperidone, 14% of those who received olanzapine and 0.0% of those who received quetiapine (Adler et al., 2004). As the majority of these studies was limited, either by their cross-sectional design or because the subjects observed had been treated with multiple medications or had a medicated history, the current study was designed to observe the effects of different neuroleptic medications, both typical and atypical, on the P50 sensory gating index of patients with never-medicated, first-episode schizophrenia.

2. Methods

2.1. Subjects

All of the participants were recruited from the Mental Health Center of Shantou University. These patients had been admitted to the Mental Health Center by family members or by themselves after experiencing some type of psychotic symptom. None of them had previously contacted psychiatric services or been medicated with any antipsychotics. The patients were administered the Structured Clinical Interview for DSM-IV by trained psychiatrists, and all of them met the DSM-IV criteria for schizophrenia or schizophreniform disorder. Those with the latter diagnosis were followed up for at least six months to confirm a diagnosis of schizophrenia. The exclusion criteria included cardiovascular or neurological disease, a history of a head injury that resulted in a loss of consciousness, meeting the DSM-IV criteria for substance dependence or meeting the diagnostic criteria for current DSM-IV Axis I mood or anxiety disorder. All of the patients began to receive antipsychotic medication once their diagnoses had been confirmed. They were treated with different antipsychotics based on a discussion with their clinical psychiatrist and family members. The psychiatrist did not know the results of the electrophysiological recordings. The normal controls were recruited from the staff of Shantou University. None of them had any personal or family history of an Axis II psychotic disorder or was taking any kind of medication. All of the subjects had normal hearing acuity and signed informed consent. The sensory gating measures for the

patient group were obtained before they received antipsychotics (at baseline) and after six weeks of antipsychotics (at endpoint). Their Positive and Negative Syndrome Scales (PANSS) were assessed with one week of P50 measures (Kay et al., 1987). However, the sensory gating measures for the normal controls were evaluated only at baseline.

Seventy-three patients and 62 normal controls entered the study. Four patients dropped out before study completion, four were treated with more than two neuroleptics, and the data for one were lost due to equipment malfunction. Therefore, 65 patients with first-episode schizophrenia ($n=53$) or schizophreniform disorder ($n=12$) and 62 normal controls finished the study. The duration of illness for the patients ranged between 0.5 and 62 months (mean 15.32±7.64; median six months). The mean age of the patients was 25.46±7.67 (ranging between 16 and 48 years), and that of the normal controls was 26.35±5.34 (ranging between 20 and 48 years) ($T=0.759$, $df=125$, $P=0.450$). The patients received antipsychotic treatment, including sulpiride ($n=24$, range of 197–1486 mg/day, mean 848.54±241.17 mg/day, chlorpromazine-equivalent dose 678.83±192.94 mg/day), clozapine ($n=17$, range of 130–516 mg/day, mean 269.35±90.16 mg/day, chlorpromazine-equivalent dose 673.38±225.4 mg/day) or risperidone ($n=24$, range of 1.2–5.2 mg/day, mean 3.76±1.02 mg/day, chlorpromazine-equivalent dose 188.00±51.00 mg/day). In the sulpiride group, two patients were also administered antidepressants (one took 20 mg of paroxetine per day, and the other took 20 mg of fluoxetine per day). In the clozapine group, three patients also took another antipsychotic, either quetiapine ($n=1$, 200 mg/average day), olanzapine ($n=1$, 10 mg/average day) or ziprasidone ($n=1$, 100 mg/average day). All of the patients treated with sulpiride or risperidone were also taking trihexyphenidyl (Artane).

2.2. P50 testing

2.2.1. Electrophysiological recordings

The electrophysiological examinations were performed at the Laboratory of Clinical Neurophysiology at the Shantou University Mental Health Center using a signal generator and the data acquisition system of a fully functional Italian-made digital 40-channel EBNeuro Sirius BB BE. Sensory gating was evaluated by recording the P50 wave of the auditory-evoked response in a paired-stimulus or conditioning-testing paradigm. All of the subjects were asked to abstain from smoking for at least 30 min prior to testing, were seated in a comfortable examination chair and instructed to relax with their eyes fixed on a point on the wall in front of them. The testing took place in a quiet, lighted room that was not electrically shielded. Eye movements were recorded via electro-oculography (EOG) with Ag/AgCl disc electrodes placed at the outer canthus and below the right eye. Recordings were obtained with a disc electrode affixed to the vertex (CZ site) and referenced to left temporal apophysis. All of the electrode resistances were less than 5 KΩ. To control background noise during stimulus presentation, 70-dB [A] broadband white noise was presented continuously throughout the session. The stimuli were generated by means of computer-driven, 90-d B pulses of 0.1 ms in duration produced by a signal generator, and a data acquisition system was used to record the ERP waveforms. The 32 pairs of auditory clicks were presented every 10 s, with a 500-ms inter-click interval. The ERP responses were amplified and band-pass filtered with a 0.1 to 300 Hz analog filter and no 50-Hz notch filter, at a sampling rate of 512 Hz, for a total of 1000 ms (100 ms before to 400 ms after the stimuli with a 500-ms gap between stimulus 1 and stimulus 2). After acquisition of the data, those trials that contained artifacts (±50 uv wave amplitude deflection) were not included in the waveform averaging. Data were analyzed offline: band-pass filtered (10–50 Hz, 12 d B/octave roll-off). The subjects were all in line with the standard and had normal hearing (subjective hearing threshold <40 dB).

2.2.2. Response analysis

The P50 component was identified as the most positive deflection 30 to 90 ms after stimulus presentation. The P50 amplitude is the absolute difference between the P50 peak and the preceding negative trough (Clementz et al., 1997; Nagamoto et al., 1991). The data from the CZ site are reported because this is the best site for distinguishing schizophrenic patients from normal subjects when using this electrode array (Cardenas et al., 1993; Clementz et al., 1998; Nagamoto et al., 1991). The computer selected the test responses within a window (±10 ms) of the conditioning stimulus response latency. The P50 testing results were analyzed by two independent neurophysiologists, both of whom were evoked potential specialists and remained blinded to the patient's diagnosis and treatment. When a significant difference was found between the findings of the two examiners, the study was reanalyzed by both, and a consensus value was obtained. The P50 gating ratios were calculated as the test stimulus response/conditioning stimulus response×100, and to minimize skewed distributions, ratios greater than 2 were assigned the value 2.

3. Statistical analysis

Because P50 data collection was available for patients with schizophrenia at both the baseline and endpoint periods, but not for the normal controls, we were unable to perform repeated measures of analysis of variance (ANOVA) for all of our data. Instead, independent-sample *t*-tests were used to test the differences of the P50 parameters between the normal controls and the patients with first-episode schizophrenia and also to examine whether there was any gender effect. A paired-samples *t*-test was used to compare the differences for the P50 parameters and PANSS scores in schizophrenia between the baseline and endpoint periods. ANOVA was performed to examine the potential differential effects of specific neuroleptics on the P50 parameters and clinical symptoms at baseline and endpoint. Correlation analyses were conducted to test the correlation among the S1, S2, PANSS and P50 gating ratios. All of the analyses were performed using SPSS software (SPSS 13.0 for Microsoft Windows).

4. Results

No gender effect was found on the P50 parameters in either the schizophrenia or normal control group (Table 1). The first-episode, never-medicated schizophrenia patients had impaired P50 sensory gating relative to the normal controls (mean=94.19% [SD=61.31%] versus mean=41.22% [SD=33.82%]). The testing amplitudes, S2, were significantly

higher in the schizophrenia patients than they were in the normal controls, although there were no significant differences in the latencies between the two groups. Bivariate correlation analysis revealed there was a significant correlation between the amplitude of the test S2 response and sensory gating in both the normal controls (r=0.697, P=0.0005) and the schizophrenia patients (r=0.542, P=0.0005). For the patient group, there was also a significant correlation between the conditioning amplitude S1 and sensory gating (r=0.388, P=0.001) (see Table 2 and Fig. 1).

There were no significant changes in the P50 sensory gating parameters between at baseline and at endpoint for the patients (paired-samples T-test, all P>0.10). However, a significant difference was found in the PANSS scores before and after antipsychotic treatment (all P<0.001). Positive symptoms were associated with the P50 gating ratio in first-episode, never-medicated schizophrenia at baseline (r=0.862, p=0.022), but not at endpoint (r=0.122, p=0.331) (Table 3).

P50 sensory gating was not significantly different among the patients receiving sulpiride, risperidone or clozapine at baseline (F=1.074, df=2,62, P=0.348) and at endpoint (F=0.441, df=2,62, P=0.646). There were also no significant differences in the P50 amplitudes or latencies following the first or second click at baseline and at endpoint (all P>0.1, Table 4).

5. Discussion

We found that first-episode, never-medicated schizophrenia patients had gating impairment and that this impaired sensory gating was related to the high S2 amplitude. Moreover, S1 amplitude was related to sensory gating in schizophrenia. These results support previous evidence that sensory gating is already impaired in the early stages of schizophrenia and may reflect a diminished capacity to "gate-in" the relevant signal and an integrative sensory disturbance (Jin et al., 1997; Boutros et al., 1999; Brockhaus-Dumke et al., 2008). In the study reported here, the sensory gating deficits were not affected by gender or antipsychotic treatment. These findings are consistent with those of two meta-analytic studies (Heinrichs, 2004; Bramon et al., 2004), according to which sensory gating deficit is one of the strongest and most reliable findings in the schizophrenia literature. Sensory gating deficits in schizophrenic patients are persistent and found in both more stable outpatients and the non-psychotic family members of patients with schizophrenia. This impairment has been considered to be one of the candidate endophenotypes for schizophrenia (Heinrichs, 2004; Bramon et al., 2004).

Table 1
Comparison of sensory gating between gender for first-episode schizophrenia and controls

P50 parameters	Schizophrenia		Control	
	Female	Male	Female	Male
	N=15	N=50	N=29	N=33
Amplitude (μv)				
Conditioning	2.06±0.86	2.33±1.46	2.34±1.16	2.63±1.70
Test	2.00±1.55	1.94±1.43	1.08±0.98	1.16±1.34
Latency (ms)				
Conditioning	56.10±12.52	56.61±12.22	57.99±11.45	54.64±10.02
Test	53.13±14.34	55.55±13.46	57.97±12.08	53.11±10.10
P50 gating ratio				
%	98.45±56.91	92.91±63.07	40.29±28.76	42.05±38.14

*the P50 parameters between female and male in first-episode schizophrenia group and controls group(T test, all P>0.1).

Table 2
Comparison of sensory gating between first-episode schizophrenia and normal controls

P50 parameters	Schizophrenia (N=65) mean±SD	Controls (N=62) mean±SD	df	T	p-value
Amplitude (μv)					
Conditioning [a]	2.27±1.34	2.50±1.47	125	0.913	0.363
Test [b]	1.95±1.12	1.45±1.18	125	3.531	0.001
Latency (ms)					
Conditioning	56.49±12.19	56.20±10.76	125	0.139	0.890
Test	54.99±13.59	55.38±11.60	125	0.177	0.862
P50 gating ratio					
%	94.19±61.31	41.22±33.82	125	5.988	0.001

[a] significant correlation between conditioning amplitude and P50 ratio in schizophrenia group (r=0.388, p=0.001).
[b] significant correlation between test amplitude and P50 ratio in schizophrenia group (r=0.542, p=0.000)and normal control group (r=0.869, p=0.000).

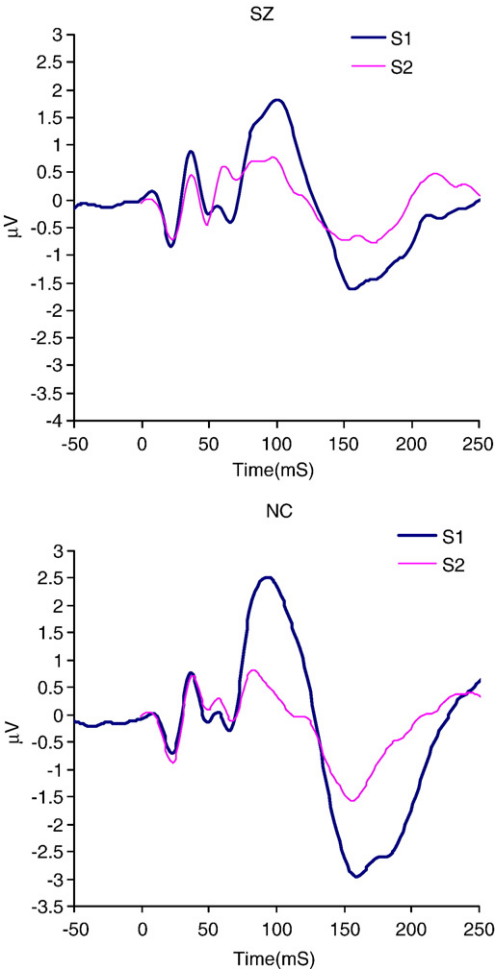

Fig. 1. Grand average for the schizophrenia group (SZ) and the normal control group (NC). Clink onset is at 0 ms. Black think line: S1 response waveform; grey line:S2 response waveform.

Table 3
Comparison of P50 parameters and PANSS between baseline and endpoint of schizophrenia

	Baseline	Endpoint			
	Mean±SD	Mean±SD	*df*	*T*	*P*-value
Amplitude (μv)					
Conditioning	2.27±1.34	2.04±1.13	64	1.09	0.280
Test	1.95±1.45	1.64±1.07	64	1.447	0.153
Latency (ms)					
Conditioning	56.48±12.91	56.70±13.28	64	0.504	0.616
Test	55.74±13.07	54.11±12.35	64	0.588	0.558
P50 gating ratio (%)	96.58±64.76	84.81±55.38	64	0.003	0.998
PANSS score					
Positive symptoms [a]	20.85±5.06	8.48±2.14	64	20.388	0.000
Negative symptoms	18.25±5.48	10.72±3.00	64	14.345	0.000
General psychopathology	44.86±5.82	23.63±4.18	64	24.11	0.000

[a] significant correlation between positive symptoms and P50 gating ratio at baseline(r=0.862, p=0.021).

It has been hypothesized that sensory gating anomalies underlie the production of positive symptoms. A delineation of the relationship between P50 gating deficits and positive symptoms may help to clarify whether sensory gating deficit is a necessary or sufficient condition for the expression of positive symptoms. In this study, we found that the relationship between P50 gating deficits and positive symptoms changed after patients received antipsychotic treatment. In a previous study, we found that the unaffected first-degree relatives of first-episode schizophrenics demonstrated sensory gating deficit and that their sensory gating ratios lay between those of the schizophrenia group and the controls (Wan et al., 2007). All of these results suggest that P50 gating deficits are not sufficient to produce the syndrome of schizophrenia, but they may reflect an intermediate phenotypic marker.

Smoking normalizes P50 suppression in people with schizophrenia, and the number of cigarettes smoked per day has been correlated with the levels of alpha-7 nicotinic receptors in the postmortem hippocampus and cortex (Adler et al., 1993; Breese et al., 2000). Pharmacological studies have demonstrated the importance of the cholinergic system in the mechanism of P50 inhibition, and one of the critical elements appears to be the cholinergic stimulation of inhibitory interneurons via the alpha-7 nicotinic receptors. Adler et al. (1998) found that nicotine lowers P50 sensory gating through diminished S2 amplitude, which is thought to reflect enhanced sensory gating through the activation of the alpha-7 nicotinic receptors. Others (Freedman et al., 1997; Leonard et al., 2002) have also reported that a marker of the gene for the alpha-7 nicotinic receptors has been linked to schizophrenia and P50 abnormalities and that the polymorphisms in the promoter region of this gene may be related to abnormal sensory gating. Our previous study also found that the three polymorphisms in the alpha-7 nicotinic receptor gene, rs2337980, rs1909884 and rs883473, were related to schizophrenia in 129 schizophrenia trios (Peng et al., 2008). Of these trios, 23 patients were recruited for the current study. Adler et al. (2004) also noted significantly lower sensory gating ratios in patients who smoked versus those who did not. These smoker and nonsmoker group differences were due primarily to the reduced P50 ratios in the patients taking clozapine who were also smokers. The acute effects of smoking were controlled for in this study by having all subjects abstain from smoking for at least 30 min prior to testing. However, the study was limited by the lack of a smoking history for the schizophrenic group. Further study should include this type of information to clarify the impact of smoking history on the sensory gating performance of patients with schizophrenia.

In the present study, we found that the typical neuroleptic sulpiride has no effect on sensory gating in schizophrenia. This result is consistent with previous reviews (Bramon et al., 2004; Potter et al., 2006). A key issue with regard to the present results is the failure to detect a beneficial effect of the atypical neuroleptics, clozapine and risperidone on the P50 sensory gating. This finding is inconsistent with two previous cross-sectional studies that found atypical neuroleptics, especially clozapine, to have enhanced sensory gating (Light et al., 2000; Adler et al., 2004). This difference may be due to the different methodologies and subject inclusion criteria adopted. For example, Light et al. (2000) and Adler et al. (2004) adopted a cross-sectional design and recruited patients with a multiple medication history, and some of their subjects were even treatment-resistant. In the present study, we recruited first-episode, never-medicated patients and adopted a prospective longitudinal design to achieve a better evaluation of the targeted effect. Our results may better

Table 4
Effects of different narcoleptic treatment on sensory gating in first-episode schizophrenia

		Sulpiride (N=24)	Risperidone (N=24)	Clozapine (N=17)	*df*	*F*	*P*
Group		Mean±SD	Mean±SD	Mean±SD			
P50 parameters							
Amplitude (μv)							
Conditioning	Baseline	2.03±1.22	2.56±1.44	2.18±1.37	2,62	0.976	0.382
	Endpoint	2.21±0.98	2.00±1.21	1.86±1.24	2,62	0.508	0.604
Test	Baseline	1.96±1.66	1.88±1.41	2.03±1.25	2,62	0.06	0.942
	Endpoint	1.71±0.89	1.46±1.11	1.80±1.23	2,62	0.553	0.578
Latency (ms)							
Conditioning	Baseline	56.48±12.91	55.21±11.75	57.74±12.32	2,62	0.316	0.73
	Endpoint	56.70±13.28	56.62±11.47	57.51±14.61	2,62	0.093	0.911
Test	Baseline	55.74±13.07	54.07±12.70	55.22±16.08	2,62	0.2	0.819
	Endpoint	54.11±12.35	54.61±10.36	58.89±15.49	2,62	1.625	0.205
P50 gating ratio (%)							
Baseline		96.58±64.76	81.15±6.87	109.21±56.39	2,62	1.074	0.348
Endpoint		84.81±55.38	95.62±85.14	105.30±62.41	2,62	0.441	0.646

support the evidence that P50 sensory gating deficit is independent of antipsychotic treatment.

However, the current results are in contradiction to the putative effect of clozapine on sensory gating. It was supposed that clozapine, which increases the release of acetylcholine in the hippocampus and has the property of 5-hydroxytryptamine3 (5-HT3) antagonism, may thereby indirectly act on the nicotinic receptor to normalize P50 sensory gating. In other studies, another atypical neucroleptic, risperidone, did not appear to capture all of the enhanced clinical effects of clozapine and had only a marginal effect on sensory gating (Yee et al., 1998; Light et al., 2000; Adler et al., 2004). However, others also found that the effect of clozapine on P50 sensory gating differed from that of nicotine and the other agents that enhance cholinergic function (e.g., Becker et al., 2004). Clozapine appears to exert its effect through increased S1 amplitude, which suggests that this medication does not enhance sensory gating, but rather operates through a different physiological mechanism (Becker et al., 2004). The underlying mechanism of this effect of clozapine is not yet fully known, but it may involve multiple neurotransmitters. In this study, we find no increased S1 amplitude in the patients who received clozapine. It should be noted, however, that our results may be limited by the small sample size ($N = 17$) and the short duration of treatment.

In conclusion, our findings indicate that there is P50 sensory gating impairment in first-episode, never-medicated schizophrenia. Typical and atypical antipsychotic treatments have no significant effect on P50 sensory gating in schizophrenia.

Role of funding source

This study was supported partially by a grant from the National "Tenth Five-year" Science and Technology Program (2002BA711A08), the Research Fund (KSCX2-YW-R-131) from the Institute of Psychology, Chinese Academy of Sciences, the National Science Fund of China (30770723), and the National Basic Research Programme (973 Programme No. 2007CB512302). These funding agents had no further role in the study design; in the collection, analysis and interpretation of the data; in the writing of the manuscript; and in the decision to submit the paper for publication.

Contributors

Xiaohong Hong and Raymond Chan designed the study and wrote up the first draft of the paper; Xihang Zhuang, Tingyun Jiang, Xiaona Wan administered the P50 paradigms to patients and analyzed the data; Xihang Zhuang, Tingyun Jiang, Xiaona Wan, Junqing Wang, Bo Xiao, Hanhui Zhou, Liyun Jian, and Bilan Weng performed clinical interview and rating on patients. All authors contributed to and have approved the final text.

Conflict of interest

The authors disclaim there is no conflicts of interest for this study.

Acknowledgements

The authors would like to acknowledge the funding sources of the "Tenth Five-year" Science and Technology Programme, the Institute of Psychology, Chinese Academy of Sciences, the National Science Fund of China, and the National Basic Research Programme of mainland China.

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