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Effects of risperidone on auditory information processing in neuroleptic-naive patients with schizophrenia spectrum disorders

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Abstract. Early effects of risperidone (2.5 ± 1 mg/day) on auditory information processing were investigated in 9 neuroleptic naive patients with schizophrenia spectrum disorders and 9 healthy controls by using event-related potentials (ERPs). ERPs were elicited during active auditory "oddball" paradigm and were recorded before and after two weeks of treatment. Baseline P3 latencies were significantly delayed in patient group. Risperidone treatment did not change P3 amplitudes and latencies. However, P2 amplitudes were reduced in parallel with the clinical improvement measured by Positive and Negative Syndrome Scale (PANSS). Although risperidone did not change neural bases of active attention after two weeks of treatment, the reduction of P2 amplitude suggests that risperidone may affect auditory information processing in patients with schizophrenia spectrum disorders who never have been exposed to antipsychotic treatment.

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INTRODUCTION

Event-related potentials (ERPs) are time-locked changes to external stimuli in electroencephalogram (EEG) providing an objective index of information processing in the human brain. One of the most widely used auditory ERP for studying neural bases of cognitive dysfunction is P3 potential. It is evoked by auditory the "odd-ball" paradigm task while the subject is reacting (pressing a button or mentally counting) on the presence of the target stimuli. P3 is usually interpreted as an electrophysiological correlate of updating of working memory (Donchin and Coles 1988). The latency of P3 reflects the speed of cognitive processing and its amplitude to the allocation of brain energy resources (Kok 1997).

Schizophrenia patients have shown abnormal P3 response with prolonged latency and/or reduced amplitude (Blackwood et al. 1987) and larger P2 component (McCarley et al. 1997, O'Donnel et al. 1994, Sandman et al. 1987) indicating disturbances in information processing. Patients with schizophrenia spectrum disorders share some phenotypic similarities with schizophrenia including personality traits (Lenzenweger 1994), neuropsychologic deficits (Kremen et al. 1994), psychophysiologic deficits (Matthysse et al. 1986), and cognitive disturbances (Bredgaard and Glenthoj 2000, Lichtermann et al. 2000). Abnormal auditory P3 responses in patients with schizophrenia spectrum disorders have confirmed similarities with schizophrenia (Kimble et al. 2000, Korostenskaja et al. 2005, Michie et al. 2002). Furthermore, Trestman and coauthors (1996) showed that the changes in auditory N1, P2, N2, and P3 components in patients with schizotypal personality disorder were intermediate between patients in schizophrenia and healthy subjects.

Usually typical antipsychotic medication does not change P3 amplitudes and latencies in schizophrenia patients (Ford et al. 1994, Umbricht et al. 1998). Atypical antipsychotics have been claimed to improve cognitive functions in schizophrenia (Meltzer and McGurk 1999, Purdon 1999). However, effects of these drugs on neural bases of cognitive dysfunction have not been consistent. Clozapine and olanzapine increased P3 amplitudes (Gonul et al. 2003, Umbricht et al. 1998). To the contrary, Gallinat and others (2001) could not find changes in P3 latency and amplitude during the olanzapine and clozapine therapy. Molina and coauthors (2004) have found no significant effect of olanzapine on P3 after long-term treatment. Risperidone treatment produced significant P3 latency reduction (Iwanami et al. 2001, Umbricht et al. 1999).

To our knowledge, only one study investigating effects of antipsychotic medication on ERPs in patients with schizophrenia spectrum disorders has been conducted up to date (Korostenskaja et al. 2005). In this study, four-week treatment of olanzapine did not change auditory P3 responses despite of clinical improvement. However, patients included in this study were chronically ill and before switching to the treatment of olanzapine, they have been receiving typical antipsychotics, possibly affecting treatment response. The aim of the present study was by using auditory ERPs to investigate effects of risperidone on auditory information processing in patients with schizophrenia spectrum disorder who never have been exposed to antipsychotic drug treatment.

METHODS

The study was performed at the Republican Vilnius Psychiatric Hospital (Vilnius, Lithuania). It was approved by Ethic Committee of the Hospital. Subjects gave their written informed consent to participate in the study.

Subjects

Nine right-handed patients with schizophrenia spectrum disorders (2 females), mean age 26 years (SD 8, range 18–39 years), and 9 right-handed healthy controls (3 females), mean age 28 years (SD 10, range 18–41 years) were investigated in this study. Diagnoses in all 9 cases were made according to the ICD-10, International Classification of Diseases (World Health Association, 1992) by clinicians using all available information. A diagnosis of paranoid schizophrenia (F20.0) was considered in 4 cases and 5 patients had schizotypal disorder (F21). All patients were hospitalized for the first time. Exclusion criteria for psychiatric patients were organic pathology of central nervous system (tumors, etc.) and history of alcohol dependence. Healthy controls had no known neurological or psychiatric disorders.

Study design

Auditory ERPs were recorded at baseline and after two weeks follow-up of risperidone treatment. All

Table I

PANSS before and after risperidone treatment

	Baseline	After risperidone treatment
PANSS, scores	97.4 ± 14.9	67.4 ± 9.5*
positive symptom scale, scores	22.1 ± 5	14.1 ± 2.3*
negative symptom scale, scores	20.2 ± 3.9	16.3 ± 4*
total psychopathology scale, scores	57.1 ± 15.2	37 ± 5.7*

(*) $P<0.05$, patients at baseline compared to follow-up

patients were neuroleptic naive. At the time of follow-up recording all patients received 2.5 ± 1 mg/day of risperidone. Patients did not receive any additional drug therapy. Clinical symptoms were evaluated with PANSS (Kay et al. 1987). For healthy controls ERPs were recorded once.

ERP recording

All data was acquired in an electrically shielded room. The recording sessions were always carried out between 9.00 A.M. and 2.00 P.M. The ERPs were recorded with the 32-channel EEG device (Galileo NT, by EBNeuro, Italy) (bandpass 0.01–30 Hz) from Cz site (according to the 10/20 International system) using Ag/AgCl electrodes. Ear electrodes served as a reference for all electrodes and the ground electrode was attached to the forehead. ERPs were acquired during active oddball paradigm. Pure tones were binaurally presented via headphones at the intensity 60dB. Standard tones had frequency of 2000 Hz and duration of 50-ms. Deviant tones had the same duration and frequency of 1000 Hz. The probability of tones was 80% for standards and 20% for deviants. During the recording at least 30 deviant stimuli were presented. Subjects were asked to count in mind all deviant stimuli and then to report the sum. The inter-stimulus interval (ISI) was 1500 ms. The analysis period was 1000 ms. The paradigm consisted of two blocks with 1-min interval. Signal rejection threshold was set for amplitude of more than 50 μV.

Data analysis

Digital filters were applied off-line (low pass filter of 30 Hz, high pass filter of 0.15 Hz). N1, P2, and P3 components were measured to deviant stimulus (N1 within 70–150-ms, P2 within 150–300-ms, and P3 within 200–500-ms post-stimulus interval). Amplitudes of all components were calculated as peak-to-peak voltage differences. Signal rejection threshold was set for amplitude of more than 50 μV. The required minimum of sweeps surviving artifact rejection (n=25) was reached for all subjects studied.

Statistical analysis

Data of two patients at the follow-up were rejected because of technical reasons. Comparisons of peak latencies and amplitudes of three ERPs components (N1, P2, P3) were performed between healthy controls and patients at baseline, between healthy controls and patients after the 2-weeks follow-up and between the patients at the baseline and after 2-weeks follow-up. Mann-Whitney U-test was used for comparison. ERPs were correlated with PANNS using Spearman correlation.

RESULTS

Psychopathology

Risperidone decreased all PANSS, total psychopathology, positive symptom and negative symptom scales (Table I).

Effects of risperidone treatment

Mean amplitudes and latencies of N1, P2 and P3 components at baseline and after 2 weeks of risperidone treatment are presented in Table II. Grand-averaged ERP waveforms are presented in Fig. 1. At the

Table II

Amplitudes and latencies of ERPs components (mean ± SD) of healthy controls and patients at baseline and follow-up

		Healthy controls (n=9)	Patients at baseline (n=9)	Patients after risperidone treatment (n=7)
N1	latency, ms	114.7 ± 14.6	124 ± 9.6	119.4 ± 17
	amplitude, μV	12.4 ± 5.3	12.3 ± 7.9	14.3 ± 10.3
P2	latency, ms	191.8 ± 13.7	185.8 ± 30	186.6 ± 17.5
	amplitude, μV	16.5 ± 8.4	17 ± 9	9.4 ± 6.4†
P3	latency, ms	319.8 ± 28.6	347.8 ± 24.4*	358.3 ± 25.9*
	amplitude, μV	21.7 ± 13.1	11.8 ± 8.6	16.4 ± 7.4

(*) P<0.05, patients at the baseline and after follow-up compared to healthy controls; (†) P<0.05, patients at follow-up compared with patients at baseline

baseline patients showed significantly longer P3 latencies than controls (U=17, Z=-2.03, P=0.04) (Table II). No significant differences in baseline N1 and P2 amplitudes or latencies between patients and controls were observed (P>0.05).

Risperidone treatment did not change P3 amplitudes or latencies (P>0.05). After treatment patients still had longer P3 latencies than controls (U=2.5, Z=-3.07, P=0.002). A significant decrease in P2 amplitude after risperidone treatment was observed (U=12, Z=2.06, P=0.04). Risperidone did not affect N1 amplitudes and latencies or P2 latencies (P>0.05).

Relationship between psychopathology and ERPs

There were no significant correlation between latencies and amplitudes of N1, P2, P3 and clinical scores measured by PANSS at baseline and follow-up.

DISCUSSION

In the current study effects of two-week risperidone treatment on neurocognitive dysfunction were explored by investigating auditory ERPs in a small sample of neuroleptic naive patients with schizophrenia spectrum disorders. Risperidone treatment did not have effects on P3 amplitudes and latencies but decreased P2 amplitudes in parallel with clinical improvement. The results of this study indicate that risperidone did not have early effects on active attention. However, the reduction of P2 amplitudes suggests that risperidone may modulate auditory information processing in patients with schizophrenia spectrum disorders who never have been exposed to antipsychotics.

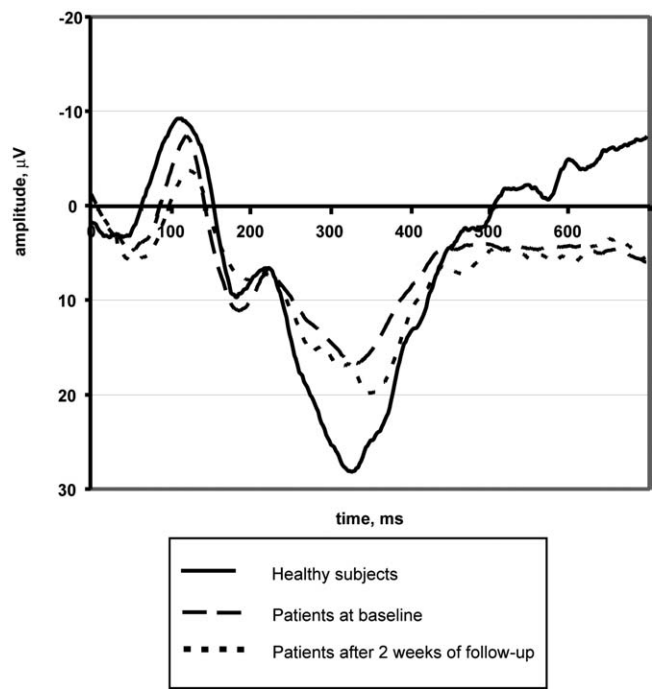

Fig. 1. Grand average of ERPs in healthy controls, patients at baseline, and patients after 2 weeks of risperidone treatment

Up to date only two studies investigating the effect of risperidone on P3 response in schizophrenia patients

have been conducted (Iwanami et al. 2001, Umbricht et al. 1999). In these studies risperidone significantly reduced P3 latency after 4 weeks (Iwanami et al. 2001) and 6–9 weeks (Umbricht et al. 1999) of treatment. Contrary to this, our study does not show changes in P3 amplitudes and latencies. Our data seem to support a view that P3 is independent from effects of antipsychotic medication thus serving as a trait marker in schizophrenia (Gonul et al. 2003, St. Clair et al. 1989) and schizophrenia spectrum disorders (Korostenskaja et al. 2005). However, in our study patients received low dose of risperidone (2.5 ± 1 mg/day) for two weeks whereas in studies of Umbricht and coauthors (1999) and Iwanami and others (2001) higher doses were used (4–6 mg/day). It is possible that different doses of risperidone lead to different treatment responses. Finally, patients included in our study had different psychopathologies. These factors may in partly explain the absence of early effect of risperidone on attention in the present study.

Our study showed reduction in P2 amplitudes following risperidone treatment. However, the functional role of P2 component is poorly understood, there is some evidence that P2 can reflect the stimulus classification process (Garcia-Larrea et al. 1992) and attention-modulated process required for the performance of an auditory discrimination task (for review see Crawley and Colrain 2004). Although baseline P2 amplitudes and latencies did not differ from those observed in healthy controls in our study, the reduction of P2 amplitude following risperidone treatment may reflect change in cognitive dysfunction in patients with schizophrenia spectrum disorders. Dopamine modulation of P2 amplitude by risperidone may in partly explain this effect. This is in line with findings of Korostenskaja and colleagues (2004), who found that administration of methylphenidate (enhancing dopamine function) to healthy subjects reduced P2 amplitude.

CONCLUSIONS

Our study showed that despite of the clinical improvement risperidone treatment did not affect neural bases of active attention measured by auditory P3 in neuroleptic-naive patients with schizophrenia spectrum disorders. Our data seem to support the view that delay of P3 could serve as a trait marker in schizophrenia spectrum disorder. However, the decrease of P2 amplitude suggests that risperidone may modulate processing of auditory information. In future, large number of patients with longer follow-up periods and different risperidone doses including more severe forms of schizophrenia spectrum disorders are needed to confirm our results about the efficacy of risperidone treatment on cognitive dysfunction.

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REFERENCES

Blackwood DH, Whalley LJ, Christie JE, Blackburn IM, St Clair DM, McInnes A (1987) Changes in auditory P3 event-related potential in schizophrenia and depression. Br J Psychiatry 150: 154–160.

Bredgaard R, Glenthoj BY (2000) Information processing and attentional dysfunctions as vulnerability indicators in schizophrenia spectrum disorders. World J Biol Psychiatry 1: 5–15.

Crawley KE, Colrain IM (2004) A review of the evidence for P2 being an independent component process: Age, sleep, and modality. Clin Neurophysiol 115: 732–734.

Donchin E, Coles MGH (1988) Is the P300 manifestation of context updating? Behav Brain Sci 11: 357–374.

Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A (1994) ERPs in schizophrenia: effects of antipsychotic medication. Biol Psychiatry 36: 153–170.

Gallinat J, Riedel M, Juckel G, Sokullu S, Frodl T, Moukhtieva R, Mavrogiorgou P, Nissle S, Müller N, Danker-Hopfe H, Hegerl U (2001) P300 and symptom improvement in schizophrenia. Psychopharmacology 158: 55–65.

Garcia-Larrea L, Lukaszevicz AC, Mauguiere F (1992) Revisiting the oddball paradigm. Non-target vs. neutral stimuli and the evaluation of ERP attentional effects. Neuropsychologia 30: 723–741.

Gonul AS, Suer C, Coburn K, Ozesmi C, Oguz A, Yilmaz A (2003) Effects of olanzapine on auditory P300 in schizophrenia. Progr Neuro-Psychopharmacol Biol Psychiatry 27: 173–177.

Iwanami A, Okajama J, Isono H, Shinoda J, Hasai K, Hata A, Fukuda M, Nakagome K, Kamijima K (2001) Effects of risperidone on event-related potentials in schizophrenic patients. Pharmacopsychiatry 34: 73–79.

Kay SR, Fiszbein A, Opler LA (1987) The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 13: 261–271.

Kimble M, Lyons M, O'Donnell B, Nestor P, Niznikievicz M, Toomey R (2000) The effect of family status and schizotypy on electrophysiologic measures of attention and semantic processing. Biol Psychiatry 47: 402–412.

Kok A (1997) Event-related potentials (ERP) reflections of mental resources: a review and synthesis. Biol Psychol 45: 19–56.

Korostenskaja M, Dubravko K, Kähkönen S (2004) Methylphenidate changes auditory information processing, combined MEG/EEG study. Clin Electroencephalogr Neurosci 35: 246.

Korostenskaja M, Dapsys K, Siurkute A, Maciulis V, Ruksenas O, Kähkönen S (2005) Effects of olanzapine on auditory P300 and mismatch negativity (MMN) in schizophrenia spectrum disorders. Prog Neuro-Psychopharmacol Biol Psychiatry 29: 543–548.

Kremen WS, Seidman LJ, Pepple JR, Lyons MJ, Tsuang MT, Faraone SV (1994) Neuropsychological risk indicators for schizophrenia: a review of family studies. Schizophrenia Bull 20: 103–119.

Lenzenweger MF (1994) Psychometric high-risk paradigms, perceptual aberrations, and schizoptypy: an update. Schizophrenia Bull 20: 121–136.

Lichtermann D, Karbe E, Maier W (2000) The genetic epidemiology of schizophrenia and of schizophrenia spectrum disorders. Eur Arch Psy Clin N 250: 304–310.

Matthysse S, Holzman PS, Lange K (1986) The genetic transmission of schizophrenia: application of Mendelian latent structure analysis to eye-tracking dysfunction in schizophrenia and affective disorder. J Psychiat Res 20: 57–76.

McCarley RW, O'Donnell B, Niznikiewicz MA, Salisbury DF, Potts GF, Hirayasu Y, Nestor PG, Shenton ME (1997) Update on electrophysiology in schizophrenia. Int Rev Psychiatry 9: 373–386.

Meltzer HY, McGurk SR (1999) The effect of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bull 25: 233–255.

Michie PT, Innes-Brown H, Todd J, Jablensky AV (2002) Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. Biol Psychiatry 52: 749–758.

Molina V, Munoz F, Martin-Loeches M, Casado P, Hinojosa JA, Iglesias A (2004) Long-term olanzapine treatment and P300 parameters in schizophrenia. Neuropsychobiology 50: 182–188.

O'Donnell BF, Hokama H, McCarley RW, Smith RS, Salisbury DF, Mondrow E, Nestor PG, Shenton ME (1994) Auditory ERPs to non-target stimuli in schizophrenia: relationship to probability, task-demands, and the target ERPs. Int J Psychophyiol 17: 219–231.

Purdon SE (1999) Cognitive improvement in schizophrenia with novel antipsychotic memdications. Schizophr Res 35(suppl.): S51–S60.

Sandman CA, Gerner R O'halloran JP, Isenhart R (1987) Event-related potentials and item recognition in depressed, schizophrenic and alcoholic patients. Int J Psychophysiol 104: 540–545.

St. Clair D, Blackwood D, Muir W (1989) P300 abnormality in schizophrenic subtypes. J Psychiatr Res 23: 49–55.

Trestman RL, Horvath T, Kalus O, Peterson AE, Coccaro E, Mitropoulou V, Apter S, Davidson M, Siever LJ (1996) Event-related potentials in schizotypal personality disorder. J Neuropsych Clin N 8: 33–40.

Umbricht D, Javitt D, Novak G, Bates J, Ollack S, Lieberman J, Kane J (1998) Effects of clozapine on auditory event-related potentials in schizophrenia. Biol Psychiatry 44: 716–725.

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.

World Health Association (1992) ICD-10: The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines. Gaskell, Royal College of Psychiatrists, England.

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