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BRIEF REPORT

Effects of risperidone on auditory event-related potentials in schizophrenia

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Abstract

Schizophrenia is associated with cognitive deficits for which treatments remain elusive. The effects of risperidone (an antipsychotic differing in some of its pharmacological properties from typical agents) on cognitive deficits have not been extensively investigated. Mismatch negativity (MMN), N2 and P3 are cognitive event-related potentials that index preattentive (MMN) and attention-dependent information processing (N2, P3) and provide a measure of cognitive deficits in schizophrenia. The effects of risperidone treatment on MMN, N2 and P3 generation in chronic schizophrenic patients were investigated in an open-label, uncontrolled study. Risperidone treatment significantly reduced psychotic symptoms. It was associated with a decrease of peak latencies, particularly pronounced for P3. However, it did not significantly affect abnormal MMN or P3 amplitudes. The results suggest an effect of risperidone on processing speed, particularly in attention-dependent tasks. These results are in agreement with findings in recent studies on the cognitive effects of risperidone.

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Introduction

Cognitive deficits are a major aspect and cause of disability in schizophrenia (Green, 1996), but effective pharmacological treatments have remained elusive. Several neuropsychological studies have reported significant effects of clozapine, risperidone and olanzapine on cognitive functioning (Green et al., 1997; Hagger et al., 1993; Hoff et al., 1996; McGurk and Meltzer, 1997; Stip and Lussier, 1996) , although other studies have failed to find such effects (Goldberg et al., 1993; Zahn et al., 1994).

Event-related potentials (ERPs) provide an objective index of cognitive dysfunction in schizophrenia, and a reliable method for assessing effects of medication on underlying brain activity. Upon presentation of auditory stimuli a negative potential peaking at approx. 100 ms, hence termed N100 or N1, followed by a positive wave with a peak latency of approx. 200 ms, called P200 or P2, are observed in an obligatory fashion. N1 and P2 are considered sensory or exogenous ERPs since their specific characteristics depend primarily on the physical features of the stimuli. If in a series of repeatedly presented standards a stimulus deviating in any physical characteristic (the so-called 'oddball' stimulus) is presented, additional ERP components termed mismatch negativity (MMN), N2 and P3 can be recorded. MMN is an early cognitive potential, occurring with a latency of approx. 100–200 ms and manifests an attention-independent process comparing the deviant stimulus to the sensory memory trace of the standard stimulus (Näätänen, 1990; Novak et al., 1990). MMN thus indexes the operation of a simple form of auditory working memory called echoic memory. In contrast, N2, a negative deflection occurring fronto-centrally with a latency of approx. 200 ms, and P3, a positive wave with an peak latency of approx. 300 ms, are attention-dependent potentials that are only observed if a specific behaviour is required upon detection of the 'oddball' or target stimulus. N2 is thought to reflect stimulus categorization (Ritter et al., 1979, 1983), whereas P3 is believed to reflect allocation of attention and activation of immediate memory (Johnson, 1986; Polich and Kok, 1995). MMN, N2 and P3 thus provide a

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sequence of potentials that index different stages (preattentive and attention-dependent) in the processing of behaviourally relevant target stimuli (Novak et al., 1990). ERP studies in schizophrenia have demonstrated abnormalities in the generation of MMN, N2 and P3 (Catts, 1995; Javitt et al., 1995; O'Donnell et al., 1993; Pritchard, 1986) indicating the presence of abnormal information processing even at the stage of the primary and secondary auditory cortex. In addition, several studies have also found increased latency of the P3 response in schizophrenia suggesting slower processing speed (Blackwood et al., 1987; Pfefferbaum et al., 1989).

Conventional antipsychotics fail to normalize abnormal amplitudes of MMN, N2 and P3, whereas they have been found to decrease P3 latency (Blackwood et al., 1987; Ford et al., 1994). In contrast, clozapine treatment is associated with an increase of deficient P3 amplitudes; however, it does not alter deficient generation of MMN (Schall et al., 1995; Umbricht et al., 1998). Thus, clozapine appears to improve attention-dependent steps in information processing without affecting deficits in early attention-independent auditory processing.

The present investigation explores the effects of risperidone, as a putative atypical antipsychotic, on cognitive dysfunction in schizophrenia as assessed by auditory ERPs using an uncontrolled study design. It is an initial attempt at answering the question whether risperidone exhibits effects on auditory ERPs that are similar to those of clozapine or more like those of conventional antipsychotics.

Subjects and methods

This study was conducted at the Hillside Hospital of the Long Island Jewish Medical Center (Glen Oaks, USA) with the necessary approval by the Ethics Committee (Internal Review Board). All subjects gave written informed consent to participate in this study. Ten chronic right-handed schizophrenic patients (M/F, 6/4; age, 33.3 ± 8.7 yr) were recruited from the in- and outpatient services of Hillside Hospital. Diagnosis was established according to criteria of DSM-III-R (American Psychiatric Association, 1987) by the primary investigator (D.U.) or by a trained nurse clinician using data obtained from patient interviews and chart reviews.

Auditory ERPs were recorded before initiation of risperidone treatment (baseline) and after 6 wk (6 patients) or 9 wk (4 patients) of treatment with risperidone, respectively. In order to assess the extent of ERP abnormalities in patients at baseline ERPs were recorded once in 12 age-matched right-handed normal controls (M/F, 10/1; age, 32.1 ± 5.2 yr).

At baseline 6 patients were treated with high potency conventional antipsychotics (3 patients with daily fluphenazine doses of 20, 20 and 10 mg, respectively; 3 patients with daily haloperidol doses of 5, 10 and 20 mg, respectively). Four patients had not been taking neuroleptics secondary to non-compliance with a prior treatment regimen for an unknown duration and were off neuroleptics at baseline. In addition 4 patients each received anticholinergic and benzodiazepines at baseline.

After the recording of baseline ERPs risperidone treatment was started and all other antipsychotic medication discontinued. Two patients received risperidone clinically, 2 patients in the context of a double-blind treatment study and 6 patients in the context of double-blind study comparing once daily to twice daily dosing of risperidone. At the time of the follow-up ERP recording all patients received 6 mg/d of risperidone. With the exception of 1 patient who received additional anticholinergic medication none of the patients was treated with concomitant psychotropic medication at follow-up.

Symptomatology was assessed with the Brief Psychiatric Rating Scale (BPRS, anchored version; Woerner et al., 1988) in 2 patients and the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) in the remainder. Due to the small study sample only the BPRS total score and BPRS psychosis factor and anergia scores (derived from PANSS scores in 8 patients) were used for analysis. Writing preference was used to assess handedness.

EEGs were recorded with a Neuroscan acquisition system and a Metrabyte EEG amplifier (bandpass 0.1–30 Hz) using a 16-electrode montage according to the 10/20 International System and stored with stimulus tags on-line on computer hard disk for further analyses. Electrodes were placed at F3, Fz, F4, left mastoid (Lm), T3, C3, Cz, C4, T4, right mastoid (Rm), T5, P3, Pz, P4, T6 and above the left outer canthus for monitoring of blinks and eye movements. An electrode placed on the nose served as reference. ERPs were acquired during active and passive auditory 'oddball' paradigms. In both conditions standard stimuli were 1000 Hz tones, deviants were tones of 1200 Hz with a probability of 0.15, randomly presented. Stimuli were of 50 ms duration with 5 ms rise/fall time, of 85 dB SPL (sound pressure level) and delivered binaurally via headphones. ISI varied randomly between 700 and 800 ms. The active paradigm always preceded the passive paradigm and consisted of two blocks with 80 deviants each. A button press within 200–1000 ms post-stimulus was considered a correct response. In the passive paradigm four blocks with 110 deviants each were presented. Subjects were watching a silent movie and told to ignore the tones.

Averages of 1024 ms with a 100 ms prestimulus baseline were constructed off-line, baseline-corrected and digitally filtered (low pass filter of 30 Hz, 6 dB down).

Table 1. Active and passive conditions of baseline and normal controls after risperidone treatment

Peak	Electron		Normal controls ($n = 12$)	Patients ($n = 10$)	
				Baseline	Follow-up
			Passive condition		
N1	Fz	Amplitude	-1.6 ± 1.19	-0.9 ± 1.1	-0.5 ± 0.9
		Latency	96 ± 10	86 ± 22	79 ± 19
P2	Fz	Amplitude	1.8 ± 1.4	2.0 ± 1.3	3.0 ± 1.2
		Latency	175 ± 25	164 ± 12	159 ± 7
MMN	Fz	Amplitude	-2.9 ± 1.1*	-1.8 ± 1.0	-2.4 ± 2.3
		Latency	173 ± 39*	123 ± 19	116 ± 16
			Active condition		
N1	Fz	Amplitude	-2.4 ± 1.2	-1.5 ± 1.6	-1.2 ± 0.8
		Latency	105 ± 13	93 ± 26	87 ± 11
P2	Fz	Amplitude	2.3 ± 2.1	1.6 ± 0.7	1.5 ± 1.5
		Latency	218 ± 29*	193 ± 25	168 ± 14‡
N2	Fz	Amplitude	-4.2 ± 3.6	-2.4 ± 4.2	-1.4 ± 4.2
		Latency	139 ± 34	150 ± 42	157 ± 42
P3	Pz	Amplitude	12.7 ± 5.7*	7.8 ± 2.8	6.1 ± 5.3
		Latency	258 ± 24†	325 ± 61	271 ± 47‡

Amplitudes in μV, latencies in ms.

* Normal controls vs. patients at baseline, t test: $p < 0.05$.

† Normal controls vs. patients at baseline, t test: $p < 0.01$.

‡ Patients at baseline vs. patients at follow-up, paired t test: $p < 0.05$.

Averages to standard and deviant stimuli in the passive condition were rereferenced to a mathematically computed average mastoid derivation for the purpose of peak measurements. In the active paradigm only sweeps associated with correct responses were included in the ERP to deviant stimuli.

In both active and passive paradigm N1 and P2 were determined from waveforms to standard stimuli at electrode Fz within a latency window of 50–150 ms post-stimulus for N1 and a latency window of 150–250 ms post-stimulus for P2. MMN latency and amplitude were determined at electrode Fz from the difference wave (ERP to deviants minus ERPs to standards) in the passive paradigm within a latency window of 100–225 ms post-stimulus. N2 was measured in the difference wave (ERP to deviant stimulus minus ERP to standard stimulus) of the active paradigm within a latency window of 100–250 ms post-stimulus. P3 was determined from the ERP to the deviant stimulus in the active paradigm within a latency window of 225–550 ms post-stimulus.

In both the passive and the active paradigm the required minimum of sweeps surviving artifact rejection (MMN = 100; N2 and P3 = 25) was not reached in 1 patient each. For both paradigms ERPs were therefore available for analyses in 9 patients.

Comparisons of latencies and peak amplitudes of the six ERP components between normal controls and patients were done with the help of unpaired t tests. To restrict the number of comparisons the effects of risperidone treatment on latencies and peak amplitudes of the various ERP components were evaluated with the help of repeated-measure ANOVAS with peak type (e.g. N1, P2, MMN) and session (baseline, follow-up) as within-subject factors. Analyses were done separately for the passive and active paradigm. Post-hoc paired t tests were used to further assess significant results. For the purpose of evaluating differences in P3 topography between controls and patients at baseline and effects of risperidone treatment on P3 topography, respectively, analyses were restricted to the 3 midline electrodes Fz, Cz and Pz and the lateralized electrodes T3/T4 and T5/T6. For all analyses α was set at 0.05, two-tailed.

Results

Passive paradigm (*Table 1*)

Comparison of patients at baseline and normal controls

Amplitudes and latencies of N1 and P2 did not differ between patients and normal controls. However, MMN amplitude was significantly smaller ($t = 2.31$, d.f. = 19, $p < 0.05$) and MMN latency significantly shorter ($t = 3.50$, d.f. = 19, $p < 0.05$) in patients than normal controls.

Effects of risperidone treatment

The peak latencies of all three ERP components were shorter at follow-up than at baseline. A repeated-measure ANOVA of peak latency with peak type (N1, P2, MMN) and session (baseline, follow-up) as repeated measures showed an effect of session that was just above the significance level [$F(1,8) = 4.66$; $p = 0.06$], but not session × peak interaction. None of the latency changes were significant when assessed individually with the help of paired t tests.

Risperidone treatment was associated with a decrease of N1 amplitude and an increase of both P2 and MMN peak amplitudes. However, there was no significant effect of session or a significant peak × session interaction in a repeated-measure ANOVA.

Active paradigm (*Table 1*)

Comparison of patients at baseline and normal controls

Patients showed smaller amplitudes of all four ERP components than controls. However, only the difference in P3 amplitude reached statistical significance ($t = 2.34$, d.f. = 19, $p < 0.05$). In addition, peak latency of P2 was significantly shorter ($t = -2.1$, *d.f.* = 19, $p < 0.05$) and P3 latency significantly longer ($t = 3.50$, d.f. = 19, $p < 0.01$) in patients than normal controls.

Comparison of P3 topography between patients and normal controls with the help of a repeated-measure ANOVA (electrodes as within-subject factor; group as between-subject factor) showed a significant group effect, but no group × electrode interaction [repeated-measure ANOVA, main effect of group: $F(1,19) = 7.04$, $p < 0.02$; group × electrode interaction: $F(6,14) = 1.03$, $p =$ ns].

Effects of risperidone treatment

With the exception of N2 latency peak latencies were shorter at follow-up than at baseline. A repeated-measure ANOVA of peak latency with peak type (N1, P2, N2, P3) and session (baseline, follow-up) as repeated measures demonstrated a significant effect of session [$F(1,8) = 5.74$; $p < 0.05$], but not session × peak interaction. Paired t tests showed that latencies of P2 and P3 were significantly shorter at follow-up than at baseline (P2: $t = 2.44$, d.f. = 8, $p < 0.05$; P3: $t = 2.73$, d.f. = 8, $p < 0.05$). At follow-up P3 latency no longer differed significantly between patients and normal controls ($t = 0.8$, d.f. = 11.2, $p =$ ns).

At follow-up the peak amplitudes of all four ERP components were smaller than at baseline. A repeated-measure ANOVA of peak amplitude with peak type (N1, P2, N2, P3) and session (baseline, follow-up) as repeated measures did not reveal any significant effects or interactions. Finally, treatment with risperidone was not associated with any significant effect on P3 topography as evaluated by a repeated-measure ANOVA with electrode sites and session as within-subject factors [main effect of session: $F(1,8) = 1.18$, $p =$ ns; session × electrode interaction: $F(3,6) = 0.79$, $p =$ ns].

Table 2. BPRS scores after risperidone treatment

	Psychopathology	
	Baseline	Follow-up
BPRS total score	51.3 ± 8.0	43.2 ± 8.9*
BPRS Psychosis factor score	17.2 ± 3.2	14.5 ± 2.8†
BPRS Anergia factor score	10.2 ± 1.9	10.0 ± 2.4

* $p < 0.05$.
† $p < 0.01$.

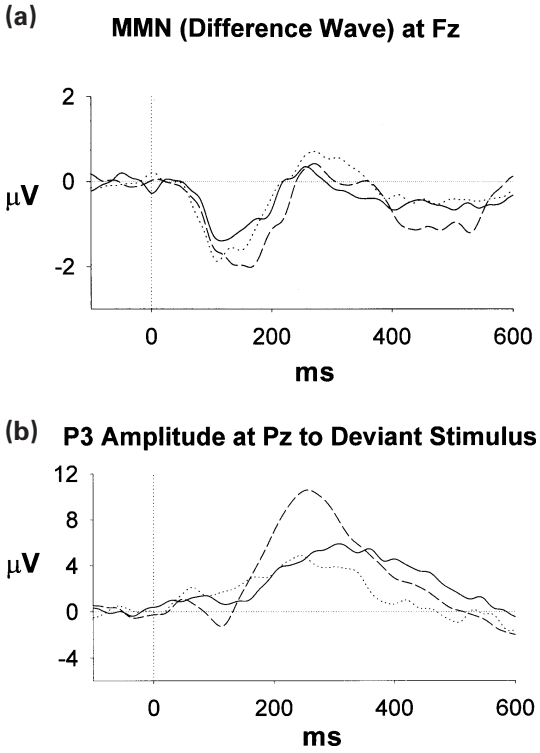

Figure 1. Grand averages of (a) Mismatch Negativity and (b) P3 in normal controls (– – –), patients at baseline (——) and patients at follow-up (·····).

Psychopathology

Treatment with risperidone was associated with significant decreases of BPRS total score and BPRS psychosis factor score, but had no significant effect on BPRS anergia factor score (Table 2). Changes in P2 and in P3 latencies

were not significantly correlated with changes in symptomatology.

Discussion

This study explored effects of risperidone treatment on neurocognitive deficits by investigating its effects on auditory ERPs in a small sample of chronic schizophrenic patients. Consistent with results of previous studies we found that patients, in comparison with age-matched controls, showed deficient generation of MMN and P3 and increased latency of P3. Risperidone treatment was associated with a shortening of peak latencies which was most pronounced in the attend condition. In particular, risperidone treatment was associated with a significant shortening of P3 latency. In contrast, risperidone treatment did not have an appreciable effect on deficient amplitudes of MMN and P3.

The shortening of peak latencies suggests an general enhancement of information processing speed by risperidone both at the preattentive and attention-dependent level. The most pronounced effect concerned a shortening of the latency of P300. In so far as P300 reflects operations such as allocation of attentional resources and updating of immediate memory (Johnson, 1986) the shortening of P300 latency associated with risperidone treatment would suggest that risperidone enhances the speed by which they are carried out. Interestingly, risperidone has been found to significantly increase reaction time compared to haloperidol (Kern et al., 1998) and in uncontrolled studies (Stip and Lussier, 1996) Although P3 latency and reaction time are manifestations of different processes they are usually highly correlated. Thus, findings concerning the relevance of abnormal reaction time may also apply to P3 latency. In cross-sectional studies reaction time has been found to predict short- and long-term outcome (Cancro et al., 1971; Zahn and Carpenter, 1978). It is thus conceivable that sustained effects on processing speed as indicated by decreased reaction time and normalized P3 latency may translate into clinically significant improvements in long-term treatment.

In recent studies we and others have demonstrated that clozapine treatment was accompanied by an increase of P3 amplitude, but did not reverse deficits in MMN generation (Schall et al., 1995; Umbricht et al., 1998), suggesting that clozapine improves attention-dependent function without affective preattentive processing. In the present study risperidone had a significant effect on latencies of P2 and P3, but did not affect P3 amplitude. To the extent that these studies can be compared to the present investigation, the results of this study would suggest that risperidone does not share the specific effects of clozapine, but may particularly improve speed of information processing – an effect not observed during clozapine treatment (Umbricht et al., 1998; Zahn et al., 1994).

Several, although not all neuropsychological studies have reported significant effects of clozapine, risperidone and olanzapine on cognitive functioning (Goldberg et al., 1993; Green et al., 1997; Hagger et al., 1993; Hoff et al., 1996; McGurk and Meltzer, 1998; Stip and Lussier, 1996; Zahn et al., 1994). To the extent that neurocognitive improvement occurs during treatment with atypical antipsychotics, electrophysiological studies will be important in analysing mechanisms underlying such effects. Our previous study on clozapine suggested a particular effect on attention-dependent information processing, while the present study indicates that risperidone improves processing speed.

In interpreting the results of this study several caveats have to be observed. Most importantly, the number of subjects investigated is small, considerably reducing the power of the study to detect small effects of risperidone and inflating the potential for type II errors. Secondly, due to the uncontrolled design of this study alternative explanations for the observed effects cannot be ruled out. In particular, the decrease in latency could simply be the result of withdrawal of conventional antipsychotics or of unspecific treatment effects. However, what mitigates against the former possibility are the results of previous studies demonstrating that treatment with conventional antipsychotics is associated with a shortening of P3 latency (Blackwood et al., 1987; Ford et al., 1994). The question to what extent the effects of risperidone observed in this study are thus comparable to, or exceed those of, conventional antipsychotics cannot be answered by this uncontrolled study.

This study is the first to investigate the effects of risperidone on neurophysiological abnormalities in schizophrenia; however, it is limited by its open and uncontrolled design, its small sample size and by the fact that not all patients could be studied in a medication-free condition at baseline. Thus, the conclusions drawn from the results must be seen as preliminary. Controlled studies in larger samples are required to answer the important issue: 'Do newer antipsychotics improve neurocognitive deficits in schizophrenia?'

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