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An evidence for lack of pseudoneglect in patients with schizophrenia: An ERP study

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HIGHLIGHTS

- We examined the effect of number magnitude on the P3 latency.
- For controls, P3 latencies were different between the targets 'one' and 'nine'.
- Patients did not show the effect of number magnitude on the P3 latency.
- The results suggest a lack of pseudoneglect in patients with schizophrenia.

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ABSTRACT

Studies have reported an altered expression of pseudoneglect in patients with schizophrenia, but no study has examined pseudoneglect in schizophrenia at the neural level. We investigated pseudoneglect using the visual P3 event-related potential and the mental number bisection (MNB) task in 21 patients and 25 controls. Using an oddball task, participants were asked to discriminate an infrequent ('one' or 'nine') from a frequent written number ('five'). The P3 ERP components were delayed to the targets on the right of the MNL ('nine') compared to the targets on the left ('one') in controls. The effect of number magnitude on the P3 latency was not observed in the patients. In MNB task, the patients did not show the normal leftward bias observed in healthy individuals. Our findings indicate a lack of pseudoneglect and the presence of an anomalous brain asymmetry in schizophrenia.

1. Introduction

Hemispheric asymmetry refers to the normal differences in the hemispheric structures or functions, and it is considered as part of the neurodevelopmental processes [1]. The right posterior parietal cortex (PPC) plays a predominant role in the spatial attention, and there is an over-attention for processing left hemi-space in healthy individuals. For example, in the line bisection task, healthy participants systematically misbisect lines to the left of their true midpoints, named pseudoneglect. Pseudoneglect is explained by the dominance of the right side of the brain in visuospatial attention [2]. In a review of the literatures, Jwell and McCourt [2] showed a significant leftward bisection error with an effect size of .44–.73.

Neuropsychological studies have indicated that the numbers are internally represented as a line, so-called the mental number line (MNL), with small numbers on the left and large numbers on the right end of the line [3,4]. The spatial nature of MNL has been used to study the representational neglect that biases attention and perception toward one hemi-field. In the mental number bisection (MNB) task [5], patients with hemi-spatial neglect tend to misplace the midpoint toward the hemispheric brain lesion. For example, when a patient with left hemi-spatial neglect is asked to say which number is the midpoint between 2 and 6, he/she might report 5, indicating a relative shift to the right.

Recent reports have indicated that the normal asymmetries are reduced or even reversed in schizophrenia [6,7]. Such abnormalities have been found in the structural and functional brain imagings [8] and the attentional functions [9]. Several studies assessed the asymmetrical attention or pseudoneglect in schizophrenia, but the results are inconsistent. For example, in the line bisection task, either rightward [10,11] or leftward [12] biases have been reported. In the MNB task, Cavezian et al. [13] found a leftward bias in the patients, but other studies did not [11,12]. The inconsistency in the results of the behavioral studies of pseudoneglect suggests the need for further explorations, which is the main aim of the present study. To the best of our knowledge, no study has investigated pseudoneglect at the neural level in patients with schizophrenia. Therefore, in the present study, we used the event-related potentials (ERPs) along with the MNB task to explore this phenomenon.

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One of the best known cognitive ERP components is the P300, which is a large and positive component in ERP. P3 is commonly elicited in two-stimulus oddball paradigm occurring 300–600 ms following the onset of the target stimulus, with maximum amplitude over the parietal electrodes [14]. Increased P3 latency and decreased P3 amplitude for the target stimulus presented on the neglected side have been reported in patients with hemi-spatial neglect [15,16]. Recently, Prifits et al. [17] employed an auditory numerical oddball task, to study the left neglect patients. Patients were asked to discriminate an infrequent stimulus ('one' or 'nine') from the frequent stimulus ('five'). Their results showed that P3 latencies were influenced by the number's relative position on MNL, with delayed to the targets on the left of MNL ('one') compared to the targets on the right ('nine').

Based on the known leftward bias in healthy individuals and behavioral evidences of the hemi-spatial neglect in schizophrenia, the present study sought to further explore the pattern of asymmetrical attention in patients with schizophrenia and healthy individuals, using the MNB task and a visual numerical oddball paradigm.

2. Methods

2.1. Participants

Twenty-five schizophrenic patients, who met the DSM-IV criteria for a lifetime diagnosis of schizophrenia, were assessed using the Scale for Assessment of Negative Symptoms (SANS) [18] and the Scale for Assessment of Positive Symptoms (SAPS) [19]. The patients did not have a history of electroconvulsive therapy within six months prior to the testing time. At the time of testing, patients were receiving antipsychotic medications. The mean chlorpromazine (CPZ) equivalent dose was 318.5 mg [20].

The control group comprised 28 participants screened for a personal and family history of psychotic illnesses. Exclusion criteria for all participants included a history of head injury, neurological disorders, and current substances abuse. In addition, none of the participants had dyscalculia in the standard clinical tests. All participants were right-handed and had normal or corrected-to-normal vision. Written informed consent was obtained from all participants, and the study was approved by the Ethics Committees of Kerman University of Medical Sciences.

2.2. Assessment procedures

2.2.1. Mental number bisection (MNB) task

The stimuli and procedures for the MNB task were designed based on Zorzi et al. [5] and Tian et al. [12] studies. The participants were presented with 96 spoken number pairs in different numerical intervals. They were asked to report orally the midpoint number between the presented pair without making a calculation. The numbers used were divided to three blocks of decades (1–9, 10–19, and 21–29). Each block comprised four interval sizes including three (e.g., 11–13), five (e.g., 11–15), seven (e.g., 11–17), and nine (e.g., 11–19). Participants were given 48 trials in an ascending order and 48 trials in a descending order.

The measure of interest in the MNB task was the difference between the true midpoint number and the participant's answer. The response was considered to have a leftward bias if the participant's answer was smaller than the true midpoint number (negative values). A rightward bias occurred when the participant's answer was higher than the true midpoint number (positive values). Individual mean biases were calculated for each interval.

2.2.2. Oddball task

Participants were seated in an electrically shielded and sound-attenuating room, with a head rest in front of a computer screen. The stimuli were Persian numbers 'one', 'five' and 'nine' presented in black and white. At the beginning of each trial, a fixation cross was presented for 200 ms, followed by the presentation of one of the numbers for 500 ms, with inter-stimulus intervals of 1700–2700 ms.The targets were the numbers 'one' and 'nine', and the non-target was the number 'five'. Participants were asked to press a key in response to the target stimuli ('one' or 'nine'), and ignore the non-target stimulus ('five'). A total of 480 non-target stimuli (80%) and 120 target stimuli (20%) were presented in a random order. All stimuli were displayed on a 19-in. computer screen, at a distance of about 65 cm from participants' eyes, resulting in a visual angle of approximately 2.5°. Reaction time and accuracy, percent of the correct responses, were recorded by pressing a key. Participants were asked not to make blinks and any other movements during trials. The actual experiment was preceded by a test trial in order to familiarize participants with the test procedure.

2.2.2.1. ERP acquisition. The experimental apparatus consisted of a Mitsar-202 system (Mitsar, Russia) and WinEEG program developed at the Institute of the Human Brain, Russian Academy of Sciences. The EEG was recorded using a 32 channel cap (Electro-Cap International, Inc.), and referenced to linked earlobes. Electrode impedance was kept below 5 kOhm. EEG was sampled at 500 Hz with filtered online .16–30 Hz band pass.

Ocular artifacts correction was performed using an independent component analysis approach. Movement artifacts were excluded from analysis by careful visual inspection of the raw EEG. After final artifact rejection, ERPs were averaged relative to stimulus onset, including 200 ms pre-stimulus to 800 ms post-stimulus. The P300 was defined as the largest positive wave following the N100–P200–N200 complex between 250 and 700 ms after stimulus onset at the Pz electrode. The P300s of other electrodes (F3, Fz, F4, C3, Cz, C4, P3, P4) were defined as the largest positive peaks within ±50 ms of the P300 at Pz. The peak latency was defined as the time from stimulus onset to the maximum peak.

2.3. Statistical analysis

Demographic and clinical data were analyzed with *t*-test for independent samples and chi-square as appropriate.

For MNB task, individual mean biases were calculated for each interval. Repeated measures ANOVA was carried out using group (schizophrenia and controls) as between-subject factor and interval size (3, 5, 7, and 9) as within-subject factor. Then, the mean biases of patients and controls for each interval size were compared with zero using one sample *t*-test.

ERP data were examined in two steps with repeated measures ANOVA. First, based on Neuthaus et al. [21], for confining the P3 amplitude to a small set of electrodes, we analyzed each group separately with the two target numbers ('one' and 'nine') and nine electrodes entered as within-subject factors. After finding parietal electrodes as the relevant leads for the aim of this study, target numbers ('one' and 'nine') and electrodes (P3, Pz, and P4) were entered as within-subject factors and group (schizophrenia and controls) as between-subject factor, for the second step of P3 analysis.

3. Results

Table 1 shows the demographic and clinical characteristics of all patients and controls. Groups were well matched for age, gender, and education.

Table 1
Demographic and clinical characteristics of the study participants.

	Patients N = 21	Controls N = 25	P
Age	34.6 (6.1)	35.4 (6.9)	NS
Education	9.8 (3.3)	9.7 (3.3)	NS
Sex – N (%males)	18 (75%)	21 (75%)	NS
Edinburgh	99.1 (2.9)	100 (0)	NS
Length of illness (year)	12.9 (7.5)	–	
Age onset of illness (year)	21.8 (5.6)	–	
Mean chlorpromazine equivalent (mg)	318.5 (165.2)	–	
SANS	35.3 (14.5)	–	
SAPS	25.3 (15.9)	–	

3.1. MNB

The model showed a significant main effect of group ($F_{1,44}$ = 9.9; p = .003; η^2 = .17). Post hoc analyses indicated that the two groups were significantly different for interval sizes of seven (p = .01) and nine (p = .01). While the main effect of the interval size was not significant ($F_{3,144}$ = .059; p = .9; η^2 = 001), the interaction effect of 'group × interval size' was significant ($F_{1,44}$ = 5.9; p = .02; η^2 = 11), indicating the pattern of performance differed significantly between patients and controls (Fig. 1). Negative values for the mean biases of controls reflect a leftward bias, while positive values for the mean biases of patients indicate a rightward bias.

Then, the mean biases of patients and controls for each interval size were compared with zero, the theoretical value of the correct answers, to examine the significance of the observed biases. Regardless of the order of presentation and the block, analyses showed that controls had significant leftward biases for the interval sizes of seven (p = .02) and nine (p = .01), but the mean biases of patients were not significantly different from zero (all p > .1).

3.2. Oddball task

3.2.1. Behavioral data

Table 2A summarizes the mean behavioral data. Repeated measure analysis was conducted on reaction time (RT), using groups (patients and controls) as between-subject factor, and target number ('one' and 'nine') as within-subject factor. The results showed a significant main effect of group ($F_{1,47}$ = 18.8; p < .001; η^2 = .28), and patients were significantly slower than controls for both target numbers (all p < .001). While the main effect of number was significant ($F_{1,47}$ = 5.5; p = .01; η^2 = 12), the interaction effect of 'group × number' was not significant ($F_{1,47}$ = .001; p = .97; η^2 = .000).

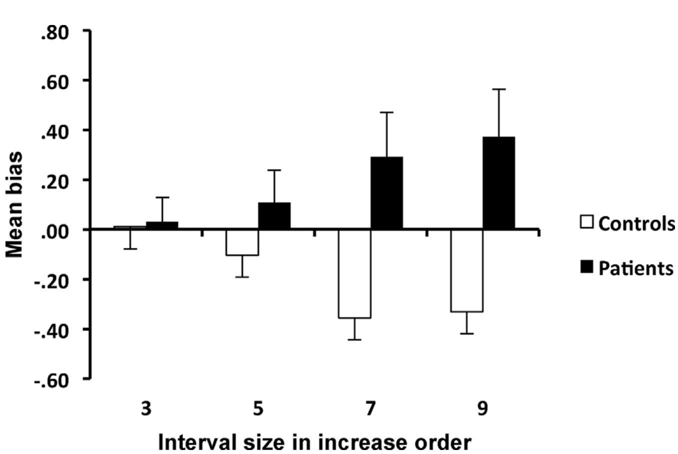

Fig. 1. Mean deviation from actual mid-number in MNB task for schizophrenia patients and controls. Positive values show shifts to the right of true midpoint. Negative values show shifts to the left of true midpoint. Error bars represent 1 SE of the mean.

For both groups, the mean RT was slower for the target 'nine' relative to the target 'one', indicating that RT significantly changes among the two target numbers, and the pattern of changes is similar between the two groups.

3.2.2. ERP data

3.2.2.1. Topographic P3 effects. In the control group, the model showed a significant main effect of 'electrode' ($F_{8,200}$ = 17.2; p < .001; η^2 = 41), but there was no significant interaction of 'electrode × number' ($F_{8,200}$ = .93; p = .4; η^2 = .04). Similarly, in the patient group, there was a significant main effect of 'electrode' ($F_{8,168}$ = 12.1; p < .001; η^2 = 36), but there was no significant interaction of 'electrode × number'. These results indicated that P3 amplitudes were highest at parietal electrodes compared with corresponding electrodes in both groups (all p < .02).

3.2.2.2. Latency analysis. The results revealed that the main effect of group reached statistically significant ($F_{1,44}$ = 4.1; p = .49; η^2 = 08), and schizophrenia patients had significantly longer latencies compared to controls. Post hoc analysis showed that the two groups differed significantly in the latency of the target number 'one' (p = .02) (Table 2B). While the main effect of number was not significant ($F_{1,44}$ = 1.9; p = 17; η^2 = 04), there was a significant interaction effect of 'group × number' ($F_{1,44}$ = 4.45; p = 04; η^2 = 09). Post hoc analysis showed that for controls, P3 latencies were significantly different between the targets 'one' and 'nine' (p = .01). In contrast, for schizophrenic patients, the comparison between latencies for the targets 'one' and 'nine' was not significant (p = .62) (Fig. 2).

3.2.2.3. Amplitude analysis. Our model showed a significant main effect of group ($F_{1,44}$ = 10.99; p = .002; η^2 = 2), and schizophrenia patients had significantly smaller mean P3 amplitudes, for both target numbers 'one' and 'nine', compared to controls. However, neither the main effects of number ($F_{1,44}$ = 1.36; p = .24; η^2 = 03) nor the interaction ($F_{1,44}$ = .23; p = .64; η^2 = 005) were significant.

3.3. Correlation analyses

In the group of patients, bivariate correlation analyses were performed between the biases in MNB for each interval size with

Table 2
Behavioral (A) and ERP measures (B) of the oddball task for each participant group.

(A)

	Patient	Control	P
Mean accuracy (%)	98.2 (2.3)	99.2 (1.8)	NS
Mean RT	557.4 (105.1)	456.9 (53.2)	<.001
RT (number 1)	550.9 (105.9)	450.3 (51.0)	<.001
RT (number 9)	563.9 (109.6)	463.6 (57.3)	<.001

(B)

Electrodes	Targets	Patients	Controls
Latency			
P3	1	467.5 (66.3)	439.3 (32.7)
	9	469.5 (57.5)	453.5 (35.1)
Pz	1	474.9 (64.1)	435.3 (37.4)
	9	469.3 (56.9)	452.9 (32.2)
P4	1	474.3 (64.1)	432.3 (36.7)
	9	467.7 (58.5)	449.5 (33.4)
Amplitude			
P3	1	7.54 (4.9)	12.07 (3.9)
	9	7.86 (4.7)	12.4 (5.1)
Pz	1	9.10 (5.3)	13.6 (4.8)
	9	9.26 (5.2)	14.2 (5.5)
P4	1	8.32 (4.8)	12.71 (4.4)
	9	8.47 (4.9)	13.3 (5.05)

Pz, parietal midline electrode; P3, left parietal electrode; P4, right parietal electrode.

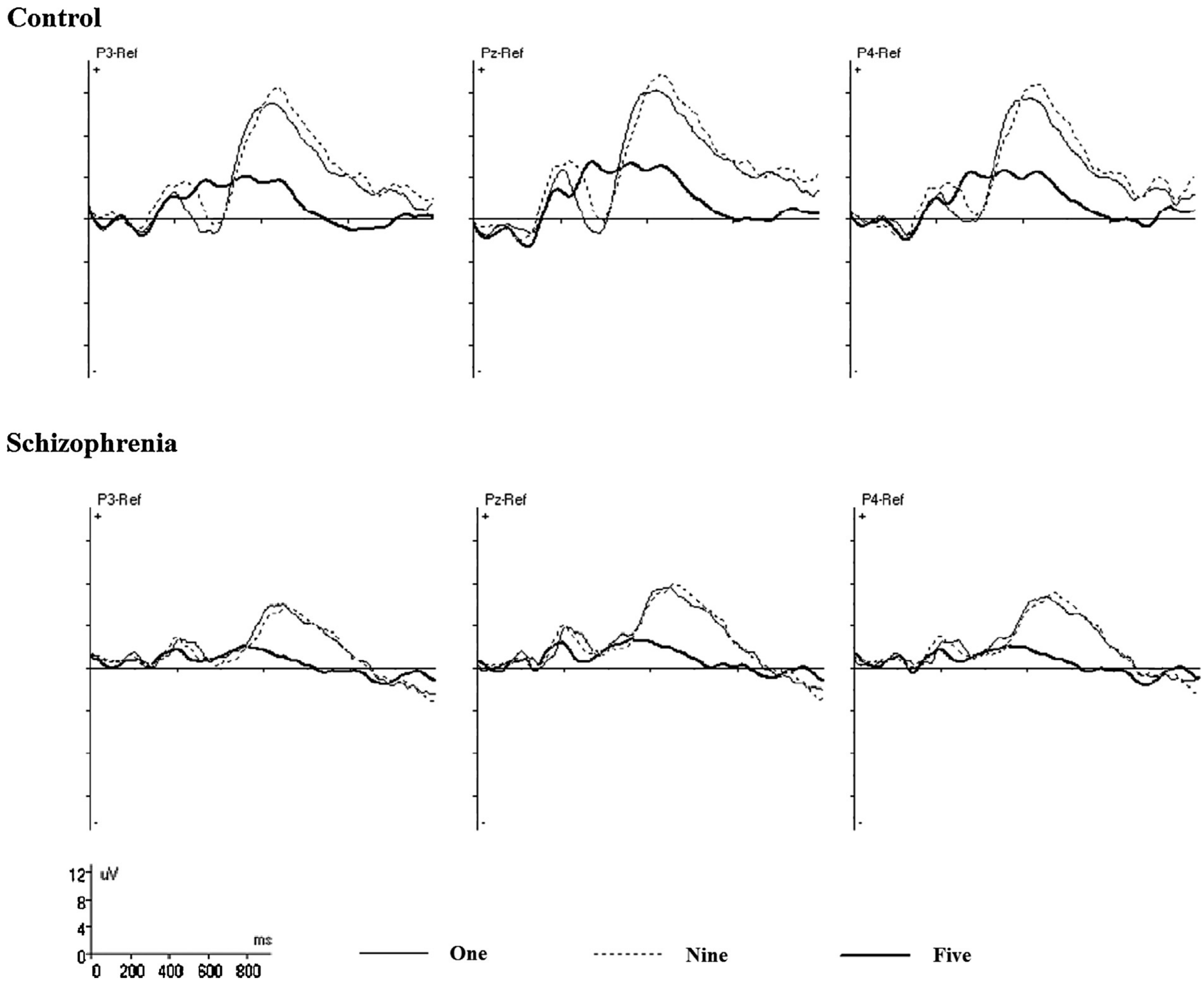

Fig. 2. Grand average ERPs at parietal electrodes for (A) control group and (B) Schizophrenia group.

the CPZ equivalent dose and clinical characteristics of the patients including SANS, SAPS, duration of disease, and age of onset. No significant correlation was found (all $p > .06$). The correlations between the ERP measures with the CPZ equivalent dose and clinical characteristics of patients were not significant (all $p > .2$).

4. Discussion

The present study aimed to explore pseudoneglect in schizophrenia at the behavioral and neural levels. At the behavioral level, the results of MNB task indicated that patients did not show the normal leftward biases observed in healthy individuals. At the neural level, consistent with the results of the MNB task, an effect of number magnitude on the P3 latency was found in healthy controls, but this effect was not observed in the patients.

At the behavioral level, the significant leftward error of the control group was comparable to the findings reported in previous studies [13,22]. This result replicates the finding that the normal individuals exhibit a modest, but significant, leftward bias. Importantly, studies have demonstrated a brain asymmetry in the spatial representation of numbers, and a role of the right cerebral hemisphere in the representation of numbers, in healthy individuals [22]. It could be expected that normal individuals pay more attention to the smaller numbers and exhibit leftward bias in MNL. However, the patients did not show the normal pattern of significant leftward bias characterizing the right hemisphere dominance for allocation of attention observed in healthy individuals. Therefore, the finding of a lack of leftward bias in schizophrenia might indicate an abnormality in the right hemisphere and in the spatial representation of numbers. Our patients also showed non-significant rightward biases in the MNB task (Fig. 1). This may be explained by great variances in the patients, so further researches with larger sample size are required.

Consistent with previous studies, in the oddball task, abnormalities in the P3 latency and amplitude were found in patients reflecting deficits in the cognitive processes. One of the important findings of this study was the effect of number magnitude on the P3 latency in controls. The P3 latency was influenced by the number's relative position on MNL, and it was longer for the numbers on the right side of MNL ('nine') compared to the number on the left side ('one'). This result indicates the over-attention of controls to the number on the left side of MNL, and it supports the right hemisphere dominant role in the spatial attention, particularly in the spatial representation of numbers. Importantly, this finding may provide a neural evidence of pseudoneglect in the neurologically intact people.

In agreement with our results in the MNB task, the patients did not show the effect of number magnitude on the P3 latency observed in controls. The P3 latencies for the numbers on the left and right sides of MNL were comparable in patients. This result suggests that the tendency of healthy controls to attend to the left side of MNL is absent in patients with schizophrenia, reflecting the abnormality in the right hemisphere.

There are mounting evidences that the right hemisphere, specifically the right PPC is involved in the spatial representation of numbers. Göbel et al. [22] found while healthy individuals underestimated the midpoint of the numerical intervals in MNL, using rTMS over the right PPC shifted the perceived midpoint of the numerical interval significantly to the right. Our finding might indicate that some aspects of the right hemisphere functions, particularly PPC, are compromised in schizophrenia. Supporting evidence comes from studies suggesting that the dysfunction of PPC is a putative candidate for many cognitive impairments in schizophrenia [23,24] such as impaired spatial attention, oculomotor control, and deficits in motor control and motor imagery [25,26].

It should be mentioned that the effect of number magnitude on the P3 latency was not represented on P3 amplitude in the healthy controls. This is not surprising, as various factors influence the P3 amplitude and latency differently [14]. The P3 amplitude is affected by perceptual and attentional variables, which had no role in our study. In addition, the P3 latency is an index of classification speed and is related to the time required to detect and evaluate a target stimulus. Importantly, P3 latency is related to how rapidly individuals can allocate attentional resources [14]. Therefore, our finding indicates that the relative position of the numbers in MNL may not affect their initial perception, but it may influence the speed of allocation of attention to them. Future researches are required to replicate this finding in the neurologically intact individuals.

The important limitation of our study was that all patients were on the medications. Tomer and Flor-Henry [27] found that while unmedicated schizophrenia patients showed inattention to the right hemi-space, medicated patients changed inattention to the left side. Particularly, in the MNB task our patients showed non-significant rightward biases. Therefore, future research are required to repeat these findings in a group of drug-naïve patients, though we did not find any correlation between CZP equivalent dose and behavioral and ERP measures.

5. Conclusion

In our study, healthy individuals underestimated the midpoint of the numerical intervals, and they exhibited longer latency for the number on the right side of MNL. However, schizophrenia patients did not show the normal pattern of over-attention to the left, neither in the MNB task nor in the number oddball task. Our results suggest a lack of normal hemispheric asymmetry and the presence of an abnormal cerebral lateralization in patients with schizophrenia. Moreover, our observations indicate that theses abnormalities extend to the neural level.

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