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Clozapine improves the orienting of attention in schizophrenia

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ABSTRACT

Attentional deficits are prominent in the cognitive profile of patients with schizophrenia. However, it remains unclear whether treatment with clozapine, an atypical antipsychotic and first-line intervention used to reduce positive and negative symptoms of psychosis, improves the attentional functions. We used the revised attention network test to measure alerting, orienting, and executive control of attention both pre- and post-treatment with clozapine in patients with schizophrenia (n = 32) and compared performance to healthy controls (n = 32). Results revealed that there were deficits in all three attentional functions pre-treatment, and while clozapine improved the orienting function in patients with schizophrenia, there was no evidence for improvement in the alerting and executive control of attention. The enhancement of the orienting function by clozapine may increase the ability of patients with schizophrenia to orient towards objects and thoughts of interest.

1. Introduction

Cognitive deficits are hallmark to schizophrenia and drive the significant disabilities in occupational, social, and economic functioning in these individuals (Keefe and Harvey, 2012). Specifically, attentional deficits are prominent in schizophrenia (Harris et al., 2007) and play a critical role in the cognitive phenotype of psychosis (Luck and Gold, 2008). Although considerable effort has been devoted to investigating the extent of attentional deficits in patients with schizophrenia, and their relation to functional, social, economic, and treatment outcomes (Meltzer and McGurk, 1999; Tamminga, 2009), whether current pharmacological interventions are effective in the treatment of attentional deficits is unclear.

Attention can be conceptualized as a set of brain functions consisting of alerting, orienting, and executive control that influence the priority of domain-specific information processing (Fan et al., 2009; Mackie et al., 2013). These attentional functions are responsible for producing and maintaining a state of readiness to process non-specific impending inputs (alerting), selecting the most relevant information from various inputs within and across modalities (orienting), and detecting and resolving conflict among competing mental processes (executive control) (Fan et al., 2002). Each function has been associated with specific brain areas and neurotransmitters (Fan and Posner, 2004). Alerting is associated with thalamus, frontal and parietal areas of right hemisphere, and is related to the locus coeruleus and norepinephrine (NE) function (Aston-Jones and Cohen, 2005; Marrocco and Davidson, 1998). Frontal eye fields, inferior parietal cortex, and acetylcholine (Ach) activity are associated with orienting (Corbetta et al., 2008; Davidson and Marrocco, 2000). Executive control of attention involves the anterior cingulate cortex and the dorsolateral prefrontal cortex (Fan et al., 2005) and is related to ventral tegmental area and dopamine (DA) function (Benes, 2000). There is consensus about the causal relation between deficits in the three attentional networks (and corresponding neurotransmission) and impaired attentional functions (Petersen and Posner, 2012).

Atypical cortical activity (Camchong et al., 2006; Davidson and Heinrichs, 2003) and dysfunctional neurotransmission have been also indicated as possible factors in the pathophysiology of schizophrenia (Horacek et al., 2006). Medications combining dopaminergic and serotoninergic antagonism (i.e., atypical antipsychotics) are the most common treatments to reduce positive symptoms of schizophrenia (Hill et al., 2010). Evidence also exists for dysfunctional cholinergic activity

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Table 1
Demographic (SD) and clinical (SD) data of schizophrenic patients (SZ) and healthy controls (HC).

	SZ	HC
N	32	32
Age	30 ± 7	28 ± 6
IQ	108 ± 11	107 ± 11
Gender	18 M/14 F	17 M/15 F
Year of education	12 ± 2	13 ± 4
Duration of disease (months)	33 (SD = 63)	
PANSS Total Pre/Post	104 ± 11/68 ± 8	
PANSS positive symptoms Pre/Post	17 ± 5/9 ± 2	
PANSS negative symptoms Pre/Post	14 ± 6/10 ± 3	
Average Clozapine Dosage	~300 ± 87 mg	

in patients with schizophrenia (McKinzie and Bymaster, 2012), and treatments targeted to cholinergic receptors have been shown to produce antipsychotic effects (Sarter et al., 2012). However, the mechanisms underlying the effectiveness of atypical antipsychotics are only partially understood, and limited evidence exists on the efficacy of these treatments on the cognitive impairment in schizophrenia (Keefe and Harvey, 2012).

There is a wealth of existing research on the attentional functions in patients with schizophrenia. Reduced sustained attention (O'Gráda et al., 2009), difficulty in orienting attention towards novel stimuli and relevant cues (Laurens et al., 2005), and impaired executive control mechanisms (Westerhausen et al., 2011) have been found in patients with schizophrenia. The majority of studies using the attention network test (ANT) have consistently found deficits in executive control (Neuhaus et al., 2011; Wang et al., 2005), orienting (Wang et al., 2005), and alerting (Backes et al., 2011) in patients with schizophrenia compared to controls, although some controversy still exists (Neuhaus et al., 2010).

Clozapine, considered to be one of the best treatments for schizophrenia (Baviera et al., 2008; Horacek et al., 2006), has a multiple receptor binding profile targeting dopaminergic D2, D1 and D4 and serotoninergic 5-HT2A and 5-HT2C receptors and noradrenaline α1, as well as cholinergic (muscarinic) receptors such as M1 and M5 (Baviera et al., 2008). Clozapine's antipsychotic effectiveness has been associated with fast dissociation from D2 receptor, preferential action against serotoninergic 5-HT2A and 2C receptor, receptor agonism of 5-HT1A, and the increase of extracellular levels of acetylcholine in the prefrontal cortex, striatum, and nucleus accumbens (Horacek et al., 2006).

There is extensive literature regarding the beneficial effects of clozapine in reducing cognitive deficits in patients with schizophrenia (Hill et al., 2010). However, the impact of treatment with clozapine on the three attentional functions has not been examined in a single paradigm. Studies investigating changes in the executive control of attention after clozapine treatment show only weak evidence of improvement due to medications (Bender et al., 2006; Bilder et al., 2002). There are also inconsistent results regarding the impact of clozapine on sustained attention deficits (Harris et al., 2007), and little is known about the relationship between the effect of antipsychotic medications and the orienting function (Keedy et al., 2009). Given the prominence and persistence of attentional impairments in patients with schizophrenia (McGurk and Meltzer, 2000), clarifying whether pharmacological interventions also treat deficits in the three attentional networks in schizophrenia is fundamental.

This study examined whether clozapine treatment reduces attentional deficits in patients with schizophrenia. Because of the broad impact of clozapine on multiple neurotransmitter systems implicated in attention, we expected a treatment effect on the three attentional functions. We

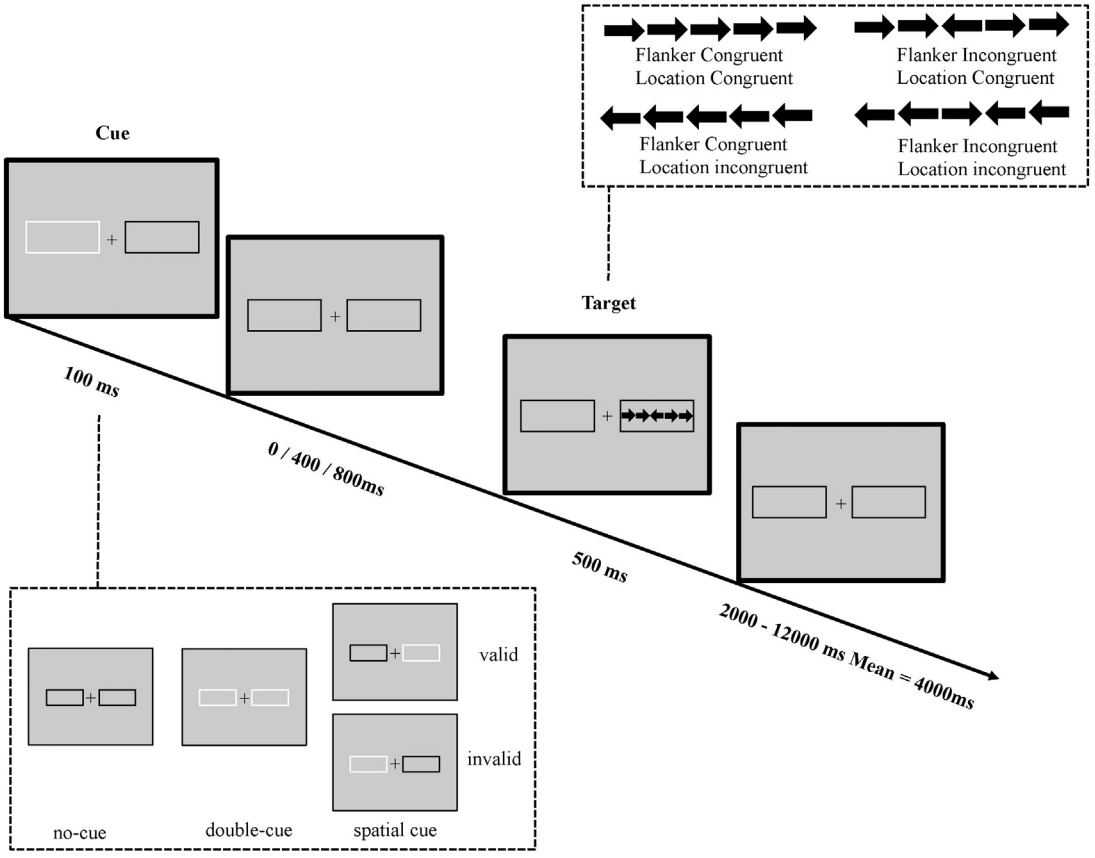

Fig. 1. Schematic of the ANT-R. In this task, participants made responses to indicate the direction of a central arrow (left or right) which was surrounded by two flanker arrows on each side, either pointing in the same direction as the target (congruent) or in the opposite direction (incongruent). Before the target appeared, a cue in the form of a box flashing on one or both sides was displayed. The cue could be valid, which predicted the target position correctly, or invalid, which predicted the opposite position. There was also a double cue condition, in which both boxes flashed to provide temporal but not spatial information, and a no cue condition, in which no cue was presented.

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predicted that patients with schizophrenia would show impairment in the alerting, orienting, and executive control of attention, and that the treatment with clozapine would reduce these attentional deficits.

2. Method

2.1. Participants

This study included 32 participants meeting DSM-IV-TR criteria for schizophrenia (mean age = 33 ± 63 months), recruited from Hefei Psychiatry Hospital affiliated with Anhui Medical University, China. Twenty-four patients were drug-naïve, while 8 had previous clozapine treatment (mean duration = 10 ± 8 months) and were off-medication for at least a period of six months. Patients eligible for clozapine treatment were recruited and were monitored for dose titration and adverse side effects. Inclusion criteria were: a) no neurological disorder (e.g., no loss of consciousness, epilepsy, Parkinson's disease or traumatic brain injury), b) no history of mental retardation, and c) no current substance/alcohol abuse. The age of patients with schizophrenia (SZ) ranged between 20 and 42 years (mean = 30 ± 7 years, 18 male), and education ranged between 8 and 17 years (mean = 12 ± 2 years). Thirty-two healthy individuals meeting the same inclusion criteria were

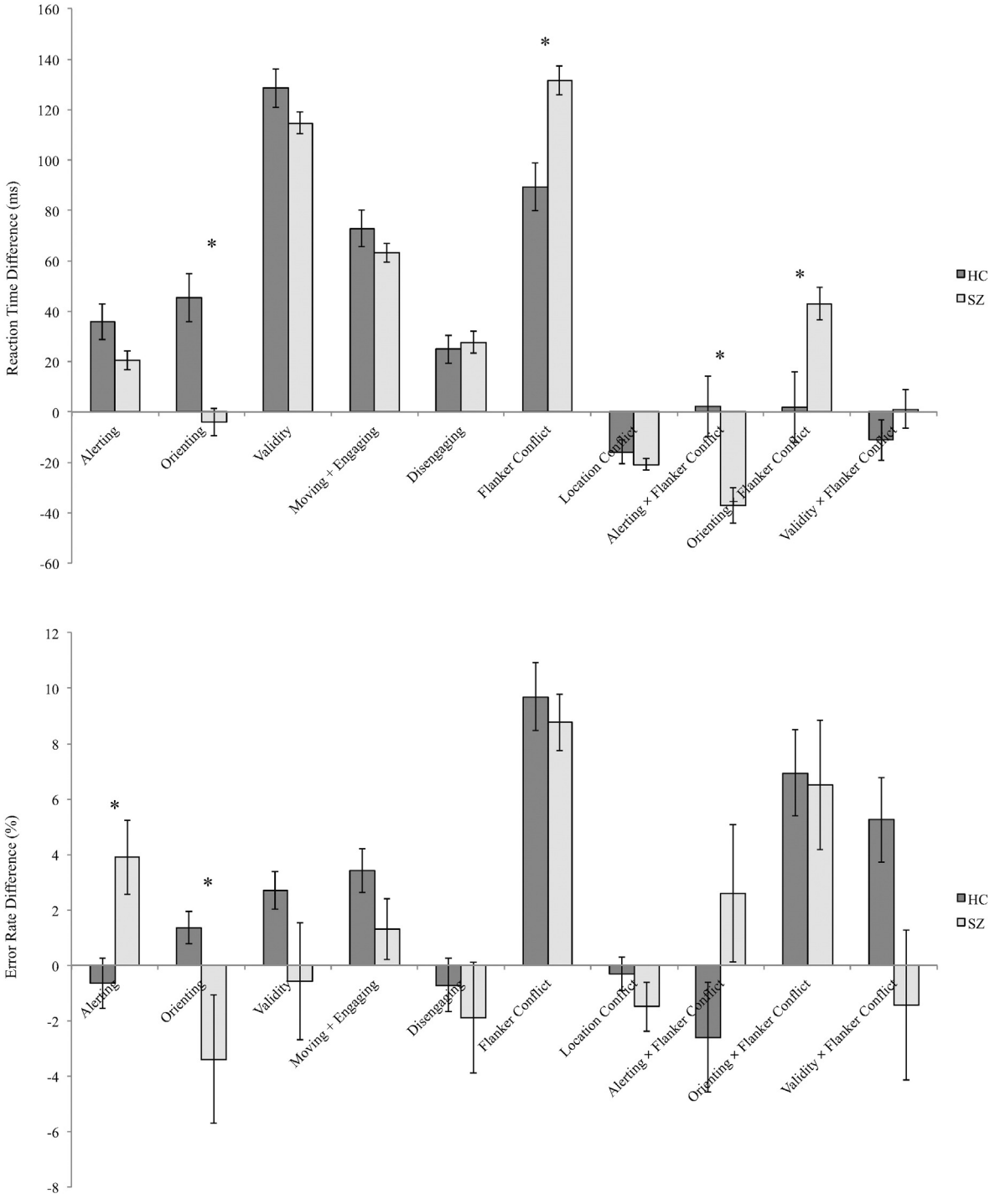

Fig. 2. The attentional effects of SZ group in comparison to the HC group in the pre-treatment session. Patients with schizophrenia showed deficits in the three attentional functions, and in the alerting by flanker conflict and orienting by flanker conflict interactions. Note * = $p < .05$; and ** = $p < .01$.

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recruited as the control group (HC). The age of HCs ranged between 21 and 44 years (mean = 28 ± 6 years, 17 male) and education ranged between 8 and 22 years (mean = 13 ± 4 years) (Table 1). There were no significant group differences in age, education, and IQ (measured with the Chinese version of the Wechsler Adult Intelligence Scale-Revised), (WAIS-R, Gong, 1992). Vision and hearing were within normal limits. Written informed consent approved by both The First Hospital of Anhui Medical University and Icahn School of Medicine at Mount Sinai was obtained from all participants prior to participation.

2.2. Procedures and measures

Staff psychiatrists at the Hefei Psychiatry Hospital conducted clinical interviews with patients with schizophrenia, and diagnosis was by consensus of at least two staff psychiatrists. Positive and negative symptoms were assessed with the Chinese version of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS — Phillips et al., 1991), administered by staff psychiatrists. Each patient with schizophrenia completed the task (see below) before and after 4 weeks of treatment (±1.5 weeks). HC also completed the task two times, separated by a 4-week interval (±1 week).

2.3. Attention network test-revised (ANT-R)

An overview of the task is presented in Fig. 1, and has been previously described (Fan et al., 2009). For a complete description of the procedure, see the Supplementary material (SM). The effects of each of the three attentional functions, as well as their interactions, are operationally defined as a comparison of the reaction time (RT) or error rate (ER) between an experimental condition and a reference condition (see Table S1 of SM for the formulae).

2.4. Data analysis

The clozapine treatment effect on the clinical symptoms of the SZ group was examined using paired-samples *t*-tests on pre- and post-treatment scores of the three PANSS scales. Repeated-measure analyses of variance (ANOVA) with group (HC, SZ) as the between-subjects factor and session (pre, post) as the within-subjects factor were performed on each attentional effect and interaction. Simple comparisons were performed to further examine significant interaction effects, differences between the pre- and post-treatment session for each group, and differences between the two groups at each session. Correlation analyses were conducted between attentional effects and pre-treatment clinical symptoms, and between changes (pre-treatment minus post-treatment) in the attentional effects and changes in the clinical symptoms after clozapine treatment. Bonferroni correction for multiple comparisons was applied to the correlation analyses, and a corrected critical α of $p < 0.01$ was used.

3. Results

Results related to the treatment effects on the positive and negative symptoms assessed by the PANSS, general performance of both HC and SZ groups to the ANT-R in the pre-treatment session are reported in the Supplementary data section. Fig. 2 shows the attentional effects in the pre-treatment session for the HC and SZ groups.

3.1. Clozapine treatment effect on attentional functions

Reported below is the examination of treatment effects on the attentional functions based on the interaction between Group and Session. For a complete list of main effects and interactions, see the SM. Fig. S1 shows the attention effects in the pre- and post-treatment sessions for the HC and SZ groups. For alerting, the Group by Session interaction was not significant for either RT ($F_{(1,62)} = 2.05$, $p = .16$) or ER ($F < 1$). For orienting, the Group by Session interaction was significant for RT ($F_{(1, 62)} = 4.35$, $p < .05$), indicating that the orienting effect increased from the pre- to the post-treatment session in the SZ group (−4 ± 54 ms vs. 20 ± 34 ms, respectively; $F_{(1, 62)} = 6.57$, $p < .05$), while the difference between the pre- and post-session was not statistically significant in the HC group (45 ± 31 ms vs. 42 ± 31 ms, respectively; $F < 1$) (Fig. 3). Further examination showed that for the valid cue and 800 ms SOA condition, the SZ group was faster in the post-treatment session compared to the pre-treatment session (pre: 777 ± 142 ms; post: 758 ± 136 ms), while no difference was present in the valid cue and 0 ms condition after the treatment (pre: 785 ± 138 ms; post: 780 ± 136 ms). This interaction was also significant for ER ($F_{(1,62)} = 5.26$, $p < .05$), indicating that the orienting effect increased from the pre- to the post-treatment session in the SZ group (−3.39 ± 13.14% vs. 1.43 ± 6.63%, respectively; $F_{(1,62)} = 7.18$, $p < .05$), while the difference in the orienting effect between the pre- and post-session in the HC group was not significantly different (1.36 ± 3.29% vs. −.91 ± 5.39%, respectively; $F_{(1,62)} = 2.02$, $p = .16$). Further examination showed that for the valid cue and 800 ms SOA condition, the SZ group made less errors in the in the post-treatment session (6.32 ± 16.56%) compared to the pre-treatment session (10.74 ± 22.28%), while no significant difference was found in the valid cue and 0 ms condition after the treatment (pre: 7.36 ± 12.45%; post: 6.71 ± 11.92%). In order to control for between-subjects differences related to the variability of the interval between the pre- and post-treatment sessions (4 weeks ± 1.5 weeks), regression analyses were conducted with the change in the orienting effect between the two sessions (post-*minus* pre) as the dependent variable and the number of days between the two sessions (post-*minus* pre) as the independent variable. Results showed no significant relationship between these two variables for both RT (r = −.08; p = .34) and error rate (r = −.08; p = .35). For the flanker conflict, the Group by Session interaction was not significant for either RT or ER (*F*s < 1).

3.2. Correlations between attentional effects and clinical symptoms: the effect of clozapine treatment

Table 2 reports the correlations between the attentional effects (calculated in both RT and ER) and the PANSS scores in the pre-treatment

Table 2
Correlations between the attentional effects and symptomatology pre-treatment (top) and between the change in the attentional effects and in the symptomatology post-treatment (bottom) for both RT (in ms) and ER (%).

	PANSS-pre			PANSS-pre		
	Total	Positive	Negative	Total	Positive	Negative
RT	%					
Global mean	−0.14	0.03	0.03	0.00	−0.13	0.17
Alerting	0.32	0.35	−0.29	0.16	−0.43	−0.28
Orienting	0.07	0.01	0.04	−0.01	−0.07	0.09
Validity	−0.26	0.01	−0.05	−0.02	−0.10	0.10
Moving + engaging	−0.04	0.08	−0.05	0.04	0.19	−0.09
Disengaging	−0.36	−0.14	0.07	−0.05	−0.20	0.16
Flanker conflict	0.36	0.25	−0.04	0.36	−0.22	−0.04
Location conflict	−0.42	0.05	0.13	0.02	0.06	−0.05
	PANSS-change			PANSS-change		
	Total	Positive	Negative	Total	Positive	Negative
RT	%					
Global mean change	0.02	−0.21	0.35	0.00	−0.10	−0.03
Alerting change	0.22	0.37	−0.43	−0.14	−0.39	0.43
Orienting change	0.18	0.03	−0.06	0.19	0.05	−0.01
Validity change	0.05	−0.03	0.07	0.12	0.04	0.02
Moving + engaging change	0.12	0.05	0.01	0.23	0.38	−0.25
Disengaging change	−0.23	−0.20	0.17	−0.01	−0.19	0.18
Flanker conflict change	0.19	−0.12	0.19	−0.25	0.15	0.18
Location conflict change	−0.27	−0.09	0.20	−0.12	−0/11	−0.15

Note: * = α < .01; (Bonferroni corrected).

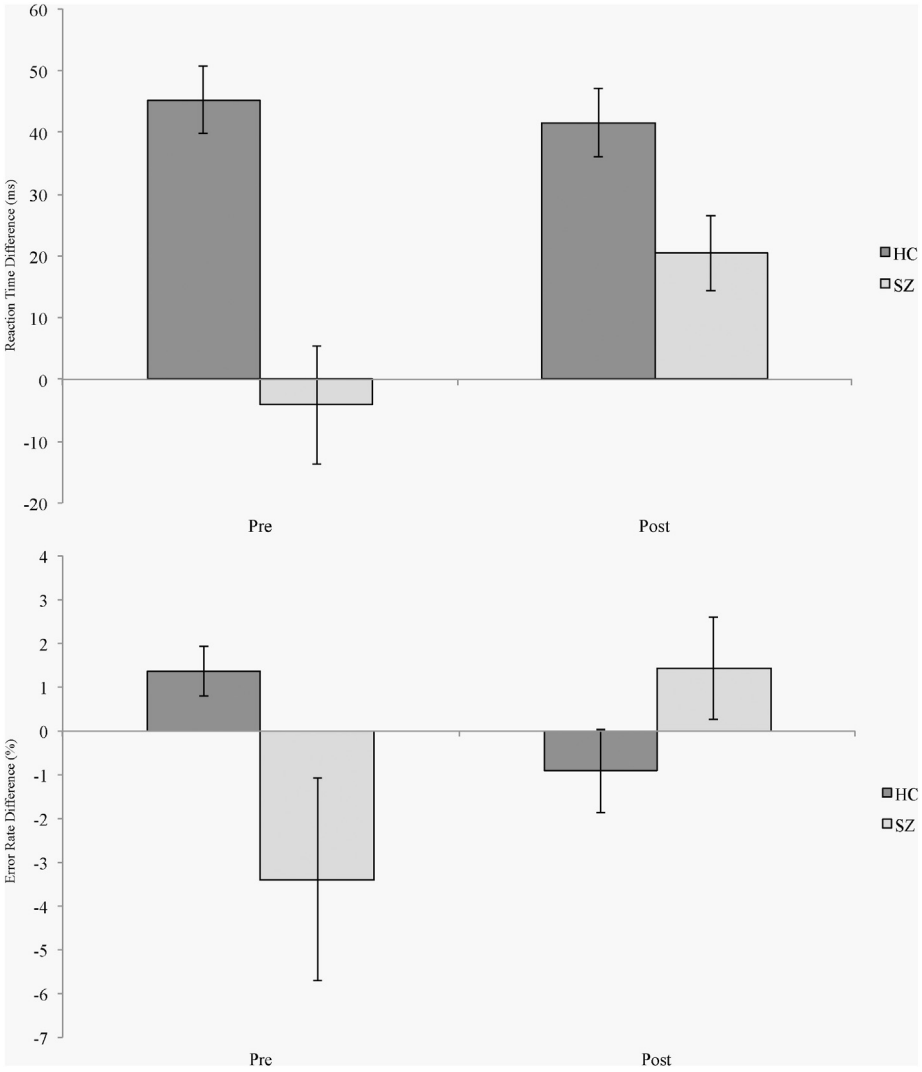

Fig. 3. The treatment effect on the orienting function. There was a significant Group by Session interaction on the orienting effect for both RT and error rate. Patients with schizophrenia (light gray) showed greater orienting effect in the post-treatment session compared to the pre-treatment session, while this difference was not significant for the HC group (dark gray).

session (PANSS-Pre) and the correlations between changes in the attentional effects and changes in the symptomatology from pre- to post-treatment. After Bonferroni correction, none of the correlations among attentional effects and clinical symptomatology were significant, indicating no significant relationship between clinical symptoms of schizophrenia and attentional functioning in this sample.

4. Discussion

The hypothesis that the three attentional functions are affected by pathology of schizophrenia was supported, consistent with previous studies showing reduced alertness (Donohoe et al., 2006), orienting (Wang et al., 2005), and executive control of attention (Westerhausen et al., 2011) associated with schizophrenia. Interestingly, our results also showed abnormal interactions among the attentional networks in patients with schizophrenia.

Based on the broad neuropharmacological impact of clozapine, we predicted a treatment effect for all three attentional functions. However, clozapine treatment selectively reduced the orienting deficit, while there was no evidence for improvement in the alerting and executive control functions. One possible mechanism by which clozapine treatment may impact the orienting function is through its effects on the cholinergic system, which has been documented in both animal models (Arnt and Skarsfeldt, 1998) and in humans (Horacek et al., 2006). There is consensus on the association between the orienting function and the cholinergic system arising from the basal forebrain (Petersen and Posner, 2012), supported by evidence that the administration of mecamylamine (a cholinergic antagonist blocking nicotinic receptors) affects orienting functions in healthy controls (Thienel et al., 2009). Nicotine administration has been shown to significantly improve attention in patients with schizophrenia (Olincy and Stevens, 2007), and the high smoking rate of patients with schizophrenia compared to the general population has been considered to reflect a form of self-medication (Levin and Rezvani, 2007) that may enhance the ability to orient their attention towards internal or external inputs. In this study we focused on changes between the pre and post-session within each group, and did not control for differences in the smoking rate between the two groups. Conversely, evidence also exists regarding the cholinergic hyperactivity associated with schizophrenia (Tandon and Greden, 1989; Tandon et al., 1991, 1993). Therefore, the effect of clozapine on the cholinergic system is still unclear, with some evidence showing that it may be an indirect Ach agonist (Ichikawa et al., 2002; Meltzer and McGurk, 1999), despite a recent report of it being a muscarinic antagonist (Rajji et al., 2015). Additionally, the enhancement of cholinergic neurotransmission in areas playing a pivotal role in attentional functions, such as the anterior cingulate cortex (Fan et al., 2003, 2005), follows the administration of dopamine antagonists (Lacroix et al., 2003). Therefore, the improvement of orienting function after clozapine treatment shown by our results

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might be related to the complex pattern of interaction between dopamine and acetylcholine neurotransmission (Demeter and Sarter, 2013).

A possible explanation for the null results regarding improvement in alerting and executive control of attention after a four-week treatment with clozapine could be due to the duration of the treatment, which may have been too short to fully exert its effect on other attentional deficits in patients with schizophrenia. However, our results are consistent with previous studies showing that deficits in sustained attention abilities and executive control of attention in patients with schizophrenia remain stable after treatment with clozapine (e.g., Bilder et al., 2002; Harris et al., 2007), while positive, negative, and other clinical symptoms are significantly reduced (Goldberg et al., 1993). Alternatively, clozapine may act on cortical and subcortical sites that are different than the brain networks responsible for the alerting and executive control functions (Minzenberg and Carter, 2012) or the effect of clozapine may not be able to compensate for brain structure abnormalities associated with schizophrenia (Lesh et al., 2015). Functional MRI investigations have revealed abnormal activation during attention tasks of regions within frontoparietal network (Belger and Barch, 2009), such as dorsolateral prefrontal (Davidson and Heinrichs, 2003) and posterior parietal cortices (Barch et al., 2002). Abnormal functional connectivity has also been found between these areas (Meyer-Lindenberg et al., 2001). Further structural and functional investigation is warranted to examine atypical cortical activity of the attentional networks and the effects of current medications in treating such abnormalities.

Despite the wealth of studies that have investigated the relationship between cognitive deficits and clinical symptoms associated with schizophrenia (Bender et al., 2006; Donohoe et al., 2006), there is still some debate about whether or not both represent independent dimensions of the disorder. In the current study, although the treatment with clozapine effectively enhanced orienting function and reduced clinical symptoms in patients with schizophrenia, the change in the orienting effect was not positively correlated with changes in the PANSS scales, indicating that changes in symptoms and in this attentional function were independent.

Our study has some limitations. Because each patient received the same medication, we are not able to determine the specificity of the clozapine treatment effect on orienting. Further, the use of a short between-sessions interval (~4 weeks) may have been responsible for the null results shown for the alerting and executive control of attention. Finally, we did not control for differences in the smoking rate between the two groups. Replications in a larger sample addressing these limitations are warranted in order to further advancing current knowledge on the mechanisms associated with the attentional networks deficits in patients with schizophrenia.

In summary, this study showed that attentional deficits in patients with schizophrenia are broad and affect both the efficiency and interactions of the attentional functions. Treatment with clozapine significantly improved the orienting function, but not the alerting and the executive control of attention. Achieving a better functional outcome for patients with schizophrenia requires that future novel antipsychotic interventions also treat deficits of the alerting and executive control functions, which have been shown to be related to functional status (Harris et al., 2007) and treatment responses (Tamminga, 2009). Developing new and wider-acting treatments for this disorder is not a trivial matter, but recognition of the value of improving cognitive functions to improve functional outcome for this population has already given way to work on new pharmacological agents for schizophrenia.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.08.009.

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