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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.

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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 serotonergic 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 serotonergic 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 serotonergic 5-HT2A and 2C receptor, receptor agonism of 5-HT1A, and the increase of extracellular levels of acetylcholine in the pre-frontal 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

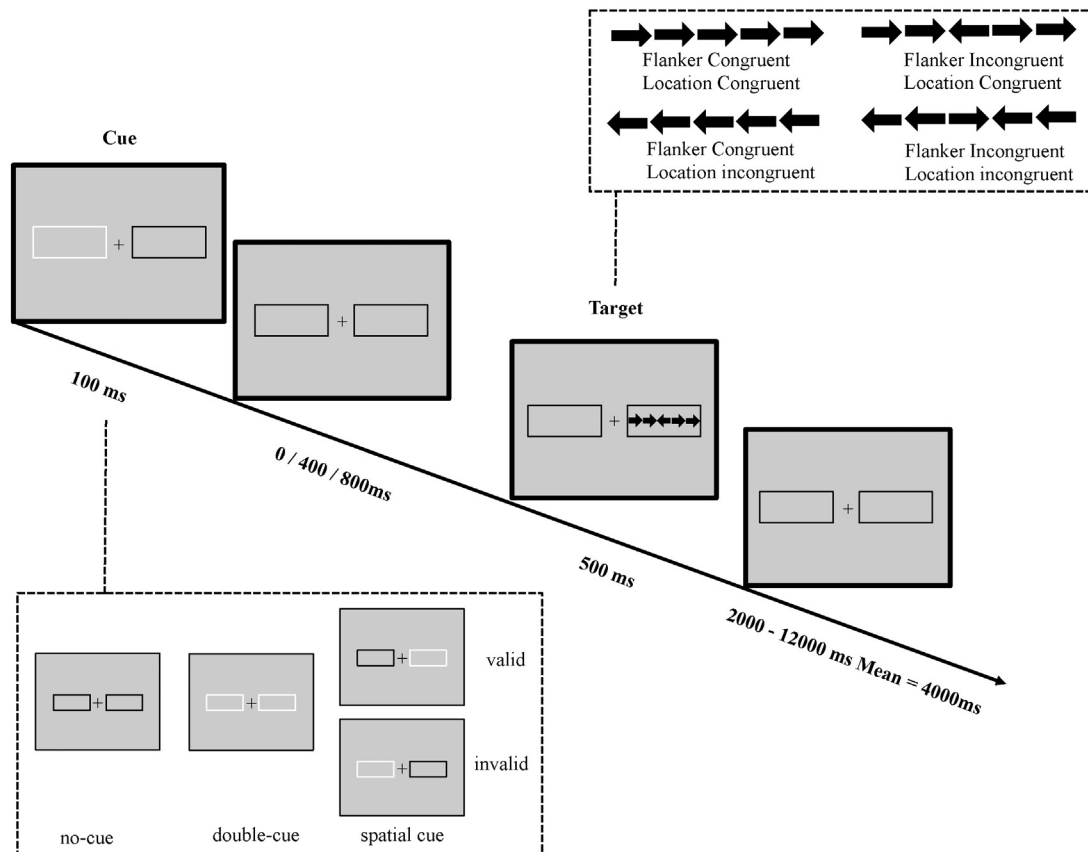


Fig. 1. Schematic of the ANT-R. In this task, participants made responses to indicate the direction of a central arrow (left or right) which was surrounded by two flanker arrows on each side, either pointing in the same direction as the target (congruent) or in the opposite direction (incongruent). Before 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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