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Deficient inhibition of return in chronic but not first-episode patients with schizophrenia

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ABSTRACT

Background: Inhibition of return (IOR) has been tested in patients with schizophrenia with contradictory results. Some studies indicated that patients with schizophrenia have normal levels of IOR; however, other studies reported delayed or blunted IOR. Inconsistency in findings might be due to differences across studies in relevant aspects associated with disease, such as heterogeneity of the disorder, different medications, onset and severity of the illness. The present study was to explore different patterns of IOR in antipsychotic medication free first-episode schizophrenia and chronic schizophrenia.

Methods: Forty two patients with first-episode schizophrenia, 44 patients with chronic schizophrenia, and 38 healthy controls were included in the study. All subjects went through a covert orienting of attention task with seven stimulus onset asynchrony (SOA) intervals (400 ms, 500 ms, 600 ms, 700 ms, 800 ms, 1200 ms and 1500 ms).

Results: Compared with healthy controls, the magnitude and onset of IOR in first-episode patients with schizophrenia were intact. However, in patients with chronic schizophrenia, there was an attenuated cuing effect especially at SOA 700 ms; in addition, there was a robust IOR until at SOAs 800 ms or above. Moreover, the illness duration and the number of psychotic episodes were significantly correlated with the validity effect at SOAs 400 ms and 600 ms.

Conclusion: Our study suggests that deficient IOR presents in chronic but not in first-episode patients with schizophrenia. IOR deficit in schizophrenia may begin during the course of illness and deteriorate over the course of illness. Our findings are consistent with the neurodegenerative model of schizophrenia.

1. Introduction

Deficits in cognitive functions are a core and enduring feature of schizophrenia, perhaps more important than positive and negative symptoms in predicting functional outcome (Friedman et al., 2001; Green, 1996; Moritz et al., 2002; Mesholam-Gately et al., 2009; Sharma and Antonova, 2003). The pattern of impairment is generalized, and across most of the cognitive domains (Green, 2006; Mesholam-Gately et al., 2009; Sharma and Antonova, 2003). Abnormality in attention is one of the most severe deficits in schizophrenia patients (Braff, 1993; Nuechterlein et al., 1992, 2006; Sharma and Antonova, 2003). Attention deficits might play a developmental role in symptom formation in schizophrenia, such as delusions and formal thought disorder (Dominguez et al., 2009; Harvey, 2000; Hemsley, 1996; Nuechterlein et al., 2006; Perry and Braff, 1994; Ross et al., 1997; Sharma and Antonova, 2003). Among various subdomains of attention, sustained attention and selective attention have been widely studied. The underlying mechanisms underlying attention dysfunction in schizophrenia patients have not been fully understood.

Healthy people orient to novel event automatically, and then disengage from it when it is task-irrelevant. When a location contains a novel stimulus, the initial response is to facilitate the processing of the novel stimulus. However, if enough time elapses, an inhibitory aftereffect will be observed in delayed responding to stimuli subsequently displayed at the originally location (Klein, 2000). Facilitatory and inhibitory effects are both important components of attention. Selection in attention often takes place through both facilitatory processing and inhibitory processing, and each is

Abbreviations: ANCOVA, analysis of covariance; ANOVA, analysis of variance; CGI, Clinical Global Impression; CS, chronic schizophrenia; FES, first-episode schizophrenia; HC, healthy controls; IOR, inhibition of return; ISI, inter-stimulus interval; MINI, Mini-International Neuropsychiatric Interview; *n*, number of subjects in the group; PANSS, Positive and Negative Syndrome Scale; SOA, stimulus onset asynchrony; RT, reaction time.

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supported by discrete neural circuitry (Fuentes and Santiago, 1999; Nestor et al., 2009; Parasuraman, 1998). Facilitatory processing selectively activates relevant information above the threshold, enabling it to control our actions. In contrast, inhibitory processing is used to prevent irrelevant stimuli from taking control of our thoughts and actions (Fuentes and Santiago, 1999; Keele and Neill, 1978).

Facilitatory processing and inhibitory processing have been observed in visual orienting tasks. Studies have shown that the effect of an exogenous cue is biphasic: early facilitation and later inhibition (Klein, 2000; Lepsien and Pollmann, 2002; Mayer et al., 2004a,b; Posner and Cohen, 1984). When the interval between cue onset and target onset (stimulus onset asynchrony, SOA) is short, the cue has a benefit, which means that participants respond more quickly to valid trials (target at the cued location) than to invalid trials (target at the uncued location). However, when the SOA is long, participants respond more slowly to valid trials than to invalid trials, this later inhibition is called inhibition of return (IOR). The crossover point — where facilitation changes to inhibition — is between 200 and 300 ms following cue onset. IOR is thought to reflect an automatic, inhibitory mechanism protecting the organism from redirecting attention to previously scanned, insignificant locations (Klein, 2000; Lupiáñez et al., 2006; Posner and Cohen, 1984; Posner et al., 1985; Taylor and Klein, 1998).

IOR of schizophrenia patients has been tested in previous studies with contradictory results (Carter et al., 1992; Fuentes et al., 1999, 2000; Fuentes and Santiago, 1999; Gouzoulis-Mayfrank et al., 2004, 2006, 2007; Huey and Wexler, 1994; Larrison-Faucher et al., 2002; Maruff et al., 1995; Nestor et al., 2009; Sapir et al., 2001). Some studies indicated that schizophrenia patients present normal levels of IOR for standard (Carter et al., 1992; Maruff et al., 1995) or relatively long SOA intervals (Fuentes et al., 1999, 2000; Fuentes and Santiago, 1999; Nestor et al., 2009); Other studies reported delayed or blunted IOR (Gouzoulis-Mayfrank et al., 2004, 2006, 2007; Huey and Wexler, 1994; Larrison-Faucher et al., 2002; Sapir et al., 2001). Inconsistency in findings might be due to differences across studies in relevant aspects associated with disease, such as heterogeneity of the disorder, different medications, onset and severity of the illness. Another factor might be the different procedures (single-cue vs. double-cue) used to measure IOR effect (Lupiáñez et al., 2006; Sapir et al., 2001, 2007; Vivas et al., 2006). The crucial difference between the two paradigms is that a component of voluntary disengagement of attention is involved in the single-cue paradigm, but not in the double-cue paradigm; however, the reflexive disengagement of attention is involved in the double-cue paradigm but not in the single-cue paradigm (Zhou and Chen, 2008).

Previous IOR-related studies in schizophrenia focused on chronic patients. So far no IOR study in first-episode schizophrenia has been reported. In addition, the participants in all previous studies except one (Gouzoulis-Mayfrank et al., 2007) were medicated schizophrenia patients; antipsychotic medication treatment seems to be relevant to IOR (Sapir et al., 2007; Vivas et al., 2006).

The present study was to explore IOR in antipsychotic medication free first-episode schizophrenia and chronic schizophrenia. We hypothesized that first-episode schizophrenia and chronic schizophrenia have different patterns of IOR.

2. Methods

2.1. Subjects

This study was conducted at the Shanghai Mental Health Center. Ninety-nine patients with schizophrenia or schizophreniform disorder, including forty-seven first-episode patients and fifty-two chronic patients, were enrolled in this study. None of them was treated with long-acting antipsychotic medications and all of them were antipsychotic medication free for at least 15 days. All of them were in relatively stable clinical condition and had the capacity to sign the consent form and participate in the study as determined by their treating psychiatrists.

Diagnosis of schizophrenia or schizophreniform disorder was confirmed by a research psychiatrist (D.L.) using MINI plus v 5.0 (Sheehan et al., 1998). The definition for first-episode schizophrenia: (1) patient was experiencing his or her first-episode of psychosis, (2) patient had been prescribed antipsychotic medication for less than 12 weeks in total, and (3) the illness duration was no more than 2 years. The definition for chronic schizophrenia: (1) the number of psychotic episode was no less than two times and (2) the course of illness was at least five years. Exclusion criteria for the study included: (1) inability to provide informed consent, (2) current substance abuse, personality disorders and mental retardation, (3) significant medical illness including severe cardiovascular, hepatic, renal disease, and (4) pregnancy or breastfeeding.

Thirty-eight healthy controls were recruited from the local community. All of them completed the structured clinical interview by a research psychiatrist (D.L.) using MINI plus v 5.0. Those with any mental disorders, neurological diseases, or positive family history were excluded. This study was approved by the Institute of Review Board of Shanghai Mental Health Center. Written informed consent was obtained from all participants.

Clinical symptoms were assessed using the Positive and Negative Symptom Scale (PANSS), which includes Positive Symptom, Negative Symptom, and General Psychopathology subscales (Kay et al., 1987, 1989); and the Clinical Global Impressions-severity scale (CGI), which assesses the severity of illness (Guy and Bonato, 1976).

2.2. Apparatus and procedure

The experiment was conducted in a dimly light, sound-attenuated room. Subjects were seated about 50 cm in front of the monitor with their heads supported by a chin rest. During the performance of task, subjects were instructed to maintain fixation on the central presented cross (+) and to detect the target using their peripheral vision. However, eye movement monitor was not used in the present study, and eye movement were not registered or deleted.

The orienting task employed in our experiment was a modified version of the IOR paradigm described by Posner and Cohen (1984), Fig. 1 illustrates our dual-cue task. All stimuli were presented in white on a black background. Each trial began with a blank display of 500 ms. Subjects were instructed to fixate the central presented cross. A peripheral cue was presented for 100 ms randomly to the left or right of fixation with equal probability. Then the central cross was brightened for 100 ms (called the central cue or the cue-back procedure). In this manner, the central cross was “cued” to ensure that participants returned their attention to fixation following the

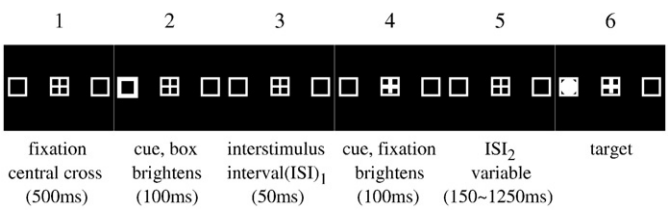

Fig. 1. The task of covert orienting and IOR (a cued trial is shown).Subjects were required to fixate the central cross and maintain fixation throughout the first five frames of the trial. Frame 1: The start of each trial, fixation on the central cross. Frame 2: A peripheral cue was presented randomly to the left or right of fixation. Frame 3: The cue offset for a brief inter-stimulus interval (ISI). Frame 4: The central fixation cue (the cue—back procedure). Frame 5: Variable ISIs including 150, 250, 350, 450, 550, 950 and 1250 ms were used and presented randomly. Frame 6: The target (circle) appeared with equal probability in the cued or uncued location, the subjects' task was to press the space key on the keyboard as soon as the target appeared.