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Aberrant functional connectivity between the thalamus and visual cortex is related to attentional impairment in schizophrenia

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ABSTRACT

Resting-state (rs) functional magnetic resonance imaging (fMRI) studies have revealed dysfunctional thalamocortical functional connectivity (FC) in schizophrenia. However, the relationship between thalamocortical FC and cognitive impairment has not been thoroughly investigated. We hypothesized that aberrant thalamocortical FC is related to attention deficits in schizophrenia. Thirty-eight patients with schizophrenia and 38 matched healthy controls underwent rs-fMRI and task fMRI while performing a Flanker task. We observed decreased left thalamic activation in patients with schizophrenia using task fMRI to determine the thalamic seed. A seed-based analysis using this seed was performed in the whole brain to assess differences in thalamocortical FC between the groups. Significantly worse performance was observed in the patient group. The rs-fMRI analysis revealed significantly increased FC between the left thalamus seed and the occipital cortices/postcentral gyri in patients when compared to controls. In the patient group, significant positive correlations were observed between the degree of FC from the left thalamus to the bilateral occipital gyri, which correspond to the visual cortex, and the Flanker effect. No significant correlation was detected in the control group. These results indicate that aberrant FC between the left thalamus and the visual cortex is related to attention deficits in schizophrenia.

1. Introduction

Cognitive impairment, a core feature of schizophrenia, is one of the most critical factors determining functional outcomes (Green et al., 2000). Although the pathophysiological mechanism of schizophrenia is unclear, it has been characterized as a neurodevelopmental disorder of brain dysconnectivity (Friston et al., 2016). There is considerable evidence suggesting that the thalamus is a crucial component of this dysconnectivity (Pergola et al., 2015).

Resting-state (rs) functional magnetic resonance imaging (fMRI) is a powerful tool for mapping functional brain networks in living human subjects. Alterations in thalamocortical functional connectivity in schizophrenia have been reported using this method. Previous studies have suggested that in schizophrenia, the brain exhibits lower connectivity between the thalamus and prefrontal cortex, as well as higher connectivity between the thalamus and sensorimotor cortex (Giraldo-Chica and Woodward, 2017).

The thalamus is composed of several nuclei. Each nucleus has a different connectivity pattern. Some nuclei establish connections between cortical and subcortical regions (cortical region–thalamic nucleus–subcortical region), whereas some establish connections between different cortical regions (cortical region–thalamic nucleus–cortical region) (Byne et al., 2009; Sim et al., 2006). The thalamus plays a significant role in corticocortical communication by controlling information processing and is involved in perceptual processing and cognitive function. Schizophrenia is characterized as a disorder of perceptual processing manifestations, such as hallucinations and impairments of cognitive function, which may reflect dysfunction in thalamocortical connectivity (Dorph-Petersen and Lewis, 2017).

Despite its importance, the correlation between thalamocortical functional connectivity and cognitive impairment has not been thoroughly investigated. Woodward and Heckers (2016) have suggested that prefrontal–thalamic functional connectivity might be related to global cognitive impairment, as assessed using the Screen for Cognitive Impairment in Psychiatry global *Z*-score for cognitive impairment in patients with psychoses.

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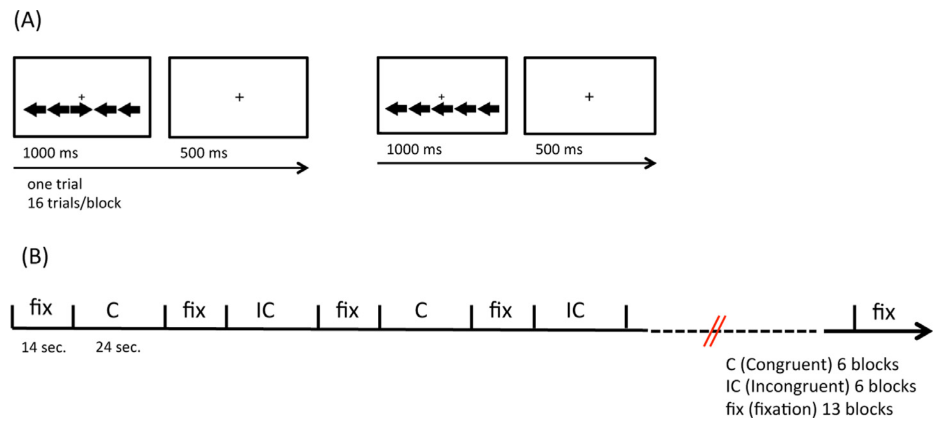

Fig. 1. Schematic illustration of incongruent (IC) and congruent (C) trials (A) and the experimental paradigm (B).

Most previous neuroimaging studies investigating the role of the thalamus set *a priori* seeds/regions of interest (ROIs) using standard atlases created based on information from different groups of subjects (Sheffield and Barch, 2016). These approaches treat the whole structure of the thalamus as a seed and ignore the thalamic sub-regions and their functions. To address this issue, we performed task fMRI to define the exact seed/ROI for the functional deficits observed in our patients based on the observation that patients with schizophrenia have thalamic hypoactivation while performing attention tasks (Pergola et al., 2015). We also performed rs-fMRI to investigate whether aberrant thalamocortical functional connectivity is responsible for attention impairment, which is considered the core cognitive impairment in patients with schizophrenia (Blokland et al., 2017).

First, we identified the region of the thalamus wherein decreased activation during the Flanker task was observed in patients with schizophrenia when compared to healthy controls. We then set this region as a seed to perform a seed-based connectivity analysis in the whole brain in each group. We investigated differences in resting-state functional connectivity between patients and controls. In the present study, we examined the correlation between aberrant thalamic functional connectivity and performance in the Flanker task.

2. Methods

2.1. Participants

Thirty-eight patients with schizophrenia (20 men and 18 women, mean age: 39 years, range: 24–48 years) and 38 healthy controls (23 men and 15 women, mean age: 36 years, range: 23–49 years) participated in this study. The patient group was composed of 30 outpatients and eight inpatients at Nagoya University Hospital and its affiliated hospitals. The patients were diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition diagnostic criteria (American Psychiatric Association, 2000) by two psychiatrists. Current clinical symptom severity was assessed using the Positive and Negative Syndrome Scale (Kay et al., 1987). All patients had been receiving antipsychotic medication. The controls had no history of psychiatric or neurological disorders (based on Structured Clinical Interview for Diagnosis, non-patient version) (First et al., 2002) and did not use any psychoactive medications. Intelligence quotient scores were estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). All participants were right-handed, as assessed using the Edinburgh Handedness Inventory (Oldfield, 1971). All procedures in this study were carried out in accordance with the Declaration of Helsinki, the participants provided written informed consent to participate, and the Nagoya University Graduate School of Medicine and Nagoya University Hospital ethics review committees approved the study.

During task fMRI pre-processing, five patients and three healthy controls were excluded from further analyses due to head motion (displacement of greater than 3 mm during the scan). Furthermore, two patients and one healthy control were excluded due to low accuracy in the Flanker task (greater than 2 standard deviations below the group mean). Two more patients were excluded due to excessive motion (translation of >2 mm in either direction of rotation of $>2^\circ$ in either direction relative to the first volume in any axis) during rs-fMRI pre-processing. Data from 29 patients and 34 healthy controls were thus analyzed.

2.2. Experimental procedure

The experimental procedure was as follows: 1) medical interview and explanation of the experiment, 2) rs-fMRI, and 3) task fMRI using the Flanker task. We used the above procedure because previous studies have suggested that functional connectivity during the resting state is affected by prior performance on a cognitive task (Stevens et al., 2010; Waites et al., 2005).

2.2.1. The Flanker task

The participants performed a computer-administered Flanker task and were asked to indicate the direction of a centrally presented arrow as quickly and accurately as possible. The stimuli comprised one target arrow and two distractor arrows on either side of the target arrow (Fig. 1(A)). In congruent trials, the distractor arrows pointed in the same direction as the target arrow (→→→→→ and ←←←←←), while in incongruent trials, the arrows pointed in opposite directions (←←→←← and →→←→→). On incongruent trials, the distractor arrows lead to response conflict and thus prolonged reaction times. The fMRI experiment was conducted in a block design comprising congruent (C) and incongruent (IC) blocks (block duration: 24 s). Each task block was interleaved with a rest block during which fixation was presented for 14 s (Fig. 1(B)). The stimulus (target and distractor arrows) appeared randomly above or below the fixation point. For each trial, the stimulus was displayed for 1000 ms and was followed by a 500 ms fixation cross (Fig. 1(A)). There were 16 trials per block and 12 blocks (six C and six IC blocks) in each run. The experiment comprised two runs of 192 trials each. Before the experiment, the participants performed a training task consisting of 15 trials (eight C and seven IC trials). Accuracy and reaction time (RT) were measured for each trial. Trials with erroneous responses were omitted from the behavioral analysis. We evaluated performance in the Flanker task by subtracting the mean RT of the C trials from the mean RT of the IC trials: [RT(IC) – RT(C)]. The difference between the two means represented the response conflict (Flanker effect). Stimulus presentation and response measurements were performed using Presentation software version 14.4 (Neurobehavioral Systems; San Francisco, CA, USA). Behavioral analysis was performed