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Behavioral evidence of delayed prediction signals during agency attribution in patients with schizophrenia

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ABSTRACT

Self-disturbance, a core feature of schizophrenia, recently has been explained from the standpoint of an abnormal sense of agency (SoA). Previous studies showed that aberrant SoA in schizophrenia arise from imprecise predictions about the sensory consequences of actions. However, the nature of the malfunctioning predictions remains unclear. We examined the temporally "delayed" nature of inadequate predictions. We studied 30 patients with schizophrenia and 30 healthy controls. Our original SoA task evaluates explicit experience of the temporal causal relationship between an intentional action and an effect on a computer screen under the presence of temporal biases. We introduced an adaptation with a "trial-by-trial" method that prolonged or shortened the temporal biases. We hypothesized that delayed prediction signals in schizophrenia could lead to a match in timing between predictions and actual outcomes, resulting in self-agency. The adjustment courses to changing temporal biases were evaluated. Patients with schizophrenia continued to feel self-agency even when the adjusted temporal bias was longer than 1000 ms. This result indicated that patient's prediction would be delayed in each trial. Our study empirically showed behavioral evidence for "delayed" prediction signals in a SoA paradigm for the first time.

1. Introduction

Alterations of self-experience including delusions of control and depersonalization have long been noted as a core feature of schizophrenia; these symptoms are generally referred to as "self-disturbances" (Sass and Parnas, 2003). Cognitive neuroscience has focused on the "self-consciousness", especially on the "sense of agency (SoA)": the attribution of oneself as the cause of one's own actions and their effects. Accordingly, self-disturbances in schizophrenia have begun to be explained from the standpoint of an abnormal SoA, and empirical studies have shown aberrant SoA in schizophrenia (Franck et al., 2001; Haggard et al., 2003; Synofzik et al., 2010; Voss et al., 2010; Hur et al., 2014). Maeda et al. showed excessive SoA in paranoid-type schizophrenia using an original agency attribution task that evaluated explicit experiences of the temporal causal relationships between an intentional action and an external event (Maeda et al., 2012). Interestingly, the reverse pattern, i.e. reduced SoA, was found in residual-type schizophrenia with predominantly negative symptoms (Maeda et al., 2013).

The most prevalent cognitive theory regarding the mechanism of aberrant SoA in schizophrenia is based on the forward model (Frith et al., 2000). In this model, it is important whether the prediction of action matches actual sensory consequences or not in the comparator. If there is a match, events are regarded as self-generated and SoA arises. If there is a mismatch, events are recognized as externally generated and SoA is lost. Previous empirical studies in schizophrenia have shown that patients have an impaired predictive mechanism in the motor domain by using sensorimotor tasks (Knoblich et al., 2004; Lindner et al., 2005; Shergill et al., 2005, 2014). Therefore, abnormal SoA in

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schizophrenia may arise from imprecise predictions about the sensory consequences of actions.

Neurophysiological studies have proposed that such malfunctioning prediction systems in patients with schizophrenia are due to failures of corollary discharge (Feinberg, 1978; Feinberg and Guazzelli, 1999; Whitford et al., 2011). Corollary discharge refers to neural signals that originate in frontal action-initiation regions, and are coincident with self-generated movements as an efference copy. This acts to suppress the sensory feedback signals caused by movements (Sperry, 1950; von Holst, 1954; Crapse and Sommer, 2008). Several studies have shown evidence for "delayed" corollary discharges on the timing of sensory feedback in the verbal domain, and demonstrated that this conduction delay was due to abnormal myelination (Ford et al., 2001; Whitford et al., 2011, 2012). In a neurophysiological experiment, when corollary discharge temporally matched actual sensory feedback, the N1 component of the event-related brain potential (ERP) elicited by the sound was attenuated; however, this N1 suppression did not occur in schizophrenia (Ford et al., 2001). This finding suggested that there is a temporal mismatch between actual corollary discharge and sensory feedback. Moreover, when sensory feedback was artificially delayed by 50 ms, N1 suppression did occur in schizophrenia (Whitford et al., 2011). This result indicated that the amount of delayed corollary discharge is estimated of approximately 50 ms (Whitford et al., 2011).

There have been no empirical studies about the nature of these "delayed" prediction signals in the context of SoA. In the present study, we try to clarify the behavioral evidence for "delayed" prediction signals in schizophrenia using the SoA paradigm. The prototype of our task was an SoA task evaluating the explicit experience of the temporal causal relationship between an intentional action and an external event with temporal biases of 0–1000 ms randomly introduced in 100-ms increments (Maeda et al., 2012, 2013). However, the present study uses a "trial-by-trial" method of adjusting temporal bias. This trial-by-trial method has proven valuable for investigating the neural substrates of SoA in healthy people and revealed that SoA was associated with activity in lateral temporoparietal areas, medial frontal areas, frontal operculum/insula regions, and posterior midline areas, including the precuneus and posterior cingulate cortex (Fukushima et al., 2013). Based on previous findings that the delay in prediction signals is approximately 50 ms in schizophrenia (Whitford et al., 2011), the adjustment range was fixed to 50 ms in the current study. In the task, if the estimated temporal bias matches the actual temporal bias in a trial and subjects report a feeling of self-agency, we prolong the temporal bias by 50 ms in the next trial. In case of healthy controls, their estimation is expected not to match the prolonged temporal bias, and no self-agency may be reported because estimation is based on the former trial. On the other hand, in schizophrenia, estimation may be delayed so it could match and offset the introduced prolonged temporal bias. Therefore, patients would report feeling self-agency even in the prolonged bias condition. Here, we hypothesized that patients with schizophrenia would continue to feel self-agency even when adjusted temporal bias is getting longer and longer, resulting in over-attribution of self-agency compared to normal control subjects.

2. Method

2.1. Participants

We recruited 30 patients (17 male; 13 female) with schizophrenia from Keio University Hospital, Ashikaga Red Cross Hospital, and Sakuragaoka Memorial Hospital, in Japan. All patients had chronic schizophrenia and were clinically stable at the time of testing. The first author (AK) or second author (TM) diagnosed all subjects according to the DSM-IV-TR criteria. To clarify the clinical status of patients, we used the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) and the Global Assessment of Functioning (GAF) score. Exclusion criteria included: (1) major brain anomaly or organic brain disease; (2) current or past substance abuse, including alcohol; (3) mental retardation; and (4) previous episodes of a mood disorder. Thirty healthy volunteers (13 male; 17 female) participated as controls. They were confirmed to have neither psychiatric nor neurological disorders, nor any first-degree relatives with neuropsychiatric disorders. Controls were matched with patients for age and gender. Demographic characteristics of participants are shown in Table 1. Education level is higher in controls than schizophrenia ($P < 0.01$). No patients dropped out or exhibited a change in psychiatric state during or after the experiment. This study was approved by the Ethics Committee at all hospitals. All subjects gave written informed consent prior to participation.

Table 1
Characteristics of participants.

	Schizophrenia ($n=30$)	Normal controls ($n=30$)
Age, years	42.5 (9.4)	39.8 (11.2)
Gender, male:female	17/13	13/17
Education, years	13.2 (2.4)	17.0 (2.8)
Outpatient/inpatient	14/16	–
Duration of illness, years	17.4 (8.3)	–
Neuroleptic dosage, HP-mg	15.5 (10.8)	–
GAF	51.0 (12.6)	–
PANSS (total score)	73.9 (17.3)	–
Positive symptoms	16.6 (6.1)	–
Negative symptoms	20.9 (6.3)	–
General psychopathology	36.3 (9.2)	–

Values are presented as means (standard deviation) unless otherwise noted. Controls were matched with patients for age and gender.

2.2. Apparatus and procedure

The experiment was controlled by E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA), and stimuli were presented on a 14.1-in. computer monitor. Participants completed two types of trials: agency condition and color condition (Fig. 1).

2.2.1. Agency condition

In the agency condition (Fig. 1a), participants were prompted with a word ("Self") indicating that the next trial would require a response about their agency experience. This prompt lasted for 1 s followed by a black screen for 500 ms. As in our previous studies (Maeda et al., 2012, 2013), a 4-mm gray square then appeared on a black background, emerging from the bottom of the screen and moving straight upward at a uniform speed (24 mm/s). An auditory cue (1000 Hz pure tone; 100 ms duration) was presented $\sim$2 s ($\pm$ 100 ms) after the square appeared. Participants were instructed to press a key with their right index finger when they perceived a cue sound. Following a short time lag after the button press, the moving square on the monitor changed its coordinates (i.e., "jumped") 25 mm upward and changed color. The square kept moving upward and disappeared out of the display. The display then presented the words "Yes–No" to prompt the participant to press a button to report whether they felt that the square's jumping was caused by their own preceding action. Participants responded using a response box in their left hand, pressing a button with the index finger to indicate "yes (Y)", and a separate button with their middle finger to indicate "no (N)". The inter-trial interval varied between 3000 and 4500 ms in steps of 500 ms. The time lag between the participant's right button press (cued by the