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Neural Substrates for Judgment of Self-Agency in Ambiguous Situations

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Abstract

The sense of agency is the attribution of oneself as the cause of one's own actions and their effects. Accurate agency judgments are essential for adaptive behaviors in dynamic environments, especially in conditions of uncertainty. However, it is unclear how agency judgments are made in ambiguous situations where self-agency and non-self-agency are both possible. Agency attribution is thus thought to require higher-order neurocognitive processes that integrate several possibilities. Furthermore, neural activity specific to self-attribution, as compared with non-self-attribution, may reflect higher-order critical operations that contribute to constructions of self-consciousness. Based on these assumptions, the present study focused on agency judgments under ambiguous conditions and examined the neural correlates of this operation with functional magnetic resonance imaging. Participants performed a simple but demanding agency-judgment task, which required them to report on whether they attributed their own action as the cause of a visual stimulus change. The temporal discrepancy between the participant's action and the visual events was adaptively set to be maximally ambiguous for each individual on a trial-by-trial basis. Comparison with results for a control condition revealed that the judgment of agency was associated with activity in lateral temporo-parietal areas, medial frontal areas, the dorsolateral prefrontal area, and frontal operculum/insula regions. However, most of these areas did not differentiate between self- and non-self-attribution. Instead, self-attribution was associated with activity in posterior midline areas, including the precuneus and posterior cingulate cortex. These results suggest that deliberate self-attribution of an external event is principally associated with activity in posterior midline structures, which is imperative for self-consciousness.

Citation: Fukushima H, Goto Y, Maeda T, Kato M, Umeda S (2013) Neural Substrates for Judgment of Self-Agency in Ambiguous Situations. *PLoS ONE* 8(8): e72267. doi:10.1371/journal.pone.0072267

Editor: Cristina Becchio, University of Turin and the Italian Institute of Technology, Italy

Received: May 3, 2013; **Accepted:** July 15, 2013; **Published:** August 19, 2013

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Funding: This study was financially supported by Grants-in-Aid for Scientific Research (grant numbers 08J06052, 23830107, 24119005 to HF, and 24330210 to SU) and a Grant-in-Aid for Scientific Research on Innovative Areas: Prediction and Decision Making (23120009 to MK, and 24120518 to SU) from JSPS (<http://www.jsps.go.jp/english/e-grants/index.html>). This research was also funded by a Health and Labour Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health from the Japanese Ministry of Health, Labour and Welfare to MK. This research was also supported by the Global COE Program "Centre for Advanced Research on Logic and Sensibility" by the MEXT of Japan and Program for the Advancement of Next Generation Research Projects, Keio University. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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Introduction

The "sense of agency", an essential aspect of self-recognition, refers to the self-attribution of the cause of one's own action, and its effects on the outside world [1–4]. The mechanisms underlying the sense of agency have primarily been proposed to involve an internal feed-forward model and a comparator mechanism, where the consequences of intentional actions are predicted by the internal feed-forward model, and then compared with the actual sensory feedback by the comparator mechanism [5–7]. The attribution of the event as self-generated is based on whether actual sensory input matches the prediction.

Importantly, the sense of agency can easily be ambiguous and uncertain in a dynamic environment. Consider a simple situation where an action–feedback discrepancy is the only source of information for an agency judgment. When the discrepancy between action and feedback is small, causation of an event can be easily attributed to the self, and when this discrepancy is large, causation can be attributed to external sources. However, there is high uncertainty when the magnitude of sensorimotor mismatch falls between these subjectively "small" and "large" amounts. As

the environment can change dynamically, judgments about agency under uncertain conditions are important to guarantee adaptive and precise behaviors. The present study focused on the judgment of agency in such ambiguous situations.

Previous studies of the sense of agency have often employed the uncertain conditions described above in their experimental manipulations [8–11]. These studies provided ambiguous conditions to decrease the relative contribution of the sensorimotor cue to judgment of agency, with the main aim of examining the effects of other sources for the judgment. For example, individuals' mental states, such as intentions, beliefs, and expectations, can also affect their sense of agency [12–15]. Additionally, multiple operations, such as implicit and explicit, and prospective and retrospective processes, have been proposed to build the sense of agency [3,16,17]. Despite these empirical and theoretical advances, however, the mechanism itself for agency judgment in purely ambiguous situations is still unclear.

It is considered that an ambiguous situation for agency judgment elicits a conflict between the perception of self-agency and non-self-agency. Thus, these potentially different judgments must be reconciled and integrated to produce a unitary sense of

agency. This judgmental process may be generated by higher-order neurocognitive activity. Furthermore, it is assumed that the ability to differentiate between self- and non-self-agency is particularly important when making a judgment about agency attribution. That is, neural activity specific to self-attribution under ambiguous conditions, as compared with that involved in non-self-attribution, may reflect higher-order critical operations related to the construction of self-consciousness. On the basis of these assumptions, the aim of the present functional magnetic resonance imaging (fMRI) study was to elucidate the neural substrates underlying agency judgment in ambiguous situations. Particularly, we examined the activities selectively associated with *self*-attribution.

Uncertainty in judgment of agency can be produced in a complex manner; for instance, several factors such as environmental cues or prediction of the consequences possibly contradict each other to make the agency judgment difficult. However, the present study did not target such heterogeneous situations. Instead, as a first step of our approach, this study manipulated ambiguity simply in terms of the degree of action–feedback discrepancy. The participants were asked whether they attributed the self as a cause of change in a visual stimulus, which exhibited a variable degree of temporal discrepancy with their own actions. This type of task often includes visuo-proprioceptive correspondence between a subject’s body movement and visual feedback [10,18–21], and is thus potentially contaminated with the sense of body-ownership being attributed to visual stimuli [17,22]. In our task, the change in visual stimulus has no spatial correspondence to the participant’s own body movement, allowing the examination of a pure sense of agency [23,24].

Furthermore, as the main feature of this study, an “adaptation method” was used on a trial-by-trial basis. This method determined the most ambiguous level of the task-relevant variable (i.e., temporal discrepancy) for each participant. Specifically, when a participant attributed self-agency to a certain magnitude of action–feedback delay, the delay in the next trial was extended so that the individual was less likely to make a self-attribution. Conversely, the delay was shortened when the subject attributed the movement in the previous trial to a “non-self” cause. We used this procedure because the temporal action–feedback discrepancy as a threshold of self/non-self discrimination depends on the individual, as does the amount of subjective ambiguity (e.g., [8,24–27]). In previous studies, the sensorimotor gap has been parametrically varied and equally applied to each participant in each experiment (e.g., [9,14,28]). However, the adaptation method in the current study allowed us to provide participants the variables that were maximally ambiguous to each individual, to optimally strengthen the relative contribution of the higher-order judgment of agency.

Previous neuroimaging studies have suggested the involvement of several specific brain regions in the processes underlying the sense of agency. Activity in regions surrounding the temporo-parietal junction (TPJ), medial frontal lobe (consisting of the supplemental motor area (SMA) and anterior cingulate cortex (ACC)), the lateral frontal cortex (dorsolateral prefrontal cortex (DLPFC) and/or ventral premotor cortex), and insula cortex has been reported in studies of agency [10,18–20,28–30]. In addition, other regions such as the precuneus and posterior cingulate cortex (PCC), extrastriate body area (EBA), and cerebellum have been reported in agency studies [13,18,21,31,32]. In particular, previous studies have consistently implicated a region surrounding the TPJ, including the inferior parietal lobule (IPL) and posterior superior temporal sulcus (pSTS), reporting that increased activation in the TPJ and adjacent areas is reliably associated with

decreases in the sense of agency [10,19–21,29,33]. The TPJ is thought to receive signals indicating a mismatch between prediction and feedback, possibly indicating a need for a subsequent action to correct the mismatch [20,21,34]. However, this region is a rare case of consistency among research works. As an example of other areas, insula activity has been proposed to be associated with self-attribution in several studies [10,19,22], while other studies reported conflicting data [20,27,33] or failed to detect a contribution of the insula to agency processing [21,33]. As such, the association of many brain areas to agency attribution remains unclear, and it is thus difficult to predict which region would contribute to agency processing when uncertainty is heightened.

In the current study, we presumed that the self-attribution in judgment of agency under uncertain conditions is mainly processed in the so-called midline cortical structure, which has recently been the subject of much research owing to its association with self-reflection and self-consciousness (e.g., [35,36]). Particularly, we were interested in the posterior part of the medial region, which includes the precuneus, PCC and retrosplenial region. As in the case of frontal midline areas (i.e., ACC and adjacent areas), the involvement of the parietal midline areas has been reported in several previous studies of agency, but the functional contribution of these areas has not been examined in detail [10,18–21,29,37,38]. Although the frontal midline areas generally contribute to action and performance monitoring [39,40], this function is not selective to self-behavior, but is shared with the perception of other individuals’ behavioral consequences [41–43]. On the other hand, even though the functional account of posterior midline areas is not yet mature, several findings have reported that the areas around the precuneus differentiate self- and other-attribution in agency judgment [18,21,29,30] and are particularly biased to self-attribution [44]. Furthermore, these areas have anatomical and functional connectivity with several other areas, including the TPJ/IPL, insula, and SMA [45,46], suggesting the existence of an integrative functional hub for agency-related areas. According to these points, we hypothesized that the posterior medial areas play a key role in the higher-order self-attribution of external events.

The present study investigated the neural activity associated with judgments of agency in a task where uncertainty was maximized. Our primary analysis focused on neural differentiation underlying self vs. non-self judgments, with the goal of uncovering the neural substrates specific to self-biased agency attribution during careful and reflective judgments. We predicted that the posterior medial regions, such as the precuneus and PCC, are essential for producing self-attribution of external events under ambiguous conditions.

Methods

Participants

Seventeen right-handed undergraduate Japanese students (6 males and 11 females, aged 19–22 years, mean \pm standard deviation of 20.88 ± 0.99 years) with no history of neurological, psychiatric, or ophthalmological disease participated in this study. All participants gave written informed consent before taking part in the study. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Keio University (No. 09004).

Tasks and Procedure

Apparatus. E-prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA) was used to present stimuli and record

responses. A Victor LCD projector (60-Hz refresh rate) was used to back-project stimuli onto a screen (approximately $20^{\circ} \times 32^{\circ}$ visual angle/ 65×105 mm) with a mirror system mounted on the magnetic resonance imager head coil. The distance between participants' eyes and the mirror was approximately 200 mm, with slight differences among participants due to variation in head size. Participants held response boxes (HHSC-2x4-C, Current Designs, Inc., PA, USA) in each hand and wore headphones (RTC2k, Resonance Technology Inc., CA, USA) in the scanner.

Agency-judgment trials. Participants completed two types of trials: agency-judgment and color-judgment (Fig. 1). In agency-judgment trials, participants were first prompted with a word ("Self?") indicating that the next trial would require an agency judgment. This prompt lasted for 1 s and was followed by a black screen for 500 ms. A 3-mm gray square then appeared on a black background, emerging from the bottom of the screen and moving straight upward at a uniform speed (~ 6.5 mm/s). A cue sound (1000-Hz pure tone with 100 ms duration) was presented ~ 2 s (± 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 delay (described in detail below) after the button press, the moving square on the monitor changed its coordinates (i.e., "jumped") 6.8 mm upward, and changed color. The square object kept moving upward and disappeared into the upper outline of the display. The display then presented the words "Yes – No" to prompt the participant to respond on the basis of their judgment of self-agency, pressing a button to report whether they felt that the changes in the square's position and color were caused by their own preceding action. Participants responded using the response box in their left hand, pressing a button with the index finger to indicate "yes", and pressing a separate button with their middle finger to indicate "no". The inter-trial interval varied between 3000 and 4500 ms in steps of 500 ms.

The temporal delay between the participant's right-button press (cued by the tone) and the following alteration of the square was initially set to 400 ms following our previous study [23]. This delay was adjusted in each subsequent trial, depending on the participant's judgment in the preceding agency-judgment trial. When participants reported "yes" in the previous trial (i.e., when they attributed the change in position of the square to self-agency), then the timing of the position change in the current trial was extended by 50 ms compared with the previous trial. If they reported "no" in the previous agency trial, the delay in the current trial was reduced by 50 ms. Using this procedure, in the first few trials, the length of the delay shifted towards a "borderline" of self and non-self judgment for each individual, and then fluctuated around that value. This means that participants were continually presented with a delay period that involved maximal uncertainty in judging self-agency. The average length (\pm standard deviation) of the delay (excluding the initial five trials) across all participants was 300.76 (± 87.91) ms.

The color of the square (after changing) also varied across trials to match the visual properties of the stimuli with the color-judgment condition described below. The color was selected randomly from the set of possible colors in the color-judgment condition, independently of the participant's performance.

Color-judgment trials. In color-judgment trials, participants judged the color of the square after its change. The color to be judged was adaptively set depending on the participant's judgment in the former color trial, in the same manner as in the agency-judgment trial.

First, the word "Red?" was presented as a prompt, indicating that a color-judgment trial was about to begin. The task-sequence in color-judgment trials was identical to that in the agency-

judgment trials, except for the timing of stimuli. In the color trials, a change in the square's position and color occurred simultaneously with the cue sound (Fig. 1). This means that the change in the color and position of the square, and the cue sound, occurred *before* the button pressing, because participants were required to press the right button after the sound, as in the agency condition. The color-judgment trials were designed to completely eliminate any implicit sense of agency, which can arise when individuals observe a temporal sequence of their action and a subsequent change in visual stimuli. In the last part of the trial, a display presented the words "Yes – No", prompting the participant to report whether the color of the square had changed to red. Participants responded with the left response box in the same way as in the agency condition.

The color of the square after changing was selected from a combination of red and blue. Decimal numbers in the 8-bit red-green-blue assignments were [250, 50, 100] for the reddest and [100, 50, 250] for the bluest color. The number of steps between these colors was the same as the number of steps of delay length in the agency condition. As with the delay length in the agency trial, the post-change color was adjusted depending on the preceding color-judgment trial. When a participant responded "yes" in the former trial, the color of the square was set one step toward blue. Conversely, when a participant reported "no" in the former trial, the color in the current trial was set one step toward red.

General procedure. After being instructed about both task conditions, participants completed ~ 10 practice trials of each type outside the scanner. Immediately before the experimental session, participants performed 5–10 additional practice trials for each task in the scanner. In the experimental sessions, participants performed 132 trials in total (66 trials for each of the two task conditions), divided into three blocks. The order of the agency- and color-judgment trials was pseudo-randomized with the restriction that the same type of trial was not presented more than three times in succession. The assignment of response keys in the task was fixed among sessions and participants.

fMRI Data Acquisition and Analysis

All images were acquired with a 3T Siemens Tim Trio scanner (Munich, Germany) having an eight-channel head coil. Scanning consisted of three experimental functional runs, with a high-resolution T1-weighted structural scan (3D MPRAGE with 1-mm isotropic resolution). Each functional run consisted of ~ 240 whole-brain T2* weighted single-shot gradient-echo planar imaging (EPI) images, collected in an oblique axial orientation (TR of 2.35 s, TE of 30 ms, FA of 90 degrees, voxel size of 3.5 mm \times 3.5 mm \times 2 mm, 44 slices (descending), slice gap of 1 mm). The first three functional volumes were discarded to allow for equilibration of net magnetization. The structural scan was coregistered to the subject's mean EPI image. The data were preprocessed and analyzed using the SPM8 software package (Wellcome Trust Centre for Neuroimaging, London, UK). Functional time images from each participant were spatially corrected for head movement, and temporally corrected for slice timing (using the middle slice acquired in time as a reference), spatially normalized to the Montreal Neurological Institute (MNI) template with a resample voxel size of 3.5 mm \times 3.5 mm \times 3.5 mm and spatially smoothed with a three-dimensional Gaussian filter (full width at half maximum of 8 mm). In addition, high-pass temporal filtering with a cut-off of 128 s was applied to remove low-frequency drift in the signal, and global changes were removed by proportional scaling.

Event-related effects were modeled using a 2 \times 2 factorial design with factors of "condition" (agency-judgment/color-judgment) and participant's "judgment" (yes/no). The first five trials for each

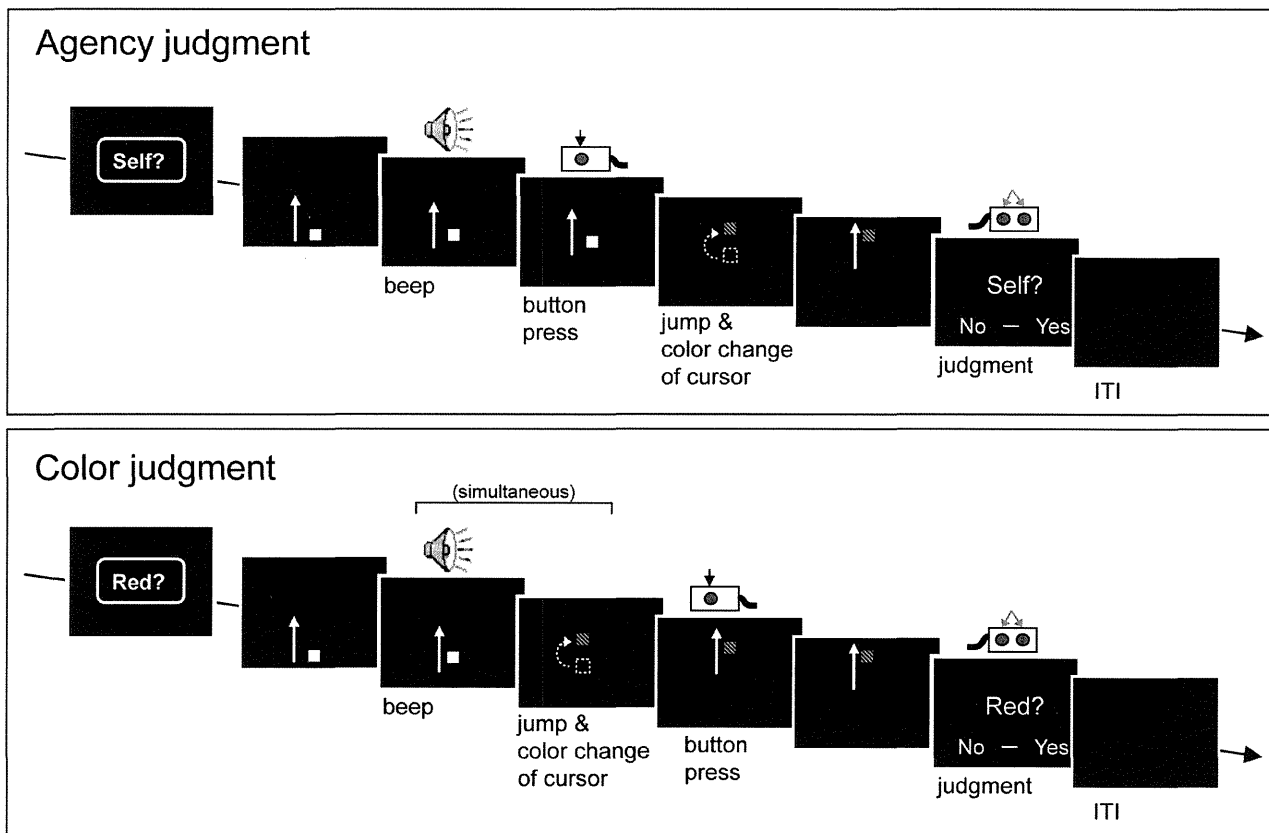


Figure 1. Task sequences. In each trial, a moving object changed its position and color at a moment proximate to the button-press response of a participant. Participants performed two types of judgment (agency-judgment and color-judgment) in a pseudo-random order. The agency-judgment condition required participants to report whether they felt they caused the change of a visual stimulus, while the color-judgment condition asked participants whether the color of the stimulus changed from gray to red. The timing of the stimulus change in the agency-judgment task and the color of the stimulus in the color-judgment task were adjusted on a trial-to-trial basis for each task. See the main text for details. doi:10.1371/journal.pone.0072267.g001

condition were discarded from the fMRI (as well as behavioral) analysis, because initial performance was unstable while task variables (delay or color) were adaptively adjusted according to individual performance. For each session, regressors for a short period immediately after the participant’s action (time-locked to the timing of the right-button press, with a duration of 2 s) in the four conditions (agency/color conditions × yes/no judgments) were modeled by convolving the canonical hemodynamic response function (HRF) with its temporal and dispersion derivatives [47]. A 2-s period of HRF modeling was selected to detect reflective processing about action–feedback events, which is assumed to take place later than automatic phasic responses at the event moment.

Statistical parametric maps were generated using the general linear model for each contrast of the *t* statistic on a voxel-by-voxel basis. Subsequent analyses of second-level group random effects were performed for the SPM contrast images of the first-level canonical HRF responses. A statistical threshold of $p < 0.001$, uncorrected, with an extent threshold of 2 voxels for multiple spatial comparisons was used across the whole brain.

Results

Behavioral Results

Reaction times (RTs) in the judgment period (measured relative to the onset of the “yes–no” prompt) are given in Table 1. Repeated-measures analysis of variance (ANOVA) with the factors

“condition” (agency-judgment/color-judgment) and “judgment” (yes/no) revealed no main effect of the condition, and no interaction between the condition and judgment. The ratio of “yes” to “no” responses was 1.06 (standard deviation of 0.22) for the agency trials and 0.93 (0.20) for the color trials, indicating that “yes” and “no” choices were reported in approximately equal numbers in both conditions. Paired *t*-tests revealed no significant differences between the two trial types ($p = 0.11$).

fMRI Results

Main effect of condition. To reveal the nature of the agency-judgment condition in the current study, the neural activity evoked in the agency trial was contrasted with that in the color-judgment trial. Increased neural activation for the agency

Table 1. Behavioral measures for each task condition.

	RT for "yes"	RT for "no"	"yes"/"no" ratio
Agency-judgment	521.05 (158.05)	462.72 (124.00)	0.51 (0.05)
Color-judgment	495.25 (160.06)	466.56 (129.38)	0.48 (0.08)

Note: Reaction times (RTs) in the judgment periods (in units of milliseconds) and the yes–no ratio of judgment for each condition are presented as means across participants. The values in parentheses are standard deviations. doi:10.1371/journal.pone.0072267.t001

condition relative to the color condition was found in the bilateral insula extending to the frontal operculum, IPL areas extending to the TPJ, the bilateral medial frontal gyrus including the SMA and dorsal anterior cingulate cortex, right middle frontal gyrus (DLPFC), and small portions of the cerebellum and PCC (Fig. 2; Table 2). In contrast, areas of stronger activation for the color condition relative to the agency condition were found predominantly in posterior regions of the brain, such as the lateral and medial occipital and inferior temporal cortex, as well as the cerebellum.

To further clarify whether the between-condition difference shown above depended on the specific judgment (i.e., “yes” or “no”) made in each trial, activation in the agency-judgment trials compared with the color-judgment trials was examined for each judgment separately (i.e., agency vs. color condition comparison in trials with “yes” (or “no”) responses only; Table 3, Fig. S1). These contrasts revealed activity in regions similar to the regions for the main effect of the condition (i.e., the task comparison analyzing both “yes” and “no” trials together). Specifically, the between-condition comparison of “yes” trials revealed significant changes in all of the same regions except the PCC and post-central gyrus, which showed no significant changes. For “no” judgments, the same between-condition contrast revealed significant differences in most of the same regions as in the analysis of all trials, including the insula-operculum continuum, the anterior medial portions (ACC and SMA), and IPL. However, the size of significant voxels was diminished relative to the same contrast with “yes” judgments, and some regions, such as the DLPFC and cerebellum, did not exhibit significant activation in “no” trials.

Simple main effect of judgment for each condition. The results above confirm that the agency-judgment condition mainly involved distributed cortical and subcortical networks that have been commonly implicated in previous agency studies (e.g., [29,48]). Following this assessment, the main aim of the present study was to examine the brain areas playing an important role in self-attribution in the deliberate judgment of agency, which is thought to be reflected in the neural activity evoked in the “yes” trials of the agency condition. To this end, a significant simple main effect of judgment (i.e., “yes” vs. “no” trials) within each

Table 2. Regions showing differential activity between task conditions (agency-judgment condition vs. color-judgment condition).

Location	Coordinates (MNI)			Z score	Voxels
	x	y	z		
<i>Agency condition – color condition</i>					
R IFG/Insula	41	25	-8	5.1	308
L Insula	-47	14	3	4.73	176
L Inferior parietal lobule	-57	-46	27	4.5	277
R Inferior parietal lobule	59	-53	38	4.34	188
L Superior temporal gyrus	-54	-53	10	4.23	16
R Medial frontal gyrus	6	28	38	4.21	218
R Middle frontal gyrus	38	28	45	3.92	36
R Superior temporal gyrus	45	7	-12	3.57	3
L Cerebellum	-26	-84	-40	3.56	4
R Postcentral gyrus	66	-28	45	3.34	7
L Posterior cingulate	-1	-39	17	3.27	2
<i>Color condition – Agency condition</i>					
L Precuneus	-19	-74	41	4.75	266
R Precuneus	41	-77	34	4.6	115
L Cerebellum	-29	-49	-22	4.26	50
R Fusiform gyrus	45	-60	-15	4.21	33
R Parahippocampal gyrus	34	-42	-12	3.99	40
R Cerebellum	3	-74	-29	3.69	10
L Inferior frontal gyrus	-43	7	31	3.61	8

doi:10.1371/journal.pone.0072267.t002

condition was analyzed separately (Table 4). For the agency condition, greater neural activity in the “yes” trials compared with the “no” trials was found in medial parietal areas (PCC and

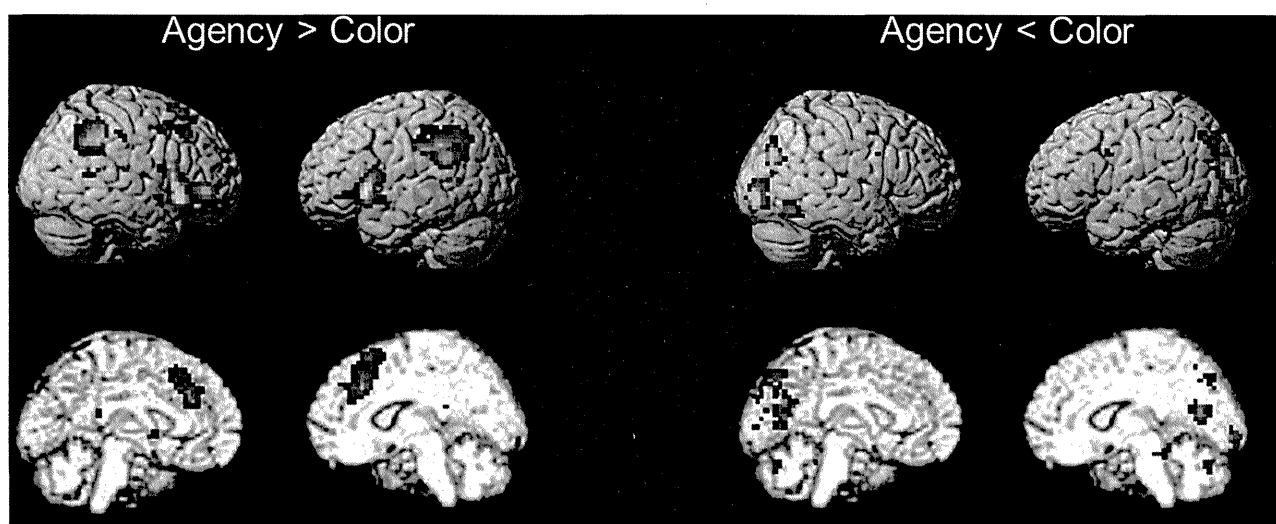


Figure 2. Regions associated with a between-condition difference. Left: A contrast of agency vs. color condition revealed a distributed neural network including the bilateral insula/operculum, IPL/TPJ, SMA/ACC, and right DLPFC. Right: A color vs. agency condition contrast revealed activity mainly among visual areas ($p < 0.001$ uncorrected, with an extent threshold of 2 voxels). doi:10.1371/journal.pone.0072267.g002

Table 3. Regions showing differential activity between conditions for each type of judgment (“yes”/“no”).

Location	Coordinates (MNI)			Z score	Voxels
	x	y	z		
<i>Agency Yes – Color Yes</i>					
R Insula	48	11	17	5.2	232
L Inferior parietal lobule	-54	-46	45	4.87	289
R Inferior parietal lobule	55	-39	48	4.63	279
L Insula	-47	7	13	4.19	106
R Medial frontal gyrus	6	28	45	4.06	146
R Middle frontal gyrus	41	11	48	3.97	55
L Superior temporal gyrus	-57	-53	10	3.91	15
L Cerebellum	-26	-70	-33	3.8	12
<i>Agency No – Color No</i>					
R Superior frontal gyrus	13	14	62	4.03	26
R Cingulate gyrus	3	28	34	3.99	56
L Insula	-47	14	3	3.92	45
R Inferior frontal gyrus	38	42	-5	3.88	84
L Supramarginal gyrus	-61	-49	27	3.66	25
L Inferior parietal lobule	-50	-63	45	3.47	3
L Middle temporal gyrus	-47	0	-29	3.45	3
L Inferior parietal lobule	-57	-28	34	3.27	5
R Supramarginal gyrus	59	-42	38	3.22	13

doi:10.1371/journal.pone.0072267.t003

precuneus) and the right anterior insula as well as the inferior occipital cortex (Fig. 3). Moreover, the same “yes” vs. “no” contrast was calculated for the color condition in examining whether medial parietal activity was specific to the agency condition. As a result, the “yes” vs. “no” contrast for the color condition detected activation in different regions of the anterior cortex, such as the middle frontal gyrus and ACC. In addition, the “no” vs. “yes” contrast for each condition revealed activation in limited portions of cortical and subcortical regions (Table 4). No overlapping regions of activation were found between the agency- and color-judgment conditions in terms of the neural differentiation of yes/no judgments.

Table 4. Regions showing differential activity between “yes” and “no” judgment for each condition.

Location	Coordinates (MNI)			Z score	Voxels
	x	y	z		
<i>Agency Yes – No</i>					
R Posterior cingulate	10	-42	20	3.82	26
R Inferior occipital gyrus	38	-91	-8	4.05	13
L Cerebellum	-22	-84	-33	3.46	4
L Precuneus	-5	-56	48	3.45	4
L Superior temporal gyrus	-33	-60	27	3.24	2
L Precentral gyrus	-36	21	41	3.19	2
R Insula	38	18	13	3.17	2
<i>Agency No – Yes</i>					
R Postcentral gyrus	48	-25	62	3.23	5
L Cingulate gyrus	-8	0	31	3.58	2
L Cerebellum	-15	-32	-15	3.16	2
<i>Color Yes – No</i>					
R Middle frontal gyrus	31	32	52	4.01	22
R Anterior cingulate	6	39	17	3.76	14
Anterior corpus callosum	10	28	-1	4.22	9
R Superior frontal gyrus	17	35	41	3.63	2
<i>Color No – Yes</i>					
R Thalamus	13	-18	6	4.22	18
R Lentiform nucleus	20	4	13	4	12
L Lentiform nucleus	-26	-4	-5	3.26	6

doi:10.1371/journal.pone.0072267.t004

Discussion

In the present study, we sought to identify the neural substrates underlying judgments of self-agency under conditions of uncertainty. To this end, we adaptively set the task-relevant variables to be maximally ambiguous for each individual. We found that attributing self-agency to an external event in our task was associated with activity in posterior midline areas.

Results of Basic Contrasts

Contrasts between the agency-judgment condition and color-judgment condition revealed significant neural activation in many

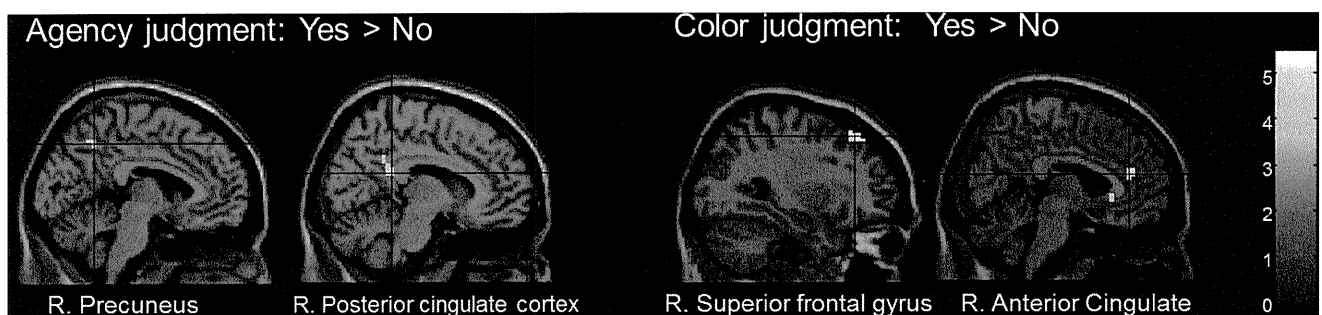


Figure 3. Activation for “Yes” versus “No” judgment in each condition. Left panels: A contrast of “yes” vs. “no” judgments for the agency-judgment condition revealed activity in posterior medial regions. Right panels: The same contrast as for the color-judgment condition revealed activation in the anterior part of the brain ($p < 0.001$ uncorrected, with an extent threshold of 2 voxels).

doi:10.1371/journal.pone.0072267.g003

of the cortical areas previously implicated in agency judgment (e.g., reviews in [29,48]). These areas included regions around the TPJ and IPL, regions around the SMA and ACC, regions around the insula and frontal operculum, and the DLPFC. The between-condition differences within each type of judgment (i.e., conducting the contrast after separating “yes” and “no” judgment trials) revealed a similar pattern of activation changes. These results suggest that the experimental paradigm in this study, in which task difficulty was adaptively determined, was appropriate for examining agency-related processing.

However, the contrast between “yes” trials and “no” trials within both conditions revealed smaller areas of significant activity, in fewer brain regions. The results of the agency-judgment condition thus indicate that a large portion of the elicited neural activity did not differentiate between trials of self- and non-self-attribution. Perhaps this was because sensorimotor discrepancy was the only cue for judging agency in the current experiment; thus, automatic feelings of agency and reflective judgments of agency may have contributed equally to decisions in the “yes” (i.e., self-attribution) and “no” (non-self-attribution) trials. On the other hand, the contrast of “yes” vs. “no” trials for the agency condition would be expected to reflect the neural correlates of the higher-order processing, which may resolve the conflicting judgment of self- and other-agency in uncertain situations. We found small areas exhibiting significant activity in regard to this contrast, which were located in the medial parietal areas, including the precuneus and PCC. The result suggests that the posterior medial areas play an important role in judgment of agency in an ambiguous situation, particularly in the case of self-attribution. We consider that these regions are critical in the operation of self-ascription, rather than in the condition of uncertainty itself. This is because those activities were detected in terms of differentiation between self- and non-self-judgment, and because the degree of uncertainty should not be different among trials.

Medial Parietal Areas Involved in Self-agency Attribution

Previous studies have occasionally reported the involvement of posterior medial regions in agency (e.g., [18–21,29,37,38]). However, as for other regions of activation detected in the current study, it is currently unclear whether these areas contribute to the sense of agency. From the considerations discussed above, we suggest that the posterior medial regions may be suitable candidates for the cognitive process of binding external inputs with a representation of the self. Several structural and functional properties of the medial parietal regions support this interpretation, as described below.

First, anatomical connectivity studies have reported that posterior medial regions do not have direct connections with primary sensory cortices, but possess connections with several sensory (and sensorimotor) association areas [44]. Although previous findings are not entirely consistent, several functional connectivity studies have reported that medial posterior areas are associated with regions thought to be involved in agency, such as the TPJ/IPL, insula, and SMA [45]. These findings suggest that posterior medial areas may play an integrative role in the agency-related network involved in the cognitive process underlying judgments of agency. Furthermore, part of the precuneus is connected to the lateral PFC [45,46], which is thought to be involved in higher-order cognitive processing (e.g., [49]). This finding supports the notion that the posterior medial area plays a critical role in the final attribution of agency, although it is still an open question as to which areas of the PFC and medial parietal are to be placed at a “higher” stage of the agency judgment.

Second, activity in medial parietal areas can also be interpreted according to their close association with consciousness and self-reflection [36,50,51]. The precuneus and PCC are closely connected to medial prefrontal regions, and have often been reported in studies of general self-reflection, as part of a network involved in mentalizing about the self and others [52–55]. Therefore, the role of medial parietal areas in self-attribution may also be related to self-reflection.

Alternatively, it is possible that the role of the medial parietal area in memory retrieval contributed to the judgment of agency in the current study. According to a recent theory, different components of the sense of agency can be characterized in terms of their temporal features, such as whether they are forward or backward processes (e.g., [3]). The automatic feeling of agency can be considered a type of predictive process, intrinsically relying on the internal feed-forward prediction of sensory consequences. Conversely, the cognitive judgment of agency can be regarded as a postdictive process; that is, interpreting the event with a *post-hoc* explanation. In accord with this notion, it is possible that the *post-hoc* judgment of agency, including the process of interest in this study, recruits memory processes involved in recall, and reflection on the action–feedback relationship occurred a short time earlier. The PCC is considered to be part of the Papez circuit, which is a network for memory encoding and retrieval [56,57]. The precuneus is also reported to be active in memory retrieval [44]. Therefore, it is possible that these areas were activated by the postdictive self-attribution of the stimuli, involving memory components that are intrinsically private and self-related.

Previous studies reported inconsistent findings regarding the association between posterior medial areas and self- and/or non-self-attribution. Several studies suggested that medial parietal regions were associated with self-attribution [18,21]. For example, Miele et al. [21] reported that the posterior precuneus and calcarine sulcus were more active when participants reported that they felt a sense of agency compared with trials in which they did not. In contrast, other studies reported that the precuneus and adjacent areas were more active when participants attributed the cause of an event to non-self-agency [29,58]. Reviewing this inconsistency, Cavanna and Trimble [44] proposed an anterior–posterior segregation of the precuneus, and suggested that self-processing occurs in the anterior part (but see [29]). Interestingly, this region corresponds to the area exhibiting activity related to explicit self-attribution in the current study. Overall, the details of previous findings regarding the relationship between medial parietal regions and agency remain controversial. The present study extended previous findings, suggesting that these regions may be involved in conscious discrimination and attribution between self- and non-self agency. The present findings could be extended by combining our paradigm with tasks used in previous studies.

Insula

In addition to medial parietal areas, areas of cortical activity differentiating between “yes” and “no” trials for the agency-judgment condition were also found in a small cluster in the right anterior insula. Brain regions frequently reported among agency studies, including the insula, are typically related with bodily processing. For example, areas around the inferior parietal lobe have been reported to integrate sensorimotor information to construct a body image, while dorsomedial frontal regions play a key role in performance monitoring [39,59–61]. The insula is thought to be primarily involved in bodily processing by receiving interoceptive signals from visceral organs [62–64]. Thus, the insula appears to contribute to basic sensorimotor processing regarding

agency. Indeed, we found the largest cluster of activity around the bilateral insula–operculum complex. At the same time, these areas did not clearly differentiate between trials resulting in self- and non-self-attribution. This may be because of the lack of variation in action–feedback discrepancy (sensorimotor cues) among trials.

However, the functional role of the tiny region of the anterior insula exhibiting significant activation in the self vs. non-self contrast remains unclear. A number of previous studies have reported that while the middle insula directly receives bodily input, the anterior portion of this region represents more abstract and subjective information of internal bodily states, generating self-reflection and self-consciousness from somatic signals (e.g., [53,65,66]). Therefore, anterior insula activation could represent a higher-order component of self-attribution, rather than low-level processes. Indeed, the insula is known to be active in processing information related to the self in various domains, such as facial recognition, action and emotion monitoring, and autobiographical memory [22,67–70]. In light of the current results and previous findings, we tentatively propose that activity in the main part of the insula may subserve the somatosensory feeling of agency, while the anterior portion might also contribute to the explicit judgment of agency. These speculative predictions require further examination.

TPJ/IPL

The temporo-parietal association areas (TPJ and IPL) are among the regions most frequently and robustly implicated in agency in previous studies (reviewed in [29]). Activity in these areas is reported to be positively correlated with action–feedback discrepancy, and to be active when individuals make an external (or non-self) attribution of an event [10,13,19,20,71].

For example, Miele et al. [21] demonstrated that the right TPJ responded to physical disturbance in visual feedback, rather than to subjective performance monitoring of participants. This and other related reports suggest, at least partially, the automaticity of TPJ involvement in detecting sensorimotor discrepancies [29,30,72]. According to these previous findings, we predicted that TPJ and adjacent areas would be more active during “no” judgment trials than during “yes” judgment trials in the current study. In the current task, however, the activity of these regions did not differentiate between “yes” and “no” judgments, as was the case for several other regions. That is, the TPJ was active not only when participants made non-self judgments, but also when they made self-attribution judgments (i.e., in “yes” trials). The participants in this study were almost always presented with a certain amount of action–feedback discrepancy. Thus, the TPJ may have been consistently activated by detecting the sensorimotor mismatch, irrespective of participants’ judgment. We propose that TPJ activity may have generated non-self attribution about an event across almost all trials, but this process might not be sufficient to make a final judgment of agency. Consequently, the final attribution is determined by activity in other areas, such as posterior medial regions. Note that we do not suggest that the TPJ (and other areas that did not differentiate self-other agency in this study) always functions in some “lower” stages in the agency judgment. Still, these areas might not play a critical role, at least in a situation where the ambiguous sensorimotor discrepancy is the only cue with which to judge agency.

DLPFC

As this study assumed a higher-order integrative process in the difficult judgment of agency, one may predict that the PFC (particularly the dorsolateral part of it) would dominantly contribute to the judgment, because the DLPFC is thought to function in various types of conscious and explicit decision-related

processing as a locus of supervisory executive function and metacognition [49,73]. In fact, several investigations reported the contribution of the PFC in agency judgments [13,28,37,74]. However, in the results of the present study, activities in the DLPFC and medial PFC were associated with agency judgment, but they did not differentiate self- and non-self-attribution of agency, as was the case in many other areas. That is, PFC regions did not appear to play an essential role in judging self-attribution in the current study. In our view, this finding is not necessarily inconsistent with popular assumptions of PFC functions as discussed below.

In reviewing the former agency studies, David et al. [48] proposed that the lateral PFC is associated with reflective and explicit judgment, rather than a pre-reflective and implicit feeling of agency. Their discussion was based on the framework of contrasting conscious vs. unconscious components. However, the present study does not fit with their scheme as it did not directly compare conscious and unconscious conditions. Instead, the current task required participants to undertake conscious processing in almost all trials by presenting similar delays that were difficult to judge. Therefore, this study does not contradict the possibility that the DLPFC is important in the conscious and reflective aspect of agency judgment.

Along another line, it is important to distinguish agency attribution from action monitoring, which is considered to be associated with PFC activity [49]. For instance, Miele et al. [21] conducted a tracking task with visual feedback involving disturbances, and revealed that the anterior PFC is activated during retrospective conscious evaluation of the task performance, rather than during execution of the task. Although their study suggested a supervisory role of the DLPFC in action control, again, this notion does not contradict our findings. We consider functional differentiation between the posterior medial regions and PFC, speculating that the former areas operate in the self-agency attribution of external stimuli, while the latter areas operate in monitoring an individual’s own action and possibly also contextual information.

Yes vs. No Contrast in the Color-judgment Task

Compared with the agency-judgment condition, the color-judgment condition was associated with significant activity in a broad range of visual areas. However, contrasting neural activity between “yes” and “no” judgment trials for the color condition showed significant changes in only a small number of regions. These findings may reflect that stimuli resulting in “yes” and “no” judgments were almost identical, and that the neural substrates involved in both types of judgment were similar, as for the agency-judgment condition. The “yes” vs. “no” comparison for the color-judgment condition revealed activity in frontal portions of the cortex that were clearly different from the medial parietal regions implicated for the agency-judgment condition, as illustrated in Fig. 3. The functional role of the areas differentiating judgments for the color condition (i.e., the neural correlates of “red-attribution”), is currently unclear. We speculatively propose that activity in these areas may subserve general perceptual decisions about external stimuli, such as those relating to monitoring or attentional networks. In any case, it is clear that the regions of activation detected by the “yes” vs. “no” contrast for the agency-judgment condition and those for the color-judgment condition were markedly distinct, in spite of the similar task properties involved. The color-judgment condition was designed to match the perceptual (both visual and auditory) and motor components involved for the agency-judgment condition. In addition, it also matched other task properties of the agency-judgment condition,

such as the amount of visual attention and task uncertainty involved, using an identical adaptive method. In fact, behavioral data (RTs and the “yes”/“no” ratios) did not differ between conditions, suggesting the validity of the color-judgment condition as a control for the agency-judgment condition. These issues and results lend further support to the notion that the brain regions discussed above contribute selectively to agency processing, rather than reflecting general information processing in perceptual judgment.

Future Directions

In this final section, it is noted what the present study did not examine and left for future investigation. As the main feature of this study was to selectively focus on the situation of uncertainty, we did not measure the neural activities for “certain” conditions in which ambiguity for agency judgment hardly exists. To further support the current findings and clarify the neural substrates for the higher-order agency-attribution in an uncertain situation, it is important to directly compare ambiguous and non-ambiguous situations, or to parametrically vary the degree of ambiguity. Subjective ambiguity reported by participants should also be included as another variable of the examination. In addition, other factors such as the level of consciousness (e.g., comparing conscious vs. unconscious aspects of judgment) and contextual cues (e.g., an individual’s belief or prediction) can be included in experimental manipulations, to relate the current approach with several lines of former investigations [17,48].

Finally, the current findings have implications for clinical research. A number of previous studies have investigated the cognitive aspects of schizophrenia, particularly the abnormal sense of agency [5,75,76]. Several recently proposed theories rely on

multiple-factor frameworks and hypothesized atypical integration of agency-related processes in schizophrenia [3,77–79]. We previously conducted a behavioral study of schizophrenia using a prototype version of the current task, reporting an aberrant sense of agency in patients with schizophrenia [23,24]. The results of the present study suggest that the abnormal sense of agency in schizophrenia may be related to dysfunction in posterior midline cortex areas, including the precuneus and posterior cingulate cortex. Moreover, knowledge of the clinical aspects of the sense of agency may be extended by applying the adaptive paradigm used in the current study, which was found to be an appropriate method for elucidating the higher-order components of self-agency.

Supporting Information

Figure S1 Regions associated with a between-condition difference in each type of judgment (“yes” and “no”). Left: The contrast of agency-judgment vs. color-judgment condition was calculated with the trials of “yes” judgments (left panels) and “no” judgments (right panels) separately. These analyses detected brain regions similar to those revealed in the simple comparison of agency vs. color condition shown in Fig. 3 (left) ($p < 0.001$ uncorrected, with an extent threshold of 2 voxels). (TIF)

Author Contributions

Conceived and designed the experiments: HF TM MK SU. Performed the experiments: HF YG SU. Analyzed the data: HF YG SU. Wrote the paper: HF YG TM MK SU.

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Reduced sense of agency in chronic schizophrenia with predominant negative symptoms



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ARTICLE INFO

Article history:

Received 4 September 2012

Received in revised form

11 April 2013

Accepted 20 April 2013

Keywords:

Self-disturbance

Sense of agency

Prediction

Post-diction

Dopamine

Glutamate

Optimal cue integration

ABSTRACT

Self-disturbances in schizophrenia have been regarded as a fundamental vulnerability marker for this disease, and have begun to be studied from the standpoint of an abnormal “sense of agency (SoA)” in cognitive neuroscience. To clarify the nature of aberrant SoA in schizophrenia, it needs to be investigated in various clinical subtypes and stages. The residual type of chronic schizophrenia with predominant negative symptoms (NS) has never been investigated for SoA. Accordingly, we investigated SoA by an original agency attribution task in NS-predominant schizophrenia, and evaluated the dynamic interplay between the predictive and postdictive components of SoA in the optimal cue integration framework. We studied 20 patients with NS-predominant schizophrenia, and compared with 30 patients with paranoid-type schizophrenia and 35 normal volunteers. NS-predominant schizophrenia showed markedly diminished SoA compared to normal controls and paranoid-type schizophrenia, indicating a completely opposite direction in agency attribution compared with excessive SoA demonstrated in paranoid-type schizophrenia. Reduced SoA was detected in experimental studies of schizophrenia for the first time. According to the optimal cue integration framework, these results indicate that there was no increase in compensatory contributions of the postdictive processes despite the existence of inadequate predictions, contrary to the exaggerated postdictive component in paranoid-type schizophrenia.

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1. Introduction

Self-disturbances have long been noted as the core psychopathology of schizophrenia, and have been regarded as a fundamental vulnerability or trait marker for this disease, because these disturbances could be present in all clinical subtypes and stages of schizophrenia (Parnas and Handest, 2003; Sass and Parnas, 2003; Nelson et al., 2008, 2009, 2012; Schultze-Lutter, 2009). However, because self-disturbances are subjective experiences and can only be described by the first-person perspective of the patient, the nature of such disturbances in schizophrenia has been hardly studied in biological research.

In recent years, self-disturbances including passivity phenomena in the First Rank Symptoms have begun to be explained and studied from the standpoint of an abnormal “sense of agency (SoA)” in cognitive neuroscience (Georgieff and Jeannerod, 1998; Frith et al., 2000; Stephens and Graham, 2000). A “SoA” is the feeling that a person causes and controls his/her own actions and their effects on the outside world, and it is one of the essential aspects of

self-consciousness (Gallagher, 2000; Haggard et al., 2002; Haggard, 2005; Tsakiris et al., 2007; Synofzik et al., 2008; Moore and Fletcher, 2012). The most prevalent theory for explaining aberrant SoA in schizophrenia has been based on the internal Forward model of action-awareness (Frith et al., 2000). Internal prediction about the sensory feedback of a movement is compared with actual sensory feedback by the “comparator” in this model. If there is a match, events are regarded as self-generated. If there is a mismatch (i.e., a prediction error), events are recognized as externally generated, and SoA is diminished or lost. Patients with schizophrenia are thought to have problems with generating adequate internal predictions about the sensory consequences of their actions, and these inadequate predictions cause the pathological inference of agency, resulting in misattribution in which the patient feels the loss of SoA and experiences that the movement is generated by external forces (Frith et al., 2000; Blakemore, 2000; Blakemore et al., 2002; Lindner et al., 2005; Shergill et al., 2005).

There are two types of tasks for probing SoA (Haggard, 2006). The agency attribution task is an *explicit* measure of SoA in which people verbally report how much they feel a sense of control over their own body or following external events. In contrast, an *implicit* measure of SoA is evaluated by the “intentional binding” effect in subjective time experience during an intentional action

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(Haggard et al., 2002; Haggard, 2006). In Haggard's experiment, subjects made voluntary key presses, which were followed 250 ms later by an auditory tone. The tone may be considered the effect of the subject's action in the external world. Subjects judged the time at which they were aware of pressing a key and the time at which they were aware of hearing the tone by using the Libet-clock method (Libet et al., 1983). The intentional binding effect refers to the subjective binding in time of voluntary actions to their sensory consequences.

Whether SoA tasks are explicit or implicit, patients with schizophrenia have an abnormally strong tendency for over-attribution of self-agency in experimental settings (Daprati et al., 1997; Franck et al., 2001; Haggard et al., 2003; Synofzik et al., 2010; Voss et al., 2010; Moore and Fletcher, 2012; Moore and Obhi, 2012; Maeda et al., 2012). Moreover, Maeda et al. (2012) identified the curious phenomenon of "backward causation," which means that patients are likely to experience SoA even when external events precede their actions. Therefore, schizophrenia patients show exaggeration of both forward and backward temporal causality with respect to their intentional actions. However, the excessive SoA in these experimental settings seems odd, because self-disturbances including passivity phenomena in the First Rank Symptoms could be explained as a reduced SoA by the Forward model. The curious contradiction between clinical symptoms and experimental findings cannot be readily explained by the Forward model and this is the most controversial issue in SoA studies in schizophrenia (Gallagher, 2004; Synofzik et al., 2008, 2010; Voss et al., 2010; Maeda et al., 2012).

Recent studies have demonstrated that SoA is not only determined by the internal predictions and comparator mechanisms in the Forward model, but also by a large variety of internal and external cues (Wegner and Sparrow, 2004; Moore and Haggard, 2008; Moore et al., 2009; Synofzik et al., 2008, 2009, 2010; Synofzik and Voss, 2010; Voss et al., 2010; Desantis et al., 2011; Moore and Fletcher, 2012; Maeda et al., 2012; Takahata et al., 2012). According to the optimal cue integration theory, emergence of SoA depends on the availability and reliability of a certain cue for adequate representation of agency (Synofzik et al., 2009; Moore and Fletcher, 2012). The dual contribution of internal signals and external cues was experimentally demonstrated by Moore et al., using the intentional binding measure of SoA. Moore et al. (2008, 2009) showed that an intentional binding effect in action awareness involves both predictive and retrospective components. The predictive component is based on internal cues, whereas the postdictive component is derived from external cues regarding the effects of an action. Moore et al. demonstrated that the intentional binding effect could occur even in the absence of the outcome of actions if predictive process based on the likelihood of the outcome is sufficiently strong. On the other hand, binding effects are determined in part by post-action information including rewards or punishments. This means that the actual outcome could influence the binding effect retrospectively, i.e., by means of postdictive processes which arise after the occurrence of the outcome of action. The postdictive component exerts more influence over SoA when the predictive component is weak (Moore and Haggard, 2008; Moore et al., 2009), and the contribution of each component changes dynamically under uncertain conditions in order to optimize adequate SoA judgments. Voss et al. (2010) provided a convincing explanation of the contradiction between clinical symptoms and experimental findings in schizophrenia. In normal controls, intentional binding arises almost entirely from the predictive mechanism. Conversely, patients with schizophrenia specifically lack a predictive mechanism of the binding effect, and the hyper-binding effect reflects their reliance on exaggerated retrospective mechanisms rather than predictive ones in experimental conditions. Therefore, stronger weighting of external cues in the postdictive process can help patients to achieve more perceptual certainty about the effects of their own actions and compensate for inadequate predictions in schizophrenia.

In previous studies, exaggerated SoA has been chiefly detected in patients with paranoid-type schizophrenia, who have prominent positive symptoms involving delusions and hallucinations, while their negative and disorganized symptoms are unremarkable (Haggard et al., 2003; Synofzik et al., 2010; Voss et al., 2010; Moore and Obhi, 2012; Maeda et al., 2012). Furthermore, previous SoA studies have employed complex tasks like the intentional binding task, restricting the participants to clinically milder and higher functioning patients with paranoid-type schizophrenia. In order to clarify whether self-disturbances in schizophrenia can be used as a vulnerability marker for this disease, it is necessary to investigate SoA in all of its clinical subtypes. However, the other chief subtype of schizophrenia, which is the residual type of schizophrenia with predominant negative symptoms (NS), has never been investigated for SoA.

In the present study, we investigated SoA in patients with NS-predominant schizophrenia compared with normal controls and patients with paranoid-type schizophrenia, and evaluated the dynamic interplay between the predictive and postdictive components of SoA by using our original agency attribution task, which is a genuine SoA task without confounding from the sense of ownership of body movements (Maeda et al., 2012). Our experiment introduced temporal biases between actions and sensory consequences in visual feedback on the computer screen, and evaluated how much subjects explicitly felt a sense of control over external events, not over bodily actions. Therefore, our method was not contaminated by any aspect of the sense of body ownership, and we regarded it as a pure SoA task. Moreover, the phenomenon of "backward causation" in our task is regarded as an explicit measure of the exaggerated contribution of the postdictive component (Maeda et al., 2012). The "backward causation" refers to the feeling that a person experiences causal effects even when the sensory consequence of an action precedes the intentional action. External events preceding intentional actions were never "prospectively" predicted by the Forward model. From the standpoint of predictive and retrospective components in the optimal cue integration framework, the curious phenomenon must be "retrospectively" or "post-dictively" inferred.

Regarding self-disturbances involved with NS, little effort has been made to explore the subjective aspects of NS or deficit symptoms (Sass and Parnas, 2003). Huber's tremendous work on the "basic symptoms (*Basissymptome*)" dealt with the *subjectively* experienced deficits of a person's own mental processes, including thinking, speech, perception, action, affect, and intention (Huber, 1983; Parnas and Handest, 2003; Gross et al., 2008). Although basic symptoms differ from NS, which are functional deficits *objectively* observed by others, basic symptoms could include subjective aspects of NS (Sass and Parnas, 2003). Loss of motivation (avolition) and reduced social communication are characteristic features of NS, and these NS would have anomalous subjective experiences, such as a diminished sense of causal efficacy on their own body and the external world, and NS-predominant patients feel detached and alienated from the vital real environment ("*Entfremdung*"). Thus, we hypothesized that patients with NS-predominant schizophrenia could also demonstrate aberrant SoA compared to healthy subjects, and evaluated the difference of SoA patterns between paranoid-type and NS-predominant schizophrenia.

2. Materials and methods

2.1. Participants

Twenty patients (12 males and eight females) with chronic residual type schizophrenia according to the DSM-IV criteria, and who predominantly presented with NS were enrolled in this study from the Keio University Hospital and Sakuragaoka Memorial Hospital in Japan. All subjects were administered the

Table 1
Characteristics of the participants.

Characteristics	NS-predominant schizophrenia	Paranoid-type schizophrenia	Normal controls
	(n=20)	(n=30)	(n=35)
Age	36.0 (10.0)	37.9 (11.9)	35.0 (10.0)
Sex	M12/F8	M21/F9	M16/F19
Education (years)	14.2 (2.2)	13.4 (2.2)	16.6 (1.5)
Outpatient/inpatient	Out 18/In 2	Out 24/In 6	–
Age at onset	23.8 (9.2)	–	–
Duration of illness (years)	12.4 (8.2)	12.7 (10.1)	–
Neuroleptic dosage (HP-mg)	11.7 (16.9)	14.0 (12.7)	–
GAF	42.7 (12.5)	58.5 (14.6)	–
PANSS			
Total score	86.9 (14.4)	73.5 (11.4)	–
Positive symptoms	16.3 (4.7)	20.4 (4.5)	–
Negative symptoms	26.3 (3.1)	15.2 (3.0)	–
General psychopathology	44.3 (9.9)	38.0 (5.9)	–

Mean (S.D.).

Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-IV). Patients with predominant NS were required to meet the following criteria: (1) NS subscale ≥ 21 on the Positive and Negative Syndrome Scale (PANSS) (Kay, 2007), (2) at least three 'moderate' scores on the NS subscale of the PANSS, and (3) clinically stable at the time of testing. The following psychiatric exclusion criteria were applied: patients suffering from (1) major brain anomalies or organic brain disease, (2) current or past substance abuse (including alcoholism), (3) mental retardation, and (4) previous episodes of mood disorder. To clarify the clinical features of the patients, we used the PANSS and the Global Assessment of Functioning (GAF) score. None of the patients dropped out or exhibited a change of psychiatric state during or after the study.

We established a new control group including 35 healthy volunteers (16 males and 19 females), with 30 data being enrolled from our previously published dataset (Maeda et al., 2012). They were confirmed to have neither psychiatric nor neurological disorders, nor any first degree relatives with neuropsychiatric disorders. In addition, 30 patients (21 males and nine females) with paranoid-type schizophrenia characterized with positive symptoms were also introduced from the previous dataset (Maeda et al., 2012). Analysis of variance (ANOVA) showed that all groups were statistically similar on demographic characteristics of age and sex. The healthy control sample differed from the NS-predominant schizophrenia and paranoid-type schizophrenia groups on years of education (controls > NS-predominant schizophrenia [$P=0.0002$], controls > paranoid-type schizophrenia [$P<0.0001$]) (corrected by the Bonferroni method for multiple comparisons), there was no difference between NS-predominant schizophrenia and paranoid-type schizophrenia on the duration of illness and neuroleptic dosage. Table 1 shows the demographic characteristics of the participants.

This study was approved by the ethics committees of Keio University and Sakuragaoka Memorial Hospital. After a complete description of the study, informed consent was obtained from each subject.

2.2. Agency attribution task (Keio Method)

We used the agency attribution task (Keio Method) devised by Maeda et al. (2012), which is a genuine SoA task that evaluates explicit experience of the temporal causal relation between an intentional action and an external event without any confounding from the sense of ownership of body movement. Each trial was run on a 14-in. computer monitor, starting with a dark screen. Then a 5-mm square piece appeared from the bottom of the screen and moved straight upward at a uniform speed (22 mm/s). Subjects were instructed to press a key with their dominant index finger immediately after they heard a target sound (beep). When the subject pressed the key, the piece on the monitor jumped 35 mm upward, with various temporal delays of 0–1000 ms in 100-ms increments (Fig. 1A). Each delay was tested 10 times. Subjects were instructed to make an agency judgment for each trial, and to answer the following question with a "yes" or "no" response: "Did you feel that you made the piece jump upward as intended?" A "yes" response meant that the subject attributed the response of the piece to his/her action, i.e., the subject experienced SoA.

In addition, to examine the experience of backward causal effect of an action to an external event ("backward causation"), "event prior to action (EPA)" trials were included in which the piece jumped when the sound occurred instead of when the key was pressed. EPA trials were done under three conditions, in which the piece jumped 100 ms before the beep, simultaneously with the beep, or 100 ms after the beep (Fig. 1B). Each EPA condition was also tested 10 times. Therefore, there were a

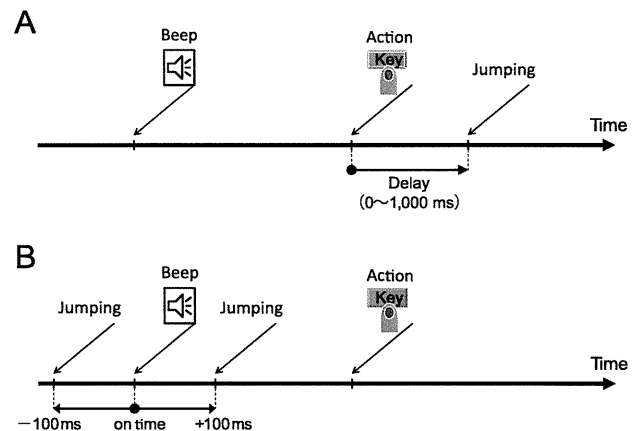


Fig. 1. Outline of the experiments. (A) Action-linked condition. Temporal delays from 0 to 1000 ms were introduced in 100-ms increments. (B) Event prior to action (EPA) condition. Movement of the piece on the screen was based on the beep sound and not on the key press, where the movement of the piece was programmed to precede their intentional actions. Three EPA conditions were tested: (1) the piece jumped 100 ms before the beep, (2) it jumped at the time of the beep, or (3) it jumped 100 ms after the beep.

total of 140 trials. Each experiment included a mixture of action-linked and EPA conditions, and the order of presentation was randomized. The inter-trial interval was constant, but the timing of the beep sound in a trial was randomly varied in order to prevent participants from predicting its occurrence.

In each trial, reaction times to beep sounds were compared between the groups, because the reaction time was considered to influence agency judgments especially in EPA conditions. Also, a normal reaction time could be regarded as validating the experiment by excluding problems with cooperation or motivation.

2.3. Statistical analysis

The number of "yes" responses was determined for each temporal delay condition in each participant, and was compared by the Kruskal–Wallis test to evaluate group difference, because scores were not normally distributed. Moreover, multiple statistical comparisons across groups were also performed using the Steel–Dwass test in order to avoid the Type I error.

In both Action-linked and EPA conditions, correlations between the total number of "yes" responses and the PANSS score, GAF score, age, gender, education, age at onset, duration of illness, and neuroleptic dose were assessed in patients with NS-predominant schizophrenia by Spearman's rank correlation analysis.

A P value less than 0.05 was considered to indicate significance in all analysis.

3. Results

3.1. Action-linked experiment (Fig. 2 right)

The mean number of "yes" responses decreased as the temporal bias became longer in all groups. The slope of the curve for agency judgment was different among groups. Patients with NS-predominant schizophrenia showed a lower peak and a steeper slope compared to normal controls and paranoid-type schizophrenia (Fig. 2 right). Remarkably, the number of "yes" responses was diminished even in no-delay condition in the Action-linked experiment. Therefore, NS-predominant patients gave fewer "yes" responses than control subjects and paranoid-type schizophrenia, suggesting that they showed under-attribution of their action effects to themselves, and resulting in a reduced SoA. The Kruskal–Wallis test demonstrated that group difference was statistically significant for all temporal delays ($P<0.05$). And then, multiple statistical comparisons across groups were performed using the Steel–Dwass test, and showed that reduced SoA in NS-predominant schizophrenia was significant for temporal biases from 0 to 700 ms compared to normal controls, and biases from 200 to 1000 ms compared to paranoid-type schizophrenia ($P<0.05$) (Table 2).

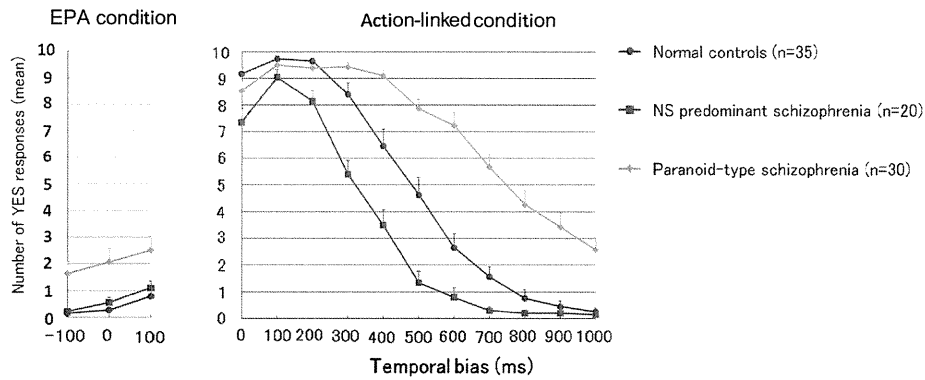


Fig. 2. Mean number of “yes” responses in each group under each of the temporal bias conditions (bars represent the standard error).

Table 2

Sense of agency judgments across groups. Results were compared among groups by the Steel–Dwass multiple comparison test.

Temporal bias (ms)	NS-predominant vs. NC	NS-predominant vs. paranoid-type	Paranoid-type vs. NC
	<i>P</i>	<i>P</i>	<i>P</i>
EPA condition			
-100	0.6532	0.0768	0.0030 ^{***}
0	0.3317	0.1877	0.0042 ^{***}
100	0.3671	0.4872	0.0469 [*]
Action-linked condition			
0	0.0041 ^{***}	0.1270	0.2973
100	0.0400 [*]	0.4603	0.2108
200	< 0.001 ^{***}	0.0051 ^{***}	0.9542
300	< 0.001 ^{***}	< 0.001 ^{***}	0.4036
400	0.0092 ^{***}	< 0.001 ^{***}	0.0117 ^{**}
500	0.0056 ^{***}	< 0.001 ^{***}	0.0031 ^{***}
600	0.0417 ^{**}	< 0.001 ^{***}	< 0.001 ^{***}
700	0.0465 ^{**}	< 0.001 ^{***}	< 0.001 ^{***}
800	0.3391	< 0.001 ^{***}	< 0.001 ^{***}
900	0.9985	< 0.001 ^{***}	< 0.001 ^{***}
1000	0.9551	< 0.001 ^{***}	< 0.001 ^{***}

* *P* < 0.05.
** *P* < 0.01.

Multiple comparisons in this study, as well as our previous study (Maeda et al., 2012), demonstrated that excessive SoA in paranoid-type schizophrenia was significant for temporal biases from 400 to 1000 ms compared to normal controls (*P* < 0.05).

There was no significant correlation between the total number of “yes” responses and the age, gender, education, duration of illness, or GAF score of the patients with NS-predominant schizophrenia. Similarly, we observed no correlation between the neuroleptic dosage and the total number of “yes” responses (*r* = 0.368, *P* = 0.111). Moreover, there was no significant correlations between the total numbers of “yes” responses and the PANSS total scores (*r* = 0.404, *P* = 0.077). However, we found a significant inverse correlation between the total number of “yes” responses and NS (*r* = -0.515, *P* = 0.020). There was significant correlation between the total number of “yes” responses and positive symptoms (*r* = 0.542, *P* = 0.014) or general psychopathology subscales (*r* = 0.509, *P* = 0.022). In order to figure out these associations, we showed the scatter plots on negative and positive symptoms (Fig. 3). There was also no significant correlation between the total number of “yes” responses and age, gender or education in the normal control group.

The reaction times (RT) to beep sounds was 277 ± 54 ms for NS-predominant schizophrenia, 304 ± 67 ms for paranoid-type schizophrenia and 273 ± 64 ms for normal controls. The one way

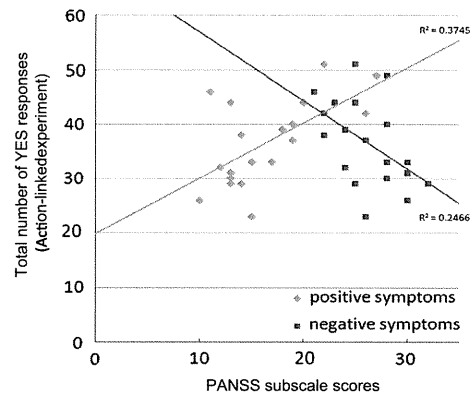


Fig. 3. Correlation between the total number of “yes” responses and PANSS subscale scores on NS and positive symptoms in NS predominant schizophrenia in the Action-linked experiment.

ANOVA showed no significant difference with respect to the mean (± S.D.) RT among groups [*F* (2, 35) = 0.885, *P* = 0.422].

3.2. EPA experiment (Fig. 2 left)

Normal controls gave very few “yes” responses under the EPA condition, and so did the patients with NS-predominant schizophrenia. The Steel–Dwass test showed that there was no significant difference of “yes” responses between NS predominant schizophrenia and controls under all EPA conditions. And, there was no difference between NS-predominant schizophrenia and paranoid-type schizophrenia.

Patients with paranoid-type schizophrenia, as well as our previous study (Maeda et al., 2012), had a significantly greater tendency to feel a SoA even in EPA conditions, indicating that these patients felt a sense of causal effect even if external events preceded their intentional actions. The Steel–Dwass test demonstrated that paranoid-type patients gave more yes responses in conditions with -100-ms biases (*P* = 0.003), no biases (*P* = 0.004), and 100-ms biases (*P* = 0.047) compared with controls.

There was no significant correlations between the total number of “yes” responses and the PANSS total scores (*r* = 0.197, *P* = 0.432), NS (*r* = -0.107, *P* = 0.674), positive symptoms (*r* = 0.331, *P* = 0.180) or general psychopathology subscales (*r* = 0.254, *P* = 0.310).

4. Discussion

In this study, SoA was examined in schizophrenia patients with predominant NS. We demonstrated that patients with NS had diminished SoA compared with healthy control subjects,

indicating that these patients under-associated causal effects of their intentional actions on subsequent events. It is intriguing that patients with NS-predominant schizophrenia demonstrated a completely opposite direction in agency judgment compared with the excessive SoA demonstrated by patients with paranoid-type schizophrenia. In addition, the phenomenon of “backward causation” was not demonstrated under EPA conditions, in contrast with paranoid-type schizophrenia. Only excessive SoA has been detected in previous studies of schizophrenia irrespective of whether agency tasks were explicit or implicit, so this is the first study in which reduced SoA was detected in patients with schizophrenia in experimental settings. According to the Forward model, the reduced SoA implies the presence of the inadequate predictions. That is, the aberrant prediction could cause the mismatch between the sensory feedback of a movement and the actual sensory feedback, and then, events are recognized as externally raised, i.e., SoA is weakened. Although it might be highly speculative, we assumed that reduced SoA compared to normal controls in each condition could represent the presence of inadequate and aberrant predictive signals in NS-predominant schizophrenia, based on the Forward model.

Furthermore, significant inverse correlation between the total number of “yes” responses and NS imply that severity of NS is related to tendency toward the reduced SoA. Moreover, positive symptoms are associated with excessive SoA in NS-predominant schizophrenia. This is consistent with previous SoA studies in paranoid-type schizophrenia which is characterized with positive symptoms. It seems very important that positive symptoms are related to tendency toward the hyper-agency even in patients with predominant-NS.

The optimal cue integration theory for SoA proposes that the emergence of SoA depends on both internal and external cues (Synofzik et al., 2008, 2009, 2010; Synofzik and Voss, 2010; Voss et al., 2010), and emphasizes the dual contribution of the predictive and retrospective components of SoA (Moore and Haggard, 2008; Moore et al., 2009; Moore and Fletcher, 2012). According to this theory, patients with schizophrenia have a problem generating adequate internal predictions, and their inadequate predictions lead to an uncertainty about SoA, resulting in an increased contribution of postdictive components based on external cues to recover agency experience (Synofzik et al., 2010; Voss et al., 2010; Maeda et al., 2012). According to this account, our surprising finding of reduced SoA in NS-predominant schizophrenia patients in the present study suggests that there is no increase in the contribution of the postdictive process by external cues in these patients despite their inadequate predictions, opposite to the exaggerated postdictive component in paranoid-type schizophrenia. In other words, the inadequate prediction is directly revealed in NS-predominant patients without appropriate compensatory postdictive contribution. This explanation is supported by the fact that we do not demonstrate the distinct manifestation of “backward causation” under EPA conditions, which is an indicator of the postdictive mechanism of SoA. Fletcher and Frith (2009) suggested that it is possible to understand self-disturbances in schizophrenia in terms of a disturbed hierarchical Bayesian framework, and speculated that the same fundamental deficit could account for both positive and NS. They suggested that the fundamental deficit, i.e., inadequate predictions, would be more profound in patients with negative features such as avolition and loss of social communications. In this state, patients might not intend to perform actions under severely inadequate predictions, and lack of a compensatory postdictive process could lead to a state where they never feel causal efficacy to their own body and external world. In other words, these patients might have lapsed into a state where decisions are difficult to make and intentional actions seem fruitless (Fletcher and Frith, 2009). Thus, the patients with

NS are detached and alienated from both the vital real environment and other people, corresponding to the symptom of “*Entfremdung*”.

Various studies have shown that positive symptoms of schizophrenia, including hallucinations and delusions, are caused by overactivity of the dopamine system (Carlsson, 1988; Davis et al., 1991; Kapur, 2003). Direct evidence of dopamine-driven enhancement of SoA was obtained in a study of the influence of a dopaminergic agent on intentional binding in patients with Parkinson's disease, which demonstrated that dopaminergic medication caused more strengthening of intentional binding during the “on” period than the “off” period (Moore et al., 2010). This indicates that the causal association between an action and its consequences was boosted by dopamine. Because previous studies have demonstrated stronger intentional binding effect in patients with paranoid-type schizophrenia (Haggard et al., 2003; Voss et al., 2010), and our earlier study showed excessive SoA in schizophrenia patients who predominantly had positive symptoms (Maeda et al., 2012), it is supposed that a hyper-dopaminergic state in schizophrenia boosts agency experiences and develop excessive SoA. In marked contrast with the positive symptoms of schizophrenia, NS are regarded as being caused by deficiency of dopaminergic function (Crow, 1980). If excessive SoA is associated with an overactive dopaminergic system, it is possible that NS-predominant patients are in a hypo-dopaminergic state and show diminished SoA in contrast to patients with paranoid-type schizophrenia.

It has also been suggested that the glutamatergic system is related to prediction error signaling in the Bayesian framework (Corlett et al., 2007, 2009, 2010, 2011). According to this hypothesis, the impact or magnitude of a prediction error is encoded by various slower modulatory neurotransmitters including dopamine. Inadequate predictions in patients with schizophrenia could lead to an excessive contribution of postdictive processes as a modulatory mechanism compensating for the fundamental prediction deficit (Synofzik and Voss, 2010; Moore and Fletcher, 2012). Thus, it is possible that fundamental prediction deficits caused by dysfunction of the glutamatergic system are modulated by excessive postdictive processes based on a hyper-dopaminergic state in schizophrenia patients with positive symptoms, which leads to excessive SoA. On the other hand, the same prediction deficits are not accompanied by dopaminergic modulation in patients with NS because of their hypo-dopaminergic state, resulting in reduced SoA. The hypothesis that dysfunction of the glutamatergic system plays an essential role in aberrant SoA in patients with schizophrenia is supported by the report that ketamine, a non-competitive glutamate receptor antagonist, induces abnormalities of SoA or the sense of body ownership (Moore et al., 2011; Morgan et al., 2011). Our findings about SoA could support the glutamatergic dysfunction theory in relation to schizophrenia (Carlsson et al., 1999; Goff and Coyle, 2001), thus shedding new light on the critical role of glutamate and dopamine in psychopharmacological models of schizophrenia.

This study had several limitations. First, it is possible that our results in NS-predominant patients might be related to nonspecific factors, including motivation and cooperation. However, the reaction time to beep sounds showed no difference among groups, indicating a minimal influence of differences in motivation and cooperation to the experiment even in the NS-predominant group. Second, our experimental protocol employed delay of stimulus to study SoA, so it is possible that aberrant SoA may have been partly due to impaired processing of temporal information. Regrettably, in this study, we did not prepare an experiment to evaluate time processing as a control task. Schizophrenia may be associated with a fundamental disturbance in the time processing, leading to dysfunction of perceptual, cognitive, and motor processes, as well

as self-consciousness. Moreover, various schizophrenic symptoms may be manifestations of those dysfunctions. Underlying impaired temporal processing which influence the abnormal SoA in schizophrenia must be fully analyzed in the future study, especially on temporal order judgment. However, SoA would differ from simple time processing, and it is important in the SoA paradigm that subjects' "intentions" could affect time perception. Therefore, it is assumed that SoA would not directly reflect simple processing of temporal information. This limitation has also been discussed in relation to the neuroanatomical basis of temporal processing (Ortuño et al., 2011; Maeda et al., 2012). Third, three patterns of temporal biases in the EPA experiment, resulting in only 30 trials, might be insufficient to detect an effect for that condition. However, in fact, the phenomenon of "backward causation" could be evoked only within limited window of temporal biases. We would like to consider whether trials in each EPA condition should be increased in the future studies. Finally, this was only a cross-sectional study, and longitudinal studies are needed from the prodromal stage of schizophrenia to the chronic stage. There have been some attempts to detect and evaluate SoA in the prodromal phase (Hauser et al., 2011a, 2011b). Our study might contribute to the development of new strategies for early diagnosis of this disorder.

In summary, we demonstrated that self-disturbances as diminished SoA exist in patients with NS-predominant schizophrenia. This is the first study to detect reduced SoA experimentally in schizophrenia patients. Taken together with data for paranoid-type schizophrenia, this finding supports the possibility that aberrant SoA representing self-disturbance could be a promising vulnerability marker for schizophrenia. Application of the cue integration framework to schizophrenia may shed light on the relation between subjective experiences that are specific symptoms of the disease and its underlying neurobiological basis.

Acknowledgments

This study was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Emergence of Adaptive Motor Function Through Interaction Between Body, Brain and Environment (Area #454)" and Grant-in-Aid for Scientific Research on Innovative Areas: Prediction and Decision Making (23120009) from the Japanese Ministry of Education, Culture, Sports, Science and Technology to MK.

All authors report no conflicts of interest in completing this study.

The authors thank Tadahiko Satoh M.D., Miwako Kashiwakura M.D., Hanako Kato M.D., and Yosuke Taniguchi M.D. of Sakuragaoka Memorial Hospital for their assistance.

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Reverse Fox Test for Detecting Visuospatial Dysfunction Corresponding to Parietal Hypoperfusion in Mild Alzheimer's Disease

American Journal of Alzheimer's Disease & Other Dementias®
201X, XX(X) 1-6
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DOI: 10.1177/1533317513511291
aja.sagepub.com



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Abstract

Background/Aim: We developed a novel visuospatial clinical task to detect parietal dysfunction in mild Alzheimer's disease (AD). **Methods:** A total of 65 outpatients, including 47 with mild AD and 18 cognitively and neuroradiologically normal individuals with subjective memory impairment (NL), performed the "Reverse Fox" test and underwent brain single photon emission tomography. Patients with AD were divided into subgroups according to the results of the Reverse Fox test (successful vs unsuccessful). **Results:** Success in the Reverse Fox test was achieved by 31.9% of patients with AD and 94.4% of NL. The unsuccessful AD subgroup had reduced perfusion of the medial parietal and bilateral temporoparietal regions compared with the successful AD subgroup. **Conclusions:** Failure in the Reverse Fox test was related to parietal hypoperfusion in patients with mild AD. Our findings suggest that the Reverse Fox test may be one of the useful supporting tools for detecting mild AD at outpatient clinic.

Keywords

Alzheimer's disease, single photon emission computed tomography, gesture imitation, screening test, visuospatial abilities

Introduction

Although memory impairment is known to be the most prominent feature of Alzheimer's disease (AD), visuospatial deficits have also been well documented in the literature on AD and could be one of the key symptoms of mild AD.¹⁻³ Patients with AD often get lost, have difficulty in understanding where they are, and have difficulty in finding objects for which they are searching.

Among various neuropsychological tests for the assessment of visuospatial function, visuoperceptual tasks based on finger (hand) positions have been employed clinically to detect cognitive decline in patients with AD. Because of visuospatial and visuomotor dysfunction, individuals with AD have difficulty in correctly positioning their hands to perform such tasks. The method of imitating the examiner's hand positions may provide a simple and effective tool for detecting AD and has already been adopted as an easy screening test for visuospatial dysfunction.⁴ Some authors have suggested that the ability to imitate hand positions is related to the severity of AD.^{5,6}

The parietal lobe is thought to play a crucial role in visuospatial function, including the assessment of hand positions. Since bilateral parietal hypoperfusion on single photon emission computed tomography (SPECT) is a characteristic feature in patients with AD,⁷⁻⁹ we hypothesized that impaired imitation of hand positions would be associated with parietal hypoperfusion in early stage AD.

In the present study, we devised the new method of hand imitation test and validated the clinical usefulness of the new

method, which is called the "Reverse Fox test," as a simple tool for detecting parietal hypoperfusion in patients with mild AD. The objectives of this study were to obtain data on the performance of patients with AD in the Reverse Fox test and to investigate the relationship between performance in this test and other neuropsychological tests as well as with regional cerebral blood flow (rCBF) measured by SPECT.

Methods

Patients

We examined 225 consecutive outpatients aged 65 to 89 years who visited the memory clinic of Keio University Hospital, between June 2009 and March 2012. Persons with mild AD and cognitively and neuroradiologically normal individuals with subjective memory impairment (NL) were included, while those with moderate or severe AD, those with other types of dementia (e.g., vascular dementia, dementia with Lewy bodies,

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or frontotemporal lobar degeneration), those with mild cognitive impairment, those with other types of brain damage, and those with psychiatric disorders (including delusional disorder, mood disorder, convulsive disorder, and substance abuse) were excluded from the study. As a result, 47 patients with mild AD (30 women) and 18 NL (14 women) were enrolled in the study (total N = 65). The mean age (\pm standard deviation) was 77.9 ± 5.2 and 75.1 ± 5.2 years in the AD and NL groups, respectively.

Patients were diagnosed as having probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.¹⁰ The severity of dementia was classified according to the Clinical Dementia Rating (CDR) scale,¹¹ and only patients with AD with a score of 0.5 or 1 were included. The NL patients presented to our memory clinic with the complaint of memory impairment, but they all maintained their activities of daily living (ADLs) and had well-preserved cognitive function based on the results of detailed neuropsychological testing. Their CDR score was 0. Although the NL group had no significant magnetic resonance image (MRI) or SPECT findings, we cannot state that they are "normal" in the strict sense because they complained of subjective cognitive impairment.¹² Thus, the individuals in this group could have had preclinical AD.¹³ However, we regard them as normal for the purpose of the present study based on the preservation of ADL and cognitive function. In the AD group, 10 (23%) of 47 patients were taking donepezil and 2 patients (4%) were taking memantine. This study was approved by the ethics committee of Keio University School of Medicine.

Reverse Fox Test

All participants were asked to imitate the shape called a Reverse Fox by using both hands. The test was done as follows.

First, the examiner instructed a participant to carefully watch the examiner's hands and then make the same shape. Subsequently, the examiner placed both hands as shown in Figure 1A. Instructions were given in a nonverbal manner without referring to a "fox." If a participant failed to copy the hand positions at this step, the test was stopped.

Next, the examiner twisted 1 hand so that the right index finger was touching the left little finger and the right little finger was touching the left index finger (Figure 1B). The examiner was careful not to give verbal instructions (such as "please make a reversed fox") that could assist the participant to compensate for visuospatial deficits.

The AD group was divided into subgroups based on their performance in the Reverse Fox test ("successful" subgroup who completed imitating the Reverse Fox hands gesture vs "unsuccessful" subgroup who failed). Then analyses were conducted using demographic data, neuropsychological test performance, and neuroimaging data comparing the successful with the unsuccessful subgroup.

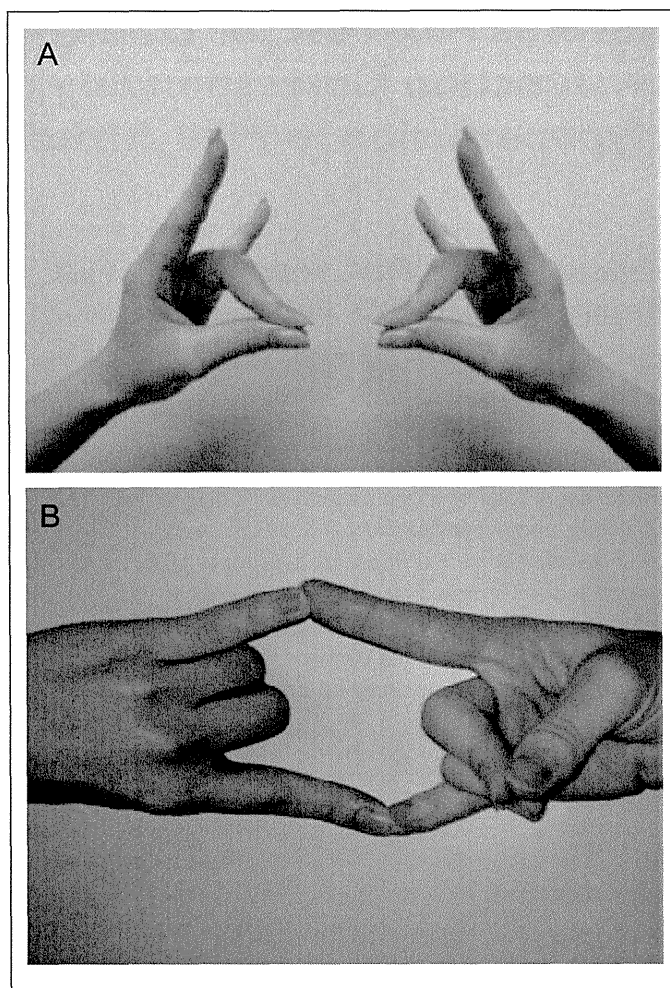


Figure 1. Demonstration of the hand positions. The examiner demonstrates (A) 2 foxes position and (B) the "Reverse Fox" position.

Clinical Evaluation

To evaluate cognitive function, detailed neuropsychological testing was performed in all patients by experienced clinical neuropsychologists [M.K. (Mika Konishi) and N.S. (Nao Sait)]. Global cognitive function was measured with the Mini-Mental State Examination and Raven's colored progressive matrices. The Rey auditory verbal learning test and the logical memory subtest of the Wechsler memory scale-revised were used to assess verbal memory, while the Rey-Osterrieth complex figure test (ROCF) was used for assessment of visual memory.¹⁴ Executive function was evaluated by using the modified Stroop test, the trail-making test, and the verbal fluency test.¹⁴ A shorter version of the geriatric depression scale was used to evaluate the subjective mood of each participant.¹⁵

Statistical analyses were performed using SPSS for Macintosh (version 18.0; SPSS Inc. Chicago, Illinois). Student *t* tests were used to compare demographic data and indices of neuropsychological performance between the AD and NL group and the successful and unsuccessful AD subgroup. All statistical tests were 2 tailed, and $P < .05$ was considered to indicate statistical significance.