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Creativity and positive symptoms in schizophrenia revisited: Structural connectivity analysis with diffusion tensor imaging

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A B S T R A C T

Both creativity and schizotypy are suggested to be manifestations of the hyperactivation of unusual or remote concepts/words. However, the results of studies on creativity in schizophrenia are diverse, possibly due to the multifaceted aspects of creativity and difficulties of differentiating adaptive creativity from pathological schizotypy_positive symptoms. To date, there have been no detailed studies comprehensively investigating creativity, positive symptoms including delusions, and their neural bases in schizophrenia. In this study, we investigated 43 schizophrenia and 36 healthy participants using diffusion tensor imaging. We used idea, design, and verbal (semantic and phonological) fluency tests as creativity scores and Peters Delusions Inventory as delusion scores. Subsequently, we investigated group differences in every psychological score, correlations between fluency and delusions, and relationships between these scores and white matter integrity using tract-based spatial statistics (TBSS). In schizophrenia, idea and verbal fluency were significantly lower in general, and delusion score was higher than in healthy controls, whereas there were no group differences in design fluency. We also found positive correlation between phonological fluency and delusions in schizophrenia. By correlation analyses using TBSS, we found that the anterior part of corpus callosum was the substantially overlapped area, negatively correlated with both phonological fluency and delusion severity. Our results suggest that the anterior interhemispheric dysconnectivity might be associated with executive dysfunction, and disinhibited automatic spreading activation in the semantic network was manifested as uncontrollable phonological fluency or delusions. This dysconnectivity could be one possible neural basis that differentiates pathological positive symptoms from adaptive creativity.

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1. Introduction

Creativity has long been thought as the ability to produce original, novel, flexible, and useful ideas that are free from established mental habit. One of the most commonly used definitions is “the production of effective novelty” (Mumford, 2003). A number of factors are thought to be related to creativity, such as divergent thinking (Guilford, 1959), openness (Dollinger et al., 2004), handedness (Shobe et al., 2009), language (Leonhard and Brugger, 1998), problem solving, adaptability, self-expression, quality of life (Runco, 2004), artistry (Bhattacharya and Petsche, 2002, 2005), magical ideation (Badzakova-Trajkov et al., 2011), and schizotypy (Fisher et al., 2004).

Both creativity and schizotypy are suggested to be manifestations of the hyperactivation of unusual or remote concepts/words (Mohr et al., 2001). Therefore, relationships between creativity and schizophrenia-spectrum disorder have been widely investigated (Sass, 2000; Nelson and Rawlings, 2010). Indeed, a study reported that schizophrenia patients tended to engage in artistic occupation (Kyaga et al., 2011). However the results of studies on creativity in schizophrenia are varied. Some studies reported enhanced mental imagery manipulation in schizophrenia using jigsaw puzzle task (Benson and Park, 2013), whereas other studies reported lower figural creativity using the Berlin Intelligence Structure Test (Jaracz et al., 2012) or lower creativity in general using design, idea, and word fluency tests (Nemoto et al., 2007) in schizophrenia. One possible reason for these inconsistencies may be found in the differences in definition and measurement methods of creativity. Furthermore, Tsakanikos et al. reported that...
increased positive schizotypy or positive symptoms had relationships with increased creativity, whereas negative schizotypy or negative symptoms could be related to reduced creativity (Tsakanikos and Claridge, 2005). Thus, the clinical background of patients should also be taken into account in respect to such inconsistencies.

In previous literature investigating the semantic priming effect, it has been suggested that enhanced automatic spreading activation in semantic networks is associated with creativity (Tsakanikos and Claridge, 2005), and might underlie some of the positive symptoms (Spitzen, 1997) such as thought disorder (Kreher et al., 2008), hallucination (Lindamer and Whitman, 1997; Korns et al., 1999), or delusion (Debrulle et al., 2007) in schizophrenia. Thus, it is reasonable to ask the following questions: what is the difference between creativity and positive symptoms, or why could hyperactivation result in innovative output in one case, but in psychotic symptoms in another? Fisher et al., in dealing with these questions, suggested that frontal lobe functions, i.e., executive functions such as monitoring, controlling, or inhibiting ability, play pivotal roles in the use of semantic information and differentiate creativity from psychopathology (Fisher et al., 2013).

Therefore, in this study, we aimed to examine creativity in schizophrenia patients with multiple creativity measures with and without semantic contents, and to investigate its impact on psychopathology, especially on positive symptoms. We predicted that overall creativity performance in schizophrenia might increase or decrease depending on the proportion of positive and negative symptoms, and that some creativity measures would positively correlate with positive symptoms. Furthermore, we hypothesized that this correlation between creativity and pathological, positive symptoms would be underpinned by the pathology of the frontal lobe structure. One of the influential hypotheses of schizophrenia, “the disconnection hypothesis” (Friston, 1998), assumes that dysconnectivity among multiple neural systems might underlie some symptoms of schizophrenia, mainly positive symptoms. We therefore utilized diffusion tensor imaging (DTI) to investigate the structural connectivity, and examined its relation with creativity and psychopathology.

2. Methods

2.1. Participants

Forty-three patients with schizophrenia (22 men and 21 women, age = 37.37 ± 8.66) were recruited. Each patient fulfilled the criteria for schizophrenia based on the Structural Clinical Interview for DSM-IV Axis I Disorders (SCID) Patients Edition, Version 2.0. None of the patients were comorbid with other mental disorders. Predicted IQ was measured using the Japanese Version of the National Adult Reading Test (JART) short form (Matsuoka et al., 2006; Matsuoka and Kim, 2007), which is thought to reflect the premorbid IQ of schizophrenia patients. Psychopathology was assessed using Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). All patients were receiving antipsychotic medication (typical [n = 3], atypical [n = 31], typical and atypical [n = 9]). Haloperidol equivalents were calculated according to the practice guideline for the treatment of schizophrenia patients (Lehman et al., 2004; Inagaki and Inada, 2008).

Thirty-six age-, gender-, handedness-, and predicted IQ-matched healthy individuals (24 men and 12 women, age = 33.86 ± 8.69) were recruited for this study as the control group. They were also evaluated using SCID Non-patient Edition, Version 2.0. They had no history of psychiatric disorders, and no first-degree relatives with psychotic episodes. Exclusion criteria for both groups were: a history of head trauma, neurological disease, severe mental disease, or substance abuse that could affect brain function. Handedness was assessed with the Edinburgh Handedness Inventory (Oldfield, 1971).

After receiving a complete description of the study, written informed consent was obtained from each participant. This study was approved by the Committee on Medical Ethics of Kyoto University, and was conducted in accordance with the Code of Ethics of the World Medical Association.

2.2. Psychological tests

We used three different fluency tests: the design fluency test and the idea fluency test from Test for Creative Thinking (TCT) Japanese version (Waseda Creativity Society, 1984; Nemoto et al., 2005), and the verbal fluency test from Brief Assessment of Cognition in Schizophrenia Japanese-language Version 3.0 (BACS-J) (Keefe et al., 2004; Kaneda et al., 2007). Two different examiners, “SS” and “MK”, kept the scores of the design and idea fluency tests of each participant and blindly chose the scores of ten participants to confirm the inter-rater reliability as performed in a previous study (Nemoto et al., 2005). We used Peters Delusions Inventory (PDI) 21-item version (Peters et al., 2004) to evaluate the participants’ delusions.

2.2.1. Design fluency test

In the design fluency test, the examiner asked the participants to produce as many different drawings for one set of four dots as possible within 3 min. After completing the task, the examiner classified the drawings into three categories: task-dependent (Design Td), the drawings based on a geometrical pattern; task-modified (Design Tm), the drawings based on the shape of a square; and task-independent (Design Ti), the rest of the drawings except for task-dependent and task-modified (Fig. 1) (Nemoto et al., 2005).

2.2.2. Idea fluency test

In the idea fluency test, the examiner asked the participants to think of as many uses for an empty tin can as possible within 2 min. In this test, we also classified the responses into three categories: task-dependent (Idea Td), ideas based on nature as a container, for example...
analyzed using SPSS 21.0.0.0 (SPSS Inc., Chicago, IL, USA). Statistical analyses were applied between differences in PDI.

2.4. Data analysis

All data were preprocessed using the program of FSL version 4.1.9 (http://www.fmrib.ox.ac.uk/fsl). Source data were corrected for eddy currents and head motion by registering all data to the first b = 0 image, with affine transformation. Fractional anisotropy (FA) maps were calculated using the DTIFIT program. For voxelwise statistical analysis, Tract-Based Spatial Statistics (TBSS) Version 1.2 was applied. Details are described in elsewhere (Fujino et al., 2014; Hirose et al., 2014).

2.4.2. Group comparisons of FA

Voxelwise permutation-based nonparametric inference (Genovese et al., 2002) was performed using the FSL Randomize version 2.5. First, we analyzed group comparisons employing the analysis of covariance design in the general linear model framework, with age and gender as nuisance covariates. Both controls-minus-patients and patients-minus-controls contrasts were performed with 10,000 permutations. The statistical threshold was set at P < .05, corrected for multiple comparisons by threshold-free cluster enhancement (TFCE) (Smith and Nichols, 2009).

2.4.3. Voxelwise correlation analyses

For significantly different psychological scales between the two groups in the above statistical tests, voxelwise multiple regression analyses were performed using TBSS to explore the white matter regions correlated with each fluency task or PDI in both groups. In these correlation analyses, the results of above-mentioned group comparisons of FA were used as masks in schizophrenia while whole brain area was included in healthy controls. We used age and gender as nuisance covariates in each model. The permutation-based nonparametric inference was performed with 10,000 permutations. The statistical threshold was set at P < .05, correcting for multiple comparisons by TFCE. The fiber tracts corresponding to clusters in the results were identified by referring to the Johns Hopkins University DTI-based White Matter Atlas (http://cmrm.med.jhmi.edu).

2.4.4. Effect of predicted IQ

To examine the possible effect of predicted IQ on psychological measures and white matter integrity, we performed correlation analyses on fluency scores and partial correlation analyses between fluency scores and PDI using predicted IQ as a control variable. We also performed the above-mentioned voxelwise correlation analyses using TBSS, adding predicted IQ as a nuisance covariate. Statistical significances were the same as mentioned above.

2.4.5. Effect of medication

To examine the possible confounding effect of medication on fluency tasks and white matter integrity, we performed correlation analyses between medication and each fluency task using SPSS, and we also performed voxelwise correlation analyses between medication and FA values using TBSS. Statistical significances were also the same as the above.

3. Results

3.1. Group comparisons and correlation analyses of fluency scores with PDI

3.1.1. Scores of fluency tasks and PDI

Demographic and clinical data are shown in Table 1a. Many patients had mild symptom severity. The scores of fluency tasks and PDI are shown in Table 1b. Inter-rater reliabilities of scoring fluency tasks between two examiners, “SS” and “MK”, were P = .98 in Idea Td, .96 in Idea Tm, .95 in Idea Ti, 1.00 in Design Td, 1.00 in Design Tm, and 1.00 in Design Ti. An independent sample t-test revealed that Idea Td, Idea Ti, Verbal C, and Verbal L were significantly lower and PDI was higher in schizophrenia than in the healthy group. There were also no significant group differences in Design Td, Design Ti, Design C, and Idea Td.

3.1.2. Correlation analyses between fluency tasks and PDI

Correlation analyses revealed that the PDI score was correlated only with Verbal L in the schizophrenia group (Table 2; Pearson’s r = 0.386, P = .011). There were no other significant correlations between fluency Table 1a

<table>
<thead>
<tr>
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<th>Hc (n = 36)</th>
<th>Sc (n = 43)</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>33.86 ± 8.66</td>
<td>37.37 ± 8.66</td>
<td>.077a</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>24/12</td>
<td>22/21</td>
<td>.164b</td>
</tr>
<tr>
<td>Handedness</td>
<td>81.94 ± 35.52</td>
<td>73.49 ± 46.70</td>
<td>.375c</td>
</tr>
<tr>
<td>Premorbid IQ</td>
<td>106.47 ± 7.62</td>
<td>102.88 ± 9.80</td>
<td>.077d</td>
</tr>
<tr>
<td>Age at onset</td>
<td>24.35 ± 8.04</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Duration of illness</td>
<td>–</td>
<td>13.01 ± 8.30</td>
<td>–</td>
</tr>
<tr>
<td>HP equivalent</td>
<td>–</td>
<td>12.10 ± 9.54</td>
<td>–</td>
</tr>
<tr>
<td>PANS positive</td>
<td>–</td>
<td>14.53 ± 5.53</td>
<td>–</td>
</tr>
<tr>
<td>PANS negative</td>
<td>–</td>
<td>16.02 ± 5.94</td>
<td>–</td>
</tr>
<tr>
<td>PANS general</td>
<td>–</td>
<td>30.88 ± 10.60</td>
<td>–</td>
</tr>
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Note: Hc: healthy control group, Sc: schizophrenia group.  

a Two-tailed t-test.  

b Gender (m/f) = 24/12.  

c Premorbid IQ was measured using Japanese adult reading test.  

d Haloperidol (HP) equivalent was calculated according to the practice guidelines for the treatment of schizophrenia patients.
3.2. Group comparisons of FA value

The patients with schizophrenia exhibited widespread FA reduction compared with healthy controls. The areas extended into bilateral deep white matter areas in the frontal, temporal, parietal, and occipital lobes, a large part of the corpus callosum (CC), and the corona radiata (Fig. 2). There were no areas with increased FA in the schizophrenia group.

3.3. Voxelwise correlation analyses

In the healthy group, there were no significant areas of correlation with Idea Tm, Idea Ti, Verbal C, Verbal L, and PDI. In the schizophrenia group, negative correlations with Verbal L were found in left frontal white matter such as forceps minor, anterior thalamic radiation (ATR), corticospinal tract, superior and anterior corona radiata, and genu and body of CC (Fig. 3a). We also found negative correlations with PDI in a widespread white matter area such as the genu, body, and splenium of CC, right superior to left forceps minor, ATR, left forceps major, posterior thalamic radiation, and anterior, superior, and posterior corona radiata (Fig. 3b). The results of these two correlation analyses showed a wide range of overlap in frontal areas, including the forceps minor, genu and body of CC, and left anterior and superior corona radiata (Fig. 4). In the additional partial correlation analysis, we found that only posterior part of CC (body and splenium) was negatively correlated with PDI using Verbal L as a control variable.

### Table 2

<table>
<thead>
<tr>
<th>PDI (Hc) Pearson's correlation coefficient</th>
<th>P-value</th>
<th>PDI (Sc) Pearson's correlation coefficient</th>
<th>P-value</th>
</tr>
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<tr>
<td>Design Td</td>
<td>0.034</td>
<td>.843</td>
<td>0.134</td>
</tr>
<tr>
<td>Design Tm</td>
<td>-0.044</td>
<td>.797</td>
<td>0.001</td>
</tr>
<tr>
<td>Design Ti</td>
<td>-0.081</td>
<td>.64</td>
<td>0.1</td>
</tr>
<tr>
<td>Idea Td</td>
<td>-0.098</td>
<td>.571</td>
<td>0.121</td>
</tr>
<tr>
<td>Idea Tm</td>
<td>-0.001</td>
<td>.995</td>
<td>0.017</td>
</tr>
<tr>
<td>Idea Ti</td>
<td>-0.177</td>
<td>.302</td>
<td>-0.048</td>
</tr>
<tr>
<td>Verbal C</td>
<td>0.052</td>
<td>.762</td>
<td>0.026</td>
</tr>
<tr>
<td>Verbal L</td>
<td>-0.155</td>
<td>.368</td>
<td>0.386</td>
</tr>
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3.4. Effect of predicted IQ

We found no significant correlations between predicted IQ and fluency scores. There was a significant partial correlation between Verbal L and PDI using predicted IQ as a control variable (P = .012). In TBSS using predicted IQ added as a nuisance covariate, we had almost the same results as we found above.

3.5. Effect of medication

We found no significant effect of medication on either fluency scores or FA values.

4. Discussion

Using comprehensive creativity scales and structural connectivity with DTI, we found decreased idea and verbal fluency in general, but retained design fluency in schizophrenia. In the schizophrenia group, phonological fluency was positively correlated with delusion severity. DTI analyses revealed correlation between frontal white matter integrity and phonological fluency, and between widespread white matter region and delusion severity in schizophrenia. These results showed substantial overlap in anterior interhemispheric connection, suggesting common neural substrates for both creativity and psychotic symptoms.

Overall decreases in idea and verbal fluency might be associated with negative symptoms such as poverty of speech, as were indicated in previous studies (Allen et al., 1993; O’Leary et al., 2000; Sumiyoshi et al., 2005). The fact that the majority of our schizophrenia subjects were chronic schizophrenia with residual negative symptoms and minimum positive symptoms might have contributed to these results.

Although verbal fluency was decreased in schizophrenia, positive correlation between phonological verbal fluency and delusions was revealed. As for the relationships between phonological fluency and schizotypy, a previous study suggested increased phonological fluency was associated with positive schizotypy (Tsakanikos and Claridge, 2005). It is suggested that increased phonological verbal fluency is associated with increased positive schizotypy or positive psychotic symptoms as a result of the automatic spreading activation between stored lexical items (Tsakanikos and Claridge, 2005). Some studies reported that the prefrontal cortex had an important role in controlling the automatic spreading activation such that the left dorsolateral prefrontal cortex was required for appropriate intrinsic word generation (Frith et al., 1991), and the left inferior prefrontal cortex inhibited the automatic spreading activation for appropriate semantic priming (Cardillo et al., 2004). Thus, the abnormal frontal white matter integrity revealed in our study may lead to disinhibited automatic spreading activation, resulting in the positive correlation between verbal fluency and delusion.

Additionally, Fisher et al. suggested that an executive function played a role in monitoring remote information resulting in innovative achievement and, as this function decreased, communication difficulties between remote concepts arose (Fisher et al., 2013), which in turn could then result in positive symptoms.

Thus, taking into consideration the above, the pathology in the frontal lobe can be linked to disinhibited verbal fluency and delusion scores in schizophrenia.

We found that FA in anterior interhemispheric connections, such as the anterior part of CC or ATR, was negatively correlated with both Verbal L and PDI. The anterior part of CC projects to frontal lobes (Berlucchi, 2012), and disruptions of this region were suggested to be involved in impairments of frontal lobe functions in neurological and psychiatric disorders (Paul et al., 2007; Berlucchi, 2012; Edwards et al., 2014). Furthermore, ATR is a pathway connecting thalamus with the prefrontal cortex. A DTI study has shown that disrupted ATR integrity was associated with enhanced creativity (Jung et al., 2010) or executive function impairments in schizophrenia (Mamah et al., 2010). Taken together,
reduced FA in the anterior part of CC and ATR indicates disrupted inter- and intrahemispheric connections projecting to frontal areas, respectively. These dysconnections might lead to impairments in executive function, resulting in positive symptoms or uncontrolled word fluency.

Design fluency was retained in schizophrenia, in contrast to one previous study indicating generally decreased fluency in schizophrenia including design fluency (Nemoto et al., 2007). Design fluency reflects a non-verbal ability and is less semantic than the others. Moreover, we used only fluency, a quantitative index, and there are other possibilities for assessing with a qualitative index, such as originality or elaboration. Consequently, design fluency might not be related to positive or negative symptoms, and be retained in our study.

This study has some limitations. First, we recruited schizophrenia patients with relatively mild symptoms, and they might not represent the general population. Second, this study is a cross-sectional study, not longitudinal, and thus it is unclear how the above-mentioned relationships progressed during the illness course. Lastly, all the patients were medicated with antipsychotics, and we could not completely rule out the effects of medications on our findings.

In conclusion, we investigated the relationships between creativity and schizophrenia, and additionally, the neural underpinnings. Our findings suggested that disrupted inter- and intrahemispheric connections projecting to frontal areas might underlie positive symptoms or uncontrolled creativity in schizophrenia. We hope our findings will contribute to a better understanding of creativity in the context of the pathophysiology of schizophrenia, and adaptive creativity, that lead to innovative achievements.

Role of funding source

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Contributors

Shuraku Son designed the study and wrote the protocol, and also managed the literature searches and analyses and wrote the first draft of the manuscript. Shuraku Son, Manabu Kubota, and Jun Miyata undertook the analysis and interpretation of clinical and psychological data. Shuraku Son performed data processing and statistical analyses, under technical supervision by Manabu Kubota, Jun Miyata, Toshihiko Aso, Shin-ichi Urayama, Hidenao Fukuyama, Toshiya Murai, and Hidehiko Takahashi. All authors contributed to and have approved the final manuscript.
Fig. 4. Overlapped significant areas between phonological fluency and delusions (P < .05, corrected by threshold-free cluster enhancement) with negative correlation with fractional anisotropy (FA) in the schizophrenia group. To aid visualization, results are thickened with bss_fil script in FSL and colored in red-yellow. Correlated areas with delusions only are shown in light blue, and those with phonological fluency only are shown in green. Results are overlaid on mean FA maps. Overlapped areas extend to forceps minor, genu and body of the corpus callosum, and left anterior and superior corona radiata.

Conflict of interest
All authors declare that they have no conflicts of interest in this study.

Acknowledgment
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