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Creativity and Positive Symptoms in Schizophrenia Revisited:

Structural Connectivity Analysis with Diffusion Tensor Imaging

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Abbreviations: tract-based spatial statistics (TBSS), diffusion tensor imaging

(DTI), Structural Clinical Interview for DSM-IV Axis I Disorders (SCID),

Japanese Version of the National Adult Reading Test (JART), Positive and

Negative Symptom Scale (PANSS), Test for Creative Thinking (TCT), Brief

Assessment of Cognition in Schizophrenia Japanese-language version 3.0

(BACS-J), Peters delusions inventory (PDI), task-dependent (Design Td),

task-modified (Design Tm), task-independent (Design Ti), category fluency

test (Verbal C), letter fluency test (Verbal L), Fractional anisotropy (FA),

threshold-free cluster enhancement (TFCE), corpus callosum (CC), anterior

thalamic radiation (ATR), Haloperidol (HP), healthy control (Hc),

schizophrenia (Sc)

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 (Nelson and Rawlings, 2010; Sass, 2000). 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

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task (Benson and Park, 2013), whereas other studies reported lower figural creativity using 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 (Spitzer, 1997) such as thought disorder (Kreher et al., 2008), hallucination (Kerns et al., 1999; Lindamer and Whitman, 1997), or delusion (Debruille 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 (21 men and 22 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, 2007; Matsuoka et al., 2006), 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 (Inagaki, 2008; Lehman et al., 2004).

Thirty-six age-, gender-, handedness-, and predicted IQ-matched healthy individuals (12 men and 24 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 (Nemoto et al., 2005; Waseda Creativity Society, 1984), and the verbal fluency test from Brief Assessment of Cognition in Schizophrenia Japanese-language version 3.0 (BACS-J) (Kaneda et al., 2007; Keefe et al., 2004). 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 three minutes. 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 usages

for an empty tin can as possible within two minutes. In this test, we also classified the

responses into three categories: task-dependent (Idea Td), ideas based on nature as a

container, for example "a pen stand"; task-modified (Idea Tm), ideas free from nature as

a container but still keeping an original form, for example "kick-the-can"; and task-independent (Idea Ti), ideas except for task-dependent and task-modified, for example "accessories."

2.2.3. Verbal (Category and Letter) fluency test

In each verbal fluency test, the examiners asked the participants to produce as many words as possible within one minute. In the category fluency test (Verbal C), representing semantic fluency, participants were asked to produce names of animals, and in the letter fluency test (Verbal L), representing phonological fluency, they were asked to produce words with an initial letter using hiragana, the Japanese cursive letters "ka" and "ta". Therefore, in total they performed three tests, each for one minute.

In each of the above fluency tests, higher scores indicate higher fluency.

2.2.4. Peters Delusions Inventory (PDI) 21-item version

This self-report questionnaire consists of 21 items assessing distress, preoccupation, and conviction related to delusional ideation and can measure delusional ideation from normal to psychiatric populations (Peters et al., 2004).

2.3. MRI acquisition and preprocessing

Diffusion-weighted data were acquired using single-shot spin-echo echo-planar sequences on a 3-Tesla MRI unit (Trio; Siemens, Erlangen, Germany) with a 40-mT/m gradient and a receiver-only 8-channel phase-array head coil. Detailed parameters are described in elsewhere (Fujino et al., 2014; Hirose et al., 2014).

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. Data analysis

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

First, independent sample t-tests were applied to examine group differences in fluency and PDI scores. Second, Pearson's correlation analyses were applied between fluency

and PDI scores. Data were analyzed using SPSS 21.0.0.0 (SPSS Inc., Chicago, IL,

USA). Statistical level was defined as $P < .05$ (two-tailed) in all analyses.

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 Tm, 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 Tm, Design Ti, 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 tasks and positive and negative symptom scores in PANSS or PDI in the two groups.

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 only posterior part of CC (body and splenium) was negatively correlated with PDI using Verbal L as a control variable.

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 two 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 (Berlucchi, 2012; Edwards et al., 2014; Paul et al., 2007). Furthermore, ATR is a pathway connecting thalamus with 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.

References

Allen, H.A., Liddle, P.F., Frith, C.D., 1993. Negative features, retrieval processes and verbal fluency in schizophrenia. Br J Psychiatry 163(6), 769-775.

Badzakova-Trajkov, G., Haberling, I.S., Corballis, M.C., 2011. Magical ideation, creativity, handedness, and cerebral asymmetries: a combined behavioural and fMRI study. Neuropsychologia 49(10), 2896-2903.

Benson, T.L., Park, S., 2013. Exceptional visuospatial imagery in schizophrenia; implications for madness and creativity. Front Hum Neurosci 7.

Berlucchi, G., 2012. Frontal callosal disconnection syndromes. Cortex 48(1), 36-45.

Bhatt, R., Laws, K.R., McKenna, P.J., 2010. False memory in schizophrenia patients with and without delusions. Psychiatry Res 178(2), 260-265.

Bhattacharya, J., Petsche, H., 2002. Shadows of artistry: cortical synchrony during perception and imagery of visual art. Cognitive Brain Res 13(2), 179-186.

Bhattacharya, J., Petsche, H., 2005. Drawing on mind's canvas: Differences in cortical integration patterns between artists and non-artists. Hum Brain Mapp 26(1), 1-14.

Cardillo, E.R., Aydelott, J., Matthews, P.M., Devlin, J.T., 2004. Left inferior prefrontal cortex activity reflects inhibitory rather than facilitatory priming. J. Cogn. Neurosci. 16(9), 1552-1561.

Debruille, J.B., Kumar, N., Saheb, D., Chintoh, A., Gharghi, D., Lionnet, C., King, S., 2007. Delusions and processing of discrepant information: An event-related brain potential study. Schizophr Res 89(1-3), 261-277.

Deese, J., 1959. On the Prediction of Occurrence of Particular Verbal Intrusions in Immediate Recall. J Exp Psychol 58(1), 17-22.

Dollinger, S.J., Urban, K.K., James, T.A., 2004. Creativity and openness: Further validation of two creative product measures. Creativity Res. J. 16(1), 35-47.

Edwards, T.J., Sherr, E.H., Barkovich, A.J., Richards, L.J., 2014. Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. Brain 137, 1579-1613.

Fisher, J.E., Heller, W., Miller, G.A., 2013. Neuropsychological differentiation of adaptive creativity and schizotypal cognition. Pers Indiv Differ 54(1), 70-75.

Fisher, J.E., Mohanty, A., Herrington, J.D., Koven, N.S., Miller, G.A., Heller, W., 2004. Neuropsychological evidence for dimensional schizotypy: Implications for creativity and psychopathology. J Res Pers 38(1), 24-31.

Friston, K.J., 1998. The disconnection hypothesis. Schizophr Res 30(2), 115-125.

Frith, C.D., Friston, K.J., Liddle, P.F., Frackowiak, R.S.J., 1991. A Pet Study of Word Finding. Neuropsychologia 29(12), 1137-1148.

Fujino, J., Takahashi, H., Miyata, J., Sugihara, G., Kubota, M., Sasamoto, A., Fujiwara, H., Aso, T., Fukuyama, H., Murai, T., 2014. Impaired empathic abilities and reduced white matter integrity in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 48, 117-123.

Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. Neuroimage 15(4), 870-878.

Guilford, J.P., 1959. Personality. McGraw-Hill, New York, NY.

Hirose, K., Miyata, J., Sugihara, G., Kubota, M., Sasamoto, A., Aso, T., Fukuyama, H., Murai, T., Takahashi, H., 2014. Fiber tract associated with autistic traits in healthy adults. J Psychiatr Res.

Inagaki, A., Inada, T, 2008. Dose equivalence of psychotropic drugs. Jpn J Clin

Psychopharmacol 11, 887–890.

Jaracz, J., Patrzala, A., Rybakowski, J.K., 2012. Creative Thinking Deficits in Patients

With Schizophrenia Neurocognitive Correlates. J. Nerv. Ment. Dis. 200(7), 588-593.

Jung, R.E., Grazioplene, R., Caprihan, A., Chavez, R.S., Haier, R.J., 2010. White matter

integrity, creativity, and psychopathology: disentangling constructs with diffusion tensor

imaging. PLoS One 5(3), e9818.

Kaneda, Y., Sumiyoshi, T., Keefe, R., Ishimoto, Y., Numata, S., Ohmori, T., 2007. Brief

Assessment of Cognition in Schizophrenia: Validation of the Japanese version.

Psychiatry Clin Neurosci 61(6), 602-609.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The Positive and Negative Syndrome Scale

(Panss) for Schizophrenia. Schizophr Bull 13(2), 261-276.

Keefe, R.S.E., Goldberg, T.E., Harvey, P.D., Gold, J.M., Poe, M.P., Coughenour, L.,

2004. The Brief Assessment of Cognition in Schizophrenia: reliability, sensitivity, and

comparison with a standard neurocognitive battery. Schizophr Res 68(2-3), 283-297.

Kerns, J.G., Berenbaum, H., Barch, D.M., Banich, M.T., Stolar, N., 1999. Word

production in schizophrenia and its relationship to positive symptoms. Psychiatry Res

87(1), 29-37.

Kreher, D.A., Holcomb, P.J., Goff, D., Kuperberg, G.R., 2008. Neural evidence for

faster and further automatic spreading activation in schizophrenic thought disorder.

Schizophr Bull 34(3), 473-482.

Kyaga, S., Lichtenstein, P., Boman, M., Hultman, C., Langstrom, N., Landen, M., 2011.

Creativity and mental disorder: family study of 300 000 people with severe mental

disorder. Br. J. Psychiatry 199(5), 373-379.

Lehman, A.F., Lieberman, J.A., Dixon, L.B., McGlashan, T.H., Miller, A.L., Perkins,

D.O., Kreyenbuhl, J., American Psychiatric, A., Steering Committee on Practice, G.,

2004. Practice guideline for the treatment of patients with schizophrenia, second edition.

Am J Psychiatry 161(2 Suppl), 1-56.

Leonhard, D., Brugger, P., 1998. Creative, paranormal, and delusional thought: A

consequence of right hemisphere semantic activation? Neuropsychiatry Neuropsychol

Behav Neurol 11(4), 177-183.

Lindamer, L.A., Whitman, R.D., 1997. Frontal lobe functioning and communication

deficits as a function of positive and negative symptoms in schizophrenia. Arch Clin

Neuropsych 12(4), 358-358.

Mamah, D., Conturo, T.E., Harms, M.P., Akbudak, E., Wang, L., McMichael, A.R.,

Gado, M.H., Barch, D.M., Csernansky, J.G., 2010. Anterior thalamic radiation integrity

in schizophrenia: A diffusion-tensor imaging study. Psychiatry Res. 183(2), 144-150.

Mason, O., Claridge, G., Jackson, M., 1995. New Scales for the Assessment of

Schizotypy. Pers Indiv Differ 18(1), 7-13.

Matsuoka, K., Kim, Y., 2007. Japanese Adult Reading Test (JART). Shinko-Igaku,

Tokyo.

Matsuoka, K., Uno, M., Kasai, K., Koyama, K., Kim, Y., 2006. Estimation of premorbid

IQ in individuals with Alzheimer's disease using Japanese ideographic script (Kanji)

compound words: Japanese version of National Adult Reading Test. Psychiatry Clin

Neurosci 60(3), 332-339.

Mohr, C., Graves, R.E., Gianotti, L.R.R., Pizzagalli, D., Brugger, P., 2001. Loose but

normal: A semantic association study. J Psycholinguist Res 30(5), 475-483.

Mumford, M.D., 2003. Where have we been, where are we going? Taking stock in creativity research. Creativity Res. J. 15(2-3), 107-120.

Nelson, B., Rawlings, D., 2010. Relating schizotypy and personality to the phenomenology of creativity. Schizophr Bull 36(2), 388-399.

Nemoto, T., Kashima, H., Mizuno, M., 2007. Contribution of divergent thinking to community functioning in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 31(2), 517-524.

Nemoto, T., Mizuno, M., Kashima, H., 2005. Qualitative evaluation of divergent thinking in patients with schizophrenia. Behav Neurol 16(4), 217-224.

O'Leary, D.S., Flaum, M., Kesler, M.L., Flashman, L.A., Arndt, S., Andreasen, N.C., 2000. Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. J Neuropsychiatry Clin Neurosci 12(1), 4-15.

Oldfield, R.C., 1971. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia 9(1), 97-113.

Paul, L.K., Brown, W.S., Adolphs, R., Tyszka, J.M., Richards, L.J., Mukherjee, P., Sherr, E.H., 2007. Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nat. Rev. Neurosci. 8(4), 287-299.

Peters, E., Joseph, S., Day, S., Garety, P., 2004. Measuring delusional ideation: The 21-item Peters et al. delusions inventory (PDI). Schizophr Bull 30(4), 1005-1022.

Roediger, H.L., Mcdermott, K.B., 1995. Creating False Memories - Remembering Words Not Presented in Lists. J Exp Psychol Learn Mem Cogn 21(4), 803-814.

Runco, M.A., 2004. Creativity. Annu Rev Psychol 55, 657-687.

Sass, L.A., 2000. Schizophrenia, modernism, and the "creative imagination": On creativity and psychopathology. Creativity Res. J. 13(1), 55-74.

Shobe, E.R., Ross, N.M., Fleck, J.I., 2009. Influence of handedness and bilateral eye movements on creativity. Brain Cogn 71(3), 204-214.

Smith, S.M., Nichols, T.E., 2009. Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. Neuroimage 44(1), 83-98.

Spitzer, M., 1997. A cognitive neuroscience view of schizophrenic thought disorder. Schizophr Bull 23(1), 29-50.

Stoneham, A.C.S., Coughtrey, A.E., 2009. The role of schizotypy and creativity in a group problem-solving task. Pers Indiv Differ 46(8), 827-831.

Sumiyoshi, C., Sumiyoshi, T., Nohara, S., Yamashita, I., Matsui, M., Kurachi, M., Niwa, S., 2005. Disorganization of semantic memory underlies alogia in schizophrenia: An analysis of verbal fluency performance in Japanese subjects. Schizophr Res 74(1), 91-100.

Tsakanikos, E., Claridge, G., 2005. More words, less words: Verbal fluency as a function of 'positive' and 'negative' schizotypy. Pers Indiv Differ 39(4), 705-713.

Waseda Creativity Society, 1984. The Handbook of TCT Creativity Tests in Japanese. Waseda University Press, Tokyo.

Table 1a. Demographic and clinical data in healthy and patient groups

	Hc (n = 36)	Sc (n = 43)	*P*-value
Age	33.86±8.66	37.37±8.66	.077[a]
Gender (m/f)	24/12	22/21	.164[b]
Handedness	81.94±35.52	73.49±46.70	.375[a]
Premorbid IQ[c]	106.47±7.62	102.88±9.80	.077
Age at onset	-	24.35±8.04	-
Duration of illness	-	13.01±8.30	-
HP equivalent[c]	-	12.10±9.54	-
PANSS positive	-	14.53±5.53	-
PANSS negative	-	16.02±5.94	-
PANSS general	-	30.88±10.69	-

Note: [a]Two-tailed t-test, [b] χ^2, [c]Premorbid IQ was measured using Japan adult reading test,

[d]Haloperidol (HP) equivalent was calculated according to the practice guidelines for the

treatment of schizophrenia patients. Hc: healthy control group, Sc: schizophrenia group

Table 1b. Scores of fluency tasks and delusional ideation in healthy and patient groups

	Hc (n = 36)	Sc (n = 43)	*P*-value
Design Td	5.03±6.06	5.56±5.75	.691
Design Tm	1.08±1.42	1.16±1.91	.837
Design Ti	3.00±3.22	2.60±2.31	.528
Idea Td	4.22±1.96	3.98±2.25	.610
Idea Tm	2.17±1.84	1.21±1.06	.008*
Idea Ti	1.53±1.83	0.67±0.94	.015*
Verbal C	22.36±6.17	17.28±4.73	< .001**
Verbal L	28.61±9.29	22.72±6.85	.002*
PDI	20.47±24.63	114.95±65.81	< .001**

Note: Two-tailed t-test was used for all analyses. Hc: healthy control group, Sc: schizophrenia group, Design: design fluency, Idea: idea fluency, Td: task-dependent, Tm: task-modified, Ti: task-independent, Verbal C: category (semantic) fluency, Verbal L: letter (phonological) fluency, PDI: Peters delusions inventory; *, significance (*P* < .05), **, (*P* < .001)

Table 2. Results of correlation analysis between fluency tasks and delusional ideation in healthy and schizophrenia groups

	PDI (Hc)		PDI (Sc)	
	Pearson's correlation coefficient	P-value	Pearson's correlation coefficient	P-value
Design Td	0.034	.843	0.134	.39
Design Tm	-0.044	.797	0.001	.997
Design Ti	-0.081	.64	0.1	.524
Idea Td	-0.098	.571	0.121	.44
Idea Tm	-0.001	.995	0.017	.916
Idea Ti	-0.177	.302	-0.048	.761
Verbal C	0.052	.762	0.026	.87
Verbal L	-0.155	.368	0.386	.011*

Note: Hc: healthy control group, Sc: schizophrenia group, Design: design fluency, Idea: idea fluency, Td: task-dependent, Tm: task-modified, Ti: task-independent, Verbal C: category (semantic) fluency, Verbal L: letter (phonological) fluency, PDI: Peters delusions inventory; *, significance ($P < .05$)

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Fig. 1. Examples of responses on design fluency test.

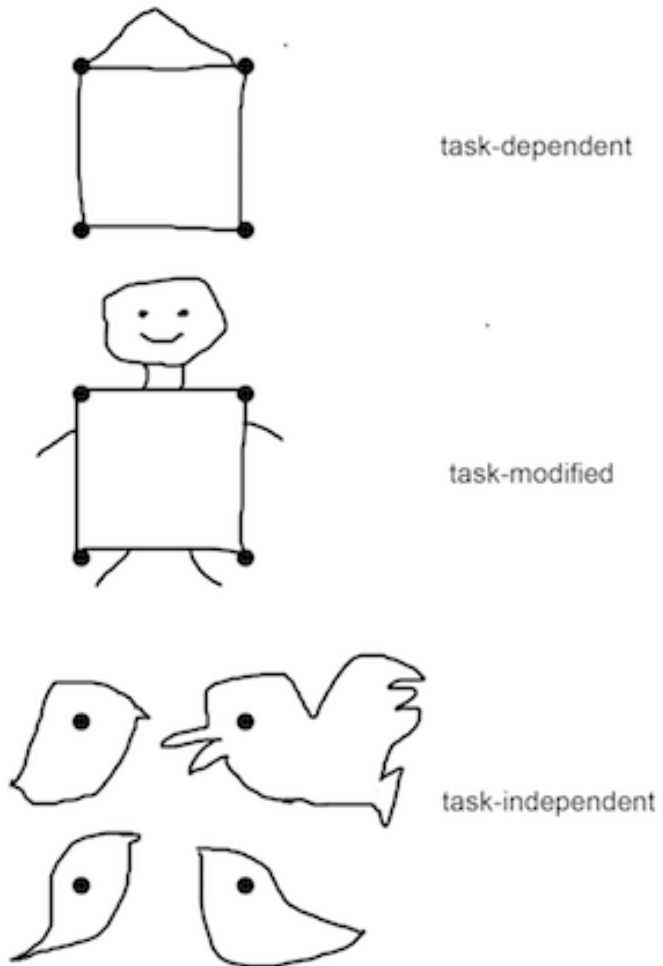task-dependent

task-modified

task-independent

Fig. 2. Regions of significant fractional anisotropy (FA) reduction in schizophrenia

relative to control group ($P < .05$, corrected by threshold-free cluster enhancement).

Schizophrenia patients exhibited widespread reduction extending to bilateral deep white

matter areas in frontal, temporal, parietal, and occipital lobes, large part of corpus

callosum, and corona radiata. Results are shown in red on mean FA maps, and FA

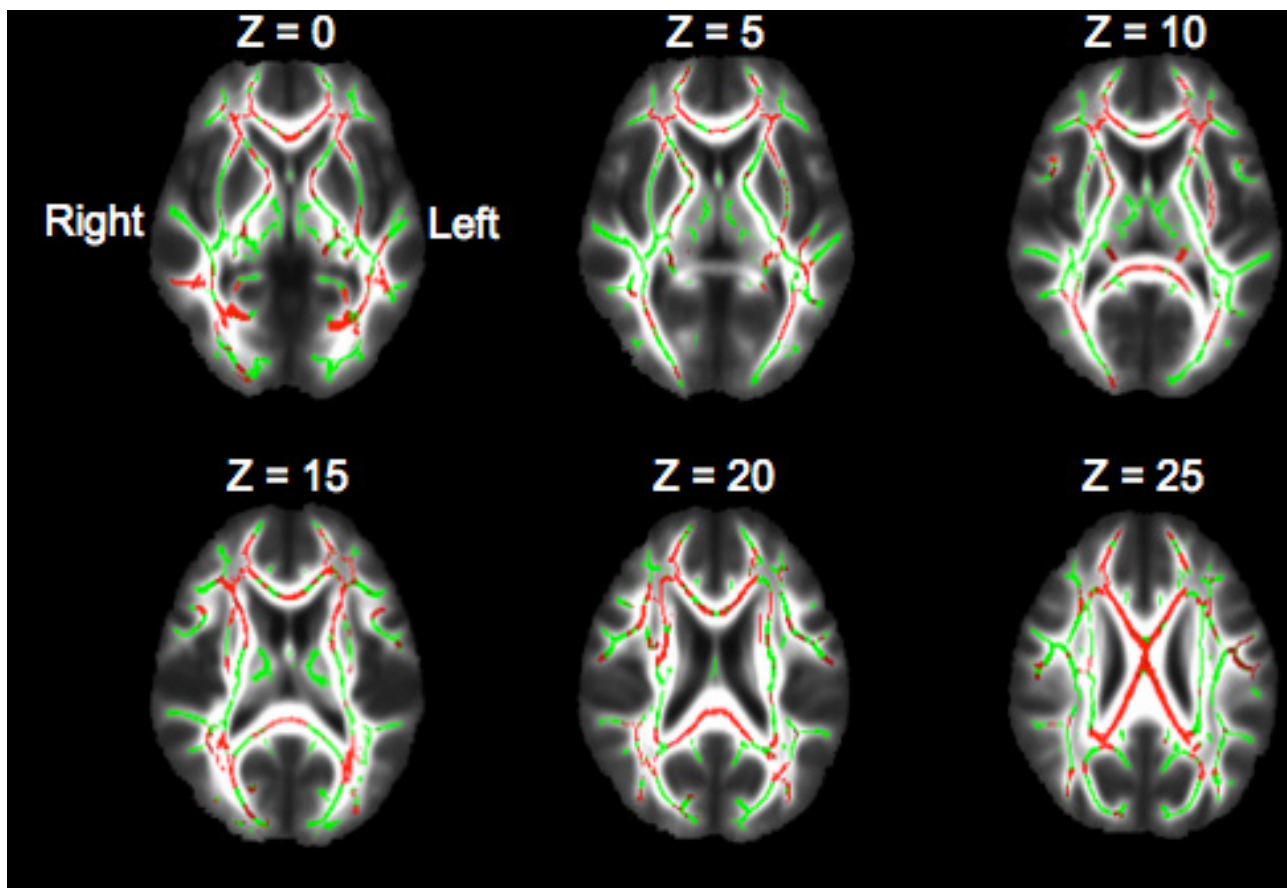skeleton in green. Axial slices from Z=0 to 25 in MNI coordinates are shown.

Fig. 3. Significant negative correlation between (a) phonological fluency and fractional anisotropy, and between (b) delusions and fractional anisotropy in the schizophrenia group ($P < .05$, corrected by threshold-free cluster enhancement). The results are shown in blue-lightblue. (a) In phonological fluency, the areas extend to the left corticospinal tract, superior corona radiata, anterior corona radiata, and genu and body of the corpus callosum. (b) In delusions, the areas extend to the right anterior corona radiata, bilateral superior corona radiata, left posterior corona radiata, genu, body, and splenium of the corpus callosum, and right forceps minor.
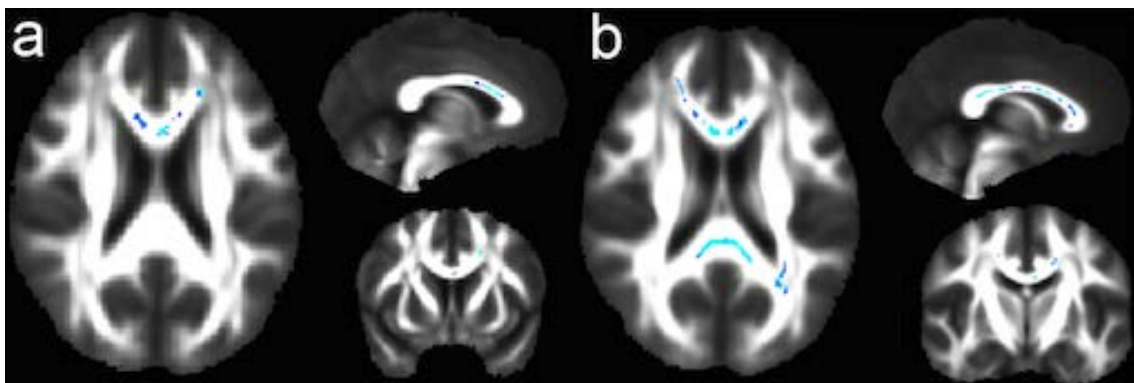
Fig. 4. Overlapped significant areas between phonological fluency and delusions (*P* < .05, corrected by threshold-free cluster enhancement) with negative correlation with fractional anisotropy (FA) in the schizophrenia group. To aid visualization, results are thickened with tbss_fill script in FSL and 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.