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Significant correlation between openness personality in normal subjects and brain myelin mapping with T1/T2-weighted MR imaging

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Abstract

Background: The objective of this study was to examine the relationship between the myelination and the psychological trait of openness to experience in young cognitively normal volunteers using regional T1-weighted (T1w)/T2w ratios on magnetic resonance imaging (MRI). It was hypothesized that axonal myelination would be related to openness, thus linking trait creativity and mental illness.

Methods: We recruited 37 healthy subjects and administered the NEO Five-Factor Inventory to assess personality factors. Regional T1w/T2w MRI values were computed as surrogate indicators of myelination status and correlations between T1w/T2w values and various personality factors (e.g., trait of openness) were calculated with a voxel-based analysis using statistical parametric mapping.

Results: Significant negative correlations were identified between the trait of openness and T1w/T2w values in the medial frontal cortex, anterior cingulate cortex, posterior cingulate cortex, and posterior insula/adjacent putamen. These

relationships remained significant even after adjusting for age, sex, and education as covariates. There were no significant correlations between other personality factors and regional volumes.

Conclusions: Individual differences in openness may be associated with variations in intra-cortical myelination, specifically in the imaginative network of the brain including the midline core ‘hubs’ of the default mode network (anterior cingulate/medial frontal cortex and posterior cingulate cortex) and regions related to motivational state (posterior insula and adjacent putamen). Signal interference related to decreased myelination may facilitate flexible imagination and the trait of openness. Our findings assist in understanding the relationship between myelination and openness, as a link between creativity and mental illness.

Keywords: Medical imaging, Psychiatry, Neuroscience

1. Introduction

Openness to experience is a personality trait that reflects a broad range of cognitive–affective styles such as absorption in sensory experience, preference for novel experiences, curiosity, and creativity (Passamonti et al., 2015). Numerous studies have consistently reported a positive relationship between openness to experience and creativity (Carson et al., 2005; Miller and Tal, 2007; Wolfradt and Pretz, 2001; Zhang and Huang, 2001). In contrast, increased openness to experience was shown in euthymic patients with bipolar disorder (BD) (Bagby et al., 1996; Nowakowska et al., 2005; Tackett et al., 2008). Recent studies have revealed associations between creativity and BD (Andreasen, 2008), and increased openness has been proposed as a trait common to patients with BD and highly creative individuals (Nowakowska et al., 2005; Srivastava et al., 2010; Strong et al., 2007). Yet, the possible mechanisms underlying this association remain unclear.

One possible biological mechanism by which increased openness to experience is linked to trait creativity and BD is altered brain myelination. Many patients with psychotic disorders such as BD have a defect in the gene that regulates production of neuregulin, a protein that regulates axonal myelination (Thomson et al., 2007), and recent brain imaging studies have revealed myelin abnormalities in patients with BD (Ishida et al., 2017; Rowley et al., 2015). In contrast, Keri (2009) reported an association between a biologically relevant polymorphism in the promoter region of the neuregulin gene and creativity in individuals with high intellectual and academic performance. Given these findings, we hypothesized that altered myelination might represent a biological substrate for openness as a link between trait creativity and BD.

It was recently proposed that the ratio of T1-weighted (T1w)-to-T2w signal on magnetic resonance imaging (MRI) is a sensitive indicator of changes in regional

myelination (Glasser and Van Essen, 2011). Therefore, we applied a T1w/T2w analysis workflow (Ganzetti et al., 2014) to structural MRI data collected from cognitively normal individuals in order to investigate the relationship between myelin content in the grey and white matter and openness to experience as a personality trait. Our findings facilitate the understanding of the relationship between myelination and the trait of openness as a link between creativity and psychosis.

2. Methods

2.1. Subjects

Thirty-seven healthy participants were recruited from the local area of northern Osaka prefecture in Japan using poster advertisements. The inclusion criteria were as follows: no history or presence of a neuropsychiatric disorder or substance abuse/dependence as per a structured psychiatric screening interview that included the Mini-International Neuropsychiatric Interview administered by a trained psychiatrist (Sheehan et al., 1998); no major structural abnormalities or signs of major vascular pathology on T1w and T2w imaging; and the absence of cognitive dysfunction as per the Mini-Mental State Examination (using a cut-off score of 27 for detecting cognitive dysfunction) (Folstein et al., 1975). The two-factor index of social position of Hollingshead was calculated from the occupation and education of each participant (Hollingshead, 1957). We administered the Revised NEO Five-Factor Inventory (NEO-FFI), a questionnaire consisting of 60 items taken from the NEO Personality Inventory Revised (NEO-PI-R) (Costa and McCrae, 1992) to assess the Big-Five personality factors (neuroticism, extraversion, openness, agreeableness, and conscientiousness). This study was approved by the medical ethics committee of the National Cerebral and Cardiovascular Center of Japan and conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all subjects prior to study participation.

2.2. MR image acquisition

MR images were acquired using a 3.0-T whole-body scanner (Signa Excite HD V12M4; GE Healthcare, Milwaukee, WI, USA) with an eight-channel phased-array brain coil. High-resolution three-dimensional T1-weighted images were acquired using a spoiled gradient-recalled sequence (repetition time [TR] = 12.8 ms, echo time [TE] = 2.6 ms, flip angle = 8°, field of view [FOV] = 256 mm; 188 sections in the sagittal plane; acquisition matrix = 256 × 256; and acquired resolution = 1 mm³). T2-weighted images were obtained using a fast-spin echo sequence (TR = 4,800 ms; TE = 101 ms; echo train length = 8; FOV = 256 mm; 74 slices in the transverse plane; acquisition matrix = 160 × 160, acquired resolution = 1 mm × 1 mm × 2 mm).

2.3. Analysis of T1w/T2w images

T1w and T2w images were preprocessed and combined using a dedicated workflow as previously described (Ganzetti et al., 2014, 2015). Image processing was conducted using the MR Tool-Multimodal Mapping tool (<http://www.bindgroup.eu/wp-content/uploads/2017/02/mrtool-v1.3.1.zip>) implemented in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK). Initially, original T2w images were co-registered to T1w images through a rigid-body transformation. Then, T1w and T2w images were separately subjected to bias correction. Input parameters for the bias correction algorithm, namely the smoothing and the regularization parameters, were set at their default values. After correcting for intensity non-uniformity, T1w and T2w images were further processed to standardize intensity using a linear scaling procedure, as previously described (Ganzetti et al., 2014, 2015). After image calibration, T1w/T2w ratios were calculated to generate calibrated T1w/T2w images. For between-group statistical comparisons, we spatially transformed T1w/T2w images into the Montreal Neurological Institute space. Grey matter (GM) and white matter (WM) components were extracted using the segmented normalized T1w image. We created both GM and WM binary mask images using the SPM Masking Toolbox (Ridgway et al., 2009) and used these mask images to perform statistical analyses with SPM12.

2.4. Statistical analysis

A voxel-based analysis was performed using SPM12 software. T1w/T2w images were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. Voxel-based analyses were performed to examine the relationship between T1w/T2w values at each voxel and Big-Five personality factors (openness, neuroticism, extraversion, agreeableness, and conscientiousness). We controlled for multiple comparisons using a cluster-extent threshold combined with a height threshold of 0.001 to identify clusters with a family-wise error-corrected p-value of < 0.05 .

Regional T1w/T2w values were calculated by averaging the values for all voxels within significant clusters from the above voxel-based analysis. Relationships between T1w/T2w values and personality factors were examined using Pearson's correlation tests. Statistical tests were 2-tailed and significance was defined as $\alpha < 0.05$. All statistical analyses were conducted using SPSS for Windows 22.0 (IBM Japan Inc., Tokyo, Japan).

3. Results

Participant characteristics are summarized in [Table 1](#). Significant negative correlations were identified between NEO-personality trait of openness scores and T1w/T2w ratios in clusters in the medial frontal cortex, anterior cingulate

Table 1. Demographic characteristics of subjects.

Characteristic	Data
Age (years)	28.1 ± 6.2 [21–45]
Female sex (n, %)	10 (27.0)
Period of education (years)	16.0 ± 0.6 [14–18]
MMSE score	29.9 ± 0.4 [28–30]
Hollingshead social score ^a	28.7 ± 2.2 [22–33]
NEO-FFI	
Openness	56.5 ± 9.2 [39–76]
Neuroticism	40.3 ± 11.5 [21–64]
Extraversion	61.3 ± 10.6 [37–80]
Agreeableness	57.3 ± 12.0 [35–80]
Conscientiousness	58.4 ± 11.9 [25–78]

Data represent the mean ± standard deviation and [range].

^a Social score = ((occupation scale score) * 7) + ((education scale score) * 4).

MMSE, Mini-Mental State Examination; NEO-FFI, NEO Five-Factor Inventory.

cortex, posterior cingulate cortex, and posterior insula/adjacent putamen (Fig. 1, Table 2). No significant correlations were identified between other personality factors and regional volumes. Table 3 shows the results of an analysis of relationships between NEO-personality traits including openness and T1w/T2w ratios in significant clusters from the voxel-based analysis. When T1w/T2w values

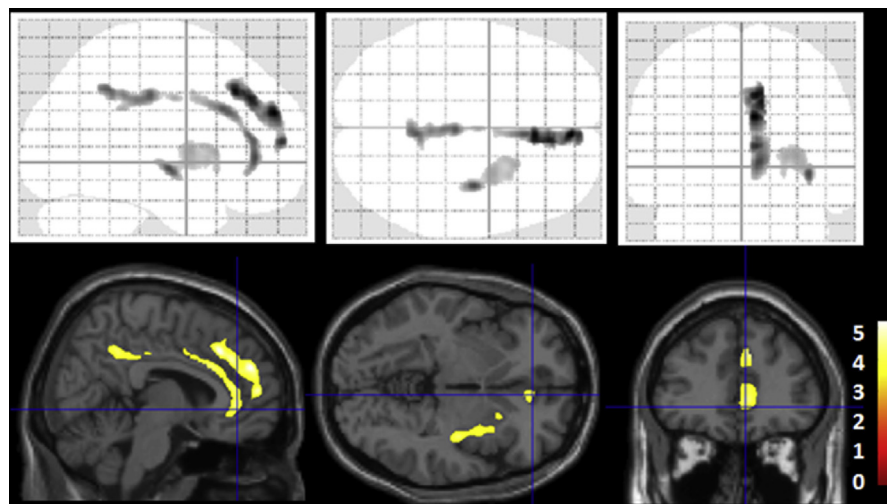


Fig. 1. Images of voxel-based maps showing significant negative correlations between T1w/T2w ratios and NEO-personality trait of openness scores. $p < 0.001$, uncorrected. Statistical parametric mapping projections were superimposed on representative sagittal ($x = 7$), transaxial ($z = -4$) and coronal ($y = 40$) magnetic resonance images.

Table 2. Clusters of regions with a significant correlation between T1w/T2w ratio and NEO-personality trait of openness score.

Comparison	Brain region	MNI coordinates (x, y, z) ^a	t-value	Cluster size (voxels)	Mean T1w/T2w value in cluster		
Positive correlation	None						
Negative correlation	Cluster #1	Medial frontal cortex (R)	6, 50, 27	4.47	3527	0.79	
			7, 27, 39	4.37			
			10, 36, 35	4.27			
	Cluster #2	Anterior cingulate cortex (R)	8, 39, 0	4.45	2422	0.78	
			6, 21, 28	4.33			
			8, 38, 10	4.27			
	Cluster #3	Insula (R)	38, -12, -6	4.43	3326	0.93	
			Putamen (R)	30, 0, 5			3.72
				25, 15, 4			3.69
	Cluster #4	Posterior cingulate cortex (R)	3, -24, 36	3.83	2331	0.77	
				5, -49, 40			3.82
				4, -39, 37			3.62

L, left hemisphere; MNI, Montreal Neurological Institute; R, right hemisphere.

^a x, y, and z reflect coordinates for the peak voxel or for other local maxima in the MNI space.

Table 3. Correlations between NEO-personality traits and T1w/T2w values in significant clusters.

	Openness	Neuroticism	Extraversion	Agreeableness	Conscientiousness
Cluster #1	-0.68 (<0.001) ^a	-0.02 (0.92)	-0.07 (0.67)	-0.02 (0.91)	0.24 (0.16)
Cluster #2	-0.65 (<0.001) ^a	0.05 (0.78)	-0.08 (0.63)	-0.23 (0.16)	0.15 (0.36)
Cluster #3	-0.55 (<0.001) ^a	0.004 (0.98)	-0.25 (0.14)	-0.02 (0.89)	0.17 (0.30)
Cluster #4	-0.64 (<0.001) ^a	0.04 (0.81)	-0.23 (0.18)	-0.12 (0.49)	0.09 (0.58)
Across all clusters	-0.70 (<0.001) ^b	0.01 (0.94)	-0.17 (0.31)	-0.09 (0.60)	0.19 (0.25)

^a $p < 0.01$ (0.05/5) was the threshold for statistical significance after adjusting for multiple comparisons.

were calculated across all significant clusters, we identified a significant positive relationship between T1w/T2w value and openness score (Table 3, Fig. 2). This relationship remained significant even after adjusting for the effects of age, sex, and education as covariates ($r = -0.56$, $p < 0.001$). In the linear regression analysis, using the openness scores as the dependent variable and the T1w/T2w values across all clusters as the independent variable, after adjusting for age, sex, and education, T1w/T2w values were negatively related to openness scores ($\beta = -0.59$, $p = 0.001$).

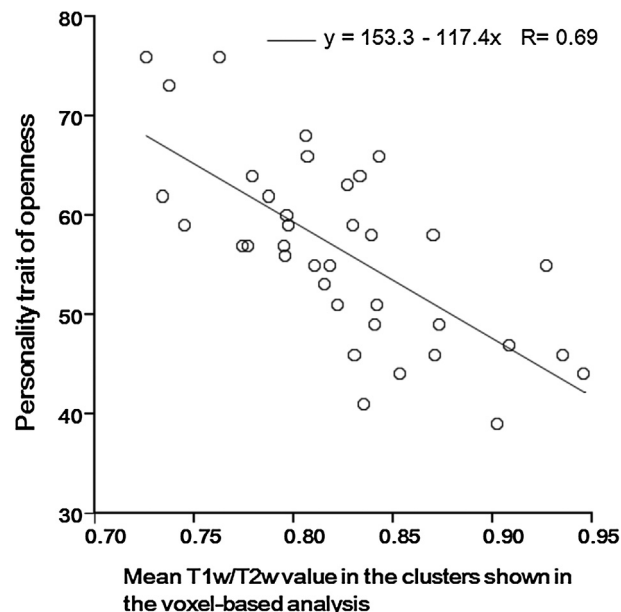


Fig. 2. Scatter plots of relationships between mean T1w/T2w values across significant clusters from the voxel-based analysis and NEO-personality trait of openness scores.

4. Discussion

The present results revealed a significant negative correlation between intra-cortical T1w/T2w ratios and the personality trait of openness in cognitively normal volunteers. Interpreting T1w/T2w ratios as a surrogate indicator of myelination, our results indirectly support the hypothesis that individual differences in openness to experience are associated with variations in intra-cortical myelination in the anterior cingulate/medial frontal cortex, posterior cingulate cortex, and posterior insula/adjacent putamen. These findings are also consistent with the hypothesis that myelination is a biological basis for the trait of openness and its role as a link between creativity and mental disorders.

The anterior cingulate medial frontal cortex and posterior cingulate cortex represent the midline core ‘hubs’ of the default mode network (DMN). In a previous study, openness to experience was positively correlated with activation in these the midline core DMN regions (Adelstein et al., 2011). The DMN has been implicated in self-generated thought such as mind wandering, future thinking, and creative idea production (Andrews-Hanna et al., 2014; Beaty et al., 2016a). Recently, Beaty et al. (2016b) found that functional organization of the DMN was related to individual differences in openness to experience using structural equation modelling and a graph theory analysis of resting-state functional MRI data. Our finding is consistent with these previous results, supporting a relationship between openness to experience and the DMN.

It has been suggested that motivation is a main factor linking creativity, creativity-related personalities, and function of the dopaminergic system (Takeuchi et al., 2017). The putamen receives dopaminergic projections from the substantia nigra and plays an important role in reward and motivation (Wise, 2004). There is also a large quantity of dopaminergic receptors expressed in the posterior insula, which has been associated with novelty-seeking behaviour (Kaasinen et al., 2004). The posterior insula and adjacent putamen are also involved in action planning in response to distress or reward (Takeuchi et al., 2017). Thus, our finding of a correlation between openness and T1w/T2w ratio in the posterior insula/adjacent putamen may indicate a relationship between openness and motivation as a component linked to creativity.

The potential mechanism of decreased intra-cortical myelination in midline DMN regions and regions related motivational state is unclear. Myelin is formed in sheets in a manner proportional to the availability of neuregulin. While large numbers of myelinated axons are found in deep white matter tracts, a substantial number is also found at the brain surface, running through layers of the cortex. An apparent decrease in intra-cortical myelination may represent fewer myelinated intra-cortical fibers or reduced myelination of individual neurons, both of which affect the performance of functional networks (Lake et al., 2016). Regarding the

relationship between intra-cortical myelination and openness as a personality trait, we speculate that signal interference resultant from reduced myelination facilitates imaginative flexibility and aesthetic interest related to the trait of openness. For example, a previous study proposed that intellectual rigidity or rigidity of knowledge is perturbed on a physiological level by mutual signal interference between improperly or insufficiently myelinated axons (Ricciardiello and Fornaro, 2013). Moderate amounts of perturbation (noise) may decrease thought rigidity and facilitate the generation of unusual ideas in imaginative networks of the brain that include the anterior cingulate/medial frontal cortex, posterior cingulate cortex, and insula/putamen; however, noise above a certain threshold may cause system chaos and the ‘fracturing’ of embodied knowledge. Fractured thinking, which is typical of mania in serious cases of BD, has been previously linked to the emergence of chaos in imaginative brain systems (Ricciardiello and Fornaro, 2013).

A negative correlation between openness and myelination was shown only in the right hemisphere. One prominent theory suggests that high creativity is associated with being able to connect distant concepts, hence promoting the combination of remotely-connected concepts into original ideas (Mednick, 1962). It is classically believed that the right hemisphere plays an important role in the processing of remote associations while the left hemisphere favors close associations (Beeman et al., 1994; Chiarello et al., 2003; Hutchison, 2003; Jung-Beeman, 2005). These notions indicate the crucial and specific contribution of the right hemisphere to creativity, which is believed to rely on the ability to combine remote concepts into novel and useful ideas, an ability which would depend on associative processing in the right hemisphere (Aberg et al., 2016). Openness, which has a strong relationship with creativity (Carson et al., 2005; Miller and Tal, 2007; Wolfradt and Pretz, 2001; Zhang and Huang, 2001), may also reside in the right hemisphere.

The present study had several limitations. First, the sample size was relatively small. Second, we lacked data that permitted a detailed examination of intellectual ability. Third, personality can also be affected by other difficult-to-quantify environmental factors such as occupation, hobbies, relationship with friends, and family structure. Fourth, this study relied on a self-report measure of personality, such that the observed effects may partially reflect differences in self-views as opposed to actual differences in personality. Future studies should address these issues and confirm our findings using observer ratings as well as self-report in a larger cohort of participants.

In conclusion, our results indicate that individual differences in openness to experience are associated with variations in regional T1w/T2w ratios in midline DMN ‘hub’ regions and regions related to motivational state, potentially representing differences in intra-cortical myelination in the imaginative network of the brain. Mutual signal interference between poorly myelinated intra-cortical

neurons may diminish thought rigidity and facilitate the generation of flexible imagination and aesthetic interest. These findings represent an important first step toward understanding the relationship between myelination and the trait of openness as a link between creativity and psychosis.

Declarations

Author contribution statement

Fumihiko Yasuno: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Takashi Kudo, Toshifumi Kishimoto: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Akihide Yamamoto, Kiwamu Matsuoka, Masato Takahashi: Performed the experiments.

Hidehiro Iida, Masafumi Ihara, Kazuyuki Nagatsuka: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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