Creative Females Have Larger White Matter Structures: Evidence from a Large Sample Study

Hikaru Takeuchi,[1]* Yasuyuki Taki,[1,2,3] Rui Nouchi,[4,5,6] Ryoichi Yokoyama,[7] Yuka Kotozaki,[8] Seishu Nakagawa,[9,10] Atsushi Sekiguchi,[2,9,11] Kunio Iizuka,[12] Yuki Yamamoto,[9] Sugiko Hanawa,[9] Tsuyoshi Araki,[6] Carlos Makoto Miyauchi,[13] Takamitsu Shinada,[9] Kohei Sakaki,[9] Yuko Sassa,[1] Takayuki Nozawa,[14] Shigeyuki Ikeda,[14] Susumu Yokota,[1] Magistro Daniele,[15] and Ryuta Kawashima[1,6,9]

[1]Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan
[2]Division of Medical Neuroimaging Analysis, Department of Community Medical Supports, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan
[3]Department of Radiology and Nuclear Medicine, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan
[4]Creative Interdisciplinary Research Division, Frontier Research Institute for Interdisciplinary Science, Tohoku University, Sendai, Japan
[5]Human and Social Response Research Division, International Research Institute of Disaster Science, Tohoku University, Sendai, Japan
[6]Department of Advanced Brain Science, Smart Ageing International Research Center, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan
[7]School of Medicine, Kobe University, Kobe, Japan
[8]Division of Clinical research, Medical-Industry Translational Research Center, Fukushima Medical University School of Medicine, Fukushima, Japan
[9]Department of Functional Brain Imaging, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan
[10]Department of Psychiatry, Tohoku Pharmaceutical University, Sendai, Japan
[11]Department of Adult Mental Health, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan
[12]Department of Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan
[13]Department of General Systems Studies, Graduate School of Arts and Sciences, The University of Tokyo, Tokyo, Japan
[14]Department of Ubiquitous Sensing, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan
[15]School of Electronic, Electrical and Systems Engineering, Loughborough University, England

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Abstract: The importance of brain connectivity for creativity has been theoretically suggested and empirically demonstrated. Studies have shown sex differences in creativity measured by divergent thinking (CMDT) as well as sex differences in the structural correlates of CMDT. However, the relationships between regional white matter volume (rWMV) and CMDT and associated sex differences have never been directly investigated. In addition, structural studies have shown poor replicability and inaccuracy of multiple comparisons over the whole brain. To address these issues, we used the data from a large sample of healthy young adults (776 males and 560 females; mean age: 20.8 years, SD = 0.8). We investigated the relationship between CMDT and WMV using the newest version of voxel-based morphometry (VBM). We corrected for multiple comparisons over whole brain using the permutation-based method, which is known to be quite accurate and robust. Significant positive correlations between rWMV and CMDT scores were observed in widespread areas below the neocortex specifically in females. These associations with CMDT were not observed in analyses of fractional anisotropy using diffusion tensor imaging. Using rigorous methods, our findings further supported the importance of brain connectivity for creativity as well as its female-specific association. *Hum Brain Mapp 38:414–430, 2017.*   © 2016 Wiley Periodicals, Inc.

Key words: creativity; structural connectivity; white matter; sex difference; voxel-based morphometry

INTRODUCTION

Creativity is commonly defined as the ability to produce work that is both novel and useful within a certain social context [Runco and Jaeger, 2012; Stein, 1953]. Creativity is typically measured by tests of divergent thinking (DT) ("information retrieval and the call for a number of varied responses to a certain item" [Guilford, 1967]). DT performance also predicts creative achievement in real life quite well [for the meta analysis, see Kim, 2008].

Previous theoretical and empirical studies have suggested that brain connectivity is essential for both creativity and creativity measured by divergent thinking (CMDT). Greater functional coherence among different brain areas during a creative task [Jausovec, 2000] and the functional connectivity of various areas involving the default mode network (the network that is more active during rest) [Beaty et al., 2014; Takeuchi et al., 2012a; Wei et al., 2013] are associated with higher creativity. Another study [Beaty et al., 2015] showed that during divergent thinking, coupling of the executive control network (the network involved in executive control) and the default mode network is observed. It was also suggested that networks of antagonistic relation tend to cooperate during creative cognition and artistic performance. The Beaty et al. [2015] study also showed that the tendency of "small world" in the network is associated with increased CMDT [Beaty et al., 2015]. A larger corpus callosum, which connects the bilateral hemispheres [Moore et al., 2009], as well as white matter microstructural properties, including higher fractional anisotropy (FA) in a wide range of areas [Takeuchi et al., 2010b], are associated with higher CMDT. However, a recent study using a larger sample suggested that there are sex differences in the association between white matter structural connectivity and CMDT [Ryman et al., 2014].

Our studies have shown that regional white matter volume (rWMV) is uniquely associated with cognitive functions and are more sensitive to cognitive functions than FA [Takeuchi et al., 2013b,c]. rWMV and FA are generally only weakly correlated [Hugenschmidt et al., 2008], suggesting that rWMV can evaluate unique relationships between structural connectivity and cognitive function that FA cannot. Furthermore, although it is difficult to evaluate the meaning of FA magnitude where fibers cross [Jones et al., 2013], there are no such drawbacks for rWMV analyses.

As for sex differences, sex differences in CMDT is an inconclusive subject. One study conducted a comprehensive review [Baer and Kaufman, 2008] on this issue and concluded "*it is unlikely that a meta-analysis would show a significant overall gender difference on these tests, but it would be noted that if there were to be an overall "winner" in the number of studies in which one gender outperformed the other, it would be women and girls over men and boys.*" However, psychological studies have shown that cognitive correlates of CMDT are different between sexes. A study reported that the association between creativity and psychopathology differs between sexes, and a positive stronger association is seen among men [Martín-Brufau and Corbalán, 2016]. An electrophysiological study also showed that a high reactivity of the α_2 rhythm was more marked during verbal creative thinking in women than in men [Matud et al., 2007]. A study reviewing functional magnetic resonance imaging also concluded that during divergent thinking, declarative memory-related regions were strongly activated in men, while regions involved in theory of mind and self-referential processing were more activated in women [Abraham et al., 2014]. These studies have also suggested gender differences in adopted strategies or cognitive styles when faced with CMDT. The recent review [Abraham, 2016] summarized the relevant findings for

these gender differences. For example, males are characterized by a stronger systemizing or analytical style, whereas female are characterized by a stronger empathizing style. Further, gender differences were found in 5- to 6-year olds in the motifs they generated during the free drawing. In addition, a study of music therapy for patients with traumatic brain injury, showed that when given the task of generating lyrics to songs, men expressed adversity and concern for the future more than women, whereas women focused on their relationships with others more than men. Conversely, there are robust sex differences in human brain structure [Cosgrove et al., 2007]. For instance, males exhibited a 10% larger total brain size [Giedd et al., 2012]. Further, males had a higher percentage of white matter area while females have a higher percentage of gray matter [Cosgrove et al., 2007]. There are also sex differences in regional gray matter volume after controlling for global effects; in particular, males showed larger hippocampus and amygdala volumes, whereas females had larger insular and many of anterior frontal regions [Ruigrok et al., 2014]. One recent study reported that males had greater FA in widespread white matter areas, whereas females had greater FA in specific areas including the parietal lobe [Inano et al., 2011]. These psychological and functional imaging studies together with sex differences in brain structure, organization, cognition, and the association between white matter connectivity and CMDT [Ryman et al., 2014] may also suggest possible sex-specific differences in rWMV correlates of CMDT.

Based on these findings, we hypothesized that CMDT is positively associated with rWMV in widespread areas and that there may be sex-specific associations. However, the aforementioned studies have not revealed the rWMV correlates of CMDT. The purpose of this study is to assess this issue and test our hypotheses. Recent reviews have suggested the problems of low sample size in the whole brain analyses [Vul et al., 2009] and in neuroscience in general [Button et al., 2013]. Particularly, low replicability of the structural analyses of low sample size has been suggested [Köhler et al., 1998]. Further, the difficulty of properly correcting the multiple comparisons in whole brain voxel-based morphometry (VBM) analyses have been suggested [Silver et al., 2012] and permutation-based methods have been shown to quite accurately correct for multiple comparisons in VBM studies [Hayasaka et al., 2004; Silver et al., 2012]. Thus, for the purpose of this study, we analyzed rWMV data from a large sample of young adults ($n = 1336$) using VBM [Ashburner and Friston, 2000]'s newest version which is implemented in SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). And, the present study also utilized rigorous permutation-based statistical methods using threshold-free cluster enhancement (TFCE) [Smith and Nichols, 2009]. Further, although we and others have investigated FA correlates of CMDT [Jung et al., 2010a; Takeuchi et al., 2010b], the findings were not consistent. Thus, in addition to sex-specific associations

between rWMV and creativity (CMDT), we also investigated microstructural (FA) correlates of CMDT and potential sex differences.

METHODS

Subjects

In total, 1,336 healthy, right-handed individuals (776 men and 560 women) participated in this study as part of our ongoing project to investigate the associations among brain imaging, cognitive functions, and aging [Takeuchi et al., 2013a,b,]. MRI scans and cognitive tests were performed on the same day in almost all cases, but in the rare instance when that was not possible, MRI scans and cognitive tests were performed separately (1–several days apart). The mean age of subjects was 20.8 years (standard deviation [SD], 1.8). All subjects were university, college, or postgraduate students or subjects who had graduated from these institutions within 1 year before the experiment and had normal vision. Written informed consent was obtained from each subject in accordance with the Declaration of Helsinki (1991). This study was approved by the Ethics Committee of Tohoku University.

DIVERGENT THINKING ASSESSMENT

The methods outlined here are reproduced from our previous studies [Takeuchi et al., 2010a,b, 2011a,b, 2012a].

The S-A creativity test [Society_For_Creative_Minds, 1969] was used to assess CMDT. J.P. Guilford generated the draft plan of this test. He also supervised the development of the test [Society_For_Creative_Minds, 1969]. The test was standardized for Japanese speakers [Society_For_Creative_Minds, 1969].

The test is used to evaluate verbal CMDT [Society_For_Creative_Minds, 1969], and it involves three types of tasks. The practice (and real) tasks are administered in the following order: (1) practice of the first task (2 min), (2) the first task (5 min), (3) practice of the second task (2 min), (4) the second task (5 min), (5) practice of the third task (2 min), and (6) the third task (5 min). Each task involves two questions. In total, the test takes 30 min. This test was administered in a group setting. The first task requires subjects to generate unique ways of using typical objects (e.g., "Other than reading, how can we use newspapers?" An example answer is "We can use them to wrap things."). The second task requires subjects to imagine desirable functions of ordinary objects (e.g., "What are the characteristics of a good TV? Write down as many characteristics as possible." An example answer is "A TV can receive broadcasts from all over the world."). The third task requires subjects to imagine the consequences of "unimaginable things" happening (e.g., "What would happen if all the mice in the world disappeared?" An example answer is "The world would become more hygienic.").

Each task requires subjects to generate as many answers as possible. Note these tasks corresponded to the three tasks (unusual use, product improvement, just suppose) of the Torrance test of creative thinking (TTCT) [Torrance, 1966], which is used in other countries. Simple correlation coefficients among the scores of the three subtasks were all $r = 0.48$–0.54. The S-A creativity test provides a total score, which was used in this study, as well as scores for the following dimensions of the creativity: (a) Fluency: Fluency is measured by the number of relevant responses to questions and is related to the ability to produce and consider several alternatives. Fluency scores are determined by the total number of questions answered after excluding inappropriate responses or responses that are difficult to understand. (b) Flexibility: Flexibility is the ability to produce responses from a wide perspective. Flexibility scores are determined by the sum of the (total) number of category types to which the responses are assigned based on a criteria table or an almost equivalent judgment. (c) Originality: Originality is the ability to produce ideas that differ from those of others. Originality scoring is based on the sum of idea categories that are weighted based on a criteria table or an almost equivalent judgment. (d) Elaboration: Elaboration is the ability to produce detailed ideas (Society for Creative Mind, 1969). Elaboration scores are determined by the sum of responses that are weighted based on a criteria table or an almost equivalent judgment. These four dimensions correspond to the same concepts as those of the TTCT [Torrance, 1966].

The total score is the sum of the originality score and that of elaboration in the version of the S-A creativity test [Society_For_Creative_Minds, 1969] used here. This is because the Fluency and Flexibility scores are highly correlated with those of Elaboration [Society_For_Creative_Minds, 1969]. Scoring of the tests was performed by the Tokyo Shinri Corporation.

The analysis was limited to the total score, and it did not include the score for each dimension. This is because in this test, the score of each dimension is highly correlated with the total score and with those of other dimensions [Takeuchi et al., 2010b]. This phenomenon is consistent with another similar divergent thinking test [Heausler and Thompson, 1988], namely TTCT [Torrance, 1966]. Heausler and Thompson [1988] concluded that the correlations among the subscales in TTCT are so high that each subscale could not meaningfully provide dissociated information. Treffinger [1985] also warned that separate interpretations of TTCT subscores should be avoided. Consistent with this notion, a previous study [Chávez-Eakle et al., 2007] that investigated the association between regional cerebral flow (rCBF) and each dimension revealed that different dimensions were correlated with rCBF in similar regions. Thus, we believe that using only the total score serves the purpose of this study. However, some studies have found specific effects of each subscale, especially originality [Takeuchi et al., 2015d]. Thus, with the

aforementioned limitation in mind, we also performed separate but identical analyses in which the total score on the S-A creativity test was replaced with each of the subscale scores.

Please refer to the appendix of our previous study for a sample and the manner in which the tests were scored [Takeuchi et al., 2010a].

S-A creativity test scores are significantly correlated with various other external measures, such as various personality factors and problem-solving abilities in daily life, suggesting its ability to predict performance in everyday situations [Shimonaka and Nakazato, 2007]. Furthermore, S-A creativity test scores are significantly correlated with the frequency of visual hypnagogic experiences, which in turn are correlated with the vividness of mental imagery [Watanabe, 1998]. Furthermore, our previous study [Takeuchi et al., 2013d] showed that S-A creativity test scores are positively correlated with extraversion, novelty seeking, motivational state, and daily physical activity level, which are consistent with the findings provided by the other measures of CMDT [Chávez-Eakle et al., 2006; King et al., 1996].

Assessment of Psychometric Measures of General Intelligence

We used Raven's Advanced Progressive Matrix (RAPM) to assess intelligence and also to adjust for the effect general intelligence has on brain structures. For more details of how RAPM was performed in our study, see our previous works [Takeuchi et al., 2010a,b].

Image Acquisition

The methods for MR image acquisition were described in our previous study [Takeuchi et al., 2012a]. All MRI data acquisition was performed using a 3-T Philips Achieva scanner. High-resolution T1-weighted structural images (T1WIs: 240×240 matrix, TR = 6.5 ms, TE = 3 ms, FOV = 24 cm, slices = 162, slice thickness = 1.0 mm) were collected using a magnetization-prepared rapid gradient echo sequence.

Diffusion-weighted data were acquired using a spin-echo EPI sequence (TR = 10,293 ms, TE = 55 ms, big delta (Δ) = 26.3 ms, little delta (δ) = 12.2 ms, FOV = 22.4 cm, $2 \times 2 \times 2$ mm^3 voxels, 60 slices, SENSE reduction factor = 2, number of acquisitions = 1). The diffusion weighting was isotropically distributed along 32 directions (b value = 1,000 s/mm^2). Additionally, three images with no diffusion weighting (b value = 0 s/mm^2) ($b = 0$ images) and one $b = 0$ image were acquired from 1,209 and 127 subjects, respectively, using a spin-echo EPI sequence (TR = 10,293 ms, TE = 55 ms, FOV = 22.4 cm, $2 \times 2 \times 2$ mm^3 voxels, 60 slices). From the collected images, FA maps and mean diffusivity (MD) maps were calculated using the commercially available diffusion tensor analysis

package on the MR consol. These procedures involved correction for motion and distortion caused by eddy currents using methods described previously [Netsch and Van Muiswinkel, 2004]. Calculations were performed according to a previously proposed method [Le Bihan et al., 2001]. MD maps were irrelevant to the purpose of this study but used in the preprocessing step as described previously [Takeuchi et al., 2013c].

Preprocessing of Structural Data

Preprocessing of the structural data was performed using Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks Inc., Natick, MA). Using the new segmentation algorithm implemented in SPM12, T1-weighted structural images of each individual were segmented into six tissues. Note for other instances in this study, SPM8 was used because of compatibility with the software of the version we used (statistical tests) or the apparent better quality of preprocessing (in cases of diffusion tensor imaging [DTI]'s preprocessing), but for VBM, SPM12 was used because of the better quality of preprocessing. In this new segmentation process, default parameters were used, except that the Thorough Clean option was used to eliminate any odd voxel, affine regularization was performed with the International Consortium for Brain Mapping template for East Asian brains, and the sampling distance was set at 1 mm. We then proceeded to the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) registration process implemented in SPM12. We used DARTEL import images of the 2 TPMs from the aforementioned new segmentation process. First, the template for the DARTEL procedures was created using imaging data from 800 participants (400 males and 400 females). The following methods were the same as in our previous study and descriptions were reproduced from our previous study [Takeuchi et al., 2015a]. Next, using this existing template, the DARTEL procedures were performed for all of the subjects in the present study. In these procedures, default parameter settings were used. The resulting images were spatially normalized to the Montreal Neurological Institute space to give images with $1.5 \times 1.5 \times 1.5$ mm^3 voxels. In addition, we performed a volume change correction (modulation) by modulating each voxel with the Jacobian determinants derived from spatial normalization, which allowed us to determine regional differences in the absolute amount of brain tissue [Ashburner and Friston, 2000]. Subsequently, all images were smoothed by convolving them with an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM).

Preprocessing of the diffusion data was performed using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK) implemented in MATLAB (Mathworks, Natick, MA). First,

using the previously validated [Takeuchi et al., 2013c] twisted methods and the new segmentation algorithm implemented in SPM8 and the information of both FA images and MD images, we segmented FA images and MD images of subjects (see this previous study for details and for the validation). Then, we basically normalized FA, gray matter segment [regional gray matter density (rGMD) map], white matter segment [regional white matter density (rWMD) map], cerebrospinal fluid (CSF) segments [regional CSF density (rCSFD) map] of diffusion images of subjects with previously validated diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL)-based registration process method that was modified to account for the signal distribution of FA within the white matter to give images with $1.5 \times 1.5 \times 1.5$ mm^3 voxel size, then normalized FA images were masked by the custom mask image that is highly likely to be the white matter and smoothed [FA images were smoothed by Gaussian Kernel of 6-mm FWHM. Details of these preprocessing procedures and their validation were presented in our previous study [Takeuchi et al., 2013c].Briefly, by accounting for FA signal variability within white matter areas in the DARTEL procedures, misalignment of the tracts was prevented. Further, by applying stringent masking of white matter areas, signal contamination from other tissues was prevented. Also, our method effectively solved or alleviated the major problems of voxel-based analyses of FA images [Smith et al., 2006].

GROUP-LEVEL STATISTICAL ANALYSIS

Statistical analyses relating to rWMV were performed using SPM8 software. We included only voxels with an rWMV signal intensity of >0.05. In whole-brain analyses, we used voxel-wise analysis of covariance (ANCOVA) with sex difference as a grouping factor (using the full factorial option of SPM8). In this analysis, age, RAPM scores, and S-A creativity test scores were covariates. These covariates were modeled so that each covariate had a unique relationship with rWMV for each sex (using the interactions option in SPM8), which enabled investigation of the effects of interaction between sex and each covariate. For the rationale of the model and why global signals were not included, see Supporting Information Methods.

Statistical analyses relating to FA were performed using SPM8 software. We confined regional analyses to areas that showed rWMD values >0.99 in the average image of the normalized rWMD images. In whole-brain analyses, we used voxel-wise ANCOVA with sex difference as a grouping factor (using the full factorial option of SPM8). In this analysis, age, RAPM scores, the number of $b = 0$ images and S-A creativity test scores were covariates. The number of $b = 0$ images (1 or 3) was included in the model because the number of $b = 0$ images affects the estimation of FA values [Jones et al., 1999]. A common effect of the number of $b = 0$ images on FA values was assumed for

TABLE I. Average, SD, and range of S-A creativity test' total and subscale scores, Raven's advanced progressive matrix scores, and age of males and females in our sample as well as the effect size and statistical values of the sex differences of these values

	Male			Female					
	average	SD	range	average	SD	range	Cohen's d	T score	P value
S–A creativity test score-Total score	37.48	10.72	7–71	39.41	9.92	7–68	0.19	−3.39	0.001
S-A creativity test score-Fluency	34.37	9.18	5–60	39.41	8.89	9–60	0.13	−2.37	0.018
S-A creativity test score-Flexibility	24.90	5.41	5–40	25.80	4.87	9–55	0.17	−3.20	0.001
S-A creativity test score-Originality	8.33	3.35	0–22	8.23	3.20	0–19	0.03	0.58	0.562
S-A creativity test score-Elaboration	29.14	8.35	7–57	31.16	7.8	5–57	0.25	−4.53	$6.56*10^{-6}$
RAPM score	28.70	3.84	13–36	28.03	3.83	15–36	0.17	3.16	0.002
Age	20.87	1.88	18–27	20.70	1.62	18–27	0.10	1.78	0.075

both sexes. This was done because there were differences in the number of $b = 0$ images between subjects, unlike in our previous study [Takeuchi et al., 2010b]. Other variables were modeled as described for the analyses of rWMV.

The main effects of S-A creativity test scores [contrasts of (the effect of the S-A creativity test score for males, that for females) were (1 1) or (−1 −1)] and the interaction between sex and S-A creativity test scores [contrasts of (the effect of the S-A creativity test for males, the effect of the S-A creativity test for females) were (−1 1) or (1 − 1)] were assessed using t-contrasts.

In addition, we also assessed the main and interaction effects of each S-A creativity test subscale. In these analyses, the total S-A creativity test score was replaced by each subscale score. As a result, we performed four additional whole-brain ANCOVAs.

Next, to examine how the significant interaction effects identified in the aforementioned analyses (see Results) were moderated by correlations between CMDT and rWMV in males and those in females, we performed multiple regression analyses using sex-specific data to test the associations between S-A creativity test scores and rWMV in males and females separately. In these analyses, the dependent variable was rWMV in each voxel and independent variables were age, RAPM scores, and S-A creativity test scores.

A multiple comparison correction of the cross-sectional analyses was performed using TFCE)[Smith and Nichols, 2009], with randomized (5,000 permutations) nonparametric permutation testing via the TFCE toolbox (http://dbm.neuro.uni-jena.de/tfce/). We applied the threshold of an FWE corrected $P < 0.05$.

RESULTS

Basic Behavioral Data

The average, SD, and range of S-A creativity test scores, RAPM scores, and age of males and females in our sample are presented in Table I. There were no significant correlations between RAPM scores and S-A creativity test scores

in males or females ($P > 0.05$, simple regression analyses). Women had higher S-A creativity test scores in this sample, and although the effect size was small (Cohen's $d = 0.19$), the difference was highly significant ($P < 0.001$).

Effects of CMDT on rWMV in Analyses Performed Using Data from Both Sexes

ANCOVA revealed no significant overall negative or positive main effects of S-A creativity test scores on rWMV in any of the regions regardless of sex. However, there were significant interaction effects of sex and S-A creativity test scores (interaction contrast of the combination of negative correlations in males and positive correlations in females) on rWMV in widespread white matter areas. The extent is presented in Figure 1 and the anatomical labeling in Table II. The associations were seen in widespread areas below the frontal, temporal, parietal, and occipital lobes as well as in the thalamus, whereas no significant associations were found in the white matter areas of the brainstem and cerebellum. Therefore, from the present results, we cannot conclude that CMDT is associated with WMV globally (in other words, in all WM areas). There were no significant results when total WMV was included as a covariate in the same way as other covariates (e.g., age).

Effects of CMDT on rWMV in Analyses Performed Using Data from Each Sex Individually

Multiple regression analysis revealed no significant correlation between S-A creativity test scores and rWMV in males. In contrast, multiple regression analysis revealed significant positive correlations between S-A creativity test scores and rWMV in widespread white matter areas in females. The extent is presented in Figure 1 and the anatomical labeling in Table III. These significant areas overlapped extensively with areas of significant interaction between sex and S-A creativity test scores.
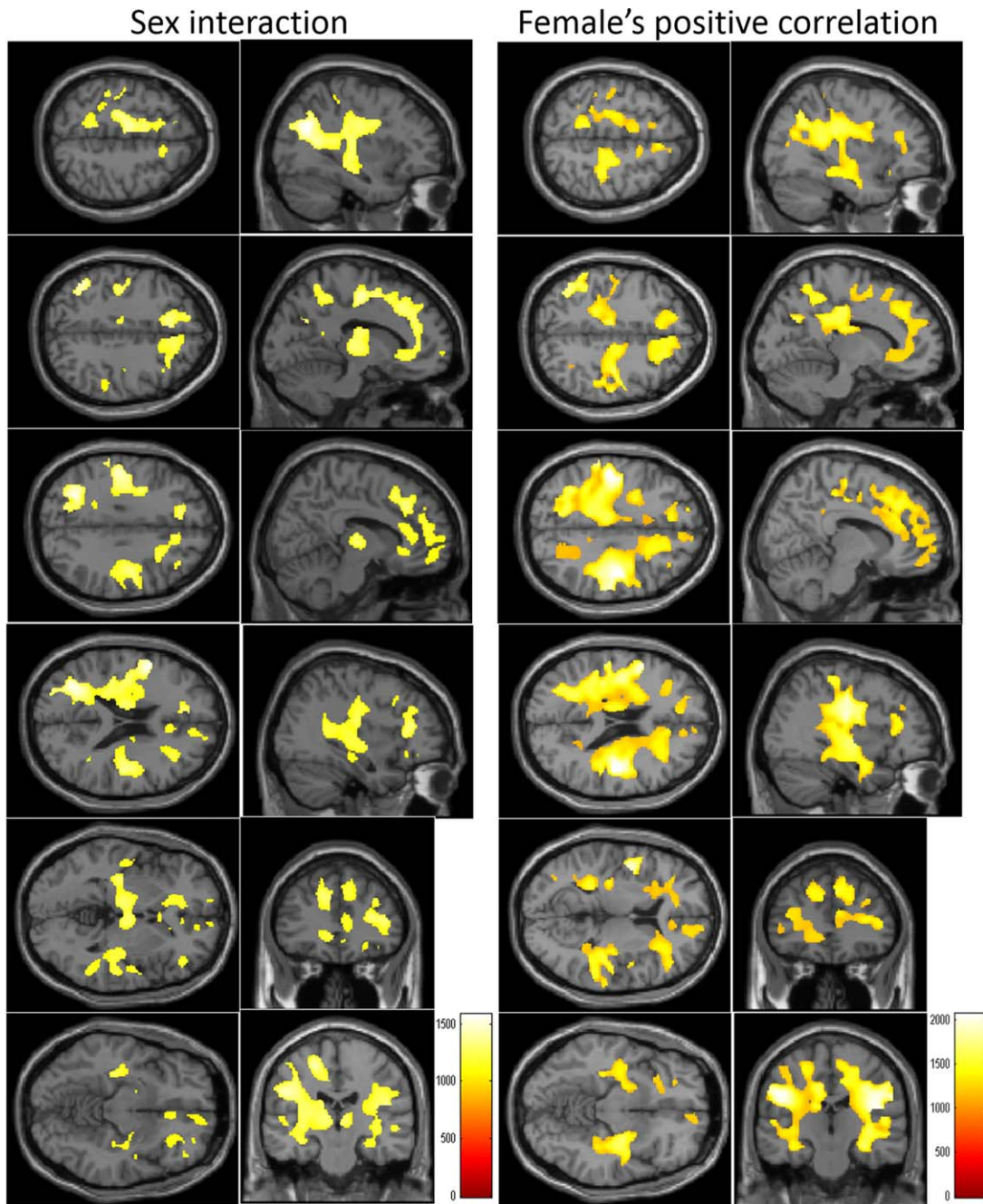
Figure 1.

Effects of interaction between CMDT and sex on rWMV. The two left columns show the areas of significant interaction effects of CMDT and sex on rWMV. The two right columns show the areas of significant positive correlation between CMDT and rWMV. The results shown were obtained using a threshold of TFCE, $P < 0.05$ corrected (FWE) based on 5,000 permutations. Regions of correlation are overlaid on a single subject T1 image of SPM. Significant sex-related interaction effects that are moderated by female-specific positive correlation between CMDT and rWMV are seen in widespread areas below the cortex.

The simple correlation coefficients between the S-A creativity test and rWMV of the major fibers are presented in Table IV. The correlation coefficients for associations between S-A creativity test scores and tWMV in males and females are presented in Table V. As can be seen from these results, the significant interaction effect of sex and S-A

TABLE II. Brain regions exhibiting significant interaction effects of S-A creativity test scores and sex on rWMV

No	Included large bundles** (number of significant voxels in the left and right side of each anatomical area)	X	y	z	TFCE value	Corrected P value (TFCE, FWE)	Cluster size (voxel)
1	Genu of the corpus callosum (658)/ Splenium of the corpus callosum (503)/ Cerebral peduncle (L:8)/Posterior limb of the internal capsule (L:730, R:8)/ Retrolenticular part of the internal capsule (L:587)/Anterior corona radiata (L:55, R:2)/Superior corona radiata (L:726)/ Posterior corona radiata (L:593)/Posterior thalamic radiation (L:515)/Sagittal stratum (L:93)/External capsule (L:147)/ Cingulum (L:8, R:145)/Stria terminalis (L:125)/Superior longitudinal fasciculus (L:1076)/Superior fronto-occipital fasciculus (L:43)/Inferior fronto-occipital fasciculus (L:47)/Tapatum (L:215)	−30	−64.5	27	1,580.96	0.017	72302
2	Anterior corona radiata (R:245)/Superior corona radiata (R:32)	45	−9	27	1,338.85	0.027	25680
3	No major fibers	7.5	28.5	37.5	1,313.20	0.029	16261
4	Posterior limb of the internal capsule (R:69)/Retrolenticular part of the internal capsule (R:440)/Superior corona radiata (R:104)/Posterior corona radiata (R:9)/ Posterior thalamic radiation (R:299)/ Sagittal stratum (R:104)/External capsule (R:124)/Cingulum (R:4)/Heschl gyrus (R:4)/Stria terminalis (R:21)/Superior longitudinal fasciculus (R:830)/Inferior fronto-occipital fasciculus (R:95)/Tapatum (R:73)	−10.5	−43.5	51	1,224.23	0.035	2363
5	No major fibers	18	57	15	1,168.59	0.040	4168
6	No major fibers	6	55.5	−6	1,094.45	0.046	1202
7	No major fibers	−7.5	57	6	1,064.64	0.049	37
8	No major fibers	−12	63	−1.5	1,063.13	0.050	57
9	No major fibers	10.5	46.5	34.5	1,062.04	0.050	41
10	Superior fronto-occipital fasciculus (R:8)	16.5	−9	21	1,061.86	0.050	44

The anatomical labels and significant clusters of major white matter fibers were determined using the ICBM DTI-81 Atlas (http://www.loni.ucla.edu/).

creativity test scores on rWMV was moderated by weak or no correlation in males and positive correlation in females.

When total WMV were included in the covariates in the same way as other covariates (e.g., age), there were no significant results.

Effects of CMDT on FA in Analyses Performed Using Data from Both Sexes

In the total cohort (both sexes), ANCOVA revealed no significant overall negative or positive main effects of S-A creativity test score on FA in any of the regions analyzed. Further, there were no significant interaction effects between S-A creativity test score and sex on FA in any region.

Effects of Each S-a Creativity Subscale Score on rWMV and FA in Analyses Using Data from Both Sexes

In the total cohort (both sexes), ANCOVAs revealed significant positive main effects of the S-A creativity test originality subscore on rWMV for the area adjacent to the right inferior parietal lobule and for the right postcentral gyrus [x, y, z = 36, −28.5, 40.5, TFCE value = 1,065.14, P = 0.047, corrected for multiple comparison using TFCE (FWE), Fig. 2]. There were no other significant main effects. As was the case for the total score, there were significant interaction effects of sex and S-A creativity test elaboration subscore (interaction contrast of the combination of positive correlations in males and negative correlations in females) on rWMV in widespread areas. There

TABLE III. Brain regions exhibiting a significant correlation between S-A creativity test scores and rWMV in females

No	Included large bundles** (number of significant voxels in the left and right side of each anatomical area)	x	y	z	TFCE value	Corrected P value (TFCE, FWE)	Cluster size (voxel)
1	Genu of the corpus callosum (351)/Body of the corpus callosum (538)/Splenium of the corpus callosum (823)/Anterior limb of the internal capsule (L:246)/Posterior limb of the internal capsule (L:148)/Retrolenticular part of the internal capsule (L:302)/Anterior corona radiata (L:1257)/Superior corona radiata (L:1559)/Posterior corona radiata (L:1259)/Posterior thalamic radiation (L:341)/Sagittal stratum (L:116)/External capsule (L:264)/Cingulum (L:461)/Heschl gyrus (L:97)/Stria terminalis (L:150)/Superior longitudinal fasciculus (L:1746)/Superior fronto-occipital fasciculus (L:160)/Inferior fronto-occipital fasciculus (L:165)/Tapatum (L:206)	45	−15	22.5	2,070.74	0.009	98,520
2	Genu of the corpus callosum (332)/Body of the corpus callosum (252)/Anterior limb of the internal capsule (R:50)/Posterior limb of the internal capsule (R:99)/Retrolenticular part of the internal capsule (R:297)/Anterior corona radiata (R:1014)/Superior corona radiata (R:1843)/Posterior corona radiata (R:185)/Posterior thalamic radiation (R:107)/Sagittal stratum (R:440)/External capsule (R:292)/Cingulum (R:153)/Stria terminalis (R:173)/Superior longitudinal fasciculus (R:1502)/Superior fronto-occipital fasciculus (R:161)/Inferior fronto-occipital fasciculus (R:186)/Uncinate fasciculus (R:89)/Tapatum (R:39)	−48	−21	31.5	2,042.42	0.009	102,090
3	Splenium of the corpus callosum (57)/Posterior corona radiata (R:122)/Tapatum (R:3)	19.5	−61.5	27	1,191.41	0.039	3476
4	Cingulum (L:62)	−4.5	18	31.5	1,111.90	0.048	618
5	Splenium of the corpus callosum (13)	12	−40.5	31.5	1,093.99	0.050	142

The anatomical labels and significant clusters of major white matter fibers were determined using the ICBM DTI-81 Atlas (http://www.loni.ucla.edu/).

were also significant interaction effects of sex and S-A creativity test fluency subscore (interaction contrast of the combination of positive correlations in males and negative correlations in females) on rWMV in several more confined white matter areas (Fig. 3 left). There were no other significant effects, but with a more lenient threshold, there were tendencies for effects of each score on rWMV of widespread areas (Fig. 3 right). ANCOVAs also revealed no significant overall main effects and no significant interaction effects of S-A creativity subscores on FA.

DISCUSSION

This study investigated the associations between individual CMDT and rWMV. We employed a large sample size, the newest preprocessing techniques, and robust permutation-based statistical techniques. Our findings showed that higher CMDT was associated with rWMV in widespread white matter areas below the cerebral neocortex, but only in females, partly congruent with our hypotheses. Finally, subscale analyses revealed a significant association pattern of the S-A elaboration subscore with rWMV similar to that of the total CMDT score, a distinct, significant association pattern of the originality subscore with rWMV, and a significant main effect of originality subscore on rWMV regardless of sex in the areas beneath the right inferior parietal lobule and right postcentral gyrus.

The present results support the notion that brain connectivity is important for CMDT and that there is a sex difference in this association. A previous theoretical review speculated that "connectivity, including the myelinated subcortical connections, might be important for creativity" [Heilman et al., 2003, p. 371] because creativity requires "transitions from one idea to another … unheard of

TABLE IV. Simple correlation coefficients (and *P* values in brackets) between S-A creativity test scores and rWMV of white matter bundles in 776 males and 560 females

	Left or median fibers		Right fibers	
	Male	Female	Male	Female
Middle cerebellar peduncle	0.004 (0.922)	0.074 (0.080)	—	—
Pontine crossing tract	0.010 (0.781)	0.058 (0.172)	—	—
Corpus callosum genu	−0.026 (0.462)	0.092 (0.030)	—	—
Corpus callosum body	0.013 (0.722)	0.081 (0.056)	—	—
Corpus callosum splenium	−0.003 (0.931)	0.099 (0.020)	—	—
Fornix	−0.007 (0.835)	−0.001 (0.977)	—	—
Corticospinal tract	0.016 (0.657)	0.057 (0.180)	0.017 (0.631)	0.050 (0.240)
Medial lemniscus	0.001 (0.986)	0.059 (0.166)	−0.004 (0.919)	0.050 (0.235)
Inferior cerebellar peduncle	−0.003 (0.942)	0.052 (0.222)	−0.009 (0.812)	0.047 (0.271)
Superior cerebellar peduncle	0.011 (0.761)	0.046 (0.272)	0.002 (0.961)	0.058 (0.168)
Cerebral peduncle	−0.013 (0.727)	0.056 (0.184)	−0.022 (0.532)	0.046 (0.281)
Anterior limb of the internal capsule	−0.007 (0.842)	0.079 (0.063)	−0.026 (0.473)	0.067 (0.115)
Posterior limb of the internal capsule	−0.047 (0.187)	0.085 (0.044)	−0.044 (0.219)	0.072 (0.087)
Retrolenticular part of the internal capsule	−0.050 (0.165)	0.096 (0.023)	−0.044 (0.218)	0.092 (0.029)
Anterior corona radiata	−0.009 (0.807)	0.107 (0.011)	−0.012 (0.734)	0.103 (0.015)
Superior corona radiata	−0.004 (0.913)	0.113 (0.007)	0.004 (0.912)	0.116 (0.006)
Posterior corona radiata	−0.012 (0.738)	0.130 (0.002)	−0.022 (0.533)	0.095 (0.025)
Posterior thalamic radiation	−0.041 (0.260)	0.089 (0.036)	−0.031 (0.381)	0.090 (0.034)
Sagittal stratum	−0.024 (0.502)	0.069 (0.104)	0.025 (0.494)	0.102 (0.015)
External capsule	−0.024 (0.510)	0.088 (0.038)	−0.007 (0.844)	0.104 (0.014)
Cingulate gyrus	−0.017 (0.645)	0.113 (0.007)	−0.032 (0.367)	0.086 (0.042)
Cingulum	−0.016 (0.664)	0.087 (0.040)	−0.019 (0.591)	0.046 (0.280)
Stria terminalis	−0.043 (0.231)	0.079 (0.062)	−0.015 (0.677)	0.067 (0.111)
Superior longitudinal fasciculus	−0.013 (0.714)	0.139 (0.001)	−0.002 (0.958)	0.134 (0.002)
Superior fronto-occipital fasciculus	−0.009 (0.803)	0.111 (0.008)	−0.033 (0.365)	0.105 (0.013)
Inferior fronto-occipital fasciculus	0.015 (0.679)	0.076 (0.071)	0.015 (0.669)	0.091 (0.032)
Uncinate fasciculus	0.002 (0.956)	0.002 (0.965)	0.018 (0.623)	0.084 (0.047)
Tapatum	−0.042 (0.246)	0.119 (0.005)	−0.018 (0.620)	0.083 (0.048)
Arcuate fasciculus.	−0.009 (0.808)	0.137 (0.001)	−0.016 (0.655)	0.136 (0.001)

The anatomical divisions of major white matter fibers were determined using the ICBM DTI-81 Atlas (http://www.loni.ucla.edu/) except in the case of the arcuate fasciculus. To construct the mask images of the arcuate fasciculus, a DTI-derived atlas (http://www. natbrainlab.com/) was used [Thiebaut de Schotten et al., 2011].

combination of elements, the subtlest associations of analogy ... where partnerships can be joined or loosened ..." according to James [James, 1890]. As summarized in the Introduction section, functional and structural studies have suggested associations between brain connectivity and CMDT. As discussed below, larger rWMV is believed to be due to microstructural and architectonic mechanisms of brain connection. Thus, the present results of female-specific positive correlation between CMDT and rWMV suggest that brain structural connectivity is important for creativity, at least in females.rWMV and FA, whose correlates of CMDT have been investigated [Takeuchi et al.,

TABLE V. Correlation coefficients (and *P* values in brackets) between total WMV and S-A creativity test score in simple regression analyses (data of each sex) and multiple regression analyses (all sample's data)

	Total WMV			
	Male *r* (*P* value)	Female *r* (*P* value)	All sample Beta (*P* value)	Differences in *r* between males and females (*P* value)
S-A creativity test score (M: 776, F: 560)	−0.023 (0.520)	0.122 (0.004)	0.025 (0.288)	0.009

Multiple regression analyses with sex as a covariate.

2010b], are only weakly associated in deep WM areas [Hugenschmidt et al., 2008] and supposed to reflect different properties of WM. The list of possible physiological mechanisms that underlie greater FA, rWMV, and cognitive abilities includes "myelination and myelin or membrane thickness and increases in the diameter of axons" [Takeuchi et al., 2013c]. Possible physiological mechanisms that lead to greater rWMV and cognitive abilities and unchanged FA are "the size and number of glial cells (forming a major portion of WM), number of axon collateral spines, or a pure increase in WM volume (or an increase in all of the physiological components of WM, while the

composites remain the same)." These mechanisms may facilitate efficient interactions among different brain regions, leading in turn to innovative combinations of ideas and better CMDT.

Higher WMV in widespread subcortical regions was associated with CMDT in females, suggesting that multiple distinct cognitive mechanisms are critical for CMDT. For example, as discussed in previous studies [Takeuchi et al., 2010a,b], the frontal lobe and the striatum are involved in cognitive flexibility [Eslinger and Grattan, 1993], which is the ability to break fixed rules or patterns and form new and better patterns of ideas, cognitive processes critical for creativity [Guilford, 1967]. Another important function of the frontal lobe assumed critical for creativity is the fluency of idea generation [Baldo et al., 2001; Dietrich, 2004]. As discussed previously [Takeuchi et al., 2010b], regions such as the inferior parietal lobule and occipital lobule are thought to be important for visual imagery [Yomogida et al., 2004], which in turn is associated with creativity [Finke, 1996]. The bilateral temporal gyri are associated with verbal functions, which are important for verbal CMDT [Friederici et al., 2009]. The temporoparietal junction is involved in the integration of multisensory information [Terhune, 2009], and integration of disparate information is thought to be an important generator of creative ideas [Spearman, 1931]. In a similar way, interhemispheric transfer of information via the corpus callosum could allow for the integration of dissimilar information stored in distant brain structures [Heilman et al., 2003]. Thus, strong direct white matter connectivity between these areas or via the corpus callosum may facilitate CMDT.

We suggest sex hormones as possible factors contributing to the females-specific relationship between rWMV and creativity. CMDT was greater in females in the present sample (Table I) and found to fluctuate with menopausal cycle and sex hormones [Krug et al., 1994].
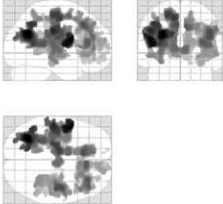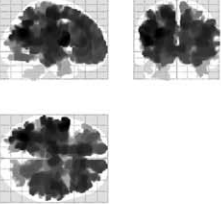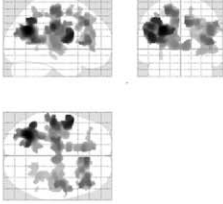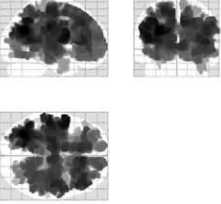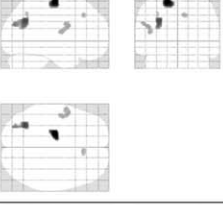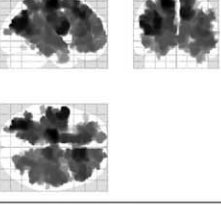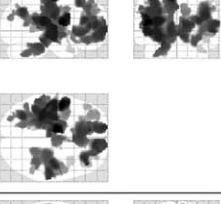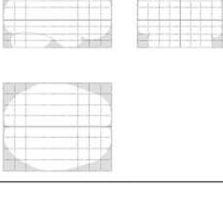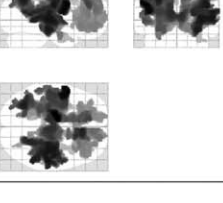
Figure 2.
Significant main effects of S-A creativity test total score and subscale scores on rWMV. The figures in the left columns show the areas with significant main effects of total score and each S-A creativity test subscale score on rWMV. The results shown were obtained using a threshold of TFCE, $P < 0.05$ corrected (FWE) based on 5,000 permutations. Regions of correlation are superimposed on a glass brain image of SPM. There were significant main effects of originality subscore on rWMV in the area adjacent to the right inferior parietal lobule and right post central gyrus. The figures in the right columns show the areas of tendencies for main effects of S-A creativity test total score and each subscale score on rWMV. The results shown were obtained using a threshold of TFCE, $P < 0.05$ uncorrected based on 5,000 permutations. Regions of correlation are superimposed on a glass brain image of SPM. There were tendencies for effects of originality subscore on rWMV in widespread areas.

Moreover, sex hormones are known to contribute to brain volume development in a sexually dimorphic manner [Peper et al., 2009]. Finally, as described in Introduction, female are characterized by a stronger empathizing style and gender differences were found in 5- to 6-year olds in the motifs they generated during the free drawing [Abraham, 2016]. Specifically, more boys drew moving objects, such as vehicles, trains, and aircraft, than girls and boys prefer cold colors, whereas more girls drew persons and flowers than boys and girls prefer warm colors. And, free drawings by the girls with a genetic disorder that is characterized by an overproduction of adrenal androgen

contained more masculine features and their drawings were not differentiable from drawings of unaffected boys [Abraham, 2016]. However, the present project does not include data on sex hormones; therefore, this is pure speculation. Future studies are needed to reveal why only females show a positive association between CMDT and WMV.

The correlations between CMDT and rWMV observed in this study were relatively weak compared to those seen in previous, conventional whole-brain multiple regression analyses investigating cognitive differences and neural indices. However, when we compare correlation strength in this way, several critical differences in analytic strategy must be considered. First, the robust associations identified in the present study were revealed by permutation tests, which are quite accurate [Silver et al., 2012]. Second, the correlation strengths of significant areas in whole-brain analyses are strongly over-fitted and far from the true strength of the associations, especially in studies with small sample sizes [Vul et al., 2009]. It should be noted that when whole-brain multiple regression analyses show significant results, they do not prove that the associations are strong or weak, just that they are not null. In fact, several structural studies of individual differences that used the data of large healthy samples ($N >$ several hundred) to investigate the associations between neuroimaging measures and establish psychological measures [Magistro et al., 2015; Schilling et al., 2012; Takeuchi et al., 2015b,c] all showed weak correlations. Moreover, the correlation coefficients in Table IV were deduced using anatomically predefined regions of interest instead of significant areas

Figure 3.

Effects of interactions between S-A creativity test scores (total score and each subscale score) and sex on rWMV moderated by negative correlations in males and positive correlations in females. The figures in the left columns show the areas of significant interaction effects of S-A creativity test total score and subscale scores on rWMV. The results shown were obtained using a threshold of TFCE, $P < 0.05$ corrected (FWE) based on 5,000 permutations. Regions of correlation are superimposed on a glass brain image of SPM. There were significant interaction effects of total score and sex on rWMV in widespread areas and significant interaction effects of elaboration subscore and sex on rWMV in widespread areas. Significant interaction effects of fluency subscore and sex on rWMV were more confined, but found in several distributed areas. The figures in the right columns show the areas of tendencies for interaction effects between S-A creativity test scores (total score of each subscale score) and sex on rWMV moderated by negative correlations in males and positive correlations in females. The results shown were obtained using a threshold of TFCE, $P < 0.05$ uncorrected based on 5,000 permutations. Regions of correlation are superimposed on a glass brain image of SPM. There were tendencies for effects of each score on rWMV in widespread areas.

in the whole-brain analyses; therefore, they are free from overfitting and should be lower than those yielded from whole-brain analyses due to the mechanism pointed out by Vul et al. [2009]. Therefore, we believe that the strengths of the correlations between individual cognitive differences and brain structural characteristics are generally low and that the results presented in Table IV more accurately reflect the true strengths.

We speculated rich white matter pathways (increased rWMV) adjacent to the anterior IPL, where significant positive main effect (regardless of sex) of originality on rWMV was observed, may facilitate individual originality through this area's functions of mental imagery and attention. The IPL is one of the areas that is most consistently activated during divergent thinking (for meta-analyses, see [Gonen-Yaacovi et al., 2013; Wu et al., 2015]). Previous studies have shown the association between CMDT and visual imagery even when the CMDT was verbal one [LeBoutillier and Marks, 2003]. Also, the IPL plays a key role in mental imagery synthesis [Yomogida et al., 2004]. Thus, one simple interpretation of our results is that rich white matter pathways in the right IPL support sharper mental imagery, which in turn facilitates creative thinking. However, one must be careful as this interpretation is speculative and the right IPL has multiple functions [Desmurget and Sirigu, 2012]. Further, the IPL is also associated with attention [Macaluso et al., 2000] and has been suggested that the activation of this area during idea generation can be interpreted as this cognitive process involves a state of focused internally directed attention [Benedek et al., 2014a]. This may be relevant, too. Nonetheless, as shown in Figure 2, the significant main effect of originality on rWMV in the area around the IPL may be only a small part of the main effect of originality on rWMV in widespread areas. Related to this, the temporoparietal junction, which is adjacent to the IPL, may also be relevant. During divergent thinking, unlike the IPL, this area is deactivated [Fink et al., 2010]. The areas of the temporoparietal junction have multiple functions and, while this area is involved in information integration, it is also involved in reorienting attention to the distractor [Benedek et al., 2014b]. The deactivation of this area is thought to prevent reorienting to irrelevant stimulation during goal-driven, top-down behavior, which may serve the executive function of task-shielding during cognitively demanding divergent thinking [Benedek et al., 2014b]. However, although this area is deactivated during divergent thinking, this area seems to be activated during conditions in which creativity is induced [Fink et al., 2010]. Given the importance of unfocused attention in creativity [Folley et al., 2003; Kasof, 1997; Necka, 1999; Rawlings, 1985], the involvement of the temporoparietal junction in originality may also be important.

Further, in this present sample of 1,336 subjects, when rWMV images were replaced by rGMV images and the same analyses were performed (i.e., same ANCOVA designs and covariates), there were no significant associations with CMDT and CMDT subscales. Among the contrasts that yielded significant results in the rWMV analyses (main positive effect of originality and interaction effect of total score and sex), there were tendencies for positive main effects of the originality subscore (regardless of sex) on rGMV in the left postcentral gyrus [$P = 0.092$, corrected for multiple comparison using TFCE (FWE)] and areas in the precuneus and right inferior parietal lobule to right postcentral gyrus ($0.1 < P < 0.15$, corrected). We suggest that failure to replicate our previous finding could be due to the use of statistical tests [Takeuchi et al., 2010a] that turned out to be inappropriate (such as the use of the cluster test for VBM toward images with relatively low smoothness), as well as instability of results due to low sample size in our previous study. Previous studies investigating associations between CMDT and gray matter amount (gray matter volume/density and cortical thickness) have also frequently suggested that CMDT is associated with the posterior midline structures, such as the precuneus/cuneus and posterior cingulate cortex. However, these studies also suffer from poor reproducibility. Including our previous study, we are aware of nine studies investigating the associations between verbal CMDT and gray matter amount [Chen et al., 2015; Cousijn et al., 2014; Fink et al., 2014; Gansler et al., 2011; Jauk et al., 2015; Jung et al., 2010b; Kühn et al., 2014; Takeuchi et al., 2010a; Zhu et al., 2013]. Among these, eight studies investigated total scores and four studies found associations between the total CMDT score and measures of gray matter amount in these areas (posterior midline structures). However, the locations were somewhat different among studies and two studies found positive associations [Kühn et al., 2014; Takeuchi et al., 2010a], while two studies found negative associations [Chen et al., 2015; Jung et al., 2010b]. The lack of any robust associations with rGMV may be partly due to the fact that CMDT is associated both with cognitive factors that are improved by greater brain volume, such as processing speed [Hong et al., 2015; Preckel et al., 2011], and with factors that lead to lower rGMV such as a tendency for psychosis [Fusar-Poli et al., 2011; Woody and Claridge, 1977]. This underscores the importance of rigorous statistical techniques as well as larger sample sizes. However, among previous different studies, there are number of methodological differences including the difference between the eastern sample in this study and the western sample in previous studies, types of dependent variables (measures used for divergent thinking as well as whether the study focused on total scores or subscores, i.e., rGMV vs. cortical thickness, etc,); thus, we cannot effectively conclude this from the present study. Other possibilities include how the scoring is performed. Our present test as well as the widely used TTCT rate originality from statistical frequency (how rare certain answers are)[Torrance, 1966], while other tests ask the scorers to rate originality [Jauk et al., 2015]. Nonetheless,

these are speculations and there is little that can be drawn from insignificant findings in the whole-brain analyses.

In the present study, there were no significant associations between CMDT and FA. This is in contrast to the findings of our previous study that showed a positive correlation between CMDT and FA in a sample of 55 young adults (who were also included in this study) [Takeuchi et al., 2010b] as well as a study by Jung et al. [2010a], which showed negative associations between FA and CMDT, using 72 subjects, in the inferior frontal white matter areas. Ryman et al. [2014] utilized DTI and performed analyses of metrics of connectivity organization, including connectivity strength, clustering, and communication efficiency using data from 83 subjects. Their results suggest female-specific negative associations between these measures and CMDT. Our present results failed to find significant findings between FA and CMDT. We cite a few possibilities for these discrepancies in the findings among studies. First, as for the findings of our previous study, as described in the Methods, our new preprocessing method effectively solved the major problems of voxel-based analyses of FA images, namely misregistration of white matter tracts and (especially) signal contamination from nonwhite matter tissues [Smith et al., 2006]. Thus, our previous findings may be explained by the associations of CMDT performance with widespread increases in rWMV (which could lead to relatively smaller areas of gray matter area), which was found only for females in the present study. Conversely, a study by Jung et al. [2010a,b] used tract-based spatial statistics (TBSS) [Smith et al., 2006] for FA analyses, and TBSS processed images substantially different from ours. Further, Ryman et al. [2014] used yet another substantially different method to preprocess DTI. Thus, these differences in preprocessing methods may explain the discrepancies in study findings, and, in the case of Ryman et al (2014)'s finding, their metrics such as those reflecting small-worldness may work in a compensatory way and rWMV measures and their metrics may associate with CMDT in an opposing way. However, these are pure speculations and, unlike the case of rGMV analyses, relevant previous studies are still lacking and more studies should be conducted. In addition, the instability of the results due to small sample sizes may explain previous findings using the sample size of 2 digits. Unlike previous studies that showed positive associations between FA and simple processing speed [Catani et al., 2003; Penke et al., 2010; Tuch et al., 2005; Vernooij et al., 2009], in the present sample, FA was not significantly related to the simple processing speed measure in any area despite far greater statistical power and the use of advanced preprocessing procedures for FA images (data not shown). However, these previous studies were characterized by either: (a) older subjects, suggesting that FA is likely to reflect the aging processes that also affect mental speed [Penke et al., 2010; Vernooij et al., 2009], and (b) small sample sizes (n = around 10) [Catani et al., 2003; Tuch et al., 2005]

lacking statistical power for robust results considering the effect size seen in structural studies using the huge sample size. On the contrary, performance on the Color–Word task was associated with rWMV in widespread white matter areas in a sample of several hundred subjects included in the present cohort [Magistro et al., 2015]. Contrary to the notion that white matter structures are associated with mental speed [Ylikoski et al., 1993] and creativity [Heilman et al., 2003], we propose that these measures are not strongly associated with white matter FA in a fully developed young adult sample like ours whose FA may not be so strongly associated with white matter maturation or aging. Instead, we propose that rWMV is the measure that best reflects the capacity for cognitive processes that have traditionally been associated with white matter structure. Not only the case of processing speed, anatomical correlates of empathizing and executive functioning showed same patterns and in a large sample, rWMV analyses showed more widespread associations with cognitive differences than FA analyses [Takeuchi et al., 2013b,c]. Other possibilities include factors we mentioned for discussions of rGMV, such as the complex psychological nature of CMDT, which associates both with factors such as psychosis and processing speed.

Our study has a limitation common to previous studies investigating the association between specific neural mechanisms and creativity, which is a study population restricted to young, healthy subjects (18- to 27- year old) with higher education levels [Jung et al., 2010b; Takeuchi et al., 2010a,b]. It must be investigated whether the present findings hold true for other populations, such as children, the less educated, and the elderly. However, restricting the study to subjects with similar characteristics is warranted given the weak associations between individual cognitive functions and brain structures [Takeuchi et al., 2015a]. Furthermore, as has been discussed previously [Takeuchi et al., 2012a], there is correlation between intelligence and creativity among subjects with relatively low intelligence [Jauk et al., 2013; Karwowski et al., 2016]. In addition, there are differences in the neural correlates of individual differences of creativity between subjects with lower intelligence and those with higher intelligence [Jauk et al., 2015; Jung et al., 2009]. Thus, focusing on more intelligent subjects may better reveal the specific neural mechanisms of creativity.

In conclusion, our study showed that CMDT is associated with rWMV across widespread white matter areas below the neocortex, but only in females. It has long been suggested that brain connectivity is important for creativity [Heilman et al., 2003]. Psychological and functional imaging studies have suggested CMDT has different cognitive psychological and neural bases, as summarized in the Introduction. Some studies on the association between CMDT structural and functional connectivity have supported this notion [Takeuchi et al., 2012a,b], whereas others found an inverse association between white matter

structural properties and CMDT in females [Ryman et al., 2014]. The present study utilized the newest preprocessing method of VBM for rWMV measurements, and specific rWMVs were shown to be strongly associated with cognitive function [Takeuchi et al., 2013c]. Through rigorous preprocessing and statistical techniques and by using a large sample, our findings further supported the importance of brain connectivity for creativity as well as its female-specific association, as well as the importance of brain connectivity beneath the right inferior parietal lobule for originality regardless of sex.

ACKNOWLEDGMENTS

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