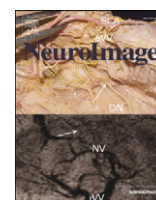


Contents lists available at [ScienceDirect](http://ScienceDirect.com)

## NeuroImage

journal homepage: [www.elsevier.com/locate/ynimg](http://www.elsevier.com/locate/ynimg)

## Cognitive and neural correlates of the 5-repeat allele of the dopamine D4 receptor gene in a population lacking the 7-repeat allele



Hikaru Takeuchi <sup>a,\*</sup>, Hiroaki Tomita <sup>b</sup>, Yasuyuki Taki <sup>a,c,d</sup>, Yoshie Kikuchi <sup>b</sup>, Chiaki Ono <sup>b</sup>, Zhiqian Yu <sup>b</sup>, Atsushi Sekiguchi <sup>c,g</sup>, Rui Nouchi <sup>f</sup>, Yuka Kotozaki <sup>e</sup>, Seishu Nakagawa <sup>g</sup>, Carlos Makoto Miyauchi <sup>h</sup>, Kunio Iizuka <sup>g,i</sup>, Ryoichi Yokoyama <sup>g,j</sup>, Takamitsu Shinada <sup>g</sup>, Yuki Yamamoto <sup>g</sup>, Sugiko Hanawa <sup>g</sup>, Tsuyoshi Araki <sup>e</sup>, Hiroshi Hashizume <sup>a</sup>, Keiko Kunitoki <sup>k</sup>, Yuko Sassa <sup>a</sup>, Ryuta Kawashima <sup>a,e,g</sup>

<sup>a</sup> Division of Developmental Cognitive Neuroscience, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

<sup>b</sup> Department of Disaster Psychiatry, International Research Institute of Disaster Science, Tohoku University, Sendai, Japan

<sup>c</sup> Division of Medical Neuroimage Analysis, Department of Community Medical Supports, Tohoku Medical Megabank Organization, Tohoku University, Japan

<sup>d</sup> Department of Nuclear Medicine and Radiology, Institute of Development, Aging and Cancer, Tohoku University, Japan

<sup>e</sup> Smart Ageing International Research Center, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

<sup>f</sup> Human and Social Response Research Division, International Research Institute of Disaster Science, Tohoku University, Sendai, Japan

<sup>g</sup> Department of Functional Brain Imaging, Institute of Development, Aging and Cancer, Tohoku University, Sendai, Japan

<sup>h</sup> Graduate School of Arts and Sciences, Department of General Systems Studies, The University of Tokyo, Tokyo, Japan

<sup>i</sup> Department of Psychiatry, Tohoku University Graduate School of Medicine, Sendai, Japan

<sup>j</sup> Japan Society for the Promotion of Science, Tokyo, Japan

<sup>k</sup> Faculty of Medicine, Tohoku University, Sendai, Japan

## ARTICLE INFO

## Article history:

Accepted 28 January 2015

Available online 3 February 2015

## ABSTRACT

The 5-repeat allele of a common length polymorphism in the gene that encodes the dopamine D4 receptor (DRD4) is robustly associated with the risk of attention deficit hyperactivity disorder (ADHD) and substantially exists in Asian populations, which have a lower ADHD prevalence. In this study, we investigated the effect of this allele on microstructural properties of the brain and on its functional activity during externally directed attention-demanding tasks and creative performance in the 765 Asian subjects. For this purpose, we employed diffusion tensor imaging, N-back functional magnetic resonance imaging paradigms, and a test to measure creativity by divergent thinking. The 5-repeat allele was significantly associated with increased originality in the creative performance, increased mean diffusivity (the measure of how the tissue includes water molecules instead of neural and vessel components) in the widespread gray and white matter areas of extensive areas, particularly those where DRD4 is expressed, and reduced task-induced deactivation in the areas that are deactivated during the tasks in the course of both the attention-demanding working memory task and simple sensorimotor task. The observed neural characteristics of 5-repeat allele carriers may lead to an increased risk of ADHD and behavioral deficits. Furthermore, the increased originality of creative thinking observed in the 5-repeat allele carriers may support the notion of the side of adaptivity of the widespread risk allele of psychiatric diseases.

© 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

## Introduction

The dopamine receptor D4 (DRD4) gene locates on chromosome 11p15.5. As summarized previously (Swanson et al., 2000), this gene has a polymorphism in a coding region—a variable number of tandem repeats (VNTR) of a 48-base pair sequence in exon 3 (Lichter et al., 1993) that codes for a variation in the third intracellular loop of the

D4 receptor. This gene is expressed in a wide range of brain areas (Mrzljak et al., 1996; Van Tol et al., 1992). A specific allele, the 7-repeat allele, of this polymorphism has been robustly associated with the risk of attention deficit hyperactivity disorder (ADHD) via multiple meta-analyses (Li et al., 2006). However, in Asian populations, the 7-repeat allele is scarce or absent (Li et al., 2006) and perhaps partly because of this, the prevalence of ADHD is quite low (Faraone and Biederman, 1998). On the other hand, another allele, the 5-repeat allele, of this polymorphism has also been shown to be associated with an increased risk of ADHD via meta-analysis, and is relatively more frequently observed in Asian samples than the 7-repeat allele (Li et al., 2006). It has been shown that the DRD4 gene's polymorphisms lead to the

\* Corresponding author at: Division of Developmental Cognitive Neuroscience, IDAC, Tohoku University, 4-1 Seiryō-cho, Aoba-ku, Sendai 980-8575, Japan. Fax: +81 22 717 7988.

E-mail address: [takehi@idac.tohoku.ac.jp](mailto:takehi@idac.tohoku.ac.jp) (H. Takeuchi).

difference in how well the receptors bind with dopamine and similar compounds (Van Tol et al., 1992), and it has been assumed this basic difference leads to the difference of the phenotype. The initial study (Van Tol et al., 1992) has just shown the inefficiency of receptors from 7-repeat alleles to bind compared with those of receptors from 2-repeat alleles and 4-repeat alleles. However, the 5-repeat allele has shown the same phenotype as the 7-repeat allele with regard to the effects on ADHD; it may therefore be assumed that the pharmacological aspects and effects of the 5-repeat allele on various characters can be parallel to those of the 7-repeat allele.

Previous genetic studies have shown the effects of the 7-repeat allele in several behavioral variables (Szekely et al., 2011) and regional gray matter structures (Durstun et al., 2005; Monuteaux et al., 2008; Shaw et al., 2007). In particular, using a large sample size, Shaw et al. (2007) have shown that the 7-repeat allele carriers have a thinner right orbitofrontal/inferior prefrontal and posterior parietal cortex. Like other polymorphisms findings, some of the initial results regarding *DRD4* polymorphism with less statistical power cannot be replicated (Kluger et al., 2002). A recent study showed a robust association between the 7-repeat allele and a slow processing speed (Szekely et al., 2011). Another interesting recent finding was the association between the 7-repeat risk allele and decreased performance of the creativity measured by a divergent thinking test in an Israeli sample (Mayseless et al., 2013). It should be noted that unlike Asian samples, the Israeli sample is known to have a high prevalence of ADHD (Cohen et al., 2013) as well as a high prevalence of the risk allele of ADHD (Mayseless et al., 2013), which is supposed to partly contribute to the cultural difference in the prevalence of ADHD (Faraone and Biederman, 1998). In the Israeli sample, this association between the 7-repeat risk allele and decreased performance of creativity measured by a divergent thinking task is despite the previously known robust association between impaired selective attention and increased divergent thinking (for the full discussion of this matter, see Takeuchi et al., 2011b).

However, to date, the following points have not been investigated. (a) The association between the polymorphism of *DRD4* and brain microstructural properties measured by diffusion tensor imaging (DTI), such as fractional anisotropy and mean diffusivity (MD); (b) the association between the polymorphism of *DRD4* and neural activity during externally directed cognitive tasks using a sample size with a statistical power that allows the analysis of this type of polymorphism ( $N > a$  few hundred at least, for estimates, see Supplemental Discussion); and (c) the neural and psychological effects of the 5-repeat allele of *DRD4* in a sample with a relatively low risk of ADHD. We investigated these issues using DTI, an n-back working memory functional magnetic resonance imaging (fMRI) paradigm, and psychological measures, in several hundred Asian samples.

The fractional anisotropy (FA) measure of DTI has proved useful in revealing the neural basis of ADHD and provided insights into the etiology of the psychiatric diseases (Konrad and Eickhoff, 2010). It also correlated with cognitive functions, including ones that were shown to be associated with the *DRD4* gene in normal adults (Jung et al., 2010a; Takeuchi et al., 2013b). On the other hand, the MD measure of DTI shows a unique property compared with MD, and reduced MD is likely to reflect the increase in tissue density due to the shape of the neuron or glias, synapse, or enhancement of tissue organization (strengthening of axonal or dendritic backbones and surrounding tissue) (Assaf and Pasternak, 2008; Sagi et al., 2012). Consistently, patients with neuronal degeneration have shown an increase in MD (Andreone et al., 2007; Kantarci et al., 2001; Nusbaum et al., 2001). In addition, further patients with ADHD show an increase in MD (Konrad and Eickhoff, 2010). Furthermore, a recent investigation elucidated a unique property of MD in the gray matter. This is partly due to its sensitivity toward neural plasticity (Abe et al., 2014; Sagi et al., 2012). More pertinent to the present study's subject is its association with dopamine. For example, MD in the dopaminergic system's areas (MDDS) has been shown to be

more sensitive to the pathology of neurodegeneration of dopaminergic systems than other MRI measures and PET measures of dopamine receptor binding (Péran et al., 2010; Seppi et al., 2004). It can sensitively detect the neural plasticity involving dopamine function change (Razek et al., 2011; Takeuchi et al., 2014c). It also shows robust correlation with the motivational state, which is highly relevant to dopamine as well as traits crucially related to dopamine (Bjørnebekk et al., 2012; Laricchiuta et al., 2013; Picerni et al., 2013; Takeuchi and Kawashima, 2013). Thus, *DRD4* polymorphism may well be associated with these DTI measures, and its investigation can reveal new insights into the effects of *DRD4* polymorphisms.

Corresponding to the three aforementioned uninvestigated issues, we hypothesized that the effect of the 5-repeat allele of *DRD4* is reflected in microstructural properties in a wide range of areas where the *DRD4* gene is expressed. We also hypothesized that it is reflected in reduced task-induced deactivation (TID) in the areas that are deactivated during attention-demanding tasks (default mode network; DMN). This is because TID in the DMN is thought to reflect inefficient attention reallocation (Takeuchi et al., 2011b) and reduced TID has been associated with increased inattentive tendencies such as increased mind wandering in nonclinical groups (Brewer et al., 2011). On the other hand, in clinical ADHD groups, the patient group tends to show a decrease in activities during attention-demanding tasks in areas of the lateral prefrontal and certain areas in the parietal cortex that are activated during the tasks, although some studies have also shown reduced TID in the DMN (Brown et al., 2012; Brown et al., 2011). Furthermore, it has been suggested that one of the reasons why the risk alleles of psychiatric diseases are widely prevalent is that these alleles have adaptive effects on several processes, such as creativity, when they are not accumulated in the individual's genome (Horrobin, 2002). Therefore, considering these and the previously reported robust association between impaired selective attention and increased creativity measured by divergent thinking, we hypothesized that the risk allele of ADHD in the present sample leads to increased divergent thinking performance.

## Material and methods

### Subjects

Seven hundred and seventy-eight healthy, right-handed individuals (433 men and 344 women;  $20.7 \pm 1.9$  years) participated in this study as part of an ongoing project investigating associations among brain imaging, cognitive functions, aging, genetics, and daily habits. Data derived from the subjects in this study are to be used in other studies irrelevant to the theme of this study. Some of the subjects who participated in this study also became subjects of intervention studies (psychological and imaging data recorded before the intervention were used in this study) (Takeuchi et al., 2013a). Psychological tests and MRI scans not described in this study were performed together with those described in this study. 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. They were recruited using advertisements on bulletin boards at Tohoku University or via email introducing the study. These advertisements and emails specified the unacceptable conditions in individuals with regard to participation in the study such as handedness (left-hand), the existence of metal in and around the body, claustrophobia, the use of certain drugs, history of head trauma, psychiatric and neurological diseases, and previous participation in related experiments. We provided a routine laboratory questionnaire to all potential experimental subjects for the assessment of psychiatric illnesses and recent drug use history. In this questionnaire, each subject answered questions related to their current or previous experiences of any list of illnesses and listed drugs that they had recently taken. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). These assessments were

performed when the (potential) subjects first came to the laboratory, and if they did not meet the aforementioned criteria, they were not included in the study. The family history of psychiatric disorders was not assessed because of its sensitive nature. 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.

#### Genotyping of subjects

Genotyping of the *DRD4* gene was performed as described in previous studies ([Pérez-Edgar et al., 2014](#)). Genomic DNA was prepared from saliva samples that were collected in the laboratory using the Oragene DNA kit (DNA Genotek, Ottawa, Ontario, Canada). For details of following procedures, see Supplemental Methods.

The genotype distributions for the full samples of 765 Asian subjects who were successfully genotyped were: 2-repeat allele/2-repeat allele ( $N = 12$ , 1.7%), 2-repeat allele/3-repeat allele ( $N = 2$ , 0.3%), 2-repeat allele/4-repeat allele ( $N = 128$ , 16.7%), 2-repeat allele/5-repeat allele ( $N = 6$ , 0.8%), 3-repeat allele/4-repeat allele ( $N = 5$ , 0.7%), 4-repeat allele/4-repeat allele ( $N = 542$ , 70.8%), 4-repeat allele/5-repeat allele ( $N = 66$ , 8.6%), 4-repeat allele/6-repeat allele ( $N = 1$ , 0.1%), and 5-repeat allele/5-repeat allele ( $N = 3$ , 0.4%). This distribution was in line with the Hardy–Weinberg equilibrium ( $P > 0.05$ ). Among all the subjects who participated in this experiment, 13 subjects failed to come for saliva sample collection, declined to offer a sample, or their sample could not be correctly processed.

In the final sample, participants were classified as 5-repeat carriers (5R+;  $n = 75$ ; 72 heterozygotes, three homozygotes, 34 females, aged  $20.9 \pm 1.8$  years) or noncarriers (5R-;  $n = 690$ , 306 females, aged  $20.7 \pm 1.8$  years). The *DRD4* genotype groups did not differ in age or sex ( $P > 0.10$ ).

The lack or scarcity of 7-repeat alleles is common in Asian or Japanese populations ([Aoki et al., 2013](#); [Li et al., 2006](#)).

#### Psychological measures

Subsequently, neuropsychological tests of basic cognitive performance and questionnaires for psychological variables relevant to ADHD or the *DRD4* gene were administered.

[A] Raven's advanced progressive matrix test ([Raven, 1998](#)), a non-verbal reasoning task. [B] A (computerized) digit span task, which is a working memory task (for details, see [Takeuchi et al., 2011b](#)). [C] Tanaka B-type intelligence test ([Tanaka et al., 2003](#)), a non-verbal mass intelligence test used for third-year junior high school and older examinees, does not include story problems but uses figures, single numbers, and letters as stimuli. In all subtests, the subjects have to solve as many problems as possible before a certain time (a few minutes). For the details of these subtests, see [Takeuchi et al. \(2013a\)](#). [D] The Stroop task ([Hakoda's version](#)) ([Hakoda and Sasaki, 1990](#); [Takeuchi et al., 2012b](#)), which measures response inhibition and impulsivity. Hakoda's version is a matching-type Stroop task requiring subjects to check whether their chosen answers are correct, unlike the traditional oral naming Stroop task. The test consists of two control tasks (Word–Color task and Color–Word task), a Stroop task, and a reverse–Stroop task. In this study, we used the Word–Color and Color–Word tasks as measures of simple PS and the Stroop and reverse–Stroop tasks as measures of inhibition. In each task, the subjects have to complete as many of the exercises as possible in 1 min. For the details of these subtests, see [Takeuchi et al. \(2014b\)](#). [E] Simple arithmetic tasks, similar to the ones constructed by [Grabner et al. \(2007\)](#), measured multiplication performance consisting of two forms of one-digit times one-digit multiplication problems (a simple arithmetic task with numbers between 2 and 9). The two forms of each task are the same, but the numbers used in the problems are ordered differently. Each form of the simple tasks have to be completed in 30 s. Average performance was used as a

performance. [F] The SA creativity test ([Society\\_For\\_Creative\\_Minds, 1969](#)), which measures creativity through divergent thinking, involves three types of tasks (generate unique ways of using typical objects, imagine desirable functions for ordinary objects, and imagine the consequences of unimaginable things happening). The SA test scores the four 4 dimensions of the creative process (fluency, originality, elaboration, and flexibility) ([Takeuchi et al., 2010a](#)). (a) Fluency—Fluency is measured by the number of relevant responses to questions and is related to the ability to produce and consider many 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 that 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\\_Minds, 1969](#)). Elaboration scores are determined by the sum of responses that are weighted based on a criteria table or an almost equivalent judgment. Please refer to our previous studies ([Takeuchi et al., 2010a, b](#)) for more extensive details, including those on the psychometric properties of this test, sample answers to the questionnaire, and the manner in which the tests were scored. [G] The cognitive reflectivity–impulsiveness questionnaire ([Takigiku and Sakamoto, 1991](#)) was used to assess individual differences in reflectivity and impulsivity. This is a self-reported questionnaire and has been previously used for measuring individual reflectivity and impulsivity ([Sasaki and Kanachi, 2005](#)). [H] The External-Preoccupation Scale ([Sakamoto, 1998](#)) was used to measure the maintenance of external focus on a specific object. Data for this scale were collected only from a subset of the subjects (678 successfully genotyped subjects). [I] The Novelty Seeking Scale, Japanese version ([Kijima et al., 1996](#)), of the Temperament Character Inventory ([Cloninger et al., 1993](#)) was used to measure novelty seeking tendency.

#### fMRI tasks

fMRI was used to map brain activity during typical cognitive tasks. The n-back task, a typical task for fMRI studies with conditions of 0-back (simple cognitive processes) and 2-back (working memory). The n-back task was performed during fMRI scanning, as described in our previous study ([Takeuchi et al., 2011a,b, 2014a](#)). We have provided the same information for the readers' sake. Participants received instructions and practiced the tasks before entering the scanner. During scanning, they viewed stimuli on a screen via a mirror mounted on a head coil. Visual stimuli were presented using Presentation software (Neurobehavioral Systems, Inc., Albany, CA, USA). A fiber-optic, light-sensitive key press interface with a button box was used to record participants' behavior.

We used a simple block design and the n-back WM task ([Callicott et al., 1999](#)) to tap brain activities during the WM task. There were two conditions (0- and 2-back). Each condition had six blocks, and all n-back tasks were performed in one session. The subjects were instructed to recall stimuli [visually presented four types of Japanese letters of vowels] seen “n” times previously (e.g., two letters shown previously for the 2-back task and the currently presented letter for the 0-back task). Two buttons were used during the 0-back task, and the subjects were asked to push the first button when the target stimuli were presented and the second button when the other stimuli were presented. During the 2-back task, the subjects were asked to push the first button when the currently presented stimuli and the stimuli presented two letters previously were the same, and to push the second button when the currently presented stimuli and the stimuli presented



two letters previously were different. Our version of the n-back task was designed to require individuals to push buttons continuously during the task period. The task level of the memory load was found to be above the stimuli for 2 s before the task started (cue phase) and remained unchanged during the task period. Each letter was presented for 0.5 s, and a fixation cross was presented for 1.5 s between each item. Each block consisted of 10 stimuli. Thus, each block lasted for 20 s. A baseline fixation cross was presented for 13 s between the task and the presentation of the next condition's task level (2 s). Thus, the rest period lasted for 15 s. There were six blocks for each 2- and 0-back condition.

### Image acquisition and analysis

MRI data acquisition was conducted using a 3 T Philips Achieva scanner. Forty-two transaxial gradient-echo images (echo time = 30 ms, flip angle = 90°, slice thickness = 3 mm, FOV = 192 mm, matrix = 64 × 64) covering the entire brain were acquired at a repetition time of 2.5 s using an echo-planar sequence. For the n-back session, 174 functional volumes were obtained. Diffusion-weighted data were acquired using a spin-echo EPI sequence (TR = 10,293 ms, TE = 55 ms, FOV = 22.4 cm, 2 × 2 × 2 mm<sup>3</sup> 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<sup>2</sup>). Additionally, using a spin-echo EPI sequence (TR = 10,293 ms, TE = 55 ms, FOV = 22.4 cm, 2 × 2 × 2 mm<sup>3</sup> voxels, 60 slices), 3 images with no diffusion weighting (*b* value = 0 s/mm<sup>2</sup>) (*b* = 0 images) were acquired. From the collected images, FA and MD maps were calculated (Takeuchi et al., 2011c).

### Preprocessing of imaging data

Preprocessing and analysis of functional activation data were performed using SPM8 implemented in Matlab. Here we describe the summary versions; however, the full details and methodological considerations have been provided in Supplemental Methods. Before analysis, BOLD images were re-aligned and re-sliced to the mean image of the BOLD images, which was then realigned to mean images of *b* = 0 images, as described previously (Takeuchi et al., 2011b). Because the mean *b* = 0 image was aligned with the FA image and MD map, the BOLD image, *b* = 0 image, FA image, and MD map were all aligned. Subsequently, using a previously validated two-step new segmentation algorithm of diffusion images and the previously validated diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL)-based registration process (Takeuchi et al., 2013c), all images, including 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, were normalized. The voxel size of normalized FA images and MD images and segmented images, was 1.5 × 1.5 × 1.5 mm<sup>3</sup>. The voxel size of normalized BOLD images was 3 × 3 × 3 mm<sup>3</sup>. Normalized rGMD maps were smoothed (3 mm full-width half-maximum) and taken to the second-level analyses of functional activities.

Next, we created average images of normalized rGMD and rWMD images from the normalized rGMD and rWMD images from the subset of the entire sample (63 subjects) (Takeuchi et al., 2013c). Subsequently, for the analyses of MD images from the normalized images of the (a) MD, (b) rGMD, and (c) rCSFD maps, we created images where areas that were not strongly likely to be gray or white matter in our averaged normalized rGMD and rWMD images (defined by “gray matter tissue probability + white matter tissue probability < 0.99”) were removed (to exclude the strong effects of CSF on MD throughout analyses). These images were then smoothed (6 mm full-width half-maximum) and carried through to the second-level analyses of MD.

Next, from the average image of normalized WM segmentation images from the 63 subjects mentioned above and from the created mask image consisting of voxels with a WM signal intensity > 0.99. We then applied this mask image to the normalized FA image; therefore, we retained only areas that are highly likely to be white matter from the normalized FA images. These images were smoothed (3 mm full-width half-maximum) and carried through to the second-level analyses of FA.

### First-level analysis of functional imaging data

Individual-level statistical analyses were performed using a general linear model (GLM). A design matrix was fitted to each participant with one regressor in each task condition (0- or 2-back in the n-back task) using a standard hemodynamic response function (HRF). The cue phases of the n-back task were modeled in the same manner, but were not analyzed further. Six parameters obtained by rigid body correction of head motion were regressed out by putting these variances into the regressor. The design matrix weighted each raw image according to its overall variability to reduce the impact of movement artifacts (Diedrichsen and Shadmehr, 2005). We removed low-frequency fluctuations with a high-pass filter, using a cut-off value of 128 s. After estimation, beta images were smoothed (3 mm full-width half-maximum) and taken to the second level analyses. For the reasons why we used lower smoothing values in functional activation analyses and used 2-back > rest and 0-back > rest contrasts instead of 2-back > 0-back contrast in this study, see Supplemental Methods.

### Statistical group-level analysis of imaging and behavioral data

Behavioral data were analyzed using SPSS 18.0 (SPSS Inc., Chicago, IL). Differences in the scores for the cognitive measures between the carriers and non-carriers of the 5-repeat allele of the *DRD4* gene were analyzed using analysis of covariance (ANCOVA). Additional covariates for each analysis were age and sex. In psychological analyses, results with a threshold of *P* < 0.05, corrected for false discovery rate (FDR) using the graphically sharpened method (Benjamini and Hochberg, 2000), were considered statistically significant. The correction for multiple comparisons using this method was applied to the results of abovementioned 16 ANCOVAs. The 16 dependent variables are psychological measures that were described in the Psychological measures subsection and are listed in Table 1 (namely RAPM, Digit span, Tanaka-B type intelligence test, Word-Color task, Reverse Stroop task, Color-Word task, Stroop task, Simple arithmetic, Total SA creativity test score, SA creativity test-fluency score, SA creativity test-flexibility, SA creativity test-originality, SA creativity test-elaboration, cognitive reflectivity-impulsivity, External-Preoccupation, and Novelty seeking). They are all hypothesized on the basis of the study hypothesis, previous studies of polymorphisms of the *DRD4* gene in the Introduction section (Durstun et al., 2005; Szekely et al., 2011), and clinical conditions of ADHD (Barkley, 1997). In particular, carriers of the risk allele of ADHD were thought to have higher divergent thinking measures (the study hypothesis in the Introduction section); lower performance in intelligence, processing speed, and working memory; and a higher tendency for attention diversion toward external stimuli, disinhibition, and novelty seeking. FDR-based methods have been shown to be more powerful and sensitive than other available approaches to multiple statistical testing (See Benjamini and Hochberg, 1995 for a full discussion; Genovese et al., 2002).

Comparing carriers and noncarriers of risk alleles and assuming that the risk is inferred even in heterozygotes of the risk alleles is correct for this polymorphism. This is because the 5-repeat allele is not so frequent in any population (0%–8%) (Li et al., 2006); thus, in any studies, homozygotes of 5-repeat alleles are rare (Comings et al., 1999; Qian et al., 2003). However, through the accumulation of these studies with the lack of homozygotes of 5-repeat alleles, meta-analysis had provided

**Table 1**Performance of psychological measures in non-carriers and carriers of the 5R allele of the dopamine receptor D4 gene (mean  $\pm$  s.e.m.).

	Non5R allele carrier	5R allele carrier	Planned contrast	<i>P</i> value <sup>a</sup> (uncorrected, FDR <sup>b</sup> )	Effect size ( $\eta^2$ )
RAPM <sup>c</sup> (score)	28.60 $\pm$ 0.14	28.84 $\pm$ 0.44	Non5R carrier > 5R carrier	(0.708, 0.598)	0.00041
Digit span (score)	35.73 $\pm$ 0.28	35.28 $\pm$ 0.69	Non5R carrier > 5R carrier	(0.351, 0.383)	0.00021
Tanaka-B type intelligence test	112.43 $\pm$ 0.44	110.62 $\pm$ 1.38	Non5R carrier > 5R carrier	(0.079, 0.135)	0.00240
Word-color task (items)	70.76 $\pm$ 0.28	68.44 $\pm$ 0.82	Non5R carrier > 5R carrier	(0.009, 0.036)	0.00717
Reverse Stroop task (items)	59.78 $\pm$ 0.31	58.99 $\pm$ 0.86	Non5R carrier > 5R carrier	(0.748, 0.598)	0.00082
Color-word task (items)	52.39 $\pm$ 0.26	51.13 $\pm$ 0.67	Non5R carrier > 5R carrier	(0.074, 0.135)	0.00339
Stroop task (items)	48.62 $\pm$ 0.26	48.41 $\pm$ 0.69	Non5R carrier > 5R carrier	(0.478, 0.441)	0.00005
Simple arithmetic (items)	31.36 $\pm$ 0.20	29.47 $\pm$ 0.63	Non5R carrier > 5R carrier	(0.002, 0.024)	0.01141
Total SA creativity test score	24.78 $\pm$ 0.22	25.25 $\pm$ 0.67	Non5R carrier < 5R carrier	(0.263, 0.323)	0.00003
SA creativity test—fluency (grade)	5.97 $\pm$ 0.06	6.00 $\pm$ 0.17	Non5R carrier < 5R carrier	(0.435, 0.435)	0.00019
SA creativity test—flexibility (grade)	6.53 $\pm$ 0.06	6.67 $\pm$ 0.18	Non5R carrier < 5R carrier	(0.213, 0.320)	0.00168
SA creativity test—originality (grade)	5.94 $\pm$ 0.07	6.43 $\pm$ 0.22	Non5R carrier < 5R carrier	(0.020, 0.048)	0.00475
SA creativity test—elaboration (grade)	6.35 $\pm$ 0.07	6.16 $\pm$ 0.20	Non5R carrier < 5R carrier	(0.820, 0.615)	0.00115
Cognitive reflectivity—impulsivity (score)	27.99 $\pm$ 0.21	26.25 $\pm$ 0.70	Non5R carrier > 5R carrier	(0.006, 0.036)	0.00839
External-preoccupation (score)	27.13 $\pm$ 0.22	25.65 $\pm$ 0.61	Non5R carrier > 5R carrier	(0.015, 0.045)	0.00669
Novelty seeking (score)	20.94 $\pm$ 0.21	21.48 $\pm$ 0.68	Non5R carrier < 5R carrier	(0.269, 0.323)	0.00067

<sup>a</sup> *P* value of one-way analyses of covariance with performance of psychological measures as dependent variables and age and sex as covariates.<sup>b</sup> False discovery rate.<sup>c</sup> Raven's advanced progressive matrix test.

convincing evidence that 5-repeat alleles increase the risk of ADHD (Li et al., 2006). Further the mechanisms of how DRD4 gene polymorphisms work in a different manner are shown to be through the relative efficiency of how efficiently agonists bind with the translated receptors (Asghari et al., 1995). In this context, the possible mechanism that two risk alleles are required to express phenotypes is ruled out because dopamine combines with the receptors of risk alleles and even a single risk allele's receptor can still function but the receptors of each allele compete with the receptors of other alleles.

In group-level imaging analyses, we tested for group-wise differences in functional activity during the attention-demanding and simple sensorimotor tasks, MD and FA, across the brain. We performed voxel-wise ANCOVAs to test group differences in functional activity analyses and MD analyses. Biological Parametrical Mapping (Casanova et al., 2007) implemented in SPM5 allowed to use these voxel-wise ANCOVAs by including images representing regional values as covariates. The analyses were performed using this software. In the analyses of MD, the dependent variables were as follows: the existence of the 5-repeat allele, the signal intensities of preprocessed (masked) rGMD and rCSFD images at each voxel, age, sex, and total intracranial volume. The analyses were limited to the gray + white matter mask that was created above. rGMD and rCSFD images were included as covariates to exclude the effects of the extent of these tissues on MD and remove the possibility that the extent of tissue instead of MD itself impacted the obtained results; however, we did not include white matter density as covariates because tissues were gray matter, white matter, or CSF in the areas relevant to the analysis.

In the analyses of functional activity, the dependent variables were as follows: the existence of the 5-repeat allele, signal intensities of preprocessed (nonmasked) rGMD images at each voxel, accuracy and RT of each task (accuracy and RT of 0-back task for 0-back task's analyses, and accuracy and RT of 2-back task for 2-back analyses), volume-level mean frame-wise displacement during the scan for the n-back task (Power et al., 2012), and total intracranial volume. For the analyses of FA, we performed normal whole-brain ANCOVA with correction for the effects of age, sex, and total intracranial volume. Analyses were limited to the white matter mask that was created above. There were no significant group (based on the existence of the 5-repeat allele) differences in these variables, which were used as covariates ( $P > 0.1$ , ANOVA). The total intracranial volume was included as a covariate, considering its effects on DTI measures (Takao et al., 2011).

Multiple comparison correction was performed using the false discovery rate (FDR) approach (Genovese et al., 2002), and areas that surpassed the extent threshold (Friston et al., 1996) based on this cluster-determining threshold were reported. Among the subjects

who were successfully genotyped for the DRD4 gene, diffusion-weighting data were successfully obtained from 756 subjects and functional activation data (including behavioral parameters) were successfully obtained from 738 subjects using the above-mentioned parameters, and were analyzed in the group-level analyses.

## Results

### Effect of the DRD4 5-repeat allele on psychological variables

Analyses of covariance corrected for the effects of age and sex revealed that 5-repeat allele carriers had a significantly lower performance in the Word-Color and simple arithmetic tasks, lower score of cognitive reflectivity (vs. impulsivity), lower score of external preoccupation, and higher score on the originality dimension of the S-A creativity task. For all results and statistical values, see Table 1.

Interestingly, 5-repeat allele carriers had significantly higher scores on the originality test; this was the only superior result for this group among performance-type cognitive tests. Visual inspection of the histogram of this originality score shows a slight deviation from the normal distribution, and with this sample size, the Kolmogorov-Smirnov test for non-normality of distribution showed significant results ( $P < 0.05$ ). However, the nonparametric test of the difference in originality scores between the two groups showed a similar statistical value ( $P = 0.024$ ); thus, the non-normality of the test fails to explain the difference.

To reveal the nature of this result, we tested the association between the score on the originality dimension of the SA creativity task and other measures after correcting for the effects of age and sex through multiple regression analyses. Results revealed that the originality dimension of the SA creativity task showed a significant positive correlation with the total score and scores on other dimensions of the SA creativity task and other cognitive tests requiring speed, e.g., Tanaka-B type intelligence test, Word-Color task, Reverse Stroop task, and simple arithmetic task ( $P < 0.05$ ), but not with others. However, these significant correlations are all positive correlations and cannot explain the specific positive association between the 5-repeat allele and the originality dimension, given that the 5-repeat allele carriers tended to show inferior performance in these tasks. In addition, to reveal the specific association of the originality dimension with other cognitive variables, we calculated the originality dimension score/fluency dimension score (originality of answers after the number of responses is adjusted), which has sometimes been used (Eisenman, 1969), and after correcting for the effects of age and sex, we investigated its association with other cognitive variables through multiple regression analyses. However, none of the

cognitive variables used in this study showed significant associations with this value ( $P > 0.05$ ).

#### Effect of the DRD4 5-repeat allele on fractional anisotropy

A whole-brain ANCOVA corrected for the effects of age, sex, and total intracranial volume revealed an absence of significant effects of the DRD4 5-repeat allele on FA.

#### Effect of the DRD4 5-repeat allele on mean diffusivity

Analyses of covariance corrected for the effects of age, sex, and total intracranial volume revealed that 5-repeat allele carriers had a significantly higher MD in: (a) the extensive cluster that spread across gray and white matter areas located mainly in and close to the frontal, parietal, and cingulate cortices; (b) anatomical cluster that spread across gray and white matter areas located mainly in and close to the amygdala, ventral tegmental area, globus pallidus, and thalamus; (c) areas located in the brainstem; and (d) anatomical cluster that spread mainly around the fusiform gyrus (Fig. 1). For the statistical values, see Table 2.

#### The performance of fMRI tasks

The subjects performed the task properly in terms of accuracy because the accuracies in both groups were higher than 99% in both the 0-back and 2-back tasks (Table 3). This means for subjects in both the groups, 2-back task conditions were not over the capacity of working memory and we did not have to take into account the nonlinear brain activation changes, which appear as the cognitive load becomes higher and after the working memory capacity is exceeded (Callicott et al., 1999). The reaction time and movements were also comparable between two groups (Table 3). Because these variables were not for validated measures to measure abilities, we did not include them in analyses to evaluate the effects of the DRD4-5-repeat allele, these variables did not exert effects on the DRD4-5-repeat allele after correction for age and sex ( $P > 0.1$ , ANCOVA). These results suggest that fMRI activation results are not explained by these variables.

#### Effect of the DRD4 5-repeat allele on functional activation

ANCOVAs corrected for confounding factors revealed that 5-repeat allele carriers had a significantly higher activity during the 0-back

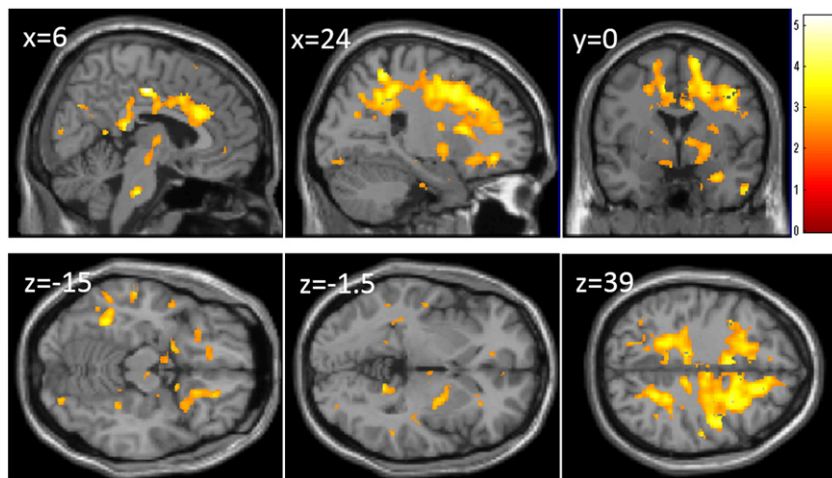
sensorimotor task in the areas of the precuneus and in the posterior cingulate cortex and anatomical cluster that spread across the thalamus, ventral tegmental area, and hippocampus (Fig. 2a, Table 4). Furthermore, ANCOVAs corrected for confounding factors revealed that 5-repeat allele carriers had a significantly higher activity (beta estimates) during the 2-back working memory task in the area of the precuneus (Fig. 2c, Table 4). Similar tendencies were observed in the posterior cingulate cortex and areas located around the hippocampus and midbrain, where significant differences were observed in the analysis of the 0-back task.

The extensive regions located around these areas showed deactivation during the wide range of externally directed attention-demanding cognitive tasks (Takeuchi et al., 2011c, See also Figs. 2b, d). This suggests that “higher activity” (beta estimates) in the extensive regions located around the precuneus in 5-repeat allele carriers actually corresponds to the reduction of TID or reduction of deactivated areas around these areas during the 0-back and 2-back tasks in 5-repeat allele carriers.

Furthermore, ANCOVAs revealed that 5-repeat allele carriers had weak tendencies of lower activity during the 2-back working memory task (but not during the 0-back task) in the areas of the caudal and rostral parts of the left dorsolateral prefrontal cortex (regions of a priori hypothesis;  $x, y, z = -21, 24, 60$ , respectively,  $t = 3.33, P < 0.001$ , uncorrected;  $x, y, z = -30, 39, 6$ , respectively,  $t = 3.27, P < 0.001$ ).

## Discussion

The present study revealed the neural and psychological effects of the DRD4 5-repeat allele in a healthy Asian sample, which is known to have a low prevalence of ADHD, as well as those of the robust risk allele (7-repeat allele) for ADHD. The 5-repeat allele was associated with worse processing speed performance, higher self-reported impulsivity, and less tendency to maintain attentional focus to the external world in this sample. These results are consistent with the previous finding of the association of slow processing speed with another risk allele (7-repeat allele) of the DRD4 gene (Szekely et al., 2011), and the association of the 5-repeat risk allele with the risk of ADHD (Szekely et al., 2011). We revealed that 5-repeat allele was significantly associated with increased originality in creative performance. Furthermore, the 5-repeat allele was significantly associated with increased MD in the widespread gray and white matter areas of the cerebral cortex, and with subcortical areas located mainly in the globus pallidus, amygdala,



**Fig. 1.** Increase in mean diffusivity in a DRD4 5-repeat allele carrier. Results are shown for a threshold of  $P < 0.05$ , corrected for multiple comparisons at false discovery rate ( $P < 0.05$ ). Findings were overlaid on a “single-subject T1” SPM5 image. The red color represents the T-score. Compared with the non-carrier of the DRD4 5-repeat allele, the 5-repeat allele carrier showed a significantly larger MD in widespread gray and white matter areas, particularly in and close to the frontoparietal areas (upper-middle, upper-right, and lower-right panels), cingulate areas (upper-left panel), amygdala (upper-right panel), ventral tegmental area and left fusiform area (lower-left panel), and globus pallidus (upper-right and lower-middle panels).



**Table 2**  
Brain regions with a significantly larger MD in 5-repeat allele carriers of the *DRD4* gene.

Included gray matter areas	Included large bundles	x	y	z	T score	Corrected P value (FDR)	Cluster size (mm <sup>3</sup> )
Angular gyrus (B)/calcarine cortex (L)/caudate (R)/anterior–middle–posterior cingulate gyrus (B)/cuneus (B)/superior–middle–inferior frontal gyrus (B)/insula (B)/lingual gyrus (L)/superior–middle occipital lobe (B)/paracentral Lobule (B)/superior–inferior parietal lobule (B)/pre-Post central gyrus (B)/putamen (R)/supplemental motor area (B)/supra marginal gyrus (R)/middle temporal gyrus (R)/superior temporal gyrus (R) (R)/superior temporal gyrus (R)	Body-Genu-splenium of the corpus callosum/ anterior limb of internal capsule (B)/posterior limb of internal capsule (R)/anterior–superior–posterior corona radiate/posterior thalamic radiation (R)/external capsule (B)/superior longitudinal fasciculus (B)/superior fronto-occipital fasciculus (L)/ inferior fronto-occipital fasciculus (R)	4.5	–16.5	43.5	5.23	0.014	132,276
Amygdala (R)/caudate (R)/Heschl gyrus (R)/Hippocampus (R)/insula (R)/globus pallidus (R)/putamen /thalamus (R)/ventral tegmental area	Cerebral peduncle (R)/internal capsule (R)/inferior longitudinal fasciculus (R)/inferior fronto-occipital fasciculus (R)/external capsule (R)/fornix (R)/inferior fronto-occipital fasciculus (R)	–6	–25.5	–37.5	4.03	0.022	1927
None	Middle cerebellar peduncle/pontine crossing tract/corticospinal tract	–45	–64.5	13.5	3.88	0.022	2200
Fusiform gyrus (L)/middle-inferior temporal gyrus (R)	None	27	–6	–3	3.30	0.022	4843

midbrain areas, brain stem, and others. This is largely consistent with our hypothesis, as discussed below. Finally, partly congruent with our hypothesis, the 5-repeat allele was associated with reduced TID in the precuneus areas in both the attention-demanding task and simple sensorimotor task; similar patterns were observed in the posterior cingulate cortex and in areas located around the midbrain and hippocampus.

The extent of the area with significant association between MD and the *DRD4* 5-repeat allele was consistent with the previously reported distribution of *DRD4*. 5-Repeat allele carriers showed increased MD in the widespread gray and white matter areas of the cerebral cortex, globus pallidus, amygdala, midbrain areas, and others. As described in the Introduction section, an increasing number of studies stress the importance of MD, and it is not surprising that physiological correlates are found in the gray matter areas. The present widespread results of diffusivity measures are congruent with the findings of the studies of polymorphisms, studies of normal development, studies of a certain disease that showed variables that were investigated in these studies affect brain mechanisms in a wide range of white matter areas (Taki et al., 2013; Tost et al., 2012; Whitwell et al., 2011) in analyses limited to white matter. Previously, a positron emission tomography (PET) study in humans showed that *DRD4* is notably expressed to a greater extent in the neocortex than in the striatum (Boy et al., 1998). Furthermore, molecular studies revealed that *DRD4* is expressed highly in the neocortex, midbrain, amygdala, and globus pallidus, and lowly expressed in the striatum and hippocampus (Mrzljak et al., 1996; Van Tol et al., 1992). Therefore, these previous findings of the distribution of the expression of *DRD4* and the present extent of the association between the *DRD4* 5-repeat allele and MD were very concordant, suggesting the validity of the present findings. Perhaps the neural mechanisms in the areas in which *DRD4* is expressed are globally affected via the *DRD4* 5-repeat allele.

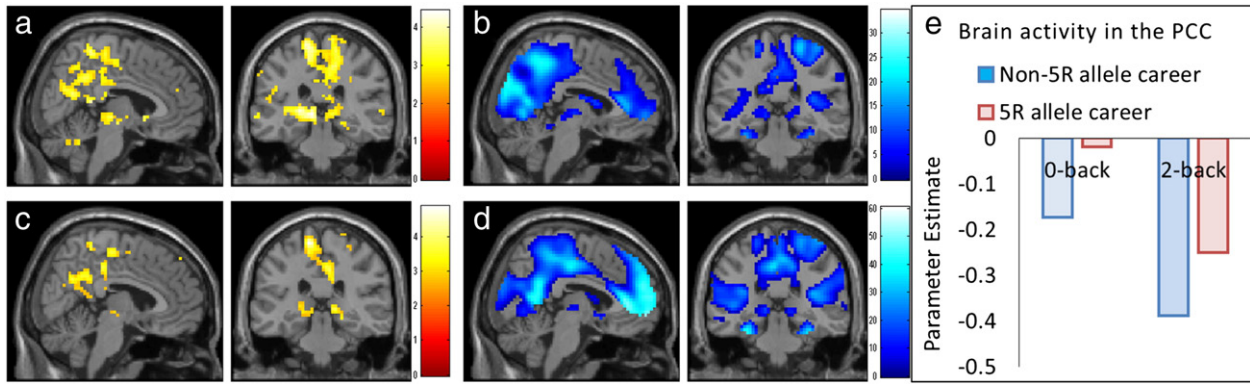
**Table 3**  
Performance of fMRI tasks in noncarriers and carriers of the 5R allele of the dopamine receptor D4 gene (mean ± s.e.m.).

	Non-5R allele carrier	5R allele carrier
0-back task: accuracy (%)	99.6 ± 0.1	99.8 ± 0.1
0-back task: reaction time (ms)	4555 ± 28	4530 ± 80
2-back task: accuracy (%)	99.2 ± 0.1	99.7 ± 0.1
2-back task: reaction time (ms)	6751 ± 68	6467 ± 206
Volumewise framewise displacement <sup>a</sup>	0.204 ± 0.002	0.203 ± 0.006

<sup>a</sup> Framewise displacement calculated by the method of Power et al. (2012).

There are several possible mechanisms via which the 5-repeat allele of *DRD4* can affect MD. MD is often believed to be a measure of overall water content (Moseley et al., 2002). Possible obstacles, such as the presence of fewer or smaller cellular structures (e.g., capillaries, synapses, and macromolecular proteins), may prevent the free diffusion of water molecules and may also be expected to cause a decrease in the MD value (Ni et al., 2010). Among normal samples, cognitive learning affects MD values after only 2 h of training in the relevant tissues and together with the results of animal experiments, an increase in the number of synaptic vesicles and swelling of astrocytes because of the increased activity has been suggested to underlie these MD changes (Johansen-Berg et al., 2012; Sagi et al., 2012). In the long run, changes in other physiological mechanisms, such as dendritic sprouting and angiogenesis, may affect MD (Johansen-Berg et al., 2012). On the other hand, the risk alleles of the *DRD4* gene are less sensitive to dopamine stimulation (Asghari et al., 1995). A regular decrease in the related neural activity in the carriers of risk alleles of *DRD4* may lead to an increase in MD through the decrease in the swelling of astrocytes, number of synaptic vesicles, dendritic sprouting, etc. The areas that exhibited significant differences in MD in the present study, as well as areas in which the *DRD4* gene was highly expressed, included areas of the mesocortical dopaminergic system and mesolimbic dopaminergic system. Neurons in the mesolimbic system project to the nucleus accumbens, hippocampus, etc. from the ventral tegmental area; this system plays a key role in the reward mechanism of the brain (Carlson, 2001). Finally, neurons in the mesocortical system project to the prefrontal cortex from the tegmental ventral area, and are involved in cognitive control and in other higher-order cognitive functions (Carlson, 2001). Blunted response in these networks may lead to the disruption of cognitive, behavioral deficits, and TID changes, suggesting the insufficient attentional reallocation (as discussed below) observed in the 5-repeat allele carriers. In addition, these physiological mechanisms can mostly impact gray and white matter and are congruent with the findings of MD found in both gray and white matters.

As discussed in our previous study (Takeuchi et al., 2011b), the reduced TID observed in the precuneus areas, posterior cingulate cortex, hippocampus, and midbrain areas in the 5-repeat allele carriers may suggest their impaired ability to suppress irrelevant cognitive activity during a cognitive task. These areas are the regions that are deactivated during cognitive tasks (Takeuchi et al., 2011b). The precuneus areas, posterior cingulate cortex, and hippocampus are supposed to be engaged in cognitive activities such as self-related mental representations and episodic memory retrieval during rest (Cavanna and Trimble, 2006). It has been argued that the magnitude of TID in these areas during cognitive tasks reflects the reallocation of



**Fig. 2.** Increase in brain activity during the cognitive tasks in a *DRD4* 5-repeat allele carrier. (a, c) Significantly larger brain activity was observed in the *DRD4* 5-repeat allele carrier (a) during the 0-back sensorimotor task, and (c) during the 2-back working memory task. Results are shown for a threshold of  $P < 0.005$ , uncorrected for visualization purposes. The findings were overlaid on a “single-subject T1” SPM5 image. The red color represents the T-score. (a) Compared with the non-carrier of the *DRD4* 5-repeat allele 5-repeat allele carrier showed significantly larger brain activity during the 0-back task in the precuneus, posterior cingulate cortex, and anatomical cluster that spread around the thalamus, midbrain area, and hippocampus. (c) Compared with the non-carrier of the *DRD4* 5-repeat allele, the 5-repeat allele carrier showed a significantly larger brain activity during the 2-back task in the precuneus. A similar tendency was observed in the posterior cingulate cortex and anatomical cluster that spread around the thalamus, midbrain area, and hippocampus. (b, d) Regions that are deactivated during the externally directed attention-demanding tasks (b, during the 0-back simple sensorimotor task, and d, during the 2-back working memory task). Results are displayed for a threshold of  $P < 0.05$ , corrected for multiple comparisons at false discovery rate ( $P < 0.05$ ). The blue color represents the T-score. (e) An activation profile of the PCC. Mean parameter estimates in two conditions and two groups, of the cluster of significant effects of the *DRD4* 5-repeat allele on brain activity during the 0-back simple sensorimotor task (Table 1) were presented.

attention from the semantic processes that occur during rest to the cognitive processes involved in performing the task (McKiernan et al., 2003). Therefore, the reduced TID observed in these areas in 5-repeat allele carriers may indicate that they are not able to inhibit or suppress cognitive activity irrelevant to the task performance (task-unrelated thought) during cognitive tasks. These neural characteristics may lead to (or reflect) an increased risk of attentional and behavioral deficits in 5-repeat allele carriers.

This type of inattentiveness that cannot suppress or filter out irrelevant information (thought) may be important for creativity measured by divergent thinking. As discussed previously (Takeuchi et al., 2011b), one speculation about the implication of the fact that individuals who are unable to suppress DMN activity is that such an inability to suppress seemingly unnecessary cognitive activity may actually help them associate two seemingly distant ideas represented in different networks. This idea of creativity has been long stated, and a vast amount of studies showed that inattentive subjects who cannot filter irrelevant information are creative (for summary, see Takeuchi et al., 2011b). The inability to suppress an irrelevant network when one network is recruited may lead to the intrusion of thoughts from the irrelevant network and may allow the combination of two isolated ideas. Consistent with this notion, a reduced TID in the areas of the DMN in subjects with higher creativity measured by divergent thinking as well as subjects at a risk of schizophrenia, which is known to be robustly associated with higher creativity measured by divergent thinking (Takeuchi et al., 2011b; Whitfield-Gabrieli et al., 2009). In addition,

some recent previous functional imaging studies of creative cognition have reported that regions of the DMN could be critically involved in creativity (Fink et al., 2010; Fink et al., 2012). Furthermore, other studies of resting state paradigms have revealed that resting state brain activity involving the DMN is important for creativity measured by divergent thinking (Takeuchi et al., 2012a; Wei et al., 2013). Some structural studies have indicated that the brain structure of the key nodes of the DMN is associated with creativity (Fink et al., 2013). In addition, DMN is thought to be critically involved in self-referential or introspective cognitive activities, such as those involving autobiographical memory, and social cognition, such as the theory of mind (Buckner et al., 2008; Fair et al., 2008; Schilbach et al., 2008). Perhaps related to this, we previously summarized the overlap or associations between self-reflection or access to self- and social cognitive functions and showed associations between social cognitive functions and creativity measured by divergent thinking (Takeuchi et al., 2014b). Based on this neuroimaging evidence, it has been pointed out the DMN is important for creative cognition (Jung et al., 2013) and the present findings may implicate the importance of the DMN itself and functions related to DMN, such as self-related cognition and social cognition (not only that of attention).

We propose possible speculative mechanisms of the association between the 5-repeat allele and originality. While subscales (dimensions) of divergent thinking tend to be highly correlated, originality shows rather distinct properties, and some previous studies have demonstrated specific changes in originality (Kharkhurin, 2008). One speculative

**Table 4**  
Difference in brain activity between non-carriers and carriers of the 5-repeat allele of the dopamine receptor D4 gene.

Lobe	Peak coordinates			T score	Corrected voxel level <i>P</i> value (FDR)	Cluster size (mm <sup>3</sup> )	
	X	Y	z				
Activity during the 0-back task							
5-repeat allele carrier > non 5-repeat allele carrier							
Bilateral thalamus/ventral tegmental area/left hippocampus	B	−9	−30	0	4.45	0.038	7776
Precuneus	B	−21	−42	60	4.33	0.038	10,125
Posterior cingulate cortex	B	18	−48	9	3.88	0.038	5481
Activity during the 2-back task							
5-repeat allele carrier > non 5-repeat allele carrier							
Precuneus	L	−12	−30	66	4.87	0.032	27



reason why originality was specifically affected in 5-repeat allele carriers is that while the originality of the idea is increased by the aforementioned mechanisms, decreased processing speed associated with the 5-repeat allele may hinder other dimensions of divergent thinking because of the association between divergent thinking and processing speed (Rindermann and Neubauer, 2004). To support the former association (DMN activity during the task and originality), we investigated the association between originality/fluency and brain activity during the task. The results indicate that the originality dimension may be specifically (after adjusting for the number of responses) associated with reduced TID in the area of the posterior cingulate cortex during the sensorimotor task, similar to the DRD4 polymorphism, but the overlap of the two is not statistically definitive (see Supplemental Methods, Supplemental Results, and Supplemental Fig. 1). However, brain lesions of certain areas irrelevant to attention processes have been shown to increase originality (Shamay-Tsoory et al., 2011). Originality is rated by how infrequent the idea is, and schizotypy, which is associated with atypical thinking patterns or experiences (Claridge et al., 1996), is known to be uniquely associated with originality of ideas (Green and Williams, 1999). Thus, the odd or atypical thinking pattern caused by certain disruptions of the brain networks may lead to originality (odd ideas). At present, these possibilities are pure speculation, and future studies are required to explore this issue more thoroughly.

There may be some incongruence between these previous findings of the association between attention-related cognition and TID in the DMN and the previous findings of brain activity of subjects with ADHD as discussed below. Although some studies have revealed a reduced TID in the DMN in subjects with ADHD during attention-demanding tasks (Brown et al., 2012), most findings have revealed reduced activation in the areas that are activated during attention-demanding tasks, particularly the lateral prefrontal areas (Burgess et al., 2010). Although we found a tendency in 5-repeat allele carriers toward reduced activation in the left lateral prefrontal cortex, due to the nature of whole-brain analysis (insignificance doesn't mean the lack of associations at all), it is not possible to say 5-repeat allele carriers are or are not associated with the reduction in brain activity in the lateral prefrontal cortex; therefore, the implications of lack of significance are statistically unclear. However, importantly, it has been shown that reduced activity in the lateral prefrontal cortex of ADHD subjects is mediated by their reduced working memory capacity (Burgess et al., 2010; Valera et al., 2010). To the best of our knowledge, no studies have reported an association between 5-repeat allele carriers (or 7-repeat allele carriers) and reduced working memory capacity. The incongruence of the lateral prefrontal cortex activity may come from this difference. In addition, because the increased cognitive load caused by the task difficulty would be expected to result in increased TID, the fact that subjects of ADHD may feel the task is difficult (and may have more cognitive load during the task) may lead to a less frequent occurrence of reduced TID in the DMN in subjects with ADHD. However, these are speculations and future studies are required to reveal this issue by, for example, focusing on subjects with ADHD with intact working memory capacity.

We failed to observe significant effects or tendency of the polymorphism of DRD4 on working memory performance as well as on general intelligence performance measured by non-verbal reasoning. This may be odd considering the implication (efficiency of attentional reallocation and suppression of task-irrelevant thoughts) of reduced TID in DMN, which was shown to be related to this polymorphism in the present study, as discussed above, as well as associations among attention, ADHD, and working memory performance (and general intelligence related to working memory capacity) (Engle et al., 1999; Martinussen et al., 2005). In studies of common polymorphisms, effects on cognitive functions tend to be weak. Thus, the lack of significance should not be treated as evidence of the lack of effects. However, we suggest one possible explanation for this result, as described above, as follows: it seems

that working memory deficit in patients with ADHD is associated with alterations in the activity of the lateral prefrontal cortex and not that of DMN (Burgess et al., 2010; Valera et al., 2010). From a neuroimaging perspective, there are various aspects of and systems in the attention system (Corbetta et al., 2008), and the suppression of task-irrelevant cognitive activity may not be so strongly associated with the performance of working memory. For example, one study reported that the correlation coefficient  $r$  of the frequency of the intrusion of task-irrelevant thoughts and working memory performance was about  $-0.23$ , explaining 5% of variance in working memory performance (Brewin and Smart, 2005). Thus, such a potentially weak indirect association between the polymorphism of the DRD4 gene and working memory performance might have resulted in the negative findings in this study.

We failed to observe significant effects of the polymorphism of DRD4 on FA. Particularly, in the whole-brain analyses, the lack of significant effects was not evidence of the lack of effects. However, the lack of significance may be incongruent with some of the previous findings, in which significant effects of polymorphisms of dopamine-related genes, such as those of catechol-O-methyltransferase (COMT) (Papenberg et al., 2014; Thomason et al., 2010), were found with a smaller sample size. Furthermore, FA is thought to reflect, in part, the degree of myelination (for details of this discussion, see Takeuchi et al., 2013b), and previous physiological studies have pointed out a profound association between the myelination process and dopamine (Káradóttir and Attwell, 2007; Lindholm and Jazin, 2007). Moreover, these previous physiological studies have suggested that the dopamine receptors D2 and D3 play key roles in mediating these associations. Thus, the lack of significance may, in part, be ascribed to the type of dopamine receptor we investigated.

There is at least a few potential pitfall or limitation of this study. This study investigated the effect of the 5-repeat allele in an Asian sample. The Asian population has a unique characteristic regarding the polymorphism of DRD4 and ADHD, as described in the "Introduction." Whether this finding is generalizable to other samples remains to be investigated. Furthermore, in this study, although we excluded subjects with psychiatric disorders on the basis of voluntary self-reports, we did not diagnose ADHD officially. The symptoms of disorders such as ADHD are known to have continuity with the normal sample (Harrington, 2001); thus, the potential inclusion of the actual ADHD is not thought to substantially alter the nature of the study. In addition, the low prevalence of ADHD in Asian and Japanese samples is well known and focusing on a high education sample plus the presented exclusion criteria may further lower the risk of ADHD (Faraone and Biederman, 2005). Consistent with this notion, the basic evaluation of another sample, which was recruited in the same manner, suggested that the sample that was recruited in the same manner as that in the present study contained few ADHD subjects (see Supplemental Methods and Supplemental Results). Nonetheless, the exact prevalence of ADHD in the present sample was not known; if available, this information may have provided some additional information. Another limitation was common to our previous studies and other studies that use college cohorts (Jung et al., 2010b; Song et al., 2008; Takeuchi et al., 2011c; Takeuchi et al., 2010a, b; Wei et al., 2013). As previously described (Takeuchi et al., 2012a), we used young healthy subjects with high educational backgrounds. Limited sampling of the full range of intellectual abilities is a common hazard when sampling from college cohorts (Jung et al., 2010b). Many possibly unique sample characteristics of college cohorts may bias some findings. Higher educational background is also known to be associated with a lower ADHD prevalence (Faraone and Biederman, 2005), which should have further lowered the risk of ADHD in the population. Whether our findings would also hold across the full range of population samples and a normal distribution must be determined using larger and more representative samples (Takeuchi et al., 2012a). Focusing on highly intellectual subjects with a low risk of ADHD was certainly warranted for the purpose of this

study, given the association between higher intelligence and higher creativity measured by divergent thinking among subjects with normal and inferior intelligence (Sternberg, 2005) and the assumption of this study that the risk allele of ADHD should lead to higher performance of creativity measures as described in the Introduction section. Finally, as can be predicted from the significance level of some of the significant results, when the present sample was split into two groups randomly, the present results of the effects of the polymorphism will not become significant in both split samples, even at an uncorrected level in psychological results. The relatively large sample is a strength of this study, and the results were congruent with the theoretical background as well as the previous meta-analyses of the clinical findings involving this polymorphism. Nonetheless, the general effects of the common polymorphism are still weak, and these results and the significance level suggest that attempts should be made to replicate the results.

This study revealed the psychological and neural effects of the 5-repeat allele of *DRD4*, which is robustly associated with the risk of ADHD. The present study newly suggested that the 5-repeat allele led to the widespread disruption of the neural networks and inefficient attentional reallocation, which was reflected in a reduced TID in the areas deactivated during cognitive tasks. These phenomena may lead to an increased risk of ADHD. Furthermore, the increased originality of creative thinking observed in the 5-repeat allele carriers may support the notion of the side of adaptivity of the widespread risk allele of psychiatric diseases (Horrobin, 2002).

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2015.01.053>.

## Acknowledgments

We thank Yuki Yamada for operating the MRI scanner, Haruka Nouchi for conducting the psychological tests, all other assistants for helping with the experiments and the study, and the study participants and all our other colleagues at IDAC, Tohoku University for their support. This study was supported by JST/RISTEX, JST/CREST, a Grant-in-Aid for Young Scientists (B) (KAKENHI 23700306) and a Grant-in-Aid for Young Scientists (A) (KAKENHI 25700012) from the Ministry of Education, Culture, Sports, Science, and Technology. The authors would like to thank Enago ([www.enago.jp](http://www.enago.jp)) for the English language review.

## References

- Abe, M., Fukuyama, H., Mima, T., 2014. Water diffusion reveals networks that modulate multiregional morphological plasticity after repetitive brain stimulation. *Proc. Natl. Acad. Sci.* 111, 4608–4613.
- Andreone, N., Tansella, M., Cerini, R., Versace, A., Rambaldelli, G., Perlini, C., Dusi, N., Pelizza, L., Balestrieri, M., Barbui, C., 2007. Cortical white-matter microstructure in schizophrenia diffusion imaging study. *Br. J. Psychiatry* 191, 113–119.
- Aoki, Y., Nishizawa, D., Kasai, S., Fukuda, K.-i., Ichinohe, T., Yamashita, S., Ikeda, K., 2013. Association between the variable number of tandem repeat polymorphism in the third exon of the dopamine  $D_{4receptor}$  gene and sensitivity to analgesics and pain in patients undergoing painful cosmetic surgery. *Neurosci. Lett.* 542, 1–4.
- Asghari, V., Sanyal, S., Buchwaldt, S., Paterson, A., Jovanovic, V., Van Tol, H.H., 1995. Modulation of intracellular cyclic AMP levels by different human dopamine *D4* receptor variants. *J. Neurochem.* 65, 1157–1165.
- Assaf, Y., Pasternak, O., 2008. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. *J. Mol. Neurosci.* 34, 51–61.
- Barkley, R.A., 1997. Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychol. Bull.* 121, 65–94.
- Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. Ser. B Methodol.* 57, 289–300.
- Benjamini, Y., Hochberg, Y., 2000. On the adaptive control of the false discovery rate in multiple testing with independent statistics. *J. Educ. Behav. Stat.* 25, 60–83.
- Bjørnebeck, A., Westlye, L.T., Fjell, A.M., Grydeland, H., Walhovd, K.B., 2012. Social reward dependence and brain white matter microstructure. *Cereb. Cortex* 22, 2672–2679.
- Boy, C., Klimke, A., Holschbach, M., Herzog, H., Muehlenstepen, H., Kops, E.R., Sonnenberg, F., Gaebel, W., Stoeklin, G., Markstein, R., 1998. Imaging dopamine *D4* receptors in the living primate brain: a positron emission tomography study using the novel *D1/D4* antagonist [ $^{11}C$ ] SDZ GLC 756. *Synapse* 30, 341–350.
- Brewer, J.A., Worhunsky, P.D., Gray, J.R., Tang, Y.-Y., Weber, J., Kober, H., 2011. Meditation experience is associated with differences in default mode network activity and connectivity. *Proc. Natl. Acad. Sci.* 108, 20254–20259.
- Brewin, C.R., Smart, L., 2005. Working memory capacity and suppression of intrusive thoughts. *J. Behav. Ther. Exp. Psychiatry* 36, 61–68.
- Brown, A.B., Biederman, J., Valera, E., Makris, N., Doyle, A., Whitfield-Gabrieli, S., Mick, E., Spencer, T., Faraone, S., Seidman, L., 2011. Relationship of *DAT1* and adult ADHD to task-positive and task-negative working memory networks. *Psychiatry Res. Neuroimaging* 193, 7–16.
- Brown, A., Biederman, J., Valera, E., Lomedico, A., Aleardi, M., Makris, N., Seidman, L.J., 2012. Working memory network alterations and associated symptoms in adults with ADHD and bipolar disorder. *J. Psychiatr. Res.* 46, 476–483.
- Buckner, R.L., Andrews-Hanna, J.R., Schacter, D.L., 2008. The brain's default network. *Ann. N. Y. Acad. Sci.* 1124, 1–38.
- Burgess, G.C., Dupue, B.E., Ruzic, L., Willcutt, E.G., Du, Y.P., Banich, M.T., 2010. Attentional control activation relates to working memory in attention-deficit/hyperactivity disorder. *Biol. Psychiatry* 67, 632–640.
- Callicott, J.H., Mattay, V.S., Bertolino, A., Finn, K., Coppola, R., Frank, J.A., Goldberg, T.E., Weinberger, D.R., 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb. Cortex* 9, 20–26.
- Carlson, N.R., 2001. *Physiology Of Behavior*. Allyn and Bacon, Boston.
- Casanova, R., Srikanth, R., Baer, A., Laurienti, P.J., Burdette, J.H., Hayasaka, S., Flowers, L., Wood, F., Maldjian, J.A., 2007. Biological parametric mapping: a statistical toolbox for multimodality brain image analysis. *Neuroimage* 34, 137–143.
- Cavanna, A.E., Trimble, M.R., 2006. The preuneus: a review of its functional anatomy and behavioural correlates. *Brain* 129, 564–583.
- Claridge, G., McCreery, C., Mason, O., Bentall, R., Boyle, G., Slade, P., Popplewell, D., 1996. The factor structure of 'schizotypal' traits: a large replication study. *Br. J. Clin. Psychol.* 35, 103–115.
- Cloninger, C.R., Svrakic, D.M., Przybeck, T.R., 1993. A psychological model of temperament and character. *Arch. Gen. Psychiatry* 50, 975–990.
- Cohen, R., Seneky, Y., Shuper, A., Inbar, D., Chodick, G., Shalev, V., Raz, R., 2013. Prevalence of epilepsy and attention-deficit hyperactivity (ADHD) disorder a population-based study. *J. Child Neurol.* 28, 120–123.
- Comings, D.E., Gonzalez, N., Wu, S., Gade, R., Muhleman, D., Saucier, G., Johnson, P., Verde, R., Rosenthal, R.J., Lesieur, H.R., 1999. Studies of the 48 bp repeat polymorphism of the *DRD4* gene in impulsive, compulsive, addictive behaviors: Tourette syndrome, ADHD, pathological gambling, and substance abuse. *Am. J. Med. Genet.* 88, 358–368.
- Corbetta, M., Patel, G., Shulman, G.L., 2008. The reorienting system of the human brain: from environment to theory of mind. *Neuron* 58, 306–324.
- Diedrichsen, J., Shadmehr, R., 2005. Detecting and adjusting for artifacts in fMRI time series data. *Neuroimage* 27, 624–634.
- Durston, S., Fossella, J., Casey, B., Pol, H.H., Galvan, A., Schnack, H., Steenhuis, M., Minderaa, R., Buitelaar, J., Kahn, R., 2005. Differential effects of *DRD4* and *DAT1* genotype on fronto-striatal gray matter volumes in a sample of subjects with attention deficit hyperactivity disorder, their unaffected siblings, and controls. *Mol. Psychiatry* 10, 678–685.
- Eisenman, R., 1969. Creativity, awareness, and liking. *J. Consult. Clin. Psychol.* 33, 157–160.
- Engle, R.W., Kane, M.J., Tuholski, S.W., 1999. Individual differences in working memory capacity and what they tell us about controlled attention, general fluid intelligence, and functions of the prefrontal cortex. *Models Of Working Memory: Mechanisms Of Active Maintenance And Executive control*. Cambridge University Press, Cambridge, pp. 102–134.
- Fair, D.A., Cohen, A.L., Dosenbach, N.U., Church, J.A., Miezin, F.M., Barch, D.M., Raichle, M.E., Petersen, S.E., Schlaggar, B.L., 2008. The maturing architecture of the brain's default network. *Proc. Natl. Acad. Sci.* 105, 4028–4032.
- Faraone, S.V., Biederman, J., 1998. Neurobiology of attention-deficit hyperactivity disorder. *Biol. Psychiatry* 44, 951–958.
- Faraone, S.V., Biederman, J., 2005. What is the prevalence of adult ADHD? Results of a population screen of 966 adults. *J. Atten. Disord.* 9, 384–391.
- Fink, A., Grabner, R.H., Gebauer, D., Reishofer, G., Koschutnig, K., Ebner, F., 2010. Enhancing creativity by means of cognitive stimulation: evidence from an fMRI study. *Neuroimage* 52, 1687–1695.
- Fink, A., Koschutnig, K., Benedek, M., Reishofer, G., Ischebeck, A., Weiss, E.M., Ebner, F., 2012. Stimulating creativity via the exposure to other people's ideas. *Hum. Brain Mapp.* 33, 2603–2610.
- Fink, A., Koschutnig, K., Hutterer, L., Steiner, E., Benedek, M., Weber, B., Reishofer, G., Papousek, I., Weiss, E.M., 2013. Gray matter density in relation to different facets of verbal creativity. *Brain Struct. Funct.* 1–7.
- Friston, K.J., Holmes, A., Poline, J.B., Price, C.J., Frith, C.D., 1996. Detecting activations in PET and fMRI: levels of inference and power. *Neuroimage* 4, 223–235.
- Genovese, C.R., Lazar, N.A., Nichols, T., 2002. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage* 15, 870–878.
- Grabner, R.H., Ansari, D., Reishofer, G., Stern, E., Ebner, F., Neuper, C., 2007. Individual differences in mathematical competence predict parietal brain activation during mental calculation. *Neuroimage* 38, 346–356.
- Green, M.J., Williams, L.M., 1999. Schizotypy and creativity as effects of reduced cognitive inhibition. *Personal. Individ. Differ.* 27, 263–276.
- Hakoda, Y., Sasaki, M., 1990. Group version of the Stroop and reverse-Stroop test: the effects of reaction mode, order and practice. *Kyoikushinrigakukenkkyu (Educ. Psychol. Res.)* 38, 389–394.
- Harrington, R., 2001. Developmental continuities and discontinuities. *Br. J. Psychiatry* 179, 189–190.
- Horrobin, D.F., 2002. *The Madness Of Adam And Eve: How Schizophrenia Shaped Humanity*. Corgi Books, London.
- Johansen-Berg, H., Baptista, C.S., Thomas, A.G., 2012. Human structural plasticity at record speed. *Neuron* 73, 1058–1060.
- Jung, R.E., Grazioplene, R., Caprihan, A., Chavez, R.S., Haier, R.J., 2010a. White matter integrity, creativity, and psychopathology: disentangling constructs with diffusion tensor imaging. *PLoS ONE* 5, e9818.

- Jung, R.E., Segall, J.M., Bockholt, H.J., Flores, R.A., Smith, S.M., Chavez, R.S., Haier, R.J., 2010b. Neuroanatomy of creativity. *Hum. Brain Mapp.* 31, 398–409.
- Jung, R.E., Mead, B.S., Carrasco, J., Flores, R.A., 2013. The structure of creative cognition in the human brain. *Front. Hum. Neurosci.* 7.
- Kantarci, K., Jack Jr., C.R., Xu, Y.C., Campeau, N.G., O'Brien, P.C., Smith, G.E., Ivnik, R.J., Boeve, B.F., Kokmen, E., Tangalos, E.G., 2001. Mild cognitive impairment and alzheimer disease: regional diffusivity of water1. *Radiology* 219, 101–107.
- Kárádóttir, R., Attwell, D., 2007. Neurotransmitter receptors in the life and death of oligodendrocytes. *Neuroscience* 145, 1426–1438.
- Kharkhurin, A.V., 2008. The effect of linguistic proficiency, age of second language acquisition, and length of exposure to a new cultural environment on bilinguals' divergent thinking. *Biling. Lang. Cogn.* 11, 225–243.
- Kijima, N., Saito, R., Takeuchi, M., Yoshino, A., Ono, Y., Kato, M., Kitamura, T., 1996. Cloninger's seven-factor model of temperament and character and Japanese version of Temperament and Character Inventory (TCI). *Arch. Psychiatr. Diagn. Clin. Eval.* 7, 379–399.
- Kluger, A., Siegfried, Z., Ebstein, R., 2002. A meta-analysis of the association between DRD4 polymorphism and novelty seeking. *Mol. Psychiatry* 7, 712–717.
- Konrad, K., Eickhoff, S.B., 2010. Is the ADHD brain wired differently? A review on structural and functional connectivity in attention deficit hyperactivity disorder. *Hum. Brain Mapp.* 31, 904–916.
- Laricchiuta, D., Petrosini, L., Piras, F., Cutuli, D., Macci, E., Picerni, E., Chiapponi, C., Caltagirone, C., Spalletta, G., 2013. Linking novelty seeking and harm avoidance personality traits to basal ganglia: volumetry and mean diffusivity. *Brain Struct. Funct.* 1–11.
- Li, D., Sham, P.C., Owen, M.J., He, L., 2006. Meta-analysis shows significant association between dopamine system genes and attention deficit hyperactivity disorder (ADHD). *Hum. Mol. Genet.* 15, 2276–2284.
- Lichter, J.B., Barr, C.L., Kennedy, J.L., Van Tol, H.H., Kidd, K.K., Livak, K.J., 1993. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Hum. Mol. Genet.* 2, 767–773.
- Lindholm, E., Jazin, E., 2007. A possible link between dopamine action and myelin dysfunction in schizophrenia. *Schizophr. Res.* 96, 271–272.
- Martinussen, R., Hayden, J., Hogg-Johnson, S., Tannock, R., 2005. A meta-analysis of working memory impairments in children with attention-deficit/hyperactivity disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 44, 377–384.
- Mayseless, N., Uzefovsky, F., Shalev, I., Ebstein, R.P., Shamay-Tsoory, S.G., 2013. The association between creativity and 7R polymorphism in the dopamine receptor D4 gene (DRD4). *Front. Hum. Neurosci.* 7, 502.
- McKiernan, K.A., Kaufman, J.N., Kucera-Thompson, J., Binder, J.R., 2003. A parametric manipulation of factors affecting task-induced deactivation in functional neuroimaging. *J. Cogn. Neurosci.* 15, 394–408.
- Monuteaux, M.C., Seidman, L.J., Faraone, S.V., Makris, N., Spencer, T., Valera, E., Brown, A., Bush, G., Doyle, A.E., Hughes, S., 2008. A preliminary study of dopamine D4 receptor genotype and structural brain alterations in adults with ADHD. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 147, 1436–1441.
- Moseley, M., Bammer, R., Illes, J., 2002. Diffusion-tensor imaging of cognitive performance. *Brain Cogn.* 50, 396–413.
- Mrzljak, L., Bergson, C., Pappy, M., Huff, R., Levenson, R., Goldman-Rakic, P., 1996. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. *Nature* 381, 245–248.
- Ni, J., Chen, S., Liu, J., Huang, G., Shen, T., Chen, X., 2010. Regional diffusion changes of cerebral grey matter during normal aging—a fluid-inversion prepared diffusion imaging study. *Eur. J. Radiol.* 75, 134–138.
- Nusbaum, A.O., Tang, C.Y., Buchsbaum, M.S., Wei, T.C., Atlas, S.W., 2001. Regional and global changes in cerebral diffusion with normal aging. *Am. J. Neuroradiol.* 22, 136–142.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Papenberg, G., Lövdén, M., Laukka, E.J., Kalpouzos, G., Keller, L., Graff, C., Köhncke, Y., Li, T.-Q., Fratiglioni, L., Bäckman, L., 2014. Magnified effects of the COMT gene on white-matter microstructure in very old age. *Brain Struct. Funct.* 1–12.
- Péran, P., Cherubini, A., Assogna, F., Piras, F., Quattrocchi, C., Peppe, A., Celsis, P., Rascol, O., Démonet, J.-F., Stefani, A., 2010. Magnetic resonance imaging markers of Parkinson's disease nigrostriatal signature. *Brain* 133, 3423–3433.
- Pérez-Edgar, K., Hardee, J.E., Guyer, A.E., Benson, B.E., Nelson, E.E., Gorodetsky, E., Goldman, D., Fox, N.A., Pine, D.S., Ernst, M., 2014. DRD4 and striatal modulation of the link between childhood behavioral inhibition and adolescent anxiety. *Soc. Cogn. Affect. Neurosci.* 9, 445–453.
- Picerni, E., Petrosini, L., Piras, F., Laricchiuta, D., Cutuli, D., Chiapponi, C., Fagioli, S., Girardi, P., Caltagirone, C., Spalletta, G., 2013. New evidence for the cerebellar involvement in personality traits. *Front. Behav. Neurosci.* 7, 133.
- Power, J.D., Barnes, K.A., Snyder, A.Z., Schlaggar, B.L., Petersen, S.E., 2012. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *Neuroimage* 59, 2142–2154.
- Qian, Q., Wang, Y., Li, J., Yang, L., Wang, B., Zhou, R., 2003. [Association studies of dopamine D4 receptor gene and dopamine transporter gene polymorphisms in Han Chinese patients with attention deficit hyperactivity disorder]. *Beijing da xue xue bao. Yi xue ban = Journal of Peking University. Health Sci.* 35, 412–418.
- Raven, J., 1998. *Manual For Raven's Progressive Matrices And Vocabulary Scales*. Oxford Psychologists Press, Oxford.
- Razek, A.A., Elmongy, A., Hazem, M., Zakareyia, S., Gabr, W., 2011. Idiopathic Parkinson disease effect of levodopa on apparent diffusion coefficient value of the brain. *Acad. Radiol.* 18, 70–73.
- Rindermann, H., Neubauer, A., 2004. Processing speed, intelligence, creativity, and school performance: testing of causal hypotheses using structural equation models. *Intelligence* 32, 573–589.
- Sagi, Y., Tavor, I., Hofstetter, S., Tzur-Moryosef, S., Blumenfeld-Katzir, T., Assaf, Y., 2012. Learning in the fast lane: new insights into neuroplasticity. *Neuron* 73, 1195–1203.
- Sakamoto, S., 1998. The preoccupation scale: its development and relationship with depression scales. *J. Clin. Psychol.* 54, 645–654.
- Sasaki, H., Kanachi, M., 2005. The effects of trial repetition and individual characteristics on decision making under uncertainty. *J. Psychol.* 139, 233–246.
- Schilbach, L., Eickhoff, S.B., Rotarska-Jagiela, A., Fink, G.R., Voegeley, K., 2008. Minds at rest? Social cognition as the default mode of cognition and its putative relationship to the Conscious. *Cogn.* 17, 457–467.
- Seppi, K., Schocke, M.F., Donnemiller, E., Esterhammer, R., Kremser, C., Scherfler, C., Diem, A., Jaschke, W., Wenning, G.K., Poewe, W., 2004. Comparison of diffusion-weighted imaging and [<sup>123</sup>I] IBZM-SPECT for the differentiation of patients with the Parkinson variant of multiple system atrophy from those with Parkinson's disease. *Mov. Disord.* 19, 1438–1445.
- Shamay-Tsoory, S., Adler, N., Aharon-Peretz, J., Perry, D., Mayseless, N., 2011. The origins of originality: the neural bases of creative thinking and originality. *Neuropsychologia* 49, 178–185.
- Shaw, P., Gornick, M., Lerch, J., Addington, A., Seal, J., Greenstein, D., Sharp, W., Evans, A., Giedd, J.N., Castellanos, F.X., 2007. Polymorphisms of the dopamine D4 receptor, clinical outcome, and cortical structure in attention-deficit/hyperactivity disorder. *Arch. Gen. Psychiatry* 64, 921–931.
- Society\_For\_Creative\_Minds, 1969. *Manual Of S-A Creativity Test*. Tokyo shinri Corporation, Tokyo.
- Song, M., Zhou, Y., Li, J., Liu, Y., Tian, L., Yu, C., Jiang, T., 2008. Brain spontaneous functional connectivity and intelligence. *Neuroimage* 41, 1168–1176.
- Sternberg, R.J., 2005. *Handbook of creativity*. Cambridge UP, New York.
- Swanson, J., Oosterlaan, J., Murias, M., Schuck, S., Flodman, P., Spence, M.A., Wasdell, M., Ding, Y., Chi, H.-C., Smith, M., 2000. Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. *Proc. Natl. Acad. Sci.* 97, 4754–4759.
- Szekely, A., Balota, D., Duchek, J., Nemoda, Z., Vereczkei, A., Sasvari-Szekely, M., 2011. Genetic factors of reaction time performance: DRD4 7-repeat allele associated with slower responses. *Genes Brain Behav.* 10, 129–136.
- Takao, H., Hayashi, N., Inano, S., Ohtomo, K., 2011. Effect of head size on diffusion tensor imaging. *Neuroimage* 57, 958–967.
- Takeuchi, H., Kawashima, R., 2013. Neural bases of individual differences of creativity measured by the divergent thinking test (symposium). Association For Psychological Science 25th Annual Convention, Washington DC, US.
- Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., Kawashima, R., 2010a. White matter structures associated with creativity: evidence from diffusion tensor imaging. *Neuroimage* 51, 11–18.
- Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., Kawashima, R., 2010b. Regional gray matter volume of dopaminergic system associate with creativity: evidence from voxel-based morphometry. *Neuroimage* 51, 578–585.
- Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., Kawashima, R., 2011a. Effects of training of processing speed on neural systems. *J. Neurosci.* 31, 12139–12148.
- Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., Kawashima, R., 2011b. Failing to deactivate: the association between brain activity during a working memory task and creativity. *Neuroimage* 55, 681–687.
- Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Fukushima, A., Kawashima, R., 2011c. Verbal working memory performance correlates with regional white matter structures in the fronto-parietal regions. *Neuropsychologia* 49, 3466–3473.
- Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Nagase, T., Nouchi, R., Fukushima, A., Kawashima, R., 2012a. Regional gray and white matter volume associated with Stroop interference: evidence from voxel-based morphometry. *Neuroimage* 59, 2899–2907.
- Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., Nouchi, R., Kawashima, R., 2012b. The association between resting functional connectivity and creativity. *Cereb. Cortex* 22, 2921–2929.
- Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Sassa, Y., Kawashima, R., 2013a. Effects of working memory-training on functional connectivity and cerebral blood flow during rest. *Cortex* 49, 2106–2125.
- Takeuchi, H., Taki, Y., Sassa, Y., Hashizume, H., Sekiguchi, A., Nagase, T., Nouchi, R., Fukushima, A., Kawashima, R., 2013b. White matter structures associated with emotional intelligence: evidence from diffusion tensor imaging. *Hum. Brain Mapp.* 34, 1025–1034.
- Takeuchi, H., Taki, Y., Thyreau, B., Sassa, Y., Hashizume, H., Sekiguchi, A., Nagase, T., Nouchi, R., Fukushima, A., Kawashima, R., 2013c. White matter structures associated with empathizing and systemizing in young adults. *Neuroimage* 77, 222–236.
- Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Sassa, Y., Kawashima, R., 2014a. Effects of multitasking-training on gray matter structure and resting state neural mechanisms. *Hum. Brain Mapp.* 35, 3646–3660.
- Takeuchi, H., Taki, Y., Sekiguchi, A., Nouchi, R., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Iizuka, K., Yokoyama, R., Shinada, T., 2014b. Creativity measured by divergent thinking is associated with two axes of autistic characteristics. *Front. Psychol.* 5 (article 921).
- Takeuchi, H., Taki, Y., Nouchi, R., Hashizume, H., Sekiguchi, A., Kotozaki, Y., Nakagawa, S., Miyauchi, C.M., Sassa, Y., Kawashima, R., 2014c. Working memory training impacts the mean diffusivity in the dopaminergic system. *Brain Struct. Funct.* <http://dx.doi.org/10.1007/s00429-014-0845-2> (Epub ahead of print).
- Taki, Y., Thyreau, B., Hashizume, H., Sassa, Y., Takeuchi, H., Wu, K., Kotozaki, Y., Nouchi, R., Asano, M., Asano, K., 2013. Linear and curvilinear correlations of brain white matter



- volume, fractional anisotropy, and mean diffusivity with age using voxel-based and region of interest analyses in 246 healthy children. *Hum. Brain Mapp.* 34, 1842–1856.
- Takigiku, K., Sakamoto, A., 1991. Cognitive reflectivity—the making of impulsiveness standard—study about the reliability and appropriateness. *The 38th Annual Meeting Of The Japanese Group Dynamics Association Collected Papers*, pp. 39–40.
- Tanaka, K., Okamoto, K., Tanaka, H., 2003. *Manual Of New Tanaka B Type Intelligence Test*. Kaneko Syobo, Tokyo.
- Thomason, M.E., Dougherty, R.F., Colich, N.L., Perry, L.M., Rykhlevskaia, E.I., Louro, H.M., Hallmayer, J.F., Waugh, C.E., Bammner, R., Glover, G.H., 2010. COMT genotype affects prefrontal white matter pathways in children and adolescents. *Neuroimage* 53, 926–934.
- Tost, H., Alam, T., Geramita, M., Rebsch, C., Kolachana, B., Dickinson, D., Verchinski, B.A., Lemaitre, H., Barnett, A.S., Trampush, J.W., 2012. Effects of the BDNF Val66Met polymorphism on white matter microstructure in healthy adults. *Neuropsychopharmacology* 38, 525–532.
- Valera, E.M., Brown, A., Biederman, J., Faraone, S.V., Makris, N., Monuteaux, M.C., Whitfield-Gabrieli, S., Vitulano, M., Schiller, M., Seidman, L.J., 2010. Sex differences in the functional neuroanatomy of working memory in adults with ADHD. *Am. J. Psychiatr.* 167, 86–94.
- Van Tol, H.H., Wu, C.M., Guan, H.-C., Ohara, K., Bunzow, J.R., Civelli, O., Kennedy, J., Seeman, P., Niznik, H.B., Jovanovic, V., 1992. Multiple dopamine D4 receptor variants in the human population. *Nature* 358, 149–152.
- Wei, D., Yang, J., Li, W., Wang, K., Zhang, Q., Qiu, J., 2013. Increased resting functional connectivity of the medial prefrontal cortex in creativity by means of cognitive stimulation. *Cortex* 51, 92–102.
- Whitfield-Gabrieli, S., Thermenos, H.W., Milanovic, S., Tsuang, M.T., Faraone, S.V., McCarley, R.W., Shenton, M.E., Green, A.I., Nieto-Castanon, A., LaViolette, P., 2009. Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia. *Proc. Natl. Acad. Sci.* 106, 1279–1284.
- Whitwell, J.L., Master, A.V., Avula, R., Kantarci, K., Eggers, S.D., Edmonson, H.A., Jack, C.R., Josephs, K.A., 2011. Clinical correlates of white matter tract degeneration in progressive supranuclear palsy. *Arch. Neurol.* 68, 753–760.
- World Medical Association, 1991. *Declaration of Helsinki*. Law, medicine & health care: a publication of the American Society of Law & Medicine 19, 264.