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White matter microstructure of the cingulum and cerebellar peduncle is related to sustained attention and working memory: A diffusion tensor imaging study

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ABSTRACT

The non-invasive imaging technique of diffusion tensor imaging (DTI) has been used to investigate the microstructural properties of white matter (WM). The present study investigated whether individual differences in the WM structure of normal subjects as measured by fractional anisotropy (FA) values correlate with cognitive performance in terms of sustained attention and working memory. Subjects underwent DTI and performed the Continuous Performance Test (CPT) and N-back task. FA values throughout the brain were correlated with behavioral performance on a voxel-by-voxel basis to investigate relationships between WM microstructure and cognitive function. The discriminability index of CPT correlated positively with FA of the right cingulum. Accuracy of the 2-back task correlated positively with FA in bilateral cerebellar peduncles. WM microstructure of the right cingulum and bilateral cerebellar peduncles appears related to cognitive function such as sustained attention and working memory in the human brain.

Diffusion tensor imaging (DTI) has recently been used to investigate the microstructural properties of white matter (WM). Unlike standard structural magnetic resonance imaging (MRI) techniques such as T1- or T2-weighted imaging, DTI measures the microstructural features of WM and permits the study of fiber connections between anatomically and functionally defined brain regions. Among the parameters obtained by this method, fractional anisotropy (FA) offers a normalized measure of diffusion anisotropy that provides information about the degree of fiber organization. Tissues with highly organized fibers oriented in the same direction (*e.g.*, the corpus callosum) generally display high FA. FA is thought to increase as a result of myelination, axonal thickness and parallel organization of axons, or combinations of these factors [3].

Several studies have indicated relationships between cognitive/motor performance and FA. In normal subjects, FA in the frontal lobe has been correlated with executive function [15]. WM diffusion anisotropy in the temporo-parietal region of the left hemisphere has been correlated with reading ability in healthy subjects [17]. In another study, normal adults who had studied a musical instrument since childhood displayed significantly greater FA in the genu of the corpus callosum than those who had not studied music [21].

In addition, various studies investigating neurological abnormalities or psychiatric disorders have demonstrated connections between WM properties and cognition. Moreover, FA in the left superior cerebellar peduncle appears to correlate with cognitive cluster score in patients with schizophrenia [18]. Patients with multiple sclerosis reportedly show correlations between Paced-Auditory Serial Addition Test scores (indicating processing speed and working memory) and FA in the corpus callosum [7].

These studies suggest that understanding which regions of WM are related to specific cognitive functions is important to elucidate the neural networks of normal and pathological brains. The present study focused on two cognitive functions for which relationships to psychiatric disorders have recently been suggested: sustained attention [20]; and working memory [4]. Attention refers to a variety of components: focusing; sustained attention; inhibiting responses to irrelevant stimuli or selective attention; and shifting attention. Sustained attention is the ability to maintain focus over time. The Continuous Performance Test (CPT) is frequently used to obtain quantitative information regarding the ability of an individual to sustain attention over time. Working memory is a construct that describes the ability to transiently store and manipulate information on-line for use in cognition or behavioral guidance. Working memory is complicated and associated with persistent neural activity in multiple brain regions.

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The processes involved include information maintenance, suppression of distraction, motor response preparation, mental timing, expectancy, monitoring of internal and external states, and preservation of alertness [10]. First, several functional MRI (fMRI) studies investigating neural correlates of sustained attention using the CPT have identified significant activation in the cingulate gyrus while subjects were engaged in a task [20]. Given these findings, we hypothesized that the WM microstructure of the cingulum is related to sustained attention. Second, fMRI studies using the N-back task have demonstrated that working memory is related to activation in the prefrontal cortex (PFC) [4]. We therefore hypothesized that the WM microstructure of the PFC is involved in working memory.

The present study investigated whether individual differences in WM structure of normal subjects as indicated by FA relate to cognitive performance in terms of sustained attention or working memory. For this purpose, subjects underwent DTI and performed the CPT and N-back task. FA values throughout the brain were correlated with behavioral performance on a voxel-by-voxel basis to investigate relationships between WM microstructure and cognitive function.

Subjects comprised 38 healthy, right-handed volunteers (mean age, 32.8 ± 6.5 years; male/female ratio, 20:18; mean duration of education, 15.8 ± 2.2 years) from the Nagoya University community. Medical interviews and Structured Clinical Interviews for DSM-IV conducted at the time of the study showed that none of the participants had any physical or psychiatric disorders. The study protocol was approved by the ethics committee at Nagoya University School of Medicine, and written informed consent was obtained from each subject prior to participation. The cognitive test battery consisted of two tasks performed on a personal computer (PC) by manipulating a mouse or numeric keypad. These tasks were performed in an experimental room outside the scanner in the fixed order of CPT and N-back task.

CPT was used to measure sustained attention or vigilance. We used CPT-Identical Pairs version (CPT-IP) software, as described previously [6]. A series of 4-digit stimuli were presented for 50 ms, with an interstimulus interval (ISI) of 950 ms. Each complete task consisted of 150 trials, 30 of which were target trials requiring a response. In this study, performance was measured by the signal detection index d-prime (d′), a measure of discriminability computed from "hits" and "false alarms".

The N-back task was used to measure working memory. We used a task that required subjects to update the mental set continually while responding to previously seen stimuli (*i.e.*, numbers). Details of this task have been described previously [4]. Stimulus duration was 0.4 s, and ISI was 1.4 s. Each test comprised 14 trials. Participants responded to stimuli using the numeric keypad of the PC. In the present study, a 2-back task was used, and performance was measured as the percentage of correct responses (accuracy, %).

DTI data were obtained using a 3-T MRI system (Siemens Trio, Erlangen, Germany) with the following parameters: spin-echo echo-planar imaging; *b*-value, 700 s/mm^2; repetition time (TR), 8500 ms; echo time (TE), 75 ms; number of averages, 4; flip angle, 90°; six non-collinear directions and one no diffusion-weighting (B0) image; matrix = 128×112; 73 slices; and voxel size = $2 \times 2 \times 2$ mm. In addition, a high-resolution whole brain T1-weighted image was acquired (magnetization-prepared rapid angle gradient echo: TR, 1420 ms; TE, 2.6 ms; flip angle, 15°; matrix, 256×256; voxel size, $0.75 \times 0.75 \times 1$ mm) for each subject.

Original Digital Imaging and Communications in Medicine (DICOM) data were converted to the analyzed format using MRI-Cro software (http://www.sph.sc.edu/comd/rorden/mricro.html). Converted data that contained one B0 and six diffusion-weighted images were further processed using the FSL diffusion toolbox (ver. 3.3; FMRIB, UK, http://www.fmrib.ox.ac.uk/fsl/). After eddy current correction, an FA image was computed for each subject. The FA image was normalized to the Montreal Neurological Institute (MNI) space using the transformation matrix obtained when the B0 image was normalized to the T2-weighted template image by an affine 12 parameter model. The normalized FA image had voxel dimensions of $91 \times 109 \times 91$ with $2 \times 2 \times 2$-mm isotropic voxels. Finally, the FA image was spatially smoothed using a 12-mm Gaussian kernel. To investigate significant clusters located in the WM, statistical analysis was conducted exclusively on the brain region in which the probability of gray matter was relatively low. For this purpose, an optimized voxel-based-morphometry method [11] was used on the high-resolution T1-weighted image. The original T1-weighted images were processed using SPM2 (Wellcome Department of Imaging Neuroscience, UK, http://www.fil.ion.ucl.ac.uk/spm/) and VBM2 (http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2/) software running under Matlab version 7.0 (MathWorks, Natick, MA). In the first step of VBM2 analysis, the customized T1 template (T1.img) and prior images of each tissue segment (gray.img/white.img/csf.img) were created. These images that had been normalized to the MNI standard space and smoothed with full-width at half-maximum (FWHM) of 8 mm represented the mean probability map for the 38 subjects. The prior WM image (white.img) was then thresholded using a value of 0.4 (range, 0–1) and the resultant image was binarized using the ImCalc function of the SPM2 software. A mask image corresponding to the WM region with a probability $\geq$0.4 was thus created. In the following statistical analyses, the inclusive masking procedure was used to restrict significant results to locations within the masking region.

Statistical analysis was performed using a multiple regression module of SPM2. The smoothed FA image for each participant was used as the dependent variable and each of the two behavioral measures (CPT-d′ or 2-back task accuracy), age, and gender were used as independent variables. Based on results from previous studies showing that performance of the CPT significantly activates the cingulate gyrus [20], we hypothesized that the FA value in WM within the cingulate region would correlate with CPT-d′. Statistical analysis was thus restricted to the combined regions of the anterior, middle and posterior cingulate gyrus. This was achieved by applying a region-of-interest (ROI) mask including these regions in the left and right hemispheres using WFU Pick-Atlas software (http://fmri.wfubmc.edu/cms/software#PickAtlas). The statistical threshold was set at $P = 0.05$, corrected for multiple comparisons (FWE) for height and $k = 50$ voxels for extent. In correlations between the FA value and 2-back task accuracy, statistical analysis was conducted for the whole brain and the threshold was set at $P = 0.0001$, uncorrected, for height and $k = 50$ voxels for extent. In addition, we analyzed mean diffusivity (MD) in the three main direction of diffusion to provide an overall evaluation of diffusion ability in each voxel. Preprocessing and statistical analysis of MD images were conducted in the same manner as for FA images, except that MD image intensity was normalized to the grand mean of all voxels and images.

In voxel-by-voxel analysis within the cingulate region, CPT-d′ showed positive correlations with FA in the right cingulum (Table 1, Fig. 1A). Additionally, in correlations between FA value and CPT-d′, statistical analysis was conducted for the whole brain without the cingulate ROI using a lenient threshold ($P = 0.001$, uncorrected for height and $k = 50$ voxels for extent) to illustrate the spatial extent of the cluster. Areas showing significant correlations between FA and CPT-d′ at the lenient threshold were located along the cingulate gyrus (Fig. 2A). Fig. 2A indicates that highly significant regions (red areas, $P < 0.05$, FWE corrected) were within the cingulate regions, with strong right lateralization.

To allow detailed examination, a spherical ROI with an 8-mm radius was placed in the right cingulum (*x*, *y*, *z* = 10, 10, 46). Mean FA and MD values of the ROI were computed in each subject. The

Table 1
Areas of significant correlation between FA and cognitive function.

Task name	Anatomical location	Coordinates (mm)			*T* value	Voxel size
		x	*y*	*z*		
CPT	Cingulum (R)	10	10	46	4.59	62
		16	−18	42	4.28	63
2-back task	Cerebellar peduncle (R)	14	−34	−34	5.05	159
	Cerebellar peduncle (L)	−16	−38	−32	4.72	100
	Occipital lobe (R)	22	−76	6	5.97	168
	Anterior cingulate (R)	14	32	−6	4.46	67

CPT: The statistical threshold was set at $P=0.05$, corrected for multiple comparisons for height and $k=50$ voxels for extent. 2-back task: We used a cluster size of more than 50 voxels and a statistical threshold of $P<0.0001$, uncorrected. R, right; L, left.

FA value extracted from the right cingulum showed positive correlations with CPT-d′ across the 38 subjects (Pearson's correlation coefficient, $r=0.37$, $P=0.02$; Fig. 3A). To investigate laterality effects on the relationship between FA and sustained attention, a spherical ROI with an 8-mm radius was placed in the left homologous part of the cingulum (x, y, $z=-10$, 10, 46) and mean FA values of the ROI were computed in each subject. Mean FA in the left cingulum did not correlate with CPT-d′ ($r=0.17$, $P=0.31$). Mean MD in the right cingulum did not correlate with CPT-d′ ($r=0.17$, $P=0.22$). FA correlated negatively with MD in the right cingulum ($r=0.43$, $P=0.007$).

In voxel-by-voxel analysis, 2-back task accuracy showed positive correlations with FA in the right cerebellar peduncle, left cerebellar peduncle, right occipital lobe, and right anterior cingulate (Table 1, Fig. 1B).

Fig. 2B shows two significant clusters, one in each of the cerebellar peduncles, superimposed on a mean FA image of the subjects. A spherical ROI with an 8-mm radius was placed in bilateral cerebellar peduncles, and mean FA and MD values within the ROI were computed in each subject. Accuracy of the 2-back task correlated positively with FA in bilateral cerebellar peduncles (right: $r=0.45$, $P=0.0005$ (Fig. 3B), left: $r=0.45$, $P=0.0005$). However, accuracy of the 2-back task did not correlate with MD in bilateral cerebellar peduncles (right: $r=0.001$, $P=0.99$; left: $r=0.01$, $P=0.94$). FA correlated negatively with FA in the right cerebellar peduncle ($r=0.47$, $P=0.003$).

To the best of our knowledge, this is the first DTI study investigating, on a voxel-by-voxel basis, whether individual differences in the WM structure of normal subjects relate to sustained attention and working memory as measured by CPT and the N-back task. In healthy subjects, several studies have indicated relationships between cognitive function and FA [21]. Based on these findings, individual differences in the WM microstructure in normal subjects may be involved in cognitive/motor performance. We demonstrated that FA of the right cingulum was positively corre-

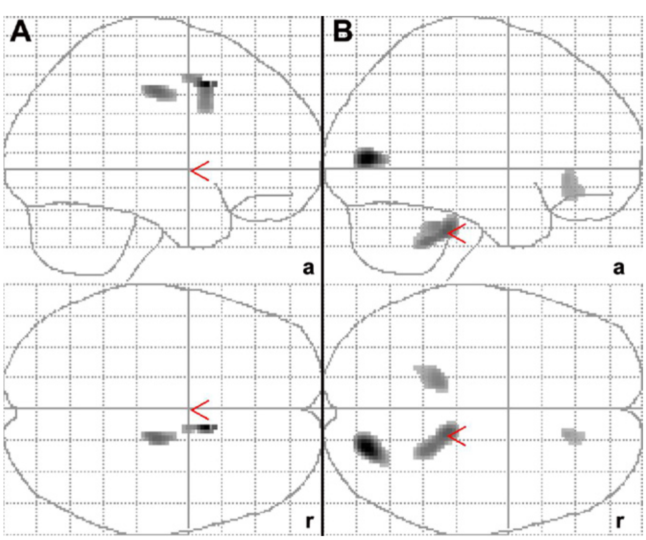

Fig. 1. (A) A 'glass brain' presentation of brain regions showing significant correlation between FA in the white matter within the cingulate region and CPT-d′ in the subjects, thresholded at $P=0.05$, corrected for multiple comparisons (FWE). Sustained attention performance was significantly correlated with FA in the right cingulum. (B) A 'glass brain' presentation of regions showing a significant correlation between FA and accuracy of the 2-back task, thresholded at $P=0.0001$, uncorrected. Working memory performance correlated significantly with FA in bilateral cerebellar peduncles, the right occipital lobe, and right anterior cingulate. a, anterior; r, right.

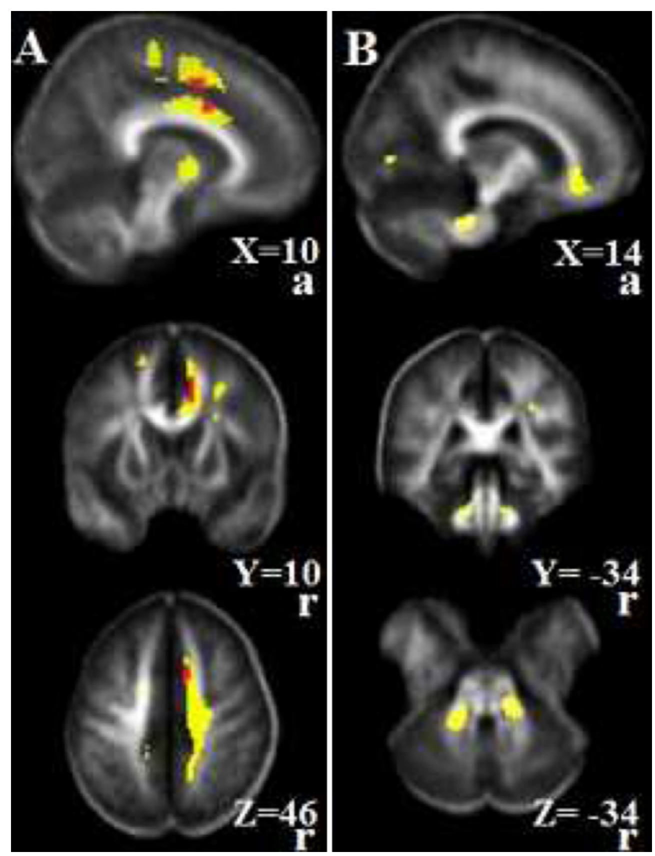

Fig. 2. (A) Yellow areas show brain regions where significant correlations between FA values and CPT-d′ were observed at $P=0.001$, uncorrected, and $k=50$ voxels without cingulate ROI mask. Red areas represent regions where correlations between FA and CPT-d′ were significant at $P=0.05$, FWE correction, with cingulate ROI mask. Highly significant regions (red areas) are thus present within the cingulate regions, with strong right lateralization. (B) Four significant clusters superimposed on a mean FA image of subjects. FA of bilateral cerebellar peduncles, the right occipital lobe, and right anterior cingulate correlated significantly with 2-back task accuracy. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

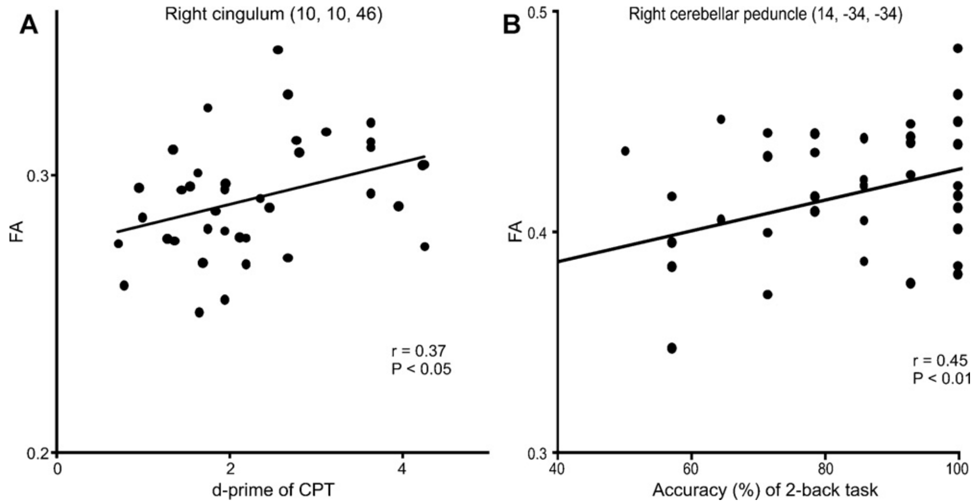

Fig. 3. (A) FA value extracted from the ROI in the right cingulum correlated positively with CPT-d′ across the 38 subjects (Pearson's correlation coefficient, $r = 0.37$, $P = 0.02$). Higher CPT-d′ was associated with better performance in the CPT. (B) Accuracy of the 2-back task was positively correlated with the FA value extracted from bilateral cerebellar peduncles (right: $r = 0.45$, $P = 0.005$; left: $r = 0.45$, $P = 0.005$). A spherical ROI with an 8-mm radius was placed in the right cingulum and bilateral cerebellar peduncles. Mean FA values of the ROI were computed in each subject.

lated with CPT-d'. Compared to MD, FA has become the consensus measure of WM microstructure throughout the DTI literature, due to its sensitivity to the changes seen with maturation, senescence, and diverse forms of brain pathology in humans [24]. A positive correlation between CPT-d′ and FA in the right cingulum indicates that individual difference in the fasciculus may contribute to sustained attention. The cingulum is the most prominent WM fiber tract underlying the cingulate gyrus and is the only communication route between the cingulate cortex and other areas of the brain, including prefrontal, parietal, and temporal areas and the thalamus [8]. The cingulate gyrus has been implicated in the attentional process in humans [5]. Several fMRI studies using CPT have shown significant activation in the right cingulate gyrus and occipital lobe while subjects are engaged in a task [12]. Since the right hemisphere might play a more prominent role than the left in human attention [16], these results suggest that the WM microstructure of the right cingulum was related to sustained attention in our subject group.

We demonstrated that FA in bilateral cerebellar peduncles, the right occipital lobe, and right anterior cingulate were positively correlated with 2-back task accuracy. This suggests that WM microstructure of these regions is related to working memory. A previous study using fMRI and the N-back task in healthy subjects demonstrated bilateral PFC activation [4]. However, FA in the PFC did not correlate with working memory performance in the present study. According to the task, differences may exist between the results of blood oxygen level-dependent fMRI and DTI investigating the microstructural properties of WM [1]. Such differences may be useful in elucidating brain function in terms of functionally connected architecture [23]. The cerebellar peduncles contain numerous neural fibers projecting from the cerebral cortex and subsequently crossing in the pons. The cerebellar nuclei also send neural fibers to the cerebral cortex and thalamus via the cerebellar peduncles, thus completing the circuit between the cerebral cortex and cerebellum [14]. Recent findings indicate that the cerebellar peduncles are involved in higher-order cognitive functions, such as working memory [22]. Cumulative evidence suggests that connections between the cerebellum and cerebral cortex may be related to cognitive function [13,22]. Given these findings, cerebellar peduncles may be involved in neural connectivity between the PFC and cerebellum in working memory performance. In the present study, WM microstructure of the right anterior cingulate and the right occipital lobe was related to working memory performance. In fMRI studies using the N-back task, significant activation was seen in the anterior cingulate during task performance [4]. The anterior cingulate has been associated with attention- or effort-related processes [2]. In a recent study, functional interactions between the prefrontal and visual association cortex were noted to contribute to top-down modulation of visual processing [9]. Moreover, an fMRI study utilizing a working memory task suggested that the visual association cortex was involved in working memory [19]. WM microstructure of the right anterior cingulate and the right occipital lobe thus appears to be related to working memory performance.

The present study shows some potential limitations. We used FA values as a measure of individual differences in the WM of normal subjects. Due to a technical problem, we were unable to investigate correlations between psychological parameters and tensor direction along the fiber directions of the cingulum and cerebellar peduncles. Future studies should therefore explore the possibility of such correlations. As the sample size was small, our analyses of relationships between FA throughout the brain and cognitive performance showed limited power. In addition, a possible limitation of voxel-wise analysis was the problem of multiple comparisons and increased risk of type 1 error. To limit this problem, we used a conservative statistical threshold of $P < 0.0001$, uncorrected in the analysis of correlations between FA value and 2-back task accuracy.

In conclusion, we found that CPT-d′ correlated positively with FA in the right cingulum and that 2-back task accuracy correlated positively with FA in bilateral cerebellar peduncles. These results indicate that the WM microstructure of the right cingulum and bilateral cerebellar peduncles appears to be related to cognitive functions such as sustained attention and working memory in the human brain.

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