

## Structural correlates of cognitive domains in normal aging with diffusion tensor imaging

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**Abstract** The involvement of brain structures in specific cognitive functions is not straightforward. In order to characterize the brain micro-structural correlates of cognitive domains, 52 healthy subjects, age 25–82 years, completed a computerized neuropsychological battery and were scanned using magnetic resonance diffusion tensor imaging. Factor analysis of 44 different cognitive scores was performed, isolating three cognitive domains—executive function, information processing speed and memory. Partial correlation was conducted between DTI parameters and each of the three cognitive domains controlling for age and motor function. Regions showing significant

correlations with cognitive domains are domain-specific and are consistent with previous knowledge. While executive function was correlated with diffusion tensor imaging (DTI) parameters in frontal white matter and in the superior longitudinal fasciculus, information processing speed was correlated with DTI parameters in the cingulum, corona radiata, inferior longitudinal fasciculus, parietal white matter and in the thalamus. Memory performance was correlated with DTI measures in temporal and frontal gray matter and white matter regions, including the cingulate cortex and the parahippocampus. Thus, inter-subject variability in cognitive performance and tissue morphology, as expressed by diffusion tensor magnetic resonance imaging, can be used to relate tissue microstructure with cognitive performance and to provide information to corroborate other functional localization techniques.

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**Keywords** Magnetic resonance imaging · Diffusion tensor imaging · Executive function · Information processing speed · Memory · Aging

### Introduction

It is widely agreed that brain function and structure are associated; however, the localization of specific functions to distinct brain structures is not straightforward.

Various studies have examined the relationship between brain structure and cognitive function, including animal studies, lesion studies and neuroimaging studies (Scoville and Milner 1957; Funahashi et al. 1989; Cabeza and Nyberg 2000). However, there are still conflicting results on the involvement of brain structures in specific cognitive functions. This has number of possible reasons. First, most of higher cognitive functions are complex and involve a

network of brain regions. Second, there is high variability in the tasks used in different studies measuring the same brain function. For example, memory function is known from lesion and neuroimaging studies to involve the hippocampus and the medial temporal lobe (Thompson and Kim 1996). However, other brain regions are known to be involved in different aspects of memory. The prefrontal cortex, mainly the dorso-lateral prefrontal cortex (D'Esposito et al. 1998), has been implicated in working memory by lesion and imaging studies. Other regions, including the cerebellum, motor areas and language areas, are involved in various learning and memory processes (Thompson and Kim 1996).

Aging is associated with a gradual, progressive decline in cognitive function. Cross-sectional and longitudinal behavioral studies have found significant declines in various functions. Among the cognitive functions that decline with aging, are executive functions, information processing speed and memory (Craik et al. 1987; Petersen et al. 1992; Youngjohn and Crook 1993; Small 2001)

Diffusion-tensor imaging (DTI) measures the magnitude and directionality of water diffusion in tissue (Basser and Pierpaoli 1998). Various DTI studies have demonstrated that DTI can characterize the brain localization of cognitive functions by correlating cognitive performance with DTI indices (Klingberg et al. 2000; Madden et al. 2004; Tuch et al. 2005; Forstmann et al. 2008; Charlton et al. 2006).

However, most of these studies focused on very specific tasks or brain regions, mainly in white matter regions. The aim of the present study was to characterize the brain localization of cognitive domains. In order to characterize specific cognitive domains, we used a broad battery of commonly used computerized neuropsychological tests to enable a comprehensive and detailed cognitive evaluation. Factor analysis of the tests scores was performed, and tests with common variability are united to one factor, thus isolating three cognitive domains: executive function, information processing speed, and memory.

Voxel-based analysis (VBA) of gray matter and white matter structures was used to characterize the micro-structural correlates of performance in the three cognitive domains identified in the factor analysis. The present study focused on a cognitively healthy population over a wide range of ages to facilitate high inter-subject variability in cognitive as well as micro-structural parameters. We correlated the scores in each cognitive domain with DTI parameters in both gray and white matter, correcting for multiple comparisons. The correlation procedure was controlled for age and for motor function.

## Methods

### Subjects

Participants were 54 cognitively healthy volunteers (ages 25–82 years, all right-handed, 32 female). Two subjects were excluded due to severe leukoaraiosis, resulting in 52 participants. Mean/median age was 51 years, with a standard deviation of 16 years. Subjects were evenly distributed over the age range. Participants were recruited from the general population by distribution of ads in community centers and in academic institutes. The local Tel Aviv-Sourasky Medical Center Helsinki Committee approved the research protocol, and all participants signed an informed consent. Inclusion and exclusion of subjects was based upon self-report. Participants had no history of neurological disease or psychological disorders, were not on neuropsychiatric medication, had no history of drug or alcohol abuse, and had intact vision. Volunteers with common age-related diseases such as diabetes, hypertension, and high levels of cholesterol were not excluded from the cohort.

### Neuropsychological tests

Participants underwent a series of computerized cognitive tests (MindStreams<sup>®</sup>, NeuroTrax Corp., Fresh Meadows, NY) that evaluate performance across an array of cognitive domains (memory, executive function, visual spatial perception, verbal function, attention, information processing speed, and motor skills) and provide measurements of accuracy and reaction time (Dwolatzky et al. 2003).

### Factor analysis

Factor analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA), as follows:

1. Factor analysis of 44 cognitive outcome parameter scores using principal component analysis (PCA) with orthogonal (VARIMAX) rotation and limiting the number of factors to 5 (although 10 factors obtained eigenvalues higher than 1) that explained 65% of the items total variance.
2. Based on the rotated component matrix, and as we aimed to extract “pure” factors, we excluded cognitive scores that contributed to more than one factor with loadings higher than 0.4. 14 scores were excluded.
3. Each factor contained cognitive scores with loadings greater than 0.4. Cronbach's alpha was used to assess the internal reliability of the factors. Factors with a Cronbach's alpha of  $\leq 0.8$  were excluded, resulting in the exclusion of two factors and the retention of three.

**Table 1** Factor analysis weights of final 20 cognitive measures, assigned to each cognitive domain

	Executive function	Memory	Information processing speed
Stroop WI RT	<b>0.82</b>	−0.15	0.32
Stroop WI RD	<b>0.80</b>	−0.14	−0.22
GoNoGo SD	<b>0.80</b>	−0.17	0.12
Stroop WOI1 RT	<b>0.74</b>	−0.33	0.10
GoNoGo RT	<b>0.72</b>	−0.11	0.33
Stroop WOI1 SD	<b>0.62</b>	0.07	0.13
NV memory rep3	−0.20	<b>0.87</b>	−0.14
NV memory rep4	−0.27	<b>0.86</b>	−0.18
NV memory delayed	−0.28	<b>0.85</b>	−0.14
NV memory rep2	−0.21	<b>0.82</b>	−0.17
NV memory rep1	0.037	<b>0.71</b>	−0.16
Verbal memory rep 1	−0.11	<b>0.47</b>	−0.33
Verbal memory delayed	−0.27	<b>0.45</b>	−0.27
Info proc 2_1 RT	0.03	−0.22	<b>0.84</b>
Info proc 2_2 RT	0.15	−0.16	<b>0.81</b>
Info proc 2_3 RT	0.25	−0.34	<b>0.64</b>
Info proc 2_3 SD	0.0005	−0.05	<b>0.48</b>

*WOI1* without interference 1 (letter color), *WI* with interference, *RT* reaction time, *RD* response time difference, *WI* minus *WOI2* (word letter), *SD* standard deviation, *Acc* accuracy, *NV* non verbal, *rep* repetition, *Info proc X\_Y* information processing, *X* number of digits, *Y* rate of presentation

4. The three factors retained were comprised of 18 cognitive scores. The scores and their factor loadings are shown in Table 1. Each factor was assigned a name describing its constituent scores: executive function, memory, and information processing speed. A detailed description of the tests is appended in Electronic Supplementary Material, briefly:

- a. The executive function factor included scores from the Go-NoGo response inhibition test and Stroop interference test. The Go-NoGo test is a continuous performance test of simple reaction time and response inhibition. In the Stroop interference test performed here, the conflicting information provided by the meaning of a word and the color of its letters lead to a decrement in performance relative to the test phases where there is no conflict and includes three phases—in phase I and II—no interference, phase III—with interference. The executive function domain is an average of reaction time (RT) in phase III with interference, response time difference (RD) between RT in phase III and phase II, RT in phase I without interference and standard deviations (SD) in phase I without interference.

- b. The memory domain included non-verbal and verbal memory tests. The verbal memory test measures immediate and delayed recognition memory for verbal paired associates. In the non-verbal memory test, participants are presented with eight black-and-white drawn pictures of simple common objects or shapes and are instructed to remember their orientation. Each of the tests included four repetitions of the study phase and a recognition test. This is followed by 10 min delayed recognition test. The memory domain included accuracy in four repetitions and delayed phase of the non-verbal memory test and accuracy in the first repetition and delayed phase of the verbal memory test.

- c. The staged information processing speed test measures information processing at increasing levels of complexity. The test is comprised of three levels of information processing load: single digits, two-digit arithmetic problems (e.g.,  $5 - 1$ ), and three-digit arithmetic problems (e.g.,  $3 + 2 - 1$ ). For each of these three levels, stimuli are presented at three different rates (speed levels), incrementally increasing as testing continues. The information processing speed domain is an average of the RT in stage 2 (two-digit arithmetic problems) in three different speed levels and SD of the RT in stage 2, level 3.

5. Calculation of factor scores: for each factor, the *z*-scores of the tests comprising it were averaged to give the factor score. These factor scores served as a covariate input for the DTI indices.

## MRI acquisition

MR imaging was performed on a 3T (GE) MRI system at the Tel Aviv-Sourasky Medical Center. The MRI protocol included conventional anatomy sequences and DTI acquired with a standard head-coil.

### Conventional anatomy sequences

$T_1$  weighted images: 3D spoiled gradient recalled echo (SPGR) sequence with the following parameters: 66 axial slices,  $TR/TE = 400/3.2$  ms, and resolution of  $1 \times 1 \times 2$  mm<sup>3</sup>, scan time of 4 min.  $T_2$  weighted images: fast spin echo  $T_2$ -weighted sequence with 24 axial slices,  $TR/TE = 4,600/85$  ms, echo train length of 32 echoes, and resolution of  $1 \times 1 \times 6$  mm<sup>3</sup>, scan time of 56 s. FLAIR images: fluid-attenuated inversion recovery sequence with 24 axial slices,  $TR/TE/TI = 9,000/140/2,100$  ms, and resolution of  $1 \times 1 \times 6$  mm<sup>3</sup>. These images were used for

screening and subjects with brain pathologies were excluded. Two subjects were excluded due to severe leukoaraiosis.

### DTI protocol

Spin-echo diffusion weighted echo planar imaging (DW-EPI) sequence was performed with 48 axial slices and resolution of  $2.5 \times 2.5 \times 2.5 \text{ mm}^3$ . Diffusion parameters were:  $\Delta/\delta = 25/19 \text{ ms}$ ,  $b$  value of  $1,000 \text{ s/mm}^2$  acquired with 19 gradient directions. The DW-EPI sequence was gated to the cardiac cycle with TR of 30 R–R intervals and TE of 88 ms.

### Image analysis

Correction of head motion image artifacts, normalization and statistical analysis were performed using the SPM software (version 2, UCL, London, UK). The image analysis routine of the diffusion tensor data included the following steps:

1. Correction of head motion using a least squares algorithm and 6-parameter (rigid body) transformations.
2. DTI analysis using in-house software written in Matlab 7.3.0 (Mathworks, Natick, MA, USA), from which axial FA and ADC maps were calculated as described previously (Basser and Pierpaoli 1998).
3. Optimized spatial normalization was applied to ensure optimal alignment. Detailed description of the normalization procedure is reported in Sasson et al. (2010) and described in Fig. 1. Briefly, an FA template was created, and the FA map of each subject was masked. The masked FA maps were normalized to the template using a 12-parameter affine transformation followed by non-linear transformations, with 1,176 parameters describing each deformation field. The same transformations were then applied to the ADC maps. The normalization procedure included smoothing of 3-mm full-width half maximum (FWHM) of the source image. A notable reduction in the standard deviation of the FA maps (Fig. 1e, g) as well as ADC maps (Fig. 1f, h) across all subjects ( $n = 52$ ) when using the optimized normalization method (Fig. 1g, h) compared with the standard normalization method (Fig. 1e, f).
4. In order to apply the random field theory (RFT) in the statistical analysis spatial smoothing was performed with a kernel at least three times the voxel size (8 mm).

### Statistical analysis

#### Voxel-based analysis

VBA is a whole brain technique that enables the detection of regionally specific differences in brain tissue

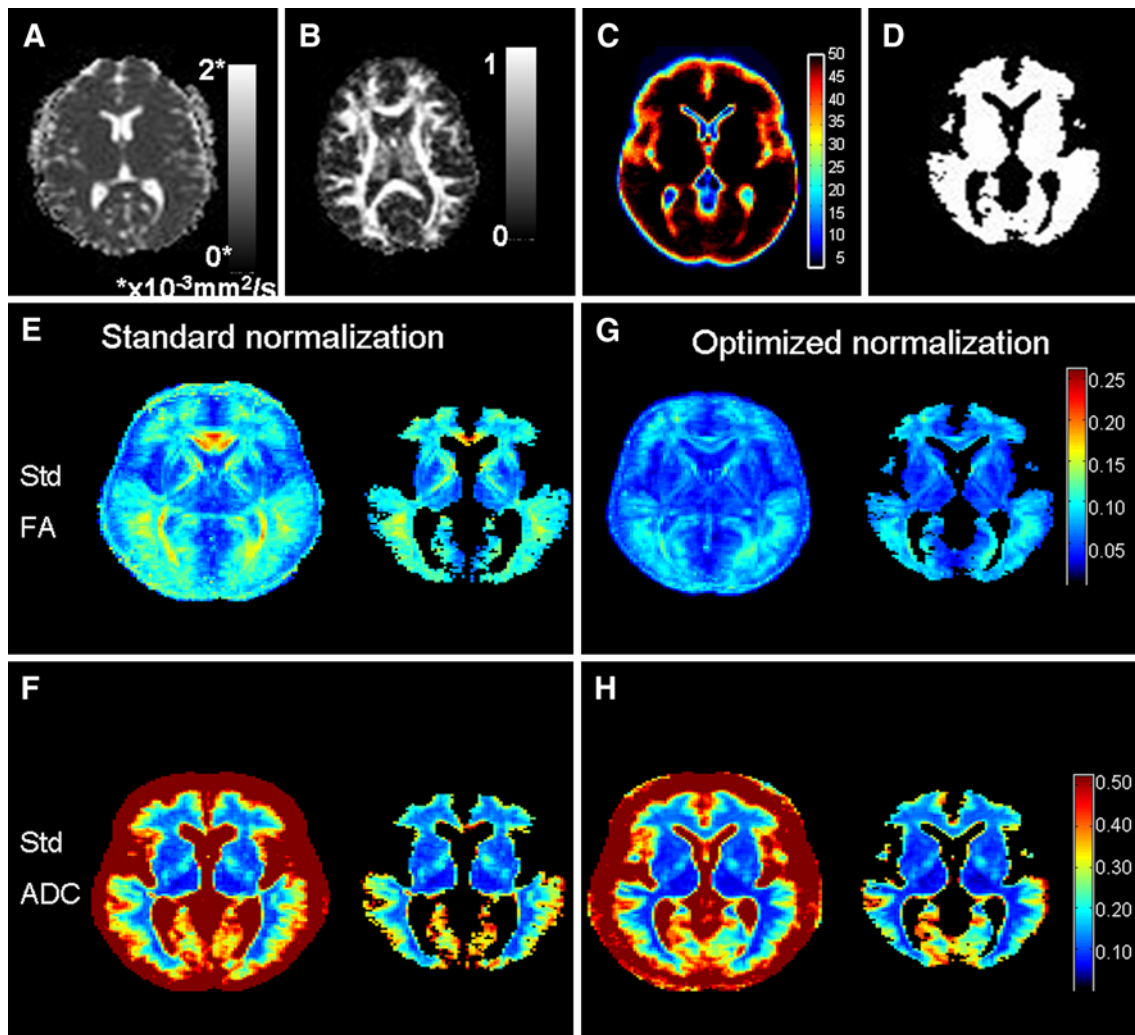
composition on a voxel-by-voxel basis (Ashburner and Friston 2000). In this work we used SPM (version 2, UCL, London, UK) to perform voxel-by-voxel correlation between the DTI indices and the cognitive factor scores (executive function, information processing speed, memory) controlling for age and motor function:

1. Partial correlation was computed between the DTI indices (ADC and FA) and each factor score for all subjects. The partial correlation was controlled for age and motor function using the multiple regression routine in SPM with each of the factor scores as covariates, and age and motor ability as constants. The statistical threshold was set at  $p < 0.005$  uncorrected. Motor function was assessed using inter-tap from the Finger Tapping test included in the computerized battery.
2. A non-cerebrospinal fluid (CSF) mask was applied: as age is related to brain atrophy, and to avoid partial volume bias in the statistical analysis, segmentation was performed on the T2 image ( $b = 0$ ) of the normalized DTI scans of all the subjects. From the segmented images, only voxels containing gray matter (GM) or WM in all subjects were included, effectively masking out the CSF regions. Areas showing partial GM or WM volume—the ventricles and in the borders around the cortex—were masked out. After masking out the CSF, cortical gray matter regions which show larger standard deviations are eliminated (Fig. 1e–h, right column).
3. The correlation analysis described above generated statistical parametric maps. False discovery rate (FDR) correction for multiple comparisons was applied on the statistical parametric maps using an in-house software written in Matlab 7.3.0 (Mathworks, Natick, MA, USA). The statistical parametric maps ( $p$  values) are presented superimposed on a T1 image from a single subject to permit informative anatomical reference. Using the statistical parametric maps for each of the correlation tests, we report significant voxels ( $p < 0.05$ , FDR corrected). The anatomic location of the significant clusters was determined using the SPM Wake Forest University Pickatlas toolbox (Maldjian et al. 2003).

## Results

### Behavioral results

Significant correlations between age and cognitive performance were found. Reaction time (RT) outcome parameters contributing to the executive function factor score increased significantly with age ( $r = 0.52$ ,  $p < 0.0001$ ),



**Fig. 1** Demonstration of the steps performed in the image analysis. **a** An example of an ADC map of one subject, in native (non-normalized) space. **b** An example of the FA map of one subject, in native space. Non-CSF mask: the mask was created in order to avoid effects of atrophy in the statistical analysis. A sum of the gray and white matter segments of all subjects ( $n = 52$ ) (following segmentation) provided specific brain regions that did not include GM or WM across all subjects: ventricles and in the borders around the cortex (**c**). Only gray and white matter regions that were found in all

subjects were included in the non-CSF mask excluding CSF regions (**d**). The mask was applied on the statistical analysis. Normalization procedure: there is a notable reduction in the standard deviation of the FA maps (**e, g**) as well as ADC maps (**f, h**) across all subjects ( $n = 52$ ) when using the optimized normalization method (**g, h**) compared to the standard normalization method (**e, f**). After masking out the CSF (using the non-CSF mask) cortical gray matter regions which show larger standard deviations are eliminated (**e–h, right column**)

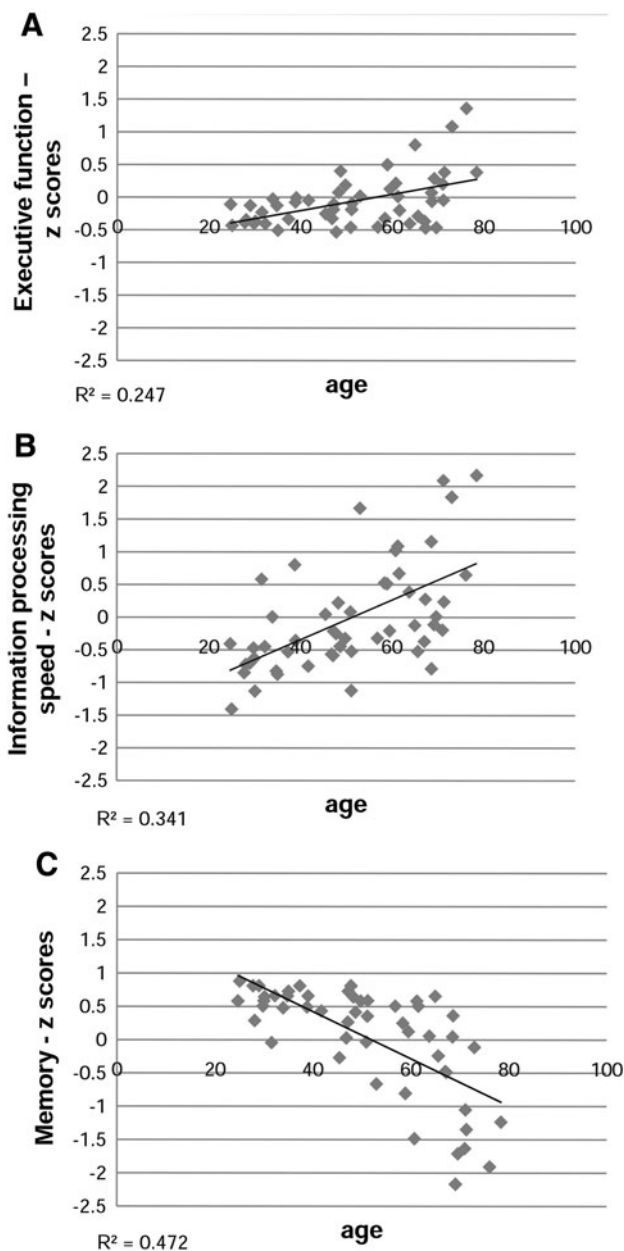
(RT) parameters contributing to the information processing speed factor score also increased significantly with age ( $r = 0.57$ ,  $p < 0.0001$ ), and Accuracy scores contributing to the memory factor score decreased significantly with age ( $r = -0.69$ ,  $p < 0.0001$ ) (Fig. 2).

#### Partial correlation of diffusion parameters with cognitive domains

Brain localization using DTI partial correlation analysis corrected for age and motor function differed for each of the three cognitive factor scores.

Positive partial correlation between the executive function factor score and ADC was found in left insular cortex, WM adjacent to left inferior frontal gyrus, left parietal and temporal parts of the superior longitudinal fasciculus (SLF). Negative partial correlation between the executive function factor score and FA was found in the left cingulum (Fig. 3; Table 2;  $p < 0.05$ , FDR corrected).

Positive partial correlation between the information processing speed factor score and ADC was found in corona radiata, left WM (ILF), and left cingulum. Negative partial correlation between the memory factor score and ADC was found mainly in temporal and frontal gray and



**Fig. 2** Age-related cognitive decline in the various cognitive domains. **a** Positive correlation between RT outcome parameters contributing to the executive function factor score and age ( $n = 52$ ,  $r^2 = 0.247$ ,  $p < 0.0001$ ). **b** Positive correlation between reaction time (RT) outcome parameters contributing to the information processing speed factor score and age ( $n = 52$ ,  $r^2 = 0.341$ ,  $p < 0.0001$ ). **c** Negative partial correlation between accuracy scores contributing to the memory factor score and age ( $n = 52$ ,  $r^2 = 0.472$ ,  $p < 0.0001$ )

white matter, including the right IFG (BA46), medial frontal gyrus (MFG), and WM adjacent to the hippocampus. Positive partial correlation between memory factor score and FA did not exceed the threshold for significance (see Fig. 5, and Table 2;  $p < 0.05$ , FDR corrected).

Negative partial correlation between the memory factor score and ADC was found mainly in temporal and frontal

gray and white matter, including the right IFG (BA46), medial frontal gyrus (MFG), and WM adjacent to the hippocampus.

## Discussion

The main finding of this study is that micro-structural parameters, measured by DTI, can characterize a cognitive domain using a broad battery of commonly used computerized neuropsychological tests. We focused on the following cognitive domains—executive function, information processing speed and memory. While executive function domain was correlated with DTI parameters in frontal white matter and in the SLF, information processing speed domain was correlated with DTI parameters in the cingulum, corona radiata, ILF, parietal white matter and in the thalamus, and memory domain was correlated in temporal and frontal gray matter and white matter regions, including the cingulate cortex and the hippocampus.

In the present study we found that correlations between cognitive performance and DTI indices were region-specific. The brain regions showing significant correlations are in line with the known localization of the cognitive tasks.

### Micro-structural morphological correlates of the executive function domain

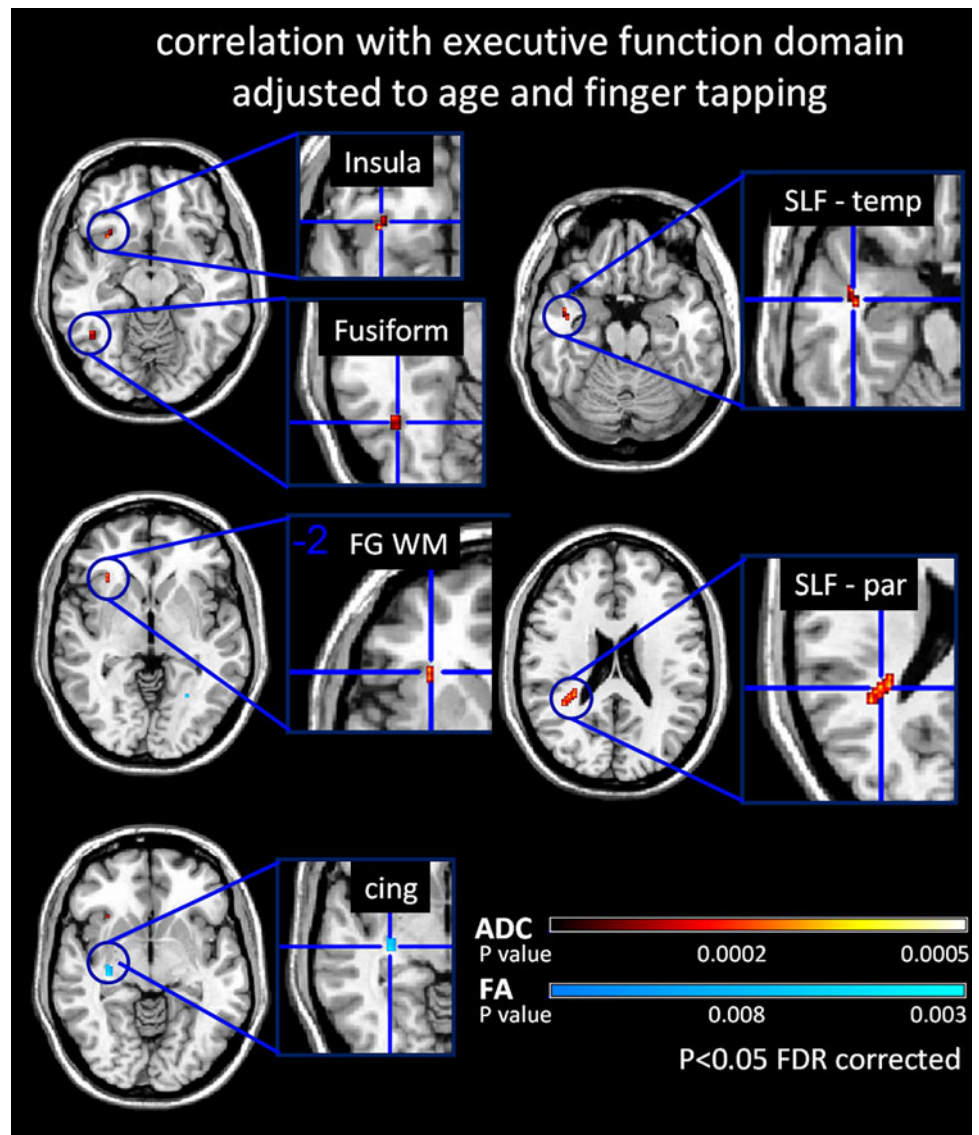
Executive function domain was correlated with ADC in left insular cortex, WM adjacent to inferior frontal gyrus, fronto-parietal parts of the SLF, and in temporal white matter.

Executive processes are implicated in complex cognition, such as novel problem solving, which involve identifying and coordinating the steps to a new goal, evaluating the intermediate outcome, and modifying the plan as needed. Executive processes are also associated with task-set control, modifying behavior as appropriate in light of changes in the environment, and involve inhibition (Carpenter et al. 2000).

Lesion studies have demonstrated that the frontal lobe is crucial for executive functions (Rowe et al. 2001; Milner 1971; Drewe 1974; Perret 1974).

However, a meta-analysis of neuroimaging and lesion studies revealed that executive functions are sensitive, but not specific, to frontal lobe functioning, meaning, both frontal and non-frontal brain regions are necessary for intact executive functions (Alvarez and Emory 2006). Non-frontal brain regions include a variety of brain regions, e.g., the anterior cingulate cortex (Bench et al. 1993; Carter et al. 1995; Pardo et al. 1990; Posner and Dehaene 1994; Posner and Petersen 1990), parietal lobe regions (Bush et al. 1998; Carter et al. 1995; Leung et al. 2000; Peterson

**Fig. 3** VBA partial correlation between DTI indices and the executive function factor score controlling for age and motor function. Positive partial correlation between the executive function factor score and ADC (shown in *red*) was found in left insular cortex, WM adjacent to left inferior frontal gyrus, left parietal parts of the superior longitudinal fasciculus SLF and in temporal white matter. Negative partial correlation between the executive function factor score and FA (shown in *cyan*) was found in left frontal white matter and in left cingulum ( $n = 52$ ,  $p < 0.05$ , FDR corrected)



et al. 1999; Taylor et al. 1997), motor areas (Bush et al. 1998; Pardo et al. 1990; Peterson et al. 1999), and temporal lobe regions (Bush et al. 1998; Carter et al. 1995; Leung et al. 2000; Pardo et al. 1990). DTI studies demonstrated a negative correlation between RT in an executive function task (task switching) and FA in left frontoparietal WM in both young and older groups (Gold et al. 2008).

Decreased FA in the frontal, temporal, and parietal lobes was associated with poorer cognitive performance in executive maze and in an attention-switching task (Grieve et al. 2007).

In DTI studies focusing on fiber tracking, it was shown that reduced integrity of specific fiber tracts are differentially correlated with declines in components of executive functions, including working memory, problem solving,

categorical task switching, and Stroop color-word interference (Madden et al. 2009; Zahr et al. 2009; Sullivan et al. 2006). In cortical association fiber tracts, correlation was found with decrement in set-shifting performance observed with age (Perry et al. 2009).

A strong significant correlation with the executive function factor score was also found in the SLF. Historically, SLF or the arcuate fasciculus (AF) has been central to the neural underpinnings of higher brain function generally and for language and language disorders in particular (Geschwind 1965a, b; Heilman et al. 1970; Lichtheim 1885; Tanabe et al. 1987). This may be relevant to the Stroop interference outcome parameters contributing to the executive function factor, as they rely upon interference between semantic and visual input.

**Table 2** VBA of DTI indices, with cognitive factor scores as covariates controlling for age

No.	Cluster		Voxel	MNI coordinates			Location			
	Cluster no.	Size	$p$ (uncor)	$x$	$y$	$z$				
1 <sup>a</sup>	1	18	0.0001	4	-44	-54	-12	Fusiform	GM	L
	2	24	0.0001	3.94	-34	20	-12	Insula(BA13)/Frontal	GM	L
									WM	L
	3		0.0001	3.93	-44	-4	-20	SLF (temporal)	WM	L
	4	31	0.0002	3.83	-32	-38	22	SLF (parietal)	WM	L
2 <sup>b</sup>	1	19	0.0005	3.45	-30	-18	-6	Cingulum	WM	L
3 <sup>c</sup>	1	40	0.000024	4.46	-20	4	46	Corona radiata (frontal)	WM	L
	2	30	0.00004	4.28	-18	-82	-16	Lingual gyrus	WM	L
	3	21	0.00014	3.91	-26	-74	-12	ILF (occipital)	WM	L
	4	12	0.00008	4.1	15	16	-18	MFG	GM	L
	4	30	0.000018	3.91	20	-18	42	Cingulum	WM	R
4 <sup>d</sup>	1	42	<0.001	4.22	43	-32	42	Cingulum (frontal)	WM	L
	2	161	0.000001	5.40	-32	-76	-6	ILF/IFOF (occipital)	WM	L
	3	19	0.000017	4.58	-34	-46	22	SLF (parietal)	WM	L
	4	13	0.00005	4.2	-8	-24	2	Thalamus	GM	L
	6	68	0.000056	4.21	4	22	-4	Anterior cingulate	GM	R
5 <sup>e</sup>	1	51	0.00015	5.93	46	24	-6	IFG	WM	R
	2	51	0.0015	3.88	-42	-28	14	Insula (BA13)	GM	L
	3	39	0.000003	5.07	50	-12	10	Insula (BA13)	GM	R
	4	26	0.000052	4.22	-8	35	27	Anterior cingulate	GM	L
	6	12	0.000015	4.5	10	46	7	Anterior cingulate	GM	R
	7	16	0.000066	4.15	38	-16	-10	Hippocampus	WM	R
	8	7	0.0001	3.9	-8	-2	32	Cingulum	WM	L

<sup>a</sup> Positive partial correlation between ADC and the executive function factor score controlling for age and motor function ( $p < 0.005$  uncorrected,  $n = 52$ )

<sup>b</sup> Negative partial correlation between FA and the executive function factor score controlling for age and motor function ( $p < 0.005$  uncorrected,  $n = 52$ )

<sup>c</sup> Positive partial correlation between ADC and the information processing speed factor score controlling for age and motor function ( $p < 0.005$  uncorrected,  $n = 52$ )

<sup>d</sup> Negative partial correlation between FA and the information processing speed factor score controlling for age and motor function ( $p < 0.005$  uncorrected,  $n = 52$ )

<sup>e</sup> Negative partial correlation between ADC and memory factor score controlling for age and motor function ( $p < 0.005$  uncorrected,  $n = 52$ )

BA brodmann area, MFG middle frontal gyrus, SLF superior longitudinal fasciculus, Corona radiata cortico pontine tract/corticospinal tract/superior thalamic radiation, ILF inferior longitudinal fasciculus, IFO inferior fronto occipital, IFG inferior frontal gyrus

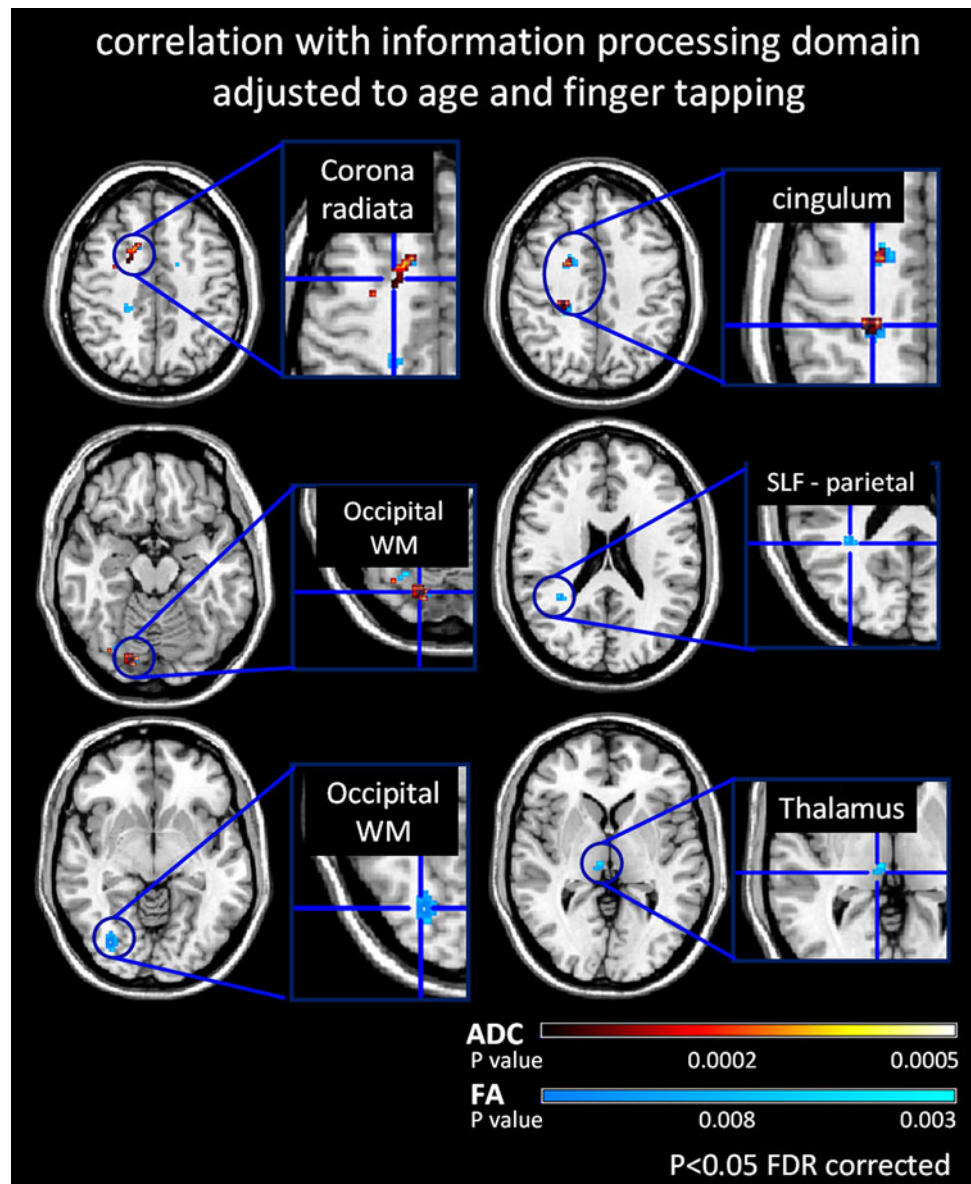
### Micro-structural morphological correlates of the information processing speed domain

The information processing speed factor score (as measured by RTs for several rates of presentation in a simple arithmetic task) was significantly correlated with DTI parameters in WM of the corona radiata, in occipital ILF, and in the medial thalamus, as well as WM adjacent to the precuneus in the parietal lobe. Information processing speed represents the response time for a relatively simple cognitive task that is time limited (Salthouse 2000). An example of information processing speed task can be simple arithmetic, known to be subserved mainly by the

parietal lobe, and more specifically the precuneus (Rocha et al. 2005; Cavanna and Trimble 2006). The correlations found in the corona radiata, a fiber bundle related to motor function, may be related to the motor response, although, as above, analysis were corrected for motor ability (as measured by finger tapping inter-tap interval using the same input device as for the other tasks). In addition, thalamic and occipital regions showed a significant correlation between information processing and DTI parameters. In some fMRI and PET studies of mental calculation, significant activation was found in the medial thalamus and in occipital regions (e.g., (Grabner et al. 2007; Cowell et al. 2000); in other studies, a role was found for occipital



**Fig. 4** VBA partial correlation between DTI indices and the information processing factor score controlling for age and motor skills. Positive partial correlation between the information processing factor score and ADC (shown in *red*) was found in corticopontine/corticospinal tract, bilateral occipital WM, inferior longitudinal fasciculus (ILF), and right cingulum. Negative partial correlation between the information processing factor score and FA (shown in *cyan*) was found in left occipital WM, parietal WM adjacent to the precuneus, anterior cingulate bilateral thalamus, and frontal WM ( $n = 52$ ,  $p < 0.05$ , FDR corrected)



regions in arithmetic, including the lingual gyrus and fusiform gyrus (Rickard et al. 2000; Dehaene et al. 1996). DTI studies found that higher average fractional anisotropy (FA) in left occipitotemporal junction was found in children trained in mental calculation (Hu et al. 2011) and that FA in the left superior corona radiata was correlated with fMRI activation in the left angular gyrus during calculation (van Eimeren et al. 2010).

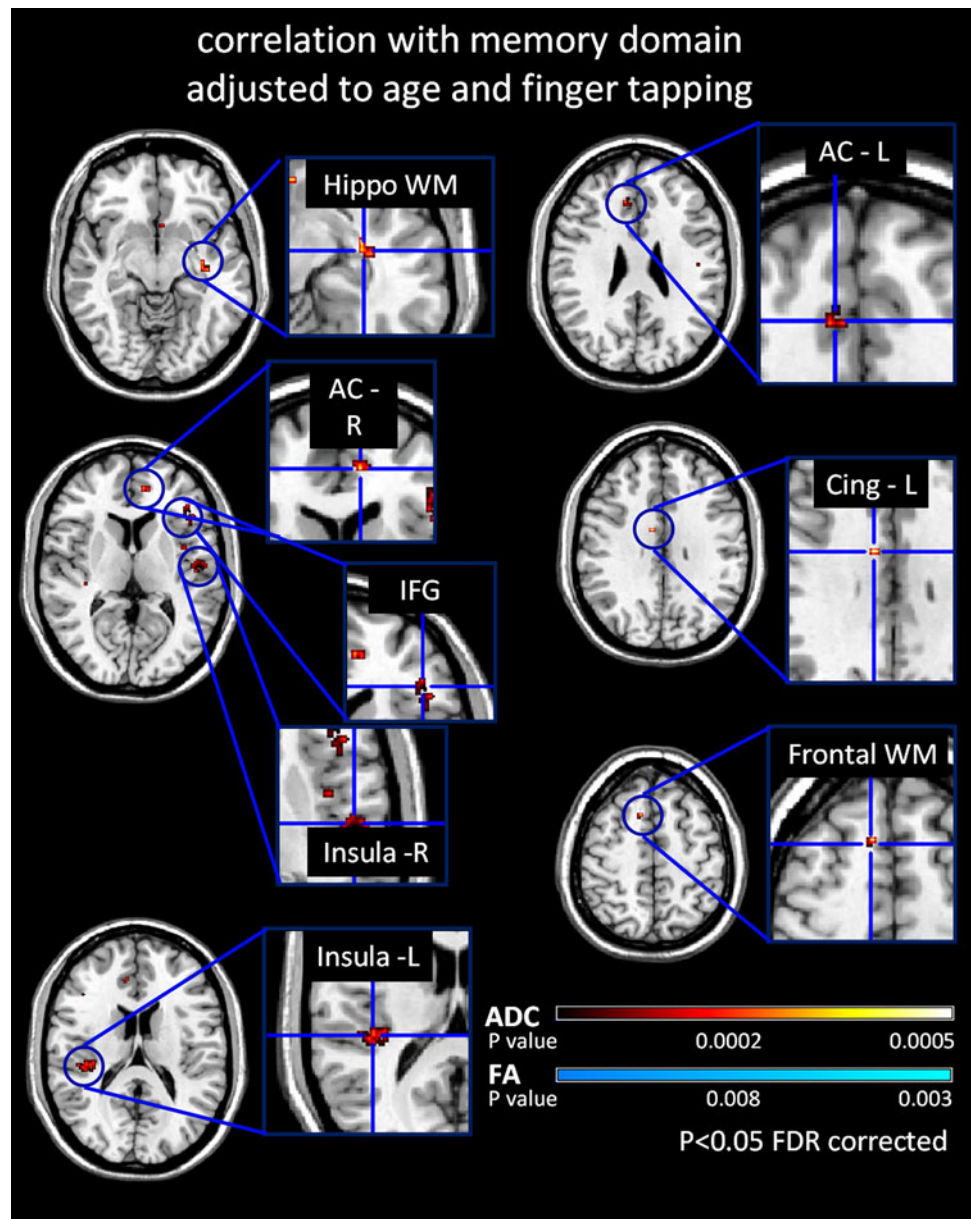
#### Micro-structural morphological correlates of the memory domain

The memory factor score was significantly correlated with ADC in frontal gray matter, in inferior frontal gyrus, middle frontal gyrus, and anterior cingulate, as well as in temporal gray matter, including the parahippocampus and

middle temporal lobe. This pattern is in line with the role of frontal and temporal regions in memory performance (Thompson and Kim 1996). Indeed, the frontal lobe is known to be essential in visual memory as demonstrated by lesion (Bauer and Fuster 1976; Funahashi et al. 1993) and functional imaging studies (D'Esposito et al. 1998; Swartz et al. 1995).

Lesion studies have substantiated the role of the parahippocampus in memory performance (Scoville and Milner 1957; Frankland and Bontempi 2005). Functional imaging studies, using PET and fMRI, have also found activation of parahippocampus during consolidation of new memories and retrieval of recently learned items. (Cabeza and Nyberg 2000; Henke et al. 1999; Constable et al. 2000; Davachi and Wagner 2002; Duzel et al. 2003; Giovanello et al. 2004; Henson 2005).

**Fig. 5** VBA partial correlation between DTI indices and the memory factor score controlling for age and motor function. Negative partial correlation between the memory factor score and ADC (shown in red) was found mainly in temporal and frontal gray and white matter, including the right inferior frontal gyrus, (BA46) middle frontal gyrus, and left superior temporal gyrus (Wernicke's area, BA22), and the parahippocampus (though this correlation did not remain significant after correction for multiple comparisons). Positive partial correlation between the memory factor score and FA did not exceed the threshold for significance ( $n = 52$ ,  $p < 0.05$ , FDR corrected)



Several DTI studies focusing on memory performance showed that performance on working memory tasks correlates with whole brain FA and ADC indices (Charlton et al. 2006) and that elderly subjects with impaired memory performance showed differences in DTI measures of anterior white matter and reduced hippocampal volume compared with subjects with preserved memory performance (Persson et al. 2006). In a longitudinal study, manual tracing of hippocampal volume showed significant reduction in those older adults with a declining memory performance as did DTI-measured FA in the anterior corpus callosum. Mean DTI measures in the anterior corpus callosum correlated negatively with activation in right prefrontal cortex during a memory task (Persson et al. 2006).

Micro-structural morphological correlates of ADC compared with morphological correlates of FA

In the present paper the structural correlates of cognitive domains show different localization between FA and ADC. FA and ADC are sensitive to different structural tissue characteristics. Higher FA values may indicate higher tissue directionality and organization, and lower ADC values may indicate higher tissue density in gray and white matter (Blumenfeld-Katzir et al. 2011; Gouw et al. 2008).

Limitations of the voxel-based correlation approach

VBA performed in the present study makes several important assumptions. The first step in VBA analysis is

spatial normalization to a template. However, it has been argued that imperfect registration of the brain maps might bias the results (Bookstein 2001). To address this problem, we performed optimized spatial normalization, based on the FA maps, which are less sensitive to volumetric differences between brains compared with normalization based on T2 ( $b = 0$ ) maps. FA reflects fine anatomical structures, while T2 maps have a strong CSF signal which reflects more gross anatomical structures. Thus, better registration of white matter structures can also be obtained with FA.

Second, it is assumed that the relationship between the tested parameters (age, memory and DTI indices) is linear. Indeed, in the behavioral findings in the present study, several of the oldest subjects showed substantially higher reaction times/lower accuracy than all other participants (Fig. 2). This is in line with some studies reporting that age-related memory decline is curve-linear, with a more rapid decline at older ages (Schaie 1996; Hultsch 1998). It is also suggested by some studies that age-related volume reduction is not homogeneous in the brain, decreasing in a linear fashion in some regions and exhibiting a quadratic or cubic decrease when regressed against age in other regions (Walhovd et al. 2005). This issue is addressed in the present study in a discussion of the relationship between cognitive performance, age and DTI indices.

## Conclusions

This study used inter-subject variability to correlate performance in three different cognitive domains—executive function, information processing speed, and memory, with DTI indices. The neurobiological correlates of the DTI indices with cognitive functions are specific to each cognitive domain and consistent with previous knowledge on the localization of these cognitive functions. To that end, tissue morphology, as expressed by diffusion tensor magnetic resonance imaging and inter-subject variability in cognitive function can be used for localization of cognitive domains and to provide converging evidence for functional localization techniques.

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