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Research report

Combined analysis of DTI and fMRI data reveals a joint maturation of white and grey matter in a fronto-parietal network

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Abstract

The aim of this study was to explore whether there are networks of regions where maturation of white matter and changes in brain activity show similar developmental trends during childhood. In a previous study, we showed that during childhood, grey matter activity increases in frontal and parietal regions. We hypothesized that this would be mediated by maturation of white matter. Twenty-three healthy children aged 8–18 years were investigated. Brain activity was measured using the blood oxygen level-dependent (BOLD) contrast with functional magnetic resonance imaging (fMRI) during performance of a working memory (WM) task. White matter microstructure was investigated using diffusion tensor imaging (DTI). Based on the DTI data, we calculated fractional anisotropy (FA), an indicator of myelination and axon thickness. Prior to scanning, WM score was evaluated. WM score correlated independently with FA values and BOLD response in several regions. FA values and BOLD response were extracted for each subject from the peak voxels of these regions. The FA values were used as covariates in an additional BOLD analysis to find brain regions where FA values and BOLD response correlated. Conversely, the BOLD response values were used as covariates in an additional FA analysis. In several cortical and sub-cortical regions, there were positive correlations between maturation of white matter and increased brain activity. Specifically, and consistent with our hypothesis, we found that FA values in fronto-parietal white matter correlated with BOLD response in closely located grey matter in the superior frontal sulcus and inferior parietal lobe, areas that could form a functional network underlying working memory function.

1. Introduction

Working memory (WM) capacity is the amount of information one can keep in mind for a short period of time [6] and develops throughout childhood and adolescence [16,19]. Development of visuo-spatial WM is associated with increased blood oxygen level-dependent (BOLD) activity in frontal and parietal cortices [31]. Brain activity measured during a spatial WM task show a similar distribution in children and adults [41,52]. The structural changes during development of WM involves maturation of white matter in the prefrontal lobe [30,40], which is one of the last brain regions to mature [18,25,48]. Additional developmental effects on brain structure, in regions important for WM, include synapse production and elimination. This occurs later in the frontal lobes than in other cortical regions [25], and reaches adult levels in mid-adolescence [24,25]. Late synapse formation can be influenced by environmental factors and occurs in relation to learning and memory [28,59], while early synapse formation seems to be mainly intrinsically regulated [8]. The prolonged development of white matter and gradual alteration in synaptic number appear to coincide with the development of cognitive capacities.

Data from diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI) have been combined in a few previous studies [55–57]. These studies show that

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a combination of the techniques can give additional information about brain organization which may change the conclusions drawn from standard imaging and give more specific information about brain injuries and organization of brain functions. However, only one of these studies combined the structural and functional data in one common analysis [56]. In that study BOLD response maps from the occipital cortex were overlaid on fractional anisotropy (FA) maps and the maps were compared visually. It was concluded that regions with low FA values were also those with highest BOLD activity.

The relationship between maturation of white matter and developmental changes in brain activity is still largely unknown. We used a new approach to investigate this question. Brain activity in the entire brain was studied by measuring the BOLD response with fMRI. These data were combined with DTI data on white matter microstructure in the same individuals. DTI is a relatively new imaging method that gives information about white matter structure. The method is based on measuring water diffusion and the directionality of diffusion (i.e. anisoptropy) within each voxel. The degree of anisotropy, e.g. FA, is calculated from the diffusion tensor. FA values range from 0 to 1 [7]. In a region with free diffusion, the FA value is 0 and the diffusion is isotropic. If the diffusion is more in one direction, i.e. anisotropic diffusion, the FA value approaches 1. The anisotropic diffusion is thought to increase as a result of myelination, axonal thickness or amount of parallel organization of axons, or a combination of these three factors [7].

Our hypothesis was that white matter maturation during development of WM would correlate with brain activity measured during performance of a WM task. We expected that white matter microstructure would correlate with brain activity in projection areas since the BOLD response is proportional to local input synaptic activity [37], which in turn may depend on the number and myelination of axons. Furthermore, afferent activity in an area may be dependent on how well the action potential is transported along the axons, and thus on fibre microstructure i.e. myelination, axonal thickness and fibre tract organization. One might therefore expect that white matter microstructure in a specific region would be positively correlated with brain activity in the cortical areas to which the axons passing through the region project.

One way of testing such a hypothesis would be to correlate the FA value in every voxel containing white matter with the BOLD value in every voxel containing grey matter. The drawback with this approach is that the information from hundreds of thousands correlation analyses would be difficult to interpret. In order to reduce the number of correlation analyses, one could select regions, or voxels, of interest in white and grey matter. But it is likely that choosing of specific anatomical regions a priori would miss regions where the developmental trends occur.

Our approach in this study was therefore to choose a smaller number of white matter regions selected in a way that ensured that in these regions there was a developmental trend. We did this by using WM scores from children of different ages as a covariate, and selecting white matter regions where we found a correlation between WM scores and FA. In the second step, we correlated FA and BOLD in an exploratory analysis. Corresponding analyses were also done starting with BOLD response values in grey matter regions that were correlated with FA values. This second analysis (BOLD to FA) was primarily performed in order to confirm findings from the first analysis.

This type of analysis would have the possibility to identify functional networks of grey and white matter regions, which have similar developmental trends. In a previous study [31], we found that brain activity in the left intraparietal cortex and the left superior frontal sulcus was positively correlated with the development of WM. One hypothesis in the present study was that this fronto-parietal network would also include the maturation of white matter microstructure in the vicinity of the grey matter areas.

In the discussion, possible mechanisms explaining the correlations between FA and BOLD response values will be presented based on previous findings on the relationship between fibre microstructure and brain activity. We will also compare our results to the existing literature on connections between regions involved in WM and relevant to our study. The findings are discussed in relation to the literature on the fronto-parietal network.

2. Materials and methods

2.1. Subjects

Twenty-three healthy, right-handed children (9 girls, 14 boys) aged 7.8–18.5 years (mean 11.9, S.D. 3.1) participated in the study. Informed consent was obtained from the parents of each participant. The study was approved by the Ethical Committee at the Karolinska Hospital, Stockholm, Sweden.

2.2. Working memory tasks

2.2.1. WM task outside the scanner

Red, filled circles were presented sequentially in a 4×4 matrix. The task was to remember and indicate the locations of every presented circle on a touch screen. The number of circles presented during each trial ranged from two to nine. The response phase was 3000 ms when two circles should be recalled and increased with 1000 ms for each additional circle. Thus, the maximal response phase was 10,000 ms. Each level consisted of two trials and the level was passed if at least one of the trials was answered
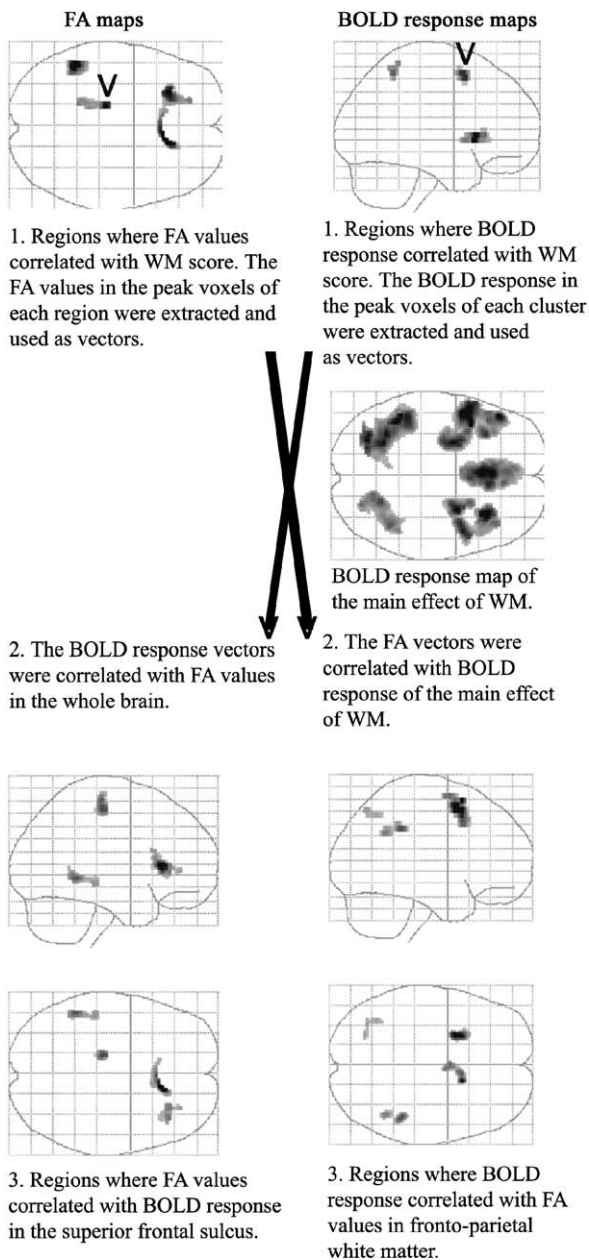
Fig. 1. Short summary of the main steps involved in the correlations of DTI and fMRI data. The images in the left column show FA maps. The images in the right column show BOLD response maps. (1) The FA and BOLD response values were extracted from the peak voxels in the regions that appeared after correlations with WM score. FA values from each subject were extracted from four regions, corresponding to four FA vectors with FA values from all subjects. BOLD response values from each subject were extracted from three regions, creating three BOLD response vectors with values from all subjects. (2) The FA and BOLD response vectors were used as covariates on BOLD response and FA maps, respectively. BOLD response values were correlated with FA values in the whole brain. FA values were correlated with BOLD response of the main effect of WM. (3) The FA map where FA values correlated with BOLD response in the superior frontal sulcus is presented as well as the BOLD response map where BOLD response correlated with the FA values in fronto-parietal white matter. The three steps presented in the figure were performed with all FA and BOLD response vectors.

correctly. The task ended when the subject failed two trials on the same level. WM score was defined as the total number of remembered circles on all levels. The task is similar to commonly used tasks for assessment of WM such as Corsi Block Tapping. The test scores for Corsi Block Tapping are quantitative and used as continuous variables and the task has a high reliability [36]. The WM score was later used as a covariate in the analysis of fMRI and DTI data.

2.2.2. WM task during scanning

The subjects were asked to remember red, filled circles presented sequentially in a 4×4 matrix. Each circle was presented for 900 ms with 500-ms intervals. After a 2000-ms delay, an unfilled cue circle appeared for 1500 ms and the subject should remember if the cue was in the same location as any of the presented circles. The subject responded by pressing a button on a response box with the right index finger. There were two levels of the task with different memory loads, one with three circles and one with five circles. The interval between trials was 1000 ms. To keep the presentation period constant on both levels the delay during presentation was longer when three circles were presented.

2.2.3. Baseline task

In the baseline task, five green filled circles were presented counter clockwise in each corner of the matrix. Two circles were presented in the same corner. The subjects were asked to look at the circles as they appeared. The same time intervals were used as for the WM task including the delay period. During the response phase a green unfilled circle appeared in the centre of the matrix. The subjects were asked to press a button on the response box with the right index finger when the green unfilled circle appeared.

2.2.4. Procedure

Before scanning the subjects, their WM scores were tested. They were also trained on the WM task to be performed in the scanner. During scanning, the stimuli were presented using E-prime® software (Psychology Software Tools, Pittsburgh, USA) and projected onto a screen in front of the scanner. On the head coil a set of mirrors were mounted so the subjects could see the screen easily. Foam pads around the head and adhesive tape on the forehead was used to restrict head movements. The memory and baseline tasks were presented alternately in 30-s epochs in two 5-min sessions.

2.3. Scanning procedures and imaging analyses

The MR scanning was performed on a 1.5-T General Electric Signa Echospeed scanner (Milwaukee, WI, USA). Functional and diffusion-weighted images, along with anatomical T1-weighted images, were collected during the same

Table 1
Regions where FA values correlated with WM score

Brain region		Coordinates			T	P	Cluster size (mm³)
		x	y	z			
Ant corpus callosum	L/R	14	27	9	5.78	<0.001	918
Temporo-occipital	L	−46	−48	0	5.39	<0.001	999
Ant frontal	L	−26	28	3	5.07	<0.001	1175
Fronto-parietal	L	−15	−22	54	4.99	<0.001	1026

Abbreviations of anatomical locations: ant, anterior; L, left hemisphere; R, right hemisphere.

scan. Total scan time for each subject was less than 45 min. The data from the MR scanning were analysed with SPM99 (Welcome Department of Cognitive Neurology, London, UK) [15].

2.3.1. fMRI data acquisition

In the fMRI experiment, 240 T2*-weighted, gradient echo, spiral echo-planar images (EPI) were acquired for each subject during two 5-min sessions (TR = 2500 ms, TE = 70 ms, 85° flip angle). The images were acquired in 18 slices with a 220×220-mm field of view and a 64×64 grid resulting in a voxel size of $3.4 \times 3.4 \times 5.0$ mm. For anatomical normalization of the functional images, T1-weighted spin-echo images were acquired (FOV = 220 ×220, 256 × 256 grid). The T1-weighted anatomical images were normalized to the MNI305 space using a template from the Montreal Neurological Institute and the SPM software. The functional images were normalized based on the normalization parameters from the anatomical images, with a final voxel size of $2 \times 2 \times 4$ mm, and smoothed with a Gaussian kernel of 6.0 mm. Motion during scanning was estimated by six parameters, representing translations and rotations in x, y and z dimensions. These parameters were used to realign the functional images to the first image in the time-series and were included as covariates in the estimation of subtraction images (see Section 2.3.3).

2.3.2. DTI data acquisition

Diffusion-weighted single shot EPI images were acquired with 20 directions of the diffusion gradient and b-value of 1000 s/mm². Pulse gating with a delay of 300 ms was included in the acquisition of the images. For each subject, eighteen 5-mm-thick slices with an inplane resolution of 1.72×1.72 mm were acquired and smoothed with a 6-mm Gaussian kernel. Five non-diffusion-weighted images ($b = 0$ s/mm²) were also collected. The mean of these five images were used to transform the anisotropy images to a common template. To increase signal-to-noise ratio, eddy current distortions and head movements were corrected before the diffusion tensor and fractional anisotropy values were calculated [3].

2.3.3. Correlation analyses

The procedure for analysing the data was as follows (Fig. 1):

(1) We generated one image per subject corresponding to the mean difference in activity during performance of the WM task and control task. This was performed in SPM by fitting the BOLD response to a box-car function describing the on- and offset of the WM task, convolved with the hemodynamic response function [15]. The contrast (WM task minus control task) of beta-values from this fixed-effect analysis will be referred to as subtraction images.

(2) From the subtraction images a statistical parametric map (SPM) was calculated to find areas activated as a main effect of WM (t test, $p < 0.05$ corrected for multiple comparisons). The subsequent correlations on BOLD response maps were restricted to the areas representing the main effect of WM.

(3) To obtain a BOLD response map where activity correlated with WM score, we used the WM scores from the test outside the scanner as a covariate in a general linear model using SPM. Due to incomplete data-files, BOLD data from two of the subjects had
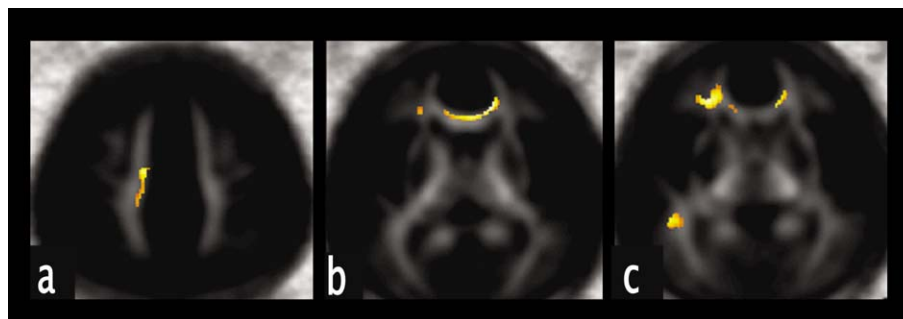

Fig. 2. Regions where FA correlated with WM score. (a) The fronto-parietal white matter region extends from precentral white matter, over the region surrounding the central sulcus and into postcentral white matter. The peak voxel in this region is located in precentral white matter. (b) The region in the anterior corpus callosum includes white matter in both the left and the right frontal lobes. (c) The temporo-occipital white matter region and the anterior frontal white matter.

Table 2
Regions where BOLD response correlated with WM score

Brain region		Coordinates			T	P	Cluster size (mm^3)
		x	y	z			
Caudate nucleus	L	− 10	18	4	4.29	0.086	304
Sup frontal sulcus	L	− 26	8	56	3.93	0.114	272
Inf parietal cortex	L	− 36	− 50	56	3.53	0.018	496

Abbreviations of anatomical locations: inf, inferior; sup, superior; L, left hemisphere.

to be excluded. To correlate FA with WM, we used the WM scores as a covariate in an analysis of white matter FA values ($T>2.54$, cluster size >15 contiguous voxels for both analyses). The FA correlation with WM score was performed on all 23 subjects.

(4) From the peak voxels in the regions that correlated with WM, the FA and BOLD response values were extracted for each subject and region. FA data from the two subjects that did not have complete BOLD data were excluded, resulting in FA and BOLD data from 21 subjects for the remaining correlation analyses. These values are referred to as FA and BOLD response vectors, respectively.

(5) The FA vectors were used as covariates in a BOLD response analysis to find regions where FA vectors from the peak voxel of each significant cluster correlated with BOLD signal activity. Similarly, the BOLD response vectors were used as covariates in an FA analysis of FA in the whole brain. In these final

exploratory correlation analyses, we used a threshold of $p<0.05$ corrected for multiple comparisons.

(6) Age was included as a covariate in the BOLD and FA analyses of WM to distinguish correlations that could be explained by age from those that could be due to inter-individual differences unrelated to age.

3. Results

3.1. Independent correlations of FA values and BOLD response with WM

The regions where FA values correlated significantly with WM score were mainly located in the left hemisphere (Table 1; Figs. 1 and 2). Three of the areas were located frontally; in the anterior corpus callosum, in fronto-parietal white matter and in anterior frontal white matter. The fourth area was in left temporo-occipital white matter.

The regions where BOLD response correlated with WM score were all located in the left hemisphere (Table 2; Fig. 1) and were found in the head of the caudate nucleus, superior frontal sulcus and inferior parietal lobe.

When age was included as a covariate in the FA analysis no significant correlations with WM score were found. However, BOLD response correlated with WM score in the inferior parietal lobe ($P=0.050$) and head of

Table 3
Regions where FA values and BOLD response correlated

FA vectors on BOLD response maps of the main effect of WM

FA vector		BOLD region		Coordinates			T	P	Cluster size (mm^3)
				x	y	z			
Temporo-occipital	L	inf parietal cortex	L	− 46	− 46	60	4.67	0.002	816
		intraparietal cortex	L	− 28	− 66	52	4.59	0.001	1024
Fronto-parietal	L	sup frontal sulcus	L	− 26	6	56	4.60	0.030	432
		intraparietal cortex	L	− 34	− 68	52	2.91	0.058*	352
Ant corpus callosum	L/R	sup frontal sulcus	L	− 26	8	56	6.98	0.011	560
		inf parietal cortex	L	− 36	− 50	60	3.37	0.011	560
Ant frontal	L	−[a]							

BOLD response vectors on whole brain FA maps

BOLD response vector		FA region		Coordinates			T	P	Cluster size (mm^3)
				x	y	z			
Caudate nucleus	L	ant corpus callosum	L/R	15	27	10	7.78	<0.001	1492
		temporo-occipital	L	− 50	− 42	− 6	4.83	<0.001	1148
Inf parietal cortex	L	ant corpus callosum	L/R	12	24	6	5.04	0.014	533
Sup frontal sulcus	L	ant corpus callosum	L/R	12	26	8	6.86	0.001	803
		temporo-occipital	L	− 50	− 45	− 3	4.52	0.055	405
		inf frontal	R	38	32	2	4.04	0.049	415
		fronto-parietal	L	− 15	− 22	54	4.76	0.080*	371

Abbreviations of anatomical locations: ant, anterior; inf, inferior; sup, superior; L, left hemisphere; R, right hemisphere.
[a] No suprathreshold clusters.
*Not significant.

the caudate nucleus ($P = 0.057$) even after the effect of age was removed.

3.2. Correlations between FA values and BOLD response

Three of the four FA vectors correlated with BOLD response in one or more regions on a BOLD response map of WM (Table 3). The FA values in the temporo-occipital white matter correlated with BOLD response in intraparietal and inferior parietal grey matter (Fig. 3). The fronto-parietal white matter FA values correlated with BOLD response in the superior frontal sulcus and intraparietal lobe (Fig. 3). The BOLD response values from the superior frontal sulcus were extracted and plotted against the FA values (Fig. 4). Finally, the FA values in the anterior corpus callosum correlated with BOLD response in the superior frontal sulcus and in the inferior parietal lobe. The FA values in the left anterior frontal white matter did not correlate with BOLD response.

All BOLD response vectors correlated with FA values in the right anterior corpus callosum (Table 3). BOLD response in the caudate nucleus and in the superior frontal sulcus also correlated with temporo-occipital white matter FA values (Fig. 3). BOLD response in the superior frontal sulcus additionally correlated with

Fig. 4. The correlation between FA values in fronto-parietal white matter ($x = -15$, $y = -22$, $z = 54$) and BOLD response values in the superior frontal sulcus (sfs) (-26 6 56).

FA values in fronto-parietal (Fig. 3) and inferior frontal white matter.

4. Discussion

In the present study we combined data from DTI and fMRI in order to identify regions of white and grey matter that show similar developmental trends. Several grey and white matter regions showed positive correlations between BOLD and FA values. In particular, and consistent with our hypothesis, we found that FA values in fronto-parietal white matter correlated with BOLD response in closely located grey matter in the superior frontal sulcus and inferior parietal lobe, areas that could form a functional network underlying WM function. The correlation of FA values in fronto-parietal white matter with BOLD response in the superior frontal sulcus was confirmed in the converse analysis where BOLD response values were used as covariates on FA maps. This correlation is primarily explained by age-related maturation of white and grey matter since WM score did not correlate with FA values or BOLD response in these regions when age-related variance was removed. The fronto-parietal correlation is shown in Fig. 1. Correlations were also found between temporo-occipital FA values and BOLD response in the head of the caudate nucleus, in the superior frontal sulcus and in the parietal cortex. FA values in the anterior corpus callosum correlated with BOLD response in the superior frontal sulcus, in the head of the caudate nucleus and in the inferior parietal lobe. BOLD response in the superior frontal sulcus also correlated with FA values in the inferior frontal lobe. The correlations between FA values in the corpus callosum and BOLD response in the superior frontal sulcus and inferior parietal cortex were confirmed in the converse analysis of BOLD response on FA maps. The remaining correlations appeared
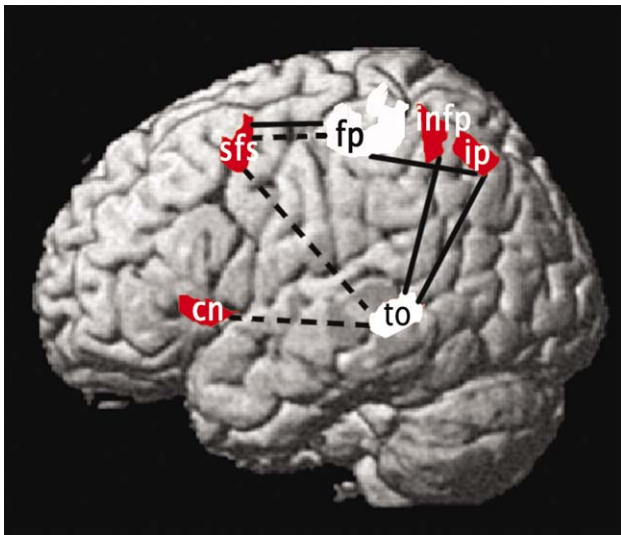

Fig. 3. Schematic presentation of the correlations between FA and BOLD regions in the left hemisphere. FA regions are displayed in white, BOLD regions in red. Both cortical and sub-cortical regions are projected onto the surface of the brain. The regions that correlated in the analysis of BOLD response vectors on FA maps, are shown with broken lines. Solid lines indicate regions that correlated when FA vectors were used as covariates in the BOLD analysis. The fronto-parietal (fp) white matter FA values correlated with BOLD response in the intraparietal (ip) cortex and in the superior frontal sulcus (sfs). FA in the temporo-occipital (to) white matter correlated with BOLD response in the caudate nucleus (cn), superior frontal sulcus and in two parietal regions located in the inferior parietal (infp) and intraparietal (ip) cortex.
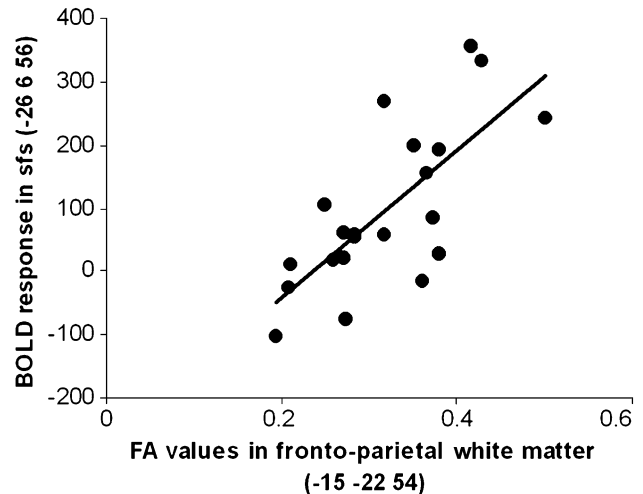
only in either of the FA and BOLD correlation analyses and could therefore be considered less robust. The correlations between WM score and BOLD response in the inferior parietal lobe and caudate nucleus could not entirely be explained by age. There was evidence for some age-related changes in brain activity in the inferior parietal lobe since the correlation with WM score in this region was weaker when the effect of age was removed. A significant amount of the brain activity changes in the caudate nucleus could better be explained by inter-individual differences in performance not related to age since the correlation with WM score was stronger when the effect of age was removed. The correlations between regions in the left hemisphere are displayed in Fig. 1.

The rationale of correlating FA values and BOLD response was the hypothesis that maturation of white matter would affect BOLD response in regions to which the maturing white matter tracts project. Previous studies have addressed the cellular mechanisms by which myelination and neural activity are related [12,33,50,51]. The speed of neural transmission depends on axon diameter and the thickness of the insulating myelin sheet [33]. The action potential spreads faster along large diameter axons and even faster along myelinated axons with the same diameter [33]. If we assume that it is development of axonal thickness and myelination that are responsible for the age-related increase in FA, this would mean that an increase in FA may possibly be associated with enhanced effectiveness of the communication between regions. Myelination may directly cause an increase in BOLD response since the BOLD signal seems to mainly reflect input activity to an area and regional processing in the dendrites within the area [37]. An alternative mechanism could be that action potentials influence the myelinogenesis during development. It has been shown that myelination is induced by action potentials in neighbouring neurons [12]. This process includes up-regulation of adenosine receptors on the oligodendrocytes, the myelin producing cells in the CNS [51]. The effect of action potential on myelinogenesis is transient and occurs during an early phase of development [12]. It could also be that specific patterns of neuronal activity controls myelination and affects the structural and functional relationship of myelinating axons by regulating the expression of cell adhesion molecules [50]. Thus, the correlations we found could be evidence of white matter maturation affecting cortical activity. However, correlations do not imply causality, and there might be other underlying biological factors related to maturation that affect both FA and BOLD that could explain the correlations. From the correlation analyses not every region was correlated with all other regions. Instead, the correlations showed that some groups of regions were more related than others, forming networks of regions that have a similar developmental trend. The development of specific networks might also be related to the development of specific functions, such as WM.

4.1. The relation of the results to known anatomical and functional data

The current knowledge of the anatomy of fibre tracts is scarce and is mainly based on tracing studies performed in non-human primates and dissections of the human brain. More data is now obtained from DTI studies [21,38] although this is still a method under development. Consequently, a large number of structural data are based on findings in non-human primates. Some of these studies show evidence for fibre connections in regions that were positively correlated in our study and will be discussed.

Below we discuss mainly the cortico-cortical connections. However, it should be added that there are common sub-cortical projection areas as well. One such common projection site is the medial pulvinar thalamic nucleus, which is connected to the posterior parietal cortex, the prefrontal cortex, the superior temporal sulcus and the anterior cingulate [20].

4.1.1. Fronto-parietal connections

In this study we found correlations between FA values in fronto-parietal white matter and BOLD response in the superior frontal sulcus and intraparietal cortex (Table 3; Fig. 3). A number of studies have explored the interconnections between the parietal and frontal areas [20]. These studies show that areas 7a, 7b and 7ip of the intraparietal cortex are connected to the dorsolateral prefrontal cortex in the macaque brain. Another study showed that areas 7a, 7ip and 7m are reciprocally connected with the principal sulcus in the prefrontal cortex and with the frontal eye field [9]. The frontal eye field is involved in control of eye movements and lies on the arcuate sulcus close to the area responsible for spatial WM. Projections from the principal sulcus and intraparietal sulcus have at least 15 common cortical targets on the ipsilateral side [46]. Among these are projections to the frontal eye field and area 7m. Connections with regions in the ipsilateral cortex are more numerous than those with contralateral cortical regions [46]. The inferior and superior parietal cortices are also connected to the dorsal areas 4 and 6 in the frontal lobes of the monkey [43]. Thus, there is strong connectivity between frontal and parietal regions that could explain our findings in the human brain.

4.1.2. Temporo-parietal and temporo-frontal connections

We found that FA values in temporo-occipital white matter correlated with BOLD response in the inferior parietal cortex, intraparietal cortex, the superior frontal sulcus and the head of the caudate nucleus (Table 3; Fig. 3).

In the macaque, fibre tracing studies also show evidence of connections between areas 7a, 7ip and 7m with the superior temporal cortex [9,20]. Furthermore, projections from the principal sulcus and the intraparietal sulcus converge on the middle third of the superior temporal sulcus [46]. Finally, Ungerleider and Desimone [53] show that, in

the macaque brain, the middle temporal lobe is connected to the intraparietal sulcus and the frontal eye field.

4.1.3. Connections with the corpus callosum

In the present study FA values in the anterior corpus callosum correlated with BOLD response in the superior frontal sulcus, the head of the caudate nucleus and in inferior parietal cortex (Table 3). The latter one of these three correlations was unexpected. It would be reasonable to expect brain activity in parietal regions to correlate with more posterior parts of the corpus callosum since this structure mainly connects homologous areas in the hemispheres. However, indirect and sub-cortical connections may explain this correlation.

There are a few reports on the relation between WM and the corpus callosum. One early study shows that WM is impaired in epileptic patients with cerebral commisurotomy in the anterior corpus callosum [58]. This study included two patients with anterior commisurotomy and eight with total commisurotomy who performed an IQ test and several verbal and non-verbal memory tests. In these patients WM was more affected than general intellectual capacity.

4.1.4. Connections with the caudate nucleus

BOLD response in the head of the caudate nucleus was found to correlate with FA values in the anterior corpus callosum and temporo-occipital white matter (Table 3; Fig. 3). The importance of the caudate nucleus in WM is seen in patients with disorders affecting the striatum, e.g., Huntington's disease [5]. These patients have altered WM functions such as planning and problem solving. The caudate nucleus is related to performance on spatial WM tasks [44]. In monkeys performing a delayed spatial alternation task, the metabolic rate in the head of the caudate nucleus increased with over 30% [35].

Most cortical areas are connected to the caudate nucleus, including temporal areas to which the activity was correlated in the present study [45]. However, one would also have expected correlations to frontal and parietal areas that were activated during WM performance [2].

The correlations with the caudate nucleus indicate activation of the oculomotor circuit which connects the caudate nucleus with the FEF, DLPFC and posterior parietal cortex (PPC). These reciprocal connections are involved in attention and preparation of motor responses in somewhat different ways: activity in the PPC and FEF can be enhanced by attentive behaviour in itself, without any requirement of saccades [10]; the DLPFC is activated when saccades are made to remembered targets [17]. Thus, the oculomotor circuit may be more heavily activated in the WM task than in the control task since the WM task demands increased attention and goal-directed saccades as well as memorization of the cues that were presented.

In this study WM capacity is defined as the amount of information one can keep in mind for a short period of time and includes cognitive abilities such as storage, rehearsal and manipulation of information which are necessary for planning, learning and reasoning [6]. Inhibitory control processes are not included in this definition of WM. However, WM and inhibitory control are closely related cognitive processes that may even share common neural substrates. Interestingly, activity in the caudate nucleus has been shown to correlate with both age and performance on a go-no-go task measuring cognitive control [14].

4.2. The fronto-parietal network

Brain activity in the superior frontal sulcus, intraparietal and inferior parietal cortex has previously been correlated with WM capacity in a subgroup of the subjects in this study [32]. In that study we could also show correlations with age in the same areas in both hemispheres. However, the correlation between WM related activity and WM score was only present in the left hemisphere. Based on our previous findings, we hypothesized that task-related activity in the frontal and parietal lobes would increase with increased WM capacity. This activity pattern has been shown in children performing spatial WM tasks [41] and has been related to development [34]. A number of neuroimaging studies on visual and spatial WM show the importance of a fronto-parietal network for task performance [26,29,39,47,52,54]. This has been confirmed in a meta-analysis on neuroimaging analyses of human WM [47].

The superior frontal sulcus was identified as a region specialized for spatial WM by Courtney et al. [11]. The superior frontal sulcus is activated during spatial WM tasks and specifically during the delay period when information is held in WM [11,22].

Anatomical overlap of activation regions in the parietal and superior frontal cortex during visuo-spatial WM tasks and spatial attention has been shown in a number of imaging studies [4,23,27]. Moreover, there is a functional overlap between spatial WM and spatial selective attention [4]. In a PET study of visuo-spatial attention, frontal and parietal cortical regions were activated during shifting attention conditions [10]. Further anatomical overlap with the fronto-parietal WM network is seen during performance on the Stroop interference task [1]. In that study a positive correlation between development and changes in brain activity was found in the left lateral prefrontal-, anterior cingulate-, and parietal cortices. The Stroop interference task measures executive functions such as interference, inhibition and conflict resolution. Several other cognitive functions, including response selection, cognitive control, episodic memory and problem solving, recruit similar regions of the frontal lobes [13]. The anatomical overlap with attention control systems and a number of cognitive abilities indicates a central role for frontal and parietal regions in cognition.

4.3. Left hemisphere lateralization

In the initial analysis, all BOLD response and FA correlations with WM were left lateralized (Tables 1 and 2). The regions where FA values and BOLD response correlated were almost exclusively located in the left hemisphere (Table 3). One explanation to the left hemisphere lateralization can be found in previous work on hemisphere maturation. These studies show that grey matter in the posterior temporal cortex [49] and white matter in the arcuate fasciculus [42] develop later in the left hemisphere. It is possible that there is a similar relationship of protracted development in the left hemisphere regions involved in WM.

5. Conclusion

We have explored a new way of combining imaging data on structural and functional properties of the brain. We were able to show positive correlations between white matter maturation, as estimated from FA, and neural activity, indicated by BOLD, in a number of regions important for WM and the development of WM. Our findings support the theory of a fronto-parietal WM network, in that fronto-parietal white matter correlated with activity in the superior frontal sulcus and in the intraparietal lobe. The results confirmed our hypothesis that white matter regions would correlate with activity in their projection areas. However, it is relevant to mention that the correlations also could be indirect since some of the regions have common projection areas or may be connected indirectly. In conclusion, we have found that combining DTI and fMRI data can be useful to identify functional networks including both white and grey matter.

Acknowledgements

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