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Diffusion Tensor Studies Dissociated Two Fronto-Temporal Pathways in the Human Memory System

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Abstract

The human memory system is composed of multiple cognitive processes. Recent functional neuroimaging studies have shown that multiple cortical areas are involved in memory encoding and retrieval. However, the underlying anatomical connections among these memory-related areas in humans remain elusive due to methodological limitations. Diffusion tensor imaging (DTI) is a new technique based on detecting the diffusion of water molecules from magnetic resonance images. DTI allows non-invasive mapping of anatomical connections and gives a comprehensive picture of connectivity throughout the entire brain. By combining functional magnetic resonance imaging (fMRI) and DTI, we show that memory related areas in the left dorso-lateral prefrontal cortex (DLPFC) and the left ventro-lateral prefrontal cortex (VLPFC) each connect with memory related areas in the left temporal cortex. This result suggests there are two pathways between prefrontal cortex and temporal cortex related to the human memory system.

Keywords

Functional Magnetic Resonance Imaging; Diffusion Tensor Imaging; Long-term memory; Prefrontal Cortex; Temporal Cortex; Connection

Introduction

The human memory system is supported by multiple processes (Squire and Zola-Morgan, 1991; Cabeza and Nyberg, 2000; Tulving, 2002; Habib et al., 2003). Recent functional neuroimaging studies have shown that areas in the prefrontal, parietal and temporal cortices are involved in memory encoding and retrieval (Tulving et al., 1994; Demb et al., 1995; Buckner et al., 1998; Buckner and Koutstaal, 1998; Wagner et al., 1998; Buckner et al., 1999; Lepage et al., 2000).

Among these memory-related areas, prefrontal cortex (PFC) is thought to subserve cognitive control processes (Goldman-Rakic, 1987; Schacter, 1987; Shimamura, 1995; Fuster, 1997; Takahashi and Miyashita, 2002), and send top-down signals to posterior cortices (Incisa

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della Rocchetta, 1993; Gazzaniga, 1995; Tomita et al., 1999; Takahashi and Miyashita, 2002). Recently, a two-stage model of PFC has been proposed (Petrides, 1994a, 1994b, 1996; Owen, Evans and Petrides, 1996). In this model, ventro-lateral prefrontal cortex (VLPFC) interacts with posterior cortices such as temporal cortex for active (or controlled) encoding and retrieval of information, whereas dorso-lateral prefrontal cortex (DLPFC) monitors and manipulates maintained information in VLPFC. Anatomical studies in nonhuman primates have shown direct corticocortical connections from VLPFC to temporal cortex (Petrides and Pandya, 2002), but direct connections from DLPFC to temporal cortex are still controversial (Seltzer and Pandya, 1989; Petrides and Pandya, 1994, 1999; Petrides, 2005).

Based on these studies we hypothesized two possibilities for the anatomical connections between PFC and temporal cortex in humans (Figure 1A); (i) Serial Pathway Model: DLPFC connects with VLPFC, and VLPFC connects with temporal cortex, but DLPFC does not connect with temporal cortex, (ii) Parallel Pathway Model: DLPFC and VLPFC both connect with temporal cortex. In this study, we performed diffusion tensor imaging (DTI) fiber tracking from functionally defined memory areas to test these two connectivity models.

DTI is a new technique based on the diffusion properties of water molecules as detected from diffusion-weighted magnetic resonance images (Basser et al., 1994). A number of fiber tracking algorithms have been developed to visualize white matter fiber tracts from DTI images (Mori et al., 1999; Jones et al., 1999; Conturo et al., 1999). Although many studies have shown anatomical connections *per se* in the human brain (Conturo et al., 1999; Basser et al., 2000; Stieltjes et al., 2001; Xu et al., 2002; Behrens et al., 2003; Lehericy et al., 2004; Powell et al., 2004), no studies to date have related memory functions with anatomical connections in the same subject within one experiment (but see Dougherty et al., 2005 and Kim et al., 2006 for connections among visual areas). Here, we show the feasibility and usefulness of such studies by combining functional magnetic resonance imaging (fMRI) and DTI in the same subject to show the anatomical network underlying memory functions in the human brain. The main goal of this study is to determine the pattern of anatomical connections between well-known memory-related activations observed in previous recognition memory studies (Buckner and Koutstaal, 1998; Buckner et al., 1998; Wagner et al., 1998; Buckner et al., 1999; Lepage et al., 2000; Habib et al., 2003). By studying anatomical connections, we hope to determine whether functional interactions between these areas are direct or indirect.

Materials and Methods

Subjects

Twenty healthy normally sighted subjects were tested (8 males and 12 females, aged 21-39, mean age 25). All subjects reported themselves to be native speakers of English, right handed, with no neurological or psychiatric histories. Written informed consent in accordance with the Declaration of Helsinki was obtained from each subject after the nature and possible consequences of the studies were explained. The procedures were approved by Boston University School of Medicine.

Stimuli

Word stimuli consisted of a pool of 216 words (upper case, 3-7 letters in length, 1-200 occurrences per million (Kucera and Francis, 1967)). We also used non-word stimuli (alphabetical stimuli) and the number sign (####) for control tasks. Alphabetical stimuli were made using random sequences of letters having the same length as the word stimuli. All stimuli were presented on a tangential screen 1.1 m from the subjects. Words were white on a black background, occupied $3.10^{\circ} \times 1.30^{\circ}$ to $7.30^{\circ} \times 1.30^{\circ}$ of visual angle and appeared at the center

of the screen. All stimuli were presented using presentation software (Neurobehavioral systems Inc., Albany, CA, USA).

Procedure

The experiment consisted of two parts, an encoding phase and a retrieval phase (Figure 1B). fMRI data were acquired during both the encoding and the retrieval phase. In the encoding phase, subjects were asked to perform 4 different “encoding” tasks: 1) make a living/nonliving judgment (deep encoding), 2) detect a given letter within a non-word letter sequence (shallow encoding), 3) press a random button, and 4) fixate on a central target. There were 48 blocks of 6 trials each in the encoding phase. Each trial lasted 4.0 seconds. At the beginning of each block, an instruction was shown that specified the type of encoding task to be performed. In the “living/nonliving” blocks, subjects decided whether or not each word was animate. In the “detection” blocks, they decided whether each word contained “E”. In both the “living/nonliving” and “detection” blocks, subjects reported their response by pressing one of two buttons held in the right hand. In the “random button press” (visuo-motor control) blocks, they looked at each non-word random letter sequence and pressed one of the two buttons held in the right hand. In the fixation blocks, they looked at the fixation cross and did not press any buttons. Each word was presented only once throughout the encoding phase. The length, the percentage of living words, and the percentage of words containing “E” were balanced across all the living/nonliving and detection blocks. The ordering of living/nonliving and detection blocks, and stimuli used in both blocks were counterbalanced across subjects. The encoding phase lasted approximately 25 minutes.

The retrieval phase (4 runs) started about 20 minutes after the end of the encoding phase. During the interval between the encoding and the retrieval phases, subjects performed a distracter task (white circle detection out of 4 circles) to disengage various strategies for encoding. In the retrieval phase, subjects performed randomly intermixed retrieval trials, visuo-motor control trials, and fixation trials. Each run consisted of 72 trials. In the retrieval trials, subjects made yes/no recognition memory judgments for previously studied and new stimuli. Subjects reported their response by pressing one of the two buttons held in the right hand. Half of the words from the encoding phase were presented again (72 words: 36 words were deep-encoded, the other 36 words were shallow-encoded), along with new words (72 words). In the visuo-motor control trials, they looked at the number sign (####) and pressed the third button that was specifically assigned for this trial type. In the fixation trials, they looked at the fixation cross and did not press any buttons. Each trial was 4.0 sec long, and the four trial types occurred with equal probability across the experiment in pseudo-random sequence. The retrieval phase lasted approximately 20 minutes.

Image acquisition

A 3 Tesla whole body scanner (Intera, Philips) was used to acquire T1-weighted anatomical images, gradient-echoEPI, and spin-echo EPI diffusion-weighted images for the DTI data sets.

Functional imaging—Parameters for functional image acquisition were as follows: repetition time (TR) = 4 sec; echo time (TE) = 35 ms; flip angle = 90°; in-plane resolution 1.8 × 1.8 mm²; FOV = 230; number of slices 36; slice thickness 4 mm. Slice orientation was axial, and the imaging volume was aligned to cover the whole brain. For each subject, conventional T1-weighted structural images were obtained to provide anatomical information. Each scanning run commenced with the acquisition of 2 dummy volumes, allowing tissue magnetization to achieve a steady state, after which functional volumes were acquired (85 volumes for each encoding run, and 73 volumes for each retrieval run).

Diffusion tensor imaging—Diffusion-Weighted Images (DWI) were acquired using multi-slice Spin Echo Echo-Planar Imaging (SE-EPI). Parameters for DTI acquisition were as follows: TR = 17.1 sec, TE = 80 msec, Matrix size 128×128, FOV 230, fat suppression, number of slices = 96, slice thickness = 1.5 mm, b = 1000 sec/mm², 15 directions, gradient strength = 0.2 G/mm, SENSE (sensitivity encoding) reduction factor = 2.0. Diffusion tensor images were taken in the identical field of view (FOV) with functional images to simplify *post hoc* spatial registration. For each subject, 16 data sets were acquired (15 diffusion weighted + 1 non-diffusion weighted images). From these data, diffusion tensors were calculated for all image pixels. A total of 4 signal averages were collected to ensure a sufficient signal-to-noise ratio (SNR) for high-quality tensor mapping. In order to compensate for motion, scan was acquired separately and then coregistered with the others before averaging. The sensitivity encoding technique (SENSE) was used, which is known to reduce susceptibility artifacts significantly (Jaermann et al., 2004). Pulse-gating was not performed.

FMRI & DTI data analyses

All functional images were analyzed with SPM99 (Wellcome Department of Neurology, UK). For each subject, the acquired images were realigned to the first volume to correct for head movement. Differences in acquisition timing between each slice were corrected for using sinc-interpolation

T1 images were acquired in the same FOV as EPI and DWI images and was normalized to the standard Talairach space (Talairach and Tournoux, 1988) by an affine transformation. The same transformation was applied to EPI and DWI images (see below). After spatial normalization, each EPI volume was resampled to 2 mm cubic voxels, smoothed spatially with a Gaussian kernel of 8 mm full-width half-maximum (FWHM), and the time-series was smoothed temporally with a 4-s FWHM Gaussian kernel. Slow signal drifts were removed by high pass filtering using cut-off periods of 300 sec for encoding and 128 sec for retrieval. For each voxel, data were best-fitted (least square) using a linear combination of regressors. The regressors were constructed to correspond to each trial type for each subject and then convolved with the standard hemodynamic response function (HRF). In the encoding phase, we did not separate correct and incorrect trials within blocks. Instead, we analysed all trials with three regressors, corresponding to deep encoding, shallow encoding and visuo-motor control. In the retrieval phase, we separated correct and incorrect trials (“Hit”, “Correct Rejection”, “Miss”, and “False Alarm”), and made five regressors, corresponding to these trial types and “visuo-motor control”. Trials in which the subject did not report a response by pressing a button in the retrieval phase (9 trials) were eliminated from further analysis. Contrasts were first performed at the single subject level and then the resulting images were taken up to the group level using t-tests. The statistical threshold was set to $p < 0.001$ as an initial height threshold and to $p < 0.05$ corrected for whole-brain multiple comparisons at cluster level, according to the SPM99 standard procedures (Friston et al., 1994). The location of each cluster was indicated by peak voxels on the normalized structural images and labeled using the nomenclature of Talairach and Tournoux (Talairach and Tournoux, 1988).

DTI images were realigned using the diffusion toolbox in SPM2. The 1st images of each run were realigned to the first image of the first run. This procedure removed eddy current-induced distortions. Then all the images were averaged across the 4 runs. For each voxel, the diffusion tensor and fractional anisotropy (FA) were calculated using standard procedures (Basser et al., 1994). We removed voxels that had extremely large residuals after fitting the 15 DWIs by an ellipsoid tensor.

Using the T maps generated by SPM99, which are the result of the random effect analysis of 20 subjects, we created starting points for DTI fiber tracking. We used a threshold $p < 0.001$ (uncorrected) and $p < 0.05$ (corrected at cluster-level) as criteria for making the starting points.

The starting points for fiber tracking were set in intervals of 1 mm in the foci of fMRI activation clusters. The coordinates of the activated clusters in Talairach coordinates were reverse normalized into each subject's coordinates, and used as the basis for fiber tracking and determining the coordinates of the end points of the fibers. Then we normalized the end points' coordinates, averaged the data across all the subjects, and superimposed the resulting maps onto the normalized T1-weighted images. The reverse normalization and normalization of the coordinates were performed in the following way. We took T1 and DWI scans in the same FOV, and using SPM99, we normalized our T1 image to the template brain. For each subject, we applied reverse conversion of normalization to the seed points, using in-house Matlab (The Mathworks Inc., Natick, MA, USA) programs. The normalization is an affine transformation, which can be expressed as: $y = C(x-x_0)+C_0+y_0$. The reverse normalization was obtained as: $x = C^{-1}(y-y_0-C_0)+x_0$, where x is the coordinate before normalization, x_0 is the origin before normalization, y is the coordinate after normalization, y_0 is the origin after normalization, C is the linear transformation matrix obtained by SPM99, and C_0 is the translation obtained by SPM99. This approach is better than normalizing DWIs directly because the resolution of DWIs was reduced when we resampled DWIs during normalization.

Fiber tracking

Diffusion tensors, fractional anisotropy (FA), and fiber tracts were calculated using custom-made Matlab programs. We used a fiber tracking algorithm based on the method described in Basser et al. (Basser et al., 2000). At every position along the fiber trajectory a diffusion tensor is interpolated and eigenvectors are computed. The eigenvector associated with the greatest eigenvalue indicates the principal direction of water diffusion. The fiber tract is propagated along this direction over a small distance (0.5 mm) to the next point where a new diffusion tensor is interpolated (linear). Fiber tracking terminates when the angle between two consecutive eigenvectors is greater than a given threshold (60°), or when the FA value is smaller than a given threshold (0.14). The criteria of $FA < 0.14-0.15$ is reported to provide the best tradeoff between fewer erroneous tracts and penetration into the white matter (Thottakara et al. 2006).

This streamline approach is based on the assumption that diffusion is locally uniform and can be accurately described by a single eigenvector. Unfortunately, this approach fails to describe crossing fibers (Alexander et al., 2001). To overcome this problem, tensorline approaches (e.g. tensor deflection) have been developed that use the entire tensor information instead of reducing it to a single eigenvector (Lazar et al., 2003). In this study, both algorithms, i.e. streamline (Basser et al., 2000) and tensor deflection (Lazar et al., 2003), were used to reconstruct 3D DTI fibers.

It is important to take into consideration that DTI fiber tracking from area A to area B does not necessarily signify a fiber connection from area A to area B. There is no way to know whether the fibers are running from A to B or B to A, because the diffusion of a water molecule does not yield directional information on the transmission of neural signals.

Group study in DTI fiber tracking

For Figure 3 and Supplementary Figures S2-S5, we performed DTI fiber tracking from all voxels in each activated cluster. We obtained the terminal points of each subject, summed them up, and superimposed them onto normalized T1-weighted anatomical images. Given the possibility of missing fibers that pass through a functionally active area, we also traced fibers between pairs of activation clusters.

Estimation of tractography error by the bootstrap method

In this study, the dispersion errors in white matter tractography were estimated by a statistical nonparametric bootstrap method (Lazar and Alexander, 2005). In each iteration, two samples were randomly selected with replacement from the pool of four independent DTI acquisitions, and were averaged. The procedure was repeated for each diffusion-encoding of the brain volume (15 directions) and for one non-diffusion weighted volume, resulting in one bootstrap DTI volume sample. The dispersion errors for the tractography were obtained by running the tractography algorithm over 100 iterations of the bootstrap DTI data set.

We made histograms of the probability of a connection to DLPFC for each and every voxel in STS/FG (Figure 5A). Using 100 bootstrap samples, we performed fiber tracking 100 times from each and all the seed points in the temporal activation. For each seed point, we examined how many times out of 100 the fibers converged onto the DLPFC activation.

A probabilistic map from a single seed point (Figure 5E) was obtained by counting how many boot-trac fibers passed each voxel. A probabilistic map from multiple seeds (Figure 5F and Supplementary Figure S7) was obtained as follows. First, we performed fiber tracking from all the seed points, for each bootstrap sample. We defined a voxel which was passed by at least one fiber as “1”, and a voxel which was not passed by any fiber as “0”. When more than one fiber passed a voxel, we defined it as “1”. We performed these procedures for 100 bootstrap samples, obtained probabilities for each voxel to be “1”, and defined this as a probabilistic map.

The probability of connections between two clusters was obtained as follows. We performed the fiber tracking for each bootstrap sample from all the seed points in cluster 1. Among those fibers for each bootstrap sample, a connection was defined when at least one fiber terminated in cluster 2, and no connection was defined when no fiber terminated in cluster 2. These procedures were done with all the 100 bootstrap samples and both directions (from cluster 1 to 2 and from cluster 2 to 1), and the probabilities between the two clusters were calculated based on how many times out of 100 iterations a connection was found.

One possible reason for observing relatively low probabilities of connections in bootstrapping was that we selected only two out of four DTI scans to estimate the fiber tracking error. This might have caused lower signal-to-noise ratio of the images.

Estimation of connection specificity by arbitrarily defined areas

We estimated the specificity in the connections between two activated clusters in the left DLPFC and the left temporal cortex in encoding. For this purpose, we examined the degree of connectivity between the DLPFC activation and arbitrarily defined non-activating regions. If the connection was specific, the degree of connectivity between DLPFC and arbitrary regions should be significantly lower than the connectivity between DLPFC and temporal cortex activation. However, the degree of connectivity could be affected by many factors, such as distances between regions, and shapes of regions. Thus, we restricted the arbitrary regions to those satisfying the following conditions: (1) all voxels were inside the brain, (2) there was no overlap with the activated regions, (3) the volume and shape of the region were exactly the same as the temporal cortex activation, (4) the distance from the DLPFC was exactly the same as the distance between the DLPFC and the temporal cortex activation. Following these conditions, the arbitrary regions were selected 100 times for each subject, allowing their overlap. Then, the number of the fibers between the DLPFC and these arbitrarily defined regions were obtained. The fibers between the left DLPFC and the newly placed cluster were tracked from any voxel in one cluster to any voxel in the other cluster in both directions.

Results

The mean percent correct in the encoding phase was $96 \pm 4\%$ (mean $\pm$ s.e.m; $n=20$) for the living/non-living judgment task, and $97 \pm 3\%$ for the detection task. They were not significantly different ($p > 0.05$; two-tailed t-test). Reaction times were 1.17 ± 0.05 sec for the living/non-living judgments task, 1.07 ± 0.05 sec for the detection task, and 0.80 ± 0.05 sec for the visuo-motor control task (mean $\pm$ s.e.m). These reaction times were significantly different ($F(2,54) = 13.8$, $p < 10^{-4}$, one-way ANOVA). In the post-hoc Tukey's t-test, the visuo-motor control task was significantly different from both the living/non-living judgments and the detection tasks ($p < 0.05$), but the living/non-living and the detection tasks were not significantly different ($p > 0.05$).

In the retrieval phase, subjects made yes/no recognition memory judgments for previously studied and new words (see Materials and Methods for details). The percent correct for words encoded with living/non-living judgment task was $77 \pm 4\%$ (mean $\pm$ s.e.m; $n=20$), which was significantly higher than the percent correct for words encoded with detection task ($69 \pm 3\%$; $p < 0.005$; two-tailed paired t-test), thus confirming that the words were more deeply encoded in living/non-living judgment task than in the detection task. The reaction time was not significantly different between deeply encoded words (1.23 ± 0.04 sec) and shallowly encoded words (1.21 ± 0.05 sec; $p = 0.3$; two-tailed paired t-test).

Functional MRI results

Figure 2A and 2C shows activated brain areas ($n=20$ subjects) found in the encoding phase ("deep encoding" versus "visuo-motor control") superimposed on T1-weighted anatomical slices (Figure 2A) and on 3D-transparent brain images (Figure 2C). Left dominant prefrontal, parietal, and temporal activation clusters were found as well as a small right prefrontal cluster (see also Table 1). This pattern is consistent with previous studies (Buckner and Koutstaal, 1998; Wagner et al., 1998; Buckner et al., 1999; Habib et al, 2003). The left dorsal prefrontal activation (a) was largely located in Brodmann's Area (BA) 46, BA9/46, BA9 on the middle frontal gyrus (MFG). Only the most ventral part was extended into BA45 on the inferior frontal gyrus (IFG). In this study, we use the term DLPFC for this activated cluster, but note that the most ventral part of the cluster includes IFG. The left VLPFC activation (b) was located in BA 45/47. The temporal cortex activation was in the superior temporal sulcus (STS) and extended into the fusiform gyrus (FG) (BA 21/22/37). Figure 2B shows the mean percent signal changes from baseline (fixation) for the three conditions in the encoding phase ($n=20$, across subject $\pm$ standard error). Our results confirmed the load-dependent activation (Kapur et al. 1994; Otten et al. 2001) in the frontal and the temporal encoding-related areas.

Fiber tracking from activated brain areas

Fiber tracking was performed from all the cortical activated areas (but not from cerebellum and brain stem) in all the 20 subjects. Figure 2D shows all the reconstructed fibers from the left DLPFC (left) and left VLPFC (right) activation in single subject. The fibers from left DLPFC and VLPFC extended to other left prefrontal regions, as well as the left parietal and temporal cortices. The fibers from the left temporal cortex activation were found to connect with the left frontal, parietal and occipital cortices. For retrieval data, please see Supplementary Figure S1 and Table S1.

Group study of DTI fiber tracking

Figure 3 shows the distribution of terminal points for reconstructed fibers in 20 subjects. The fibers were tracked from areas in the left DLPFC (top row), VLPFC (middle row) and temporal cortex (bottom row) that were activated during the encoding phase. The terminal points converged on a large number of memory-related areas also activated during the encoding phase.

These areas include: left VLPFC (h), right VLPFC (k), left medial frontal (o, s), left superior frontal (t) and left temporal cortex (f) (see also **Table S1**). In addition, some fibers terminated in areas activated during the retrieval phase (e.g. i and p). We also found connections to the left hippocampus/parahippocampal region (c). The activated areas in the left DLPFC, VLPFC, and the left temporal cortex were all connected with the left hippocampus/parahippocampal region. We performed this group analysis for all the other activated areas. The results in Fig. 3 suggest that activated areas in the left DLPFC and VLPFC both have connections with the left temporal cortex activation (see **Figure S2** and **S3** for complete continuous slices of this group study for the encoding and retrieval clusters). The activation in the left DLPFC, VLPFC, STS and intraparietal sulcus (IPS) each connected with the hippocampus/ parahippocampal region (Figure 3, **S2, S3**).

Connections between memory-related areas

We examined connections between pairs of activation clusters in each subject (Figure 4A, B, Table 2). Fibers were obtained using any voxel in the starting cluster (as a seed) to any voxel within the end cluster, going in either direction. Figure 4A shows the connections found between the activated areas in the left DLPFC and the left temporal cortex for the encoding phase. Figure 4B shows the connections between the left VLPFC and the left temporal cortex activation for the encoding phase. We performed this analysis on the data obtained from all 20 subjects. The most dorsal part (BA 9) of the left DLPFC cluster connected with the dorsal part (BA21, 22) of the left temporal cortex cluster. In some subjects, there were also connections between the ventral part of the DLPFC cluster and the temporal cortex cluster. Fibers between VLPFC and STS also exhibited different pathways passing through more ventral parts. These fiber pathways were consistent across subjects.

Table 2 summarizes the connectivity data between each pair of clusters for the entire group of subjects (For retrieval, see Supplementary Table S2). In obtaining the data for Table 2, we used both the streamline and tensor deflection algorithms. The connections between the left DLPFC and the left temporal cortex, and between the left VLPFC and the left temporal cortex were found in more than 10 out of 20 subjects with both the streamline (from the left DLPFC to the left temporal cortex: 18 subjects; from the left VLPFC to the left temporal cortex: 14 subjects) and tensor deflection algorithms (from the left DLPFC to the left temporal cortex: 20 subjects; from the left VLPFC to the left temporal cortex: 18 subjects) in encoding. (For other connections, see Supplementary Figure S6.)

Estimations of tractography error

We estimated the error of fiber tracking between the left DLPFC and the left temporal cortex using a bootstrap method (Lazar and Alexander, 2005) (see Materials and Methods). First, we made histograms of the probability of a connection to DLPFC for each and every voxel in STS/FG (Figure 5A; see Materials and Methods). Thirty-three continuous seed points in the temporal cortex (a green region in Figure 5C) showed greater than 50 % probability of a connection to DLPFC. The seed cluster volume was 33 mm³ (1mm sampling of seed points), corresponding to 0.7 % of the entire temporal cortex activation (4848 mm³). It is clear that these seed points did not distribute diffusively across the whole activated cluster, but were rather confined in a specific region. The Talairach coordinates of these 33 voxels were located in STS (x, y, z = -54 ± 5, -40 ± 2, -1 ± 2). These results indicate that the locations in temporal cortex that had connections with DLPFC were very specific.

We showed the results of boot-trac from a single seed point (Talairach: x, y, z = -49, -41, 0; from a green region in Figure 5C) in two ways. First, all the fibers for 100 bootstraps are shown in Figure 6D. Most of the fibers (78 %) went to the DLPFC, gradually diverging by the distance from the seed point in the temporal cortex activation. To assess uncertainty of this probability,

we performed boot-trac analysis 1000 times. By shuffling the orders of the 1000 boot-trac samples 1000 times, an error for each iteration was obtained (Figure 5B). At 100 iterations of boot-trac, the error was less than 5%. Second, the boot-trac from the same seed is shown as a probabilistic map (Figure 5E; see Materials and Methods). This figure shows how many times, out of 100, the boot-trac fibers passed through each voxel. The probabilities were almost 100 % around the seed point in the temporal cortex activation, but soon went down less than 50 %. This is because of the divergence of the tracked fibers, which depends on the distance from the seed point, as displayed in Figure 5D.

We obtained a probabilistic map of connections from all 33 seed points with a connection probability greater than 50% (Figure 5F; see Materials and Methods). These seed points are located in restricted locations, so they could compensate for the low probability of one seed point. The results indicate that the fiber tracking from those 33 seed points reached the DLPFC activation with a probability of more than 80 %. The terminal location was the posterior end of the DLPFC cluster (around x, y, z = -49, 3, 36 in the Talairach coordinate), around the precentral sulcus to the middle frontal gyrus. This result indicates that not only the seed points, but also the terminal points were in very restricted locations within the activation. Figure 5F shows the probabilities of fibers from 33 voxels in the temporal cortex to anywhere in the whole brain. Although we did not selectively show the fibers that reached the DLPFC activation, high probabilities were found only along the pathway from the temporal cortex to DLPFC. Thus, the specificity of this pathway was remarkable. We also obtained probabilistic maps (Supplementary Figure S7, **upper row**) from all the voxels in the temporal cortex activation, similar to Figure 5F. All subjects' results (n=20) were averaged after normalization (Supplementary Figure S7, **lower row**).

The boot-tracked fibers were diverging by the distance from the seed points, but in many cases, as shown in Figure 5D, most of the fibers reached the DLPFC activation. To see this observation quantitatively, we examined the probability of connections between any voxel in the temporal cortex and any voxel in the DLPFC (see Materials and Methods). We found the connection with a probability of 100% in this subject.

We performed this latter analysis for 18 subjects who showed connections between these regions. The existence of this pathway was crucial to distinguishing between the two models (the Serial and Parallel Pathway Models) mentioned above. Ten subjects out of the 18 subjects showed more than 50% probabilities for the connections between the left DLPFC and the left temporal cortex. The probability for the existence of this connection was very high in these 10 subjects ($86.3 \pm 18.0\%$, n=10). This result validates our major finding on the direct pathway between DLPFC and the temporal cortex activation.

Estimations of the connection specificity using arbitrary defined areas

We also examined the specificity of the connections between DLPFC and the temporal cortex. Arbitrary regions satisfying the selection criteria (see Materials and Methods) were used 100 times for each subject. Then, the number of fibers between the DLPFC and those arbitrarily defined regions were obtained (see the histogram in Figure 6A). There was no connection between the DLPFC cluster and 55% of the random clusters. The median of the number of fibers between the DLPFC cluster and the random clusters was found to be 0, which is significantly different from the observed number of fibers (57 fibers; $P < 10^{-16}$; Wilcoxon signed rank test). The random clusters that had more fibers than the actual number of fibers (57 fibers) were only 5%, and all of them were found in the precuneus in this particular subject.

We performed the same kind of analyses in all 18 subjects who had fibers between DLPFC and temporal cortex clusters. Eleven out of 18 subjects showed a significantly larger number of actual fibers relative to fibers generated from random clusters ($P < 0.001$; Wilcoxon signed

rank test). At the population level, we made histograms of the number of actual fibers (black bars in Fig. 6B) and the median number of fibers from random clusters (white bars in Fig. 6B) for 18 subjects, and found a significant difference ($P < 0.001$, Wilcoxon Signed Rank Test, $n=18$). These analyses confirmed that the connections between DLPFC and temporal cortex activation were specific. Only some restricted areas ($14.0 \pm 3.6\%$; average $\pm$ standard error; $n=18$) located in the right PFC (BA9/46) and precuneus (BA7) showed more connections with the left DLPFC cluster.

Anatomical network among memory-related areas

A summary of the fiber tracking results among the activation clusters in 20 subjects is shown in Figure 7. Fibers found in more than half of all 20 subjects with both the streamline and tensor deflection algorithms were shown as arrows in solid lines. The dotted arrow indicates the pathways found in more than 10 subjects only by tensor deflection. (Some arrows are omitted. For a complete table of connections, see Table 2 and Supplementary Table S2).

Discussion

By combining fMRI and DTI *in vivo*, we demonstrated that two fronto-temporal anatomical pathways between functionally defined memory-related areas. Many functional neuroimaging studies have suggested that the fronto-temporal pathway is involved in deep encoding processing and retrieval efforts with the top-down signaling (Buckner et al., 1998; Takahashi and Miyashita, 2002). Consistent with functional correlation studies that have suggested interaction between frontal and temporal cortices (Rajah et al., 1999; Koechlin et al., 2003), our study demonstrated direct anatomical connections between these areas. In encoding, more than half of all the subjects showed the connections from both the left DLPFC and left VLPFC activation to the left temporal cortex activation, which supports the Parallel Pathway Model described in the introduction. In retrieval, the connection between the DLPFC and the temporal cortex is still controversial and depends on the algorithms of fiber tracking (the streamline and the tensor deflection), while the left VLPFC activation was connected with the activated area in the left temporal cortex in more than half of the subjects with using both algorithms.

Furthermore, we examined the connections from/to the medial temporal cortex such as the hippocampus/parahippocampal area. Although there is a consensus on the medial temporal lobe structures important for declarative memory (Squire and Zola-Morgan, 1991; Takahashi et al., 2002), it is still under debate how these structures exactly contribute to memory. In our study, the activation in the left DLPFC, VLPFC, STS and intraparietal sulcus (IPS) all connected with the hippocampus/ parahippocampal region. This suggests that hippocampus/ parahippocampal region play a fundamental role in the human memory function.

In the past decade, functional neuroimaging studies have significantly advanced our understanding of human cognitive functions. However, the advance in human brain anatomy has been limited. The combination of fMRI and DTI presented in this study will increase our understanding of the functional neuroanatomy underlying many other cognitive functions in humans.

Comparison with previous human and animal studies

In non-human primates, many connections have been studied in detail. DLPFC (BA 46, 9/46, 9) has reciprocal connections with a multimodal region in the temporal cortex, called area TPO, located at the upper bank of the superior temporal sulcus (Seltzer and Pandya, 1989), but not with the inferior temporal cortex (Petrides and Pandya, 2002). In VLPFC (BA 45, 47/12), BA 45 is strongly connected with the area TPO (Seltzer and Pandya, 1989), whereas BA 47/12 is strongly linked with the inferotemporal visual association cortex (Ungerleider et al.,

1989; Petrides and Pandya, 2002). The temporal cortex activation observed in the encoding phase of this study was located in the STS (BA 21, 22) and the FG (BA 37). The fusiform gyrus is considered a visual association area, whereas STS is considered a multimodal region and presumably the homologue of monkey area TPO (Calvert et al., 2000; Beauchamp et al., 2004; Beauchamp, 2005). Although we presented word stimuli to the subjects visually, verbal memory is multimodal in nature, which is consistent with temporal activation in visual and multimodal association areas. In humans, we found connections between DLPFC (BA 46, 9) and **temporal cortex** activations. The fibers ended mostly in STS (Figure 5A). This appears to be homologues to connections between DLPFC and area TPO in the monkey brain. Human VLPFC (BA 45, 47) was also connected with the STS activation, which is also consistent with previous monkey studies. Our findings suggest that there are two pathways between PFC and temporal cortex related to human verbal memory: one between DLPFC and temporal cortex, and another between VLPFC and temporal cortex. The similar pathways between PFC and the temporal multimodal region in the monkey brain suggest that such dual control systems might also be important for multimodal memory function in non-human primates.

We showed that left DLPFC is connected with STS, the intraparietal sulcus (IPS), and the anterior cingulate cortex. In monkeys, connections with the prefrontal region around the principal sulcus (PS) were found in the STS, IPS, and the cingulate cortex (Pandya and Kuypers, 1969). Similarly, connections were also found between IPS and the temporal cortex in monkeys (Pandya and Kuypers, 1969; Mesulam et al., 1977; Cavada and Goldman-Rakic, 1989), which is consistent with our results. From the occipital cortex, we showed fascicles to IPS. These pathways are also known in monkeys between the IPS and inferior occipital gyrus (Seltzer and Pandya, 1980).

We showed hippocampal connections with a focus on activation identified in the DLPFC, VLPFC, STS and IPS. In monkeys, hippocampal connections were also found with the dorsolateral prefrontal cortex (BA9/46) (Goldman-Rakic et al., 1984; Nauta, 1964), the inferior parietal sulcus (BA7) and the inferior temporal cortex (Seltzer and Pandya, 1983; Van Hoesen et al., 1979).

Roles of the connections between DLPFC and the temporal cortex

On the basis of lesion studies in nonhuman primates (Petrides, 1991), neuroimaging studies in humans (Petrides, Alivisatos, Evans and Meyer, 1993; Petrides, Alivisatos, Meyer and Evans, 1993), and connection studies in nonhuman primates (Petrides and Pandya, 1994), the two-stage model of PFC (Petrides, 1994a, 1994b, 1996; Owen, Evans and Petrides, 1996) was suggested: the Ventro-Lateral Prefrontal Cortex (VLPFC) is thought to interact with posterior cortices such as the temporal cortex for active (or controlled) encoding and retrieval of information, while the Dorso-Lateral Prefrontal Cortex (DLPFC) is hypothesized to monitor and manipulate the maintained information in VLPFC. In this study, we found that there are two front-temporal pathways between the left DLPFC and the left temporal cortex, and between the left VLPFC and the left temporal cortex. This result suggests that there is a direct interaction between DLPFC and temporal cortex.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

(A) Two possible models of connections between the prefrontal and temporal cortices. (i) Serial Pathway Model: DLPFC connects with VLPFC, but not with the temporal cortex, and VLPFC connects with the temporal cortex, (ii) Parallel Pathway Model: DLPFC and VLPFC both connect with the temporal cortex.

(B) Experimental design for functional imaging in encoding (left) and retrieval (right). In encoding, there are four conditions: living/nonliving, detection, visuo-motor control, and fixation. In retrieval, there are retrieval trials and visuo-motor control trials (see text and Materials and Methods for further details).

Figure 2.

(A-D) Activation and fiber tracking from the activated areas in the encoding phase in the comparison “deep encoding versus visuo-motor control”.

(A) Activated clusters (20 subjects, random effect analysis, $p < 0.001$, uncorrected; $p < 0.05$ corrected for whole-brain multiple comparisons at cluster level, only cortical activation clusters are displayed) are superimposed on T1-weighted normalized brain slices. The left hemisphere of the brain corresponds to the left side of the image. A color bar for T values of activated areas is shown at the bottom of the left. Z coordinates of Talairach space are shown on the top of each slice. (a) Left DLPFC (BA9/46/45), (b) left VLPFC (BA45/47/insula), (c) medial frontal

gyrus (BA6), (d) right VLPFC (BA45/46), (e) left superior frontal gyrus (BA6), (f) left intraparietal sulcus (BA7) and (g) left STS and FG (BA21/22/37). BA: Brodmann's Area.

(B) The mean percent signal changes (across subject $\pm$ standard error) for the three conditions in the encoding phase. The bars in the left side show activation levels from "Deep" condition, the bars in the middle from "Shallow" condition, and the bars in the right from "Visuo-motor Control" condition.

(C) Activated clusters using the same threshold as (A) are shown as red superimposed on a sagittal view (top) and an axial view (bottom) of a brain. (a)-(g) represent the same areas as shown in (A).

(D) All the reconstructed fibers from the left DLPFC (left) and left VLPFC (right) in single subject are shown as green in a sagittal view (top) and an axial view (bottom). The activated areas are shown as yellow.

Figure 3.

The average results of 20 subjects' terminal points of DTI fiber tracking. The left hemisphere of the brain corresponds to the left side of the image. The terminals of the tracked fibers are shown as yellow to green. The colors indicate the number of subjects whose fiber tracking from any seed points terminated in the voxel (see color bar). Terminal points of fibers from encoding activation in the left DLPFC (**top row**), left VLPFC (**middle row**) and the left STS (**bottom row**). The end points of fiber tracking converged in (a) left inferior frontal gyrus (BA47), (b) left anterior to posterior insula, (c) left hippocampus/parahippocampal formation, (d) bilateral brain stem, (e) left inferior occipital gyrus (BA18), (f) left STS and FG (BA21/22/37), (g) left inferior frontal gyrus (BA44/45), (h) left frontal operculum (BA47), (i) left striatum, (j) left thalamus, (k) right inferior frontal gyrus (BA46), (l) left superior to middle frontal gyri (BA9/10), (m) left occipital gyrus (BA19), (n) left medial frontal gyrus (BA9), (o) left supplementary motor area (BA8), (p) left precuneus (BA7), (q) left middle frontal gyrus (BA6), (r) left inferior parietal gyrus (BA40), (s) left supplementary motor area (BA6), (t) left superior frontal gyrus (BA6), and (u) left postcentral gyrus.

Figure 4.

Fibers between two activation clusters in five different subjects. **(A)** Reconstructed fibers between the left DLPFC (BA9/8/46/45) and left STS to FG (BA21/22/37) in the encoding phase. **(B)** Reconstructed fibers between the left VLPFC and the left STS to FG (BA21/22/37) in the encoding phase. (A: Anterior, P: posterior, D: dorsal, V: ventral, L: left, R: right). Fibers were tracked in both directions. For summary, see Table 2 and S2. (For connections between other clusters, see Supplementary Figure S7.)

Figure 5.

(A) A histogram of the probability of a connection to DLPFC for every voxel in STS/FG of one subject. All the seed points of more than 50% of probability (red bars) were found in a small specific region in the temporal cortex. (B) Boot-trac analysis with 1000 iterations from a voxel (-49, -41, 0) in a single subject. Estimated probabilities of a connection to DLPFC were plotted against number of iterations (blue line). The averages (red line) and errors (SD) of probabilities at each iteration were estimated by shuffling the orders of the 1000 boot-trac samples (see the main text). (C) The locations of the continuous thirty-three seed points that showed more than 50 % of probability (green in the temporal cortex activation). (A: anterior, P: posterior, D: dorsal, V: ventral). (D) All the fibers for 100 bootstraps from a single seed point at (-49, -41, 0). (E) A probabilistic map of the connection from a single seed point (Talairach: x, y, z = -49, -41, 0). The voxels with more than 10 % probabilities were color-coded. (F) A probabilistic map of the connection from the 33 seed points of high probabilities in the temporal cortex (green). Voxels that showed more than 50 % were color-coded.

Figure 6.

(A) A histogram of the numbers of the fibers between the DLPFC cluster and each of the 100 random clusters for one subject. (B) Histograms of actual numbers of fibers from DLPFC to the temporal cortex (black bars) and median numbers of fibers from DLPFC to random clusters (white bars) for 18 subjects.

Figure 7.

Summary of the fiber tracking results between the activation clusters. (A) Encoding, (B) Retrieval. The pathways found in more than 10 subjects both by streamline and tensor deflection algorithms are shown as solid arrows, while a dotted arrow indicates the pathways found in more than 10 subjects only by tensor deflection. (For a complete table of connections, see Table 2 and Supplementary Table S2). DLPFC: dorso-lateral prefrontal cortex, VLPFC: ventro-lateral prefrontal cortex, SFG: superior frontal gyrus, STS: superior temporal sulcus, FG: fusiform gyrus, AC: anterior cingulate cortex, SMA: supplementary motor area, OTC: occipito-temporal cortex.

Regions activated in the memory tasks. Only clusters with a significant activity of $p < 0.05$ corrected for whole-brain multiple comparisons are reported. The coordinates and their T-values are at the peak voxels in each cluster, and the coordinates and approximate Brodmann's area (BA) are indicated in the Talairach and Tournoux atlas space. 1 voxel=8mm³.

Table 1

Contrasts	Cluster size	T value	Coordinate (mm)			z	L/R	Brodmann's area (BA)
			x	y				
Encoding Deep vs. Control	1347	7.12	-44	30		18	L	BA9/46/45
	606	5.73	-44	-42		-8	L	BA21/22/37
	306	5.27	-34	-58		58	L	BA7
	277	5.21	-32	32		6	L	BA46/10/47
	107	4.70	-34	-4		70	L	BA6
	93	4.61	-2	24		58	L/R	BA6
	89	4.60	40	28		14	R	BA45/46
	69	4.56	28	-88		0	R	BA17/18
								middle frontal gyrus (DLPFC)
								superior temporal sulcus & fusiform gyrus (STS/FG)
								intraparietal sulcus (IPS)
								inferior frontal gyrus (VLPFC)
								superior frontal gyrus (SFG)
								medial frontal gyrus (SMA)
								inferior frontal gyrus (VLPFC)
								inferior occipital gyrus

Connection patterns that show how many subjects have connections between each pair of activated clusters in encoding (deep encoding versus control). The streamline algorithm (numbers outside of the parenthesis) and the tensor deflection algorithm (numbers inside of the parenthesis) were used.

Table 2

	L BA9/46/45 (DLPFC)	L BA45/47 (VLPFC)	L BA22/37 (MTG/FG)	L BA7 (IPS)	L BA6 (SFG)	R BA45/46 (VLPFC)	R BA17/18
L BA45/47	20 (20)						
L BA22/37	18 (20)	14 (18)					
L BA7	9 (12)	8 (7)	15 (19)				
L BA6	14 (19)	3 (6)	4 (2)	2 (1)			
R BA45/46	7 (11)	2 (4)	1 (1)	0 (1)	0 (0)		
R BA17/18	1 (2)	1 (1)	3 (4)	1 (3)	0 (1)	1 (10)	
Med BA6	8 (12)	2 (0)	1 (5)	1 (3)	2 (2)	0 (5)	2 (2)