

Fiber density between rhinal cortex and activated ventrolateral prefrontal regions predicts episodic memory performance in humans

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The prefrontal cortex (PFC) is assumed to contribute to goal-directed episodic encoding by exerting cognitive control on medial temporal lobe (MTL) memory processes. However, it is thus far unclear to what extent the contribution of PFC-MTL interactions to memory manifests at a structural anatomical level. We combined functional magnetic resonance imaging and fiber tracking based on diffusion tensor imaging in 28 young, healthy adults to quantify the density of white matter tracts between PFC regions that were activated during the encoding period of a verbal free-recall task and MTL subregions. Across the cohort, the strength of fiber bundles linking activated ventrolateral PFC regions and the rhinal cortex (comprising the peri- and entorhinal cortices) of the MTL correlated positively with free-recall performance. These direct white matter connections provide a basis through which activated regions in the PFC can interact with the MTL and contribute to interindividual differences in human episodic memory.

functional MRI | tractography | hippocampus | perirhinal cortex | entorhinal cortex

Episodic memory (1) is the ability to encode, store, and recall events in their spatial and temporal context. Human lesion studies (2, 3) have demonstrated that episodic memory function is critically dependent on the hippocampus and neighboring structures of the medial temporal lobe (MTL), and functional neuroimaging experiments have shown that episodic memory encoding is associated with activations of the MTL and regions of the prefrontal cortex (PFC) (1, 4, 5).

During encoding, both MTL and PFC regions show stronger activity for items that are later recalled compared with items that are forgotten [difference because of memory (DM)] (for reviews see refs. 6 and 7). It had long been hypothesized that coactivation of PFC and MTL structures might indicate that both regions cooperate during encoding and that activated PFC regions might be anatomically connected to MTL structures by white matter tracts (8). Via these fiber tracts, PFC regions might exert top-down control on MTL structures (9, 10) that act as gateways to the hippocampus, most notably the entorhinal and perirhinal cortices (ERC and PRC, respectively, jointly referred to as the rhinal cortex) (7).

Although intriguing, the possibility of a direct anatomically based functional interaction between PFC regions and the ERC and PRC during successful encoding is not without doubt. Activity patterns that reflect successful encoding in functional MRI (fMRI) studies are most frequently observed in the ventrolateral and dorsolateral PFC (VLPFC and DLPFC, respectively) (6, 7). However, studies in nonhuman primates suggest that the strongest PFC projections to the ERC and PRC arise in the orbitofrontal cortex (11–13). In contrast, structural connectivity between DLPFC/VLPFC and the MTL is light (10–13). Therefore, the question whether prefrontal areas that show encoding-related ac-

tivity patterns are connected with the ERC and PRC is particularly relevant in humans.

Diffusion tensor imaging (DTI) allows in vivo tracking of subcortical white matter fiber bundles that connect distant cortical structures (14, 15). Previous studies have demonstrated a relationship between fractional anisotropy (FA) measures obtained from DTI and memory performance in patients with mild cognitive impairment, and a possible relationship between reduced FA and cognitive dysfunction in temporal lobe epilepsy and schizophrenia (16–18). In young, healthy adults, FA in temporal lobe white matter has been related to true vs. false recognition performance (19).

It is, however, unclear to what extent these findings relate to specific fiber tracts connecting PFC regions to the MTL. DTI-based fiber tracking allows one to specifically assess white matter tracts linking distant brain regions (20). A recent study used combined fMRI/DTI to assess the functional connectivity of parietal and medial temporal cortices during memory retrieval (21), suggesting that interindividual functional anatomical variability during cognitive tasks can be accounted for during fiber tracking by combining these two imaging modalities.

To investigate the contribution of PFC-MTL white matter connections to episodic memory encoding, we performed event-related fMRI during the encoding periods of a verbal free-recall task and DTI-based fiber tracking in the same 28 young, healthy participants. During fMRI scanning, participants studied words at deep (semantic) and shallow (phonemic) levels of processing (LOP) and were instructed to freely recall the words after a brief period of distraction (Fig. S1) (22). Activation maxima of the LOP and subsequent memory effects in the DLPFC and VLPFC were used as seed regions for DTI-based tracking of fiber tracts linking the PFC to the ERC and PRC. We also included fiber tracts to the parahippocampal cortex (PHC), a region that has also been related to successful memory encoding (8). Fiber tract reconstruction was performed using a Monte Carlo simulation algorithm that repeatedly searches for probable paths through the determined diffusion tensor matrix (23). The number of paths detected for a given number of path calculation starts was used as

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a measure of neuronal structural connectivity and related back to memory performance. Our analyses were confined to tracks traversing through the uncinate fascicle, and we did not consider tracks that traverse through the splenium (24) because of the difficulty in tracing this long pathway.

Results

Behavioral Results. The average percentages of recalled items in the deep and shallow study conditions are displayed in Table S1. There was a strong, significant effect of the LOP on the proportion of remembered items ($F_{1,27} = 63.67$; $P < 0.001$; one-way ANOVA for repeated measures). Reaction times were significantly shorter for shallowly studied items than for deeply studied items ($F_{1,27} = 6.65$; $P = 0.016$; two-way ANOVA for repeated measures), but there was no reaction time difference as a function of subsequent recall and no interactive effect of subsequent recall and LOP on reaction times (all, $P > 0.339$).

Functional MRI Results. Brain activity differences related to the LOP. Irrespective of subsequent recall, deep study processing was associated with increased activations in the bilateral dorsomedial PFC [Brodmann Area (BA) 6, 8, 9], the left inferior frontal gyrus (BA 47) (Fig. S2), as well as portions of the left parietal and temporal cortex, replicating earlier results with the same paradigm (22) and with different study tasks (25). Prefrontal activations for deeply relative to shallowly studied items were consistently observed at the single-subject level, and the local maxima in the dorsomedial and ventrolateral PFC showed very little variability across subjects.

Brain activity related to subsequent recall. Similar to previously reported observations (8, 22, 25), successful encoding of words (i.e., subsequently recalled vs. subsequently forgotten) was associated with increased activations of the MTL and PFC, including dorsolateral and ventrolateral PFC regions (Fig. 1A). The distinct

group-level clusters in the DLPFC and VLPFC were consistent between the studied cohort and an independent cohort investigated with the same paradigm (Fig. S3). Similar to the LOP effect, left PFC activation was robustly observed at the single-subject level; however, unlike LOP-related activations, individual local maxima within the left DLPFC and VLPFC varied across subjects (Figs. 1C and 2B).

Fiber-Tracking Results. Fiber tracts were reconstructed from individual activation peaks within the four fMRI-derived seed regions in the PFC (DLPFC DM, VLPFC DM, dorsomedial and ventrolateral LOP regions) to the three anatomically segmented regions of interest (ROIs) within the MTL (Fig. 2A and B). Fig. 2C displays representative fiber tracts linking the MTL and memory-related PFC regions in a single subject. The absolute number of fiber tracts showed high interindividual variability in our cohort, which was observed at comparable magnitudes by all three raters. Type 3 intraclass correlations revealed interrater reliabilities of $0.680 < r < 0.994$ (all, $P < 0.001$). Fig. 3A displays example fiber tracts from three participants linking the VLPFC DM seed region to the segmented PRC in three representative subjects.

Table S2 displays the average strengths of the tracts linking prefrontal seed regions to the MTL ROIs. The VLPFC DM seed region showed highest fiber density to the PRC (mean number of tracked paths = 63.3; SD 56.4), followed by the ERC (47.4; SD 60.1) and PHC (7.6; SD 7.3). Paired t tests showed that the numbers of tracts from the VLPFC and DLPFC DM seed regions were significantly higher to the PRC than to the ERC and PHC, and the numbers of tracts to the ERC was significantly higher than to the PHC (all, $P < 0.001$). Fiber tract strengths from the VLPFC DM seed to the PRC and ERC, respectively, were strongly correlated ($r = 0.934$; $P < 0.001$), but did not correlate with the number of tracts to the PHC (all $P > 0.300$). On the other hand, the numbers of fiber tracts from the DLPFC

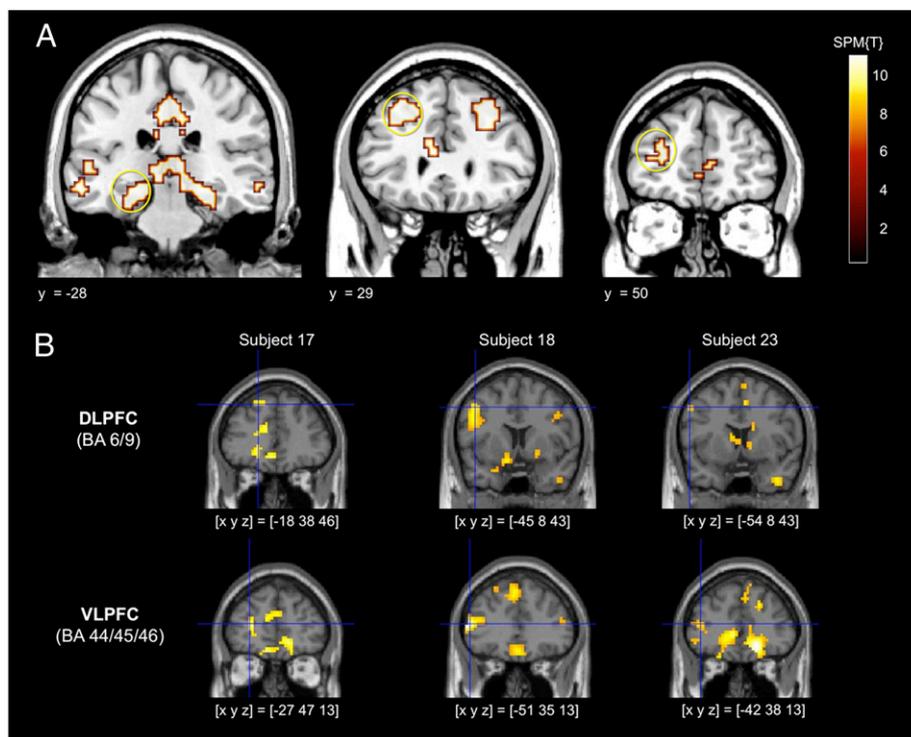


Fig. 1. Activations related to the LOP and successful memory encoding (DM). (A) Successful memory formation (i.e., subsequently recalled vs. subsequently forgotten items) was associated with activation of the left hippocampal formation (Left) and left DLPFC (Center) and VLPFC (Right). Coordinates are given in Montreal Neurological Institute space; $P < 0.05$, whole-brain family-wise error-corrected. (B) Examples from single subjects illustrating interindividual variability of local maxima of DLPFC and VLPFC activations during successful memory formation.

DTI-Based Fiber Tracking. DTI and calculation of DTI maps were performed as described previously (48, 49). Fiber tracts were reconstructed using a double-step probabilistic approach (23). Briefly, a Monte Carlo simulation algorithm that repeatedly searches for probable paths through the determined diffusion tensor matrix was implemented in Matlab. An estimate of the voxel-specific probability distribution of axonal connections was used to calculate the probabilities of all allowable propagation steps. Each step was chosen by drawing randomly from this distribution.

Cortical regions of the MTL (ERC, PRC, PHC) were manually outlined individually on T1 images, as described by Pruessner et al. (50). Prefrontal LOP and DM start regions for fiber tracking were seeded to the individual local maxima in the left PFC ROIs. These ROIs were defined based on the most prominent PFC activations in an independent cohort (LOP ROIs: dorsomedial PFC, Broca's area/BA 47; DM ROIs: DLPFC/BAs 6, 8, 9, VLPFC/BAs 44, 45, 46).

Tractographic analysis between functionally defined individual prefrontal seed regions and the three anatomically defined MTL ROIs (ERC, PRC, PHC) was performed in the left hemisphere, as previous encoding studies with verbal stimuli have yielded predominantly left PFC and MTL activations (8, 22, 25).

Within each predefined start region, the number of paths detected for a given number of path calculation starts was used as a measure of neuronal connectivity within the axonal tract being considered. To ensure that only paths within the tract being considered were counted, anatomically defined filter conditions

were imposed (for a related approach, see ref. 51). Specifically, we set a cutoff value of 30 double jumps between start point and target region. This value was decreased stepwise if fibers appeared that did not belong to the observed path. This procedure was carried out by three independent raters who were all blinded concerning the behavioral results. Type 3 intraclass correlation coefficients were computed to assess interrater reliability, and the average number of paths resulting from the three ratings was used for statistical analysis.

Statistical Analysis. In a preliminary stepwise linear regression analysis, the percentage of recalled words was used as dependent variable, with the strengths of all fiber tracts and MTL ROI volumes as independent variables. We next computed Pearson's correlation coefficients for all 12 fiber tracts and memory performance for the entire group (Fig. 2B). The correlations were then computed in two subgroups of 14 subjects each, to verify robustness of the relationship between fiber tract strengths and behavioral performance.

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