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 entrorhinal 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 activity 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. 1*A*). 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. 1*C* and 2*B*).

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. 2 *A* and *B*). Fig. 2*C* 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. 3*A* 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

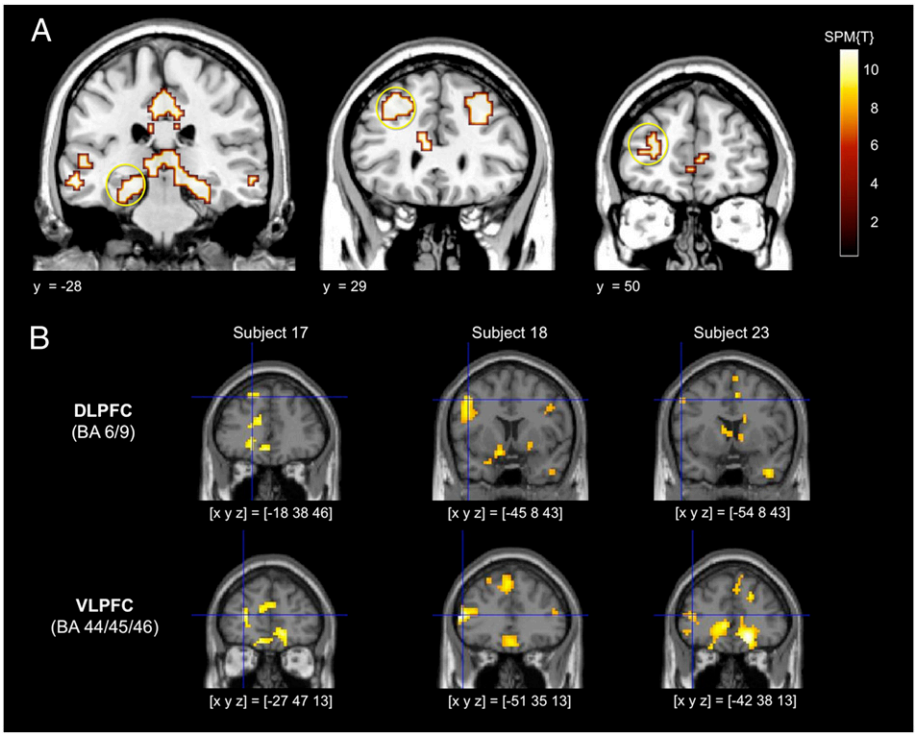

Fig. 1. Activations related to the LOP and successful memory encoding (DM). (*A*) Successful memory formation (i.e., subsequently recalled vs. subsequently forgotten items) was associated with activation of the left hippocampal formation (*Left*) and left DLPFC (*Center*) and VLPFC (*Right*). Coordinates 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.

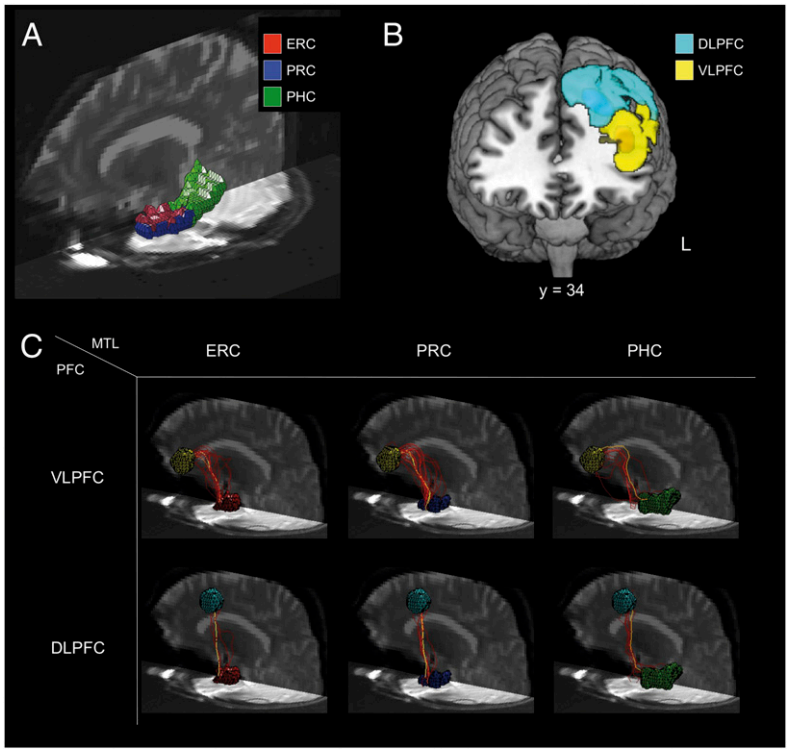

Fig. 2. ROI selection and fiber-tracking results. (*A*) Representative medio-temporal ROIs from a single subject. The ERC (red), PRC (blue), and PHC (green) were manually segmented from the subjects' individual T1-weighted MRIs. (*B*) Localization of the fMRI-based PFC DM seed region. All PFC starting regions for fiber tracking were seeded around the local maxima of activation during deep vs. shallow processing (LOP) or successful encoding (DM), respectively. The picture shows the distribution (mean ± 1 and 2 SD) of the DLPFC (cyan) and VLPFC (yellow) DM seed regions of the study subjects. (*C*) Fiber-tracking results. The figure displays the fiber tracts linking the fMRI-based DLPFC and VLPFC DM seed regions and the three anatomically selected MTL regions. Results from a representative subject are shown. In all subjects, fiber tracking yielded connections of comparable anatomical location, but of variable strength.

DM seed to the MTL regions were all positively correlated (all $r > 0.534$; all, $P < 0.003$).

Correlation of Fiber Tract Strength and Memory Performance. To assess which fiber tract strengths best explained successful recall performance, we first performed a stepwise linear regression analysis for the entire cohort with memory performance as the dependent variable and the fiber tracts linking the peak activations in the four prefrontal seed regions with the three MTL ROIs as independent variables. We also included the volumes of the MTL ROIs to exclude them as confounding factors. Only the strength of the fiber tract linking the VLPFC-DM seed region to the PRC ($\beta = 0.682$, $P < 0.001$) remained in the model.

Next, we computed Pearson's correlations to assess the strength of the correlation between fiber tract strengths and recall performance, both independently of LOP and separately for the deep and shallow study. Successful memory encoding (i.e., proportion of recalled items) correlated positively with the strengths of the fiber tracts linking the VLPFC DM seed region with the PRC ($r = 0.682$, $P < 0.001$) and ERC ($r = 0.622$, $P < 0.001$), both correlations surviving Bonferroni correction for all 12 correlations computed (Fig. 3*B*). Both correlations were significant, separately, for the deep and shallow study conditions, also surviving Bonferroni correction (Fig. 3*C*).

To verify the reliability of this relationship, we performed a random split-half of the cohort. In both subcohorts of 14 subjects, the correlations between the strengths of the VLPFC-DM to the PRC and VLPFC-DM to the ERC fiber tracts and the proportion of successfully recalled items were positive and significant (cohort 1, PRC: $r = 0.587$, $P = 0.027$; cohort 1, ERC: $r = 0.631$, $P = 0.016$; cohort 2, PRC: $r = 0.758$, $P = 0.002$; cohort 2, ERC: $r = 0.629$, $P = 0.016$; all, P two-tailed). Correlations of the fiber tract strengths between the other PFC and MTL regions were not significant or not reliable when applying a split-half (see *SI Results*).

Importantly, there was no significant correlation between the volumes of segmented MTL regions and recall performance (see *SI Results*). Hence, the correlations between density of the fiber tracts linking the VLPFC-DM seed region to the PRC and ERC and recall performance cannot be attributed to variability in MTL gray matter.

Discussion

As in earlier fMRI studies (6, 7), our data show stronger activity in MTL and PFC for subsequently recalled items compared with forgotten items. PFC and MTL coactivations have been suggested to reflect cooperative interaction of these regions during encoding, and our results provide a putative structural anatomical correlate for such an interaction. More strikingly, our findings show that the strength of white matter connectivity between the ventrolateral PFC, PRC, and ERC correlates with explicit recall performance. Taken together, our findings provide an anatomical substrate through which goal-directed PFC representations might exert top-down control onto MTL memory processing.

PFC-MTL Connectivity. We observed DM effects in the ventrolateral and dorsolateral PFC, compatible with earlier fMRI studies (6, 7). For all participants, both the DLPFC (comprising BA 6, 8, 9) and VLPFC (comprising BA 44, 45, 46) activations were observed, although individual local maxima showed a degree of variability (Figs. 1*B* and 2*B*). We did not observe consistent differences in the prefrontal distribution of DM effects for deep and

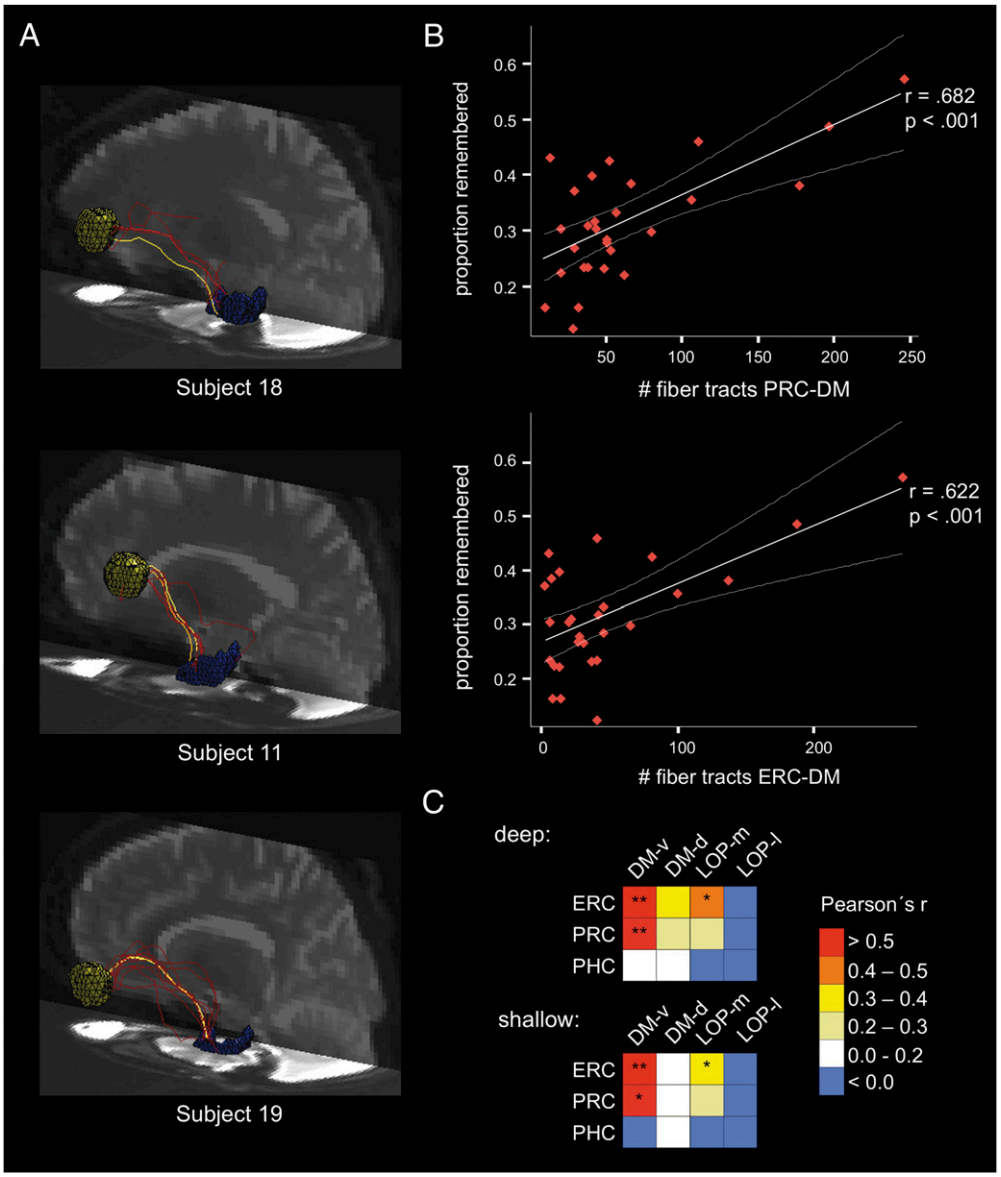

Fig. 3. Interindividual variability of fiber tract strengths and correlation with memory performance. (*A*) Example fiber tracts linking a VLPFC DM seed region to the PRC. The number of tracts was highly variable across subjects, ranging from 10.0 to 245.7 (mean over three raters). (*B*) The numbers of fiber tracts linking VLPFC DM seed regions to the PRC (*Upper*) and ERC (*Lower*) were significantly correlated with successful memory formation. The correlations survived a split-half (see *Results*). (*C*) Correlation of fiber tract strengths and memory performance, separated by LOP. Of all fiber tracts, only the tracts linking seed regions in the VLPFC DM ROI to the ERC and PRC were reliably associated with memory performance during both deep and shallow study. DM-d, dorsolateral subsequent memory seed region; DM-v, ventrolateral subsequent memory seed region; LOP-l, lateral functional LOP seed region; LOP-m, medial functional LOP ROI. *$P < 0.05$, uncorrected; **$P < 0.05$, Bonferroni-corrected and significant after split-half.

shallow study, compatible with earlier studies reporting overlapping DM-effects for both task conditions (26–28).

In nonhuman primates, the strongest projections to the ERC and PRC arise in the orbitofrontal cortex. In contrast, projections between the dorsolateral and ventrolateral PFC and the rhinal cortex are sparse (10–13). For example, Walker's area 46 (which is more extensive than human BA 46) has sparse projections to the ERC, as do areas 9, 8, and 6 (12, 13). A similar picture emerges for the PRC (11). There are projections to the fundus of the rhinal cortex, which originate from the DLPFC (10).

Compatible with the sparse but existent connectivity in nonhuman primates, we observed that PFC regions exhibiting DM-related activations showed reliable white matter tracts to the ERC and PRC. The regions in both DLPFC and VLPFC showed the highest fiber density to the PRC, followed by the ERC. Connectivity of DLPFC and VLPFC with the PHC was lower than with the ERC and PRC, which is at odds with primate studies, where the DLPFC particularly shows marked reciprocal connectivity with the PHC (11). We might have underestimated the fiber density between these regions because our analyses were confined to the uncinate fascicle and adjacent tracts, although pathways to the PHC may predominantly transverse through the splenium by joining the cingulum bundle (24). Indeed, areas 46, 9/46, and the medial extension of area 9 send MTL projections through this pathway (24). Future studies of anatomical PFC-MTL connectivity should therefore consider connectivity within this pathway in relation to memory performance. A further direction for future research might be the comparison of PFC-MTL connectivity to other fiber tracts from the PFC to distant brain regions (see *SI Discussion*).

PFC-MTL Connectivity Correlated with Memory Performance. Recall performance was predicted primarily by PFC-PRC white matter tract connectivity. VLPFC-PRC and VLPFC-ERC connectivity were highly correlated, and both were reliably associated with memory performance, although connectivity of the PFC and PHC showed no correlation with memory performance at all. Fiber tract densities were higher for the VLPFC than for the DLPFC regions, and only the fiber tracts linking the VLPFC DM seed to ERC and PRC showed a correlation with recall performance. These findings are compatible with the proposal that the VLPFC may play a particularly important role in establishing successful encoding (7). Notably, this observation was specific to the more lateral region of the VLPFC activated during successful encoding (BA 44, 45, 46), but no correlation with recall performance was observed for the fiber tracts linking the inferior-medial portion of the VLPFC activated as a function of LOP (Broca's area, BA 47) to the ERC and PRC.

The exact functional contributions of the DLPFC vs. VLPFC to memory encoding are thus far unclear. Studies in PFC lesion patients have reported impaired performance in free recall (29–32) and in complex memory tasks like source memory (33) or associative learning (34–36), but recognition memory impairment after PFC lesions or VLPFC transcranial magnetic stimulation is modest (32, 37). These impairments have been attributed to deficits in cognitive control of information selection and organization rather than a primary memory deficit (7).

Selection involves directing attention toward goal-relevant information and task-appropriate responses (9, 38, 39), and organization refers to spontaneous clustering of recall output according to the semantic relationships within a categorized word list (30, 34, 40–42). VLPFC regions might predominantly contribute to selection, whereas the DLPFC might contribute predominantly to organization processes (7). Because our word lists did not contain systematic semantic relationships, it is conceivable that cognitive control pertaining to spontaneous semantic organization would not benefit recall performance much. We speculate that this may explain why fiber tract density with DLPFC DM seed regions showed no reliable correlations with recall performance. However, it is possible that a stronger correlation may emerge when semantic organization would benefit recall performance. It should also be noted that part of the projections from DLFPC to the rhinal cortex transverse through the fronto-occipital fascicle (10), and we thus may have underestimated the DLPFC to MTL connectivity by restricting our analyses to the connections that transverse through the uncinate fascicle. This restriction may have been one reason why, despite the fact that we have identified significant fiber connectivity between DLPFC and MTL, we did not observe a significant correlation of that connectivity with recall performance.

Memory Impairment and White Matter Connectivity. Previous studies directed at the relationship between fronto-temporal white matter integrity have largely focused on patient populations (16–18). Here we could demonstrate that fiber tract strength of these connections contributes considerably to interindividual variability of memory performance in young, healthy adults, with fiber tract strength of the VLPFC DM activation to rhinal connection explaining ~42.5% of the variance (Fig. 3*B*). In one previous study in young, healthy adults, temporal lobe white matter ultrastructure, as determined with FA, had been related to true- vs. false-recognition memory (19). In that study, however, no correlations with memory performance was observed for white matter tracts linking the MTL and the PFC. One reason for this might be that the white matter tracts identified in this study might be less likely to be detected with voxel-wise analysis of FA images and require explicit delineation by fiber tracking. Furthermore, the seed regions in the PFC were chosen based upon individual activation during successful memory encoding. This approach takes into account the considerable interindividual variability of memory-related prefrontal activations.

Direct Connectivity Between the PFC and Rhinal Cortex: Functional Implications. Within the MTL, the ERC and PRC are major gateways for the hippocampus (11). ERC and PRC functions in memory are best understood within the processing hierarchy of MTL structures (43–46). Information flow from the cerebral cortex is funneled to the ERC through the PHC and PRC, which are likely to provide input about spatial- and object-based information, respectively (47). It is evident that ERC and PRC function will be strongly dependent on the content of the preprocessed input they receive along these processing hierarchies (47).

However, although the connectivity and processing hierarchy within the MTL is important for the memory-coding properties of the PRC and ERC, it leaves unanswered how attentional mechanisms can bias information selection from different input pathways toward forming goal-directed rather than entirely stimulus-driven episodic memories. Such top-down attentional control of memory by the PFC has been postulated (9), but its anatomical substrate in humans has remained elusive. We propose that the direct connectivity of ventrolateral and dorsolateral PFC regions with the PRC and ERC that we have identified here may be this anatomical substrate, and hence allow a top-down attentional control mechanism through which goal-directed prefrontal selection biases can influence the rhinal gating of information.

Conclusions

We show that free-recall performance in a verbal encoding task is correlated with the strength of white matter connections linking VLPFC regions activated during successful memory formation with the rhinal cortex. The strength of anatomical connectivity between the PFC and MTL thus seems to capture interindividual variability of memory performance in healthy humans. This convergence between functional activity patterns and anatomical connectivity between the PFC and MTL closes a long-standing gap in human memory research as to the mechanisms through which goal-directed representations in the PFC could exert attentional control biases on MTL processing.

Materials and Methods

Twenty-eight young, healthy participants (age range 19–31, 16 female) participated in the experiment. Details are available in *SI Materials and Methods*.

Functional MRI Experiment. We used an encoding task followed by free recall (Fig. S1) (22). The experiment consisted of three scanning sessions, each containing three study phases with a deep (pleasantness judgment) and shallow (syllable counting) study task, respectively. Study lists of 20 words were presented (stimulus duration, 1 s; interstimulus interval, 2.75 s). After a distracter task (four moderately difficult arithmetic operations), subjects were prompted to freely and overtly recall all studied words they could remember. The duration of the free-recall phase was 90-s. Echo-planar images were acquired on a GE Signa MRI system (General Electric) (repetition time = 2.0 s, echo time = 35 ms). Images consisted of 23 axial slices [64 × 64, voxel size = 3.13 × 3.13 × 6 mm (5-mm slice thickness + 1-mm gap)]; each session contained 540 volumes. Statistical parametric mapping (SPM8, Wellcome Trust Center for Neuroimaging, London, United Kingdom) was used for preprocessing and data analysis. Echo-planar images were corrected for acquisition delay, realigned, normalized (voxel size: 3 × 3 × 3 mm), smoothed (8 × 8 × 8 mm), and high-pass-filtered (128 s). Single-subject statistical analysis was performed using a general linear model with separate covariates for the conditions of interest (deep remembered, deep forgotten, shallow remembered, shallow forgotten), the speech events (overt response in free recall), rigid-body movement parameters derived from realignment, the distracter task, and a constant (the mean over scans). Group analysis was computed by submitting the contrasts of interest to a two-way ANOVA model, treating subjects as random effect. Planned *t*-test comparisons were carried out to assess effects of LOP and later memory. The significance level was set to 0.05 (whole-brain corrected for family-wise error), with a minimum of 10 adjacent voxels.

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. 2*B*). 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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