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Inter-Individual Variation in Fronto-Temporal Connectivity Predicts the Ability to Learn Different Types of Associations

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Abstract

The uncinate fasciculus connects portions of the anterior and medial temporal lobes to the lateral orbitofrontal cortex, so it has long been thought that this limbic fiber pathway plays an important role in episodic memory. Some types of episodic memory are impaired after damage to the uncinate, while others remain intact. Because of this, the specific role played by the uncinate fasciculus in episodic memory remains undetermined. In the present study, we tested the hypothesis that the uncinate fasciculus is involved in episodic memory tasks that have high competition between representations at retrieval. To test this hypothesis, healthy young adults performed three tasks: Experiment 1 in which they learned to associate names with faces through feedback provided at the end of each trial; Experiment 2 in which they learned to associate fractals with cued locations through feedback provided at the end of each trial; and Experiment 3 in which unique faces were remembered in a paradigm with low retrieval competition. Diffusion tensor imaging and deterministic tractography methods were used to extract measures of uncinate fasciculus microstructure. Results revealed that microstructural properties of the uncinate, but not a control tract, the inferior longitudinal fasciculus, significantly predicted individual differences in performance on the face-name and fractal-location tasks. However, no relationship was observed for simple face memory (Experiment 3). These findings suggest that the uncinate fasciculus may be important for adjudicating between competing memory representations at the time of episodic retrieval.

Keywords

orbitofrontal cortex; white matter; limbic; diffusion imaging; faces; proper names; associative memory; temporal pole; uncinate fasciculus

1. Introduction

Correct recall of episodic memories relies on the function of medial temporal lobe structures, especially the entorhinal cortex and hippocampal formation, along with control

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structures in portions of the frontal lobe. There is long-standing interest in understanding how fiber pathways that connect these regions function in episodic memory. Over 30 years ago, it was proposed that a white matter tract called the *uncinate fasciculus* (UF) played a key role in episodic memory. Markowitsch (1982) wrote, “The task of the uncinate fascicle will be to guide and channel this information flow to the prefrontal cortex and to transmit preprocessed information back to the temporal cortex for the final act of representation”. This fiber pathway creates a direct structural connection between portions of the anterior and medial temporal lobes (including the uncus, temporal pole, entorhinal cortex, perirhinal cortex, and amygdala) and the lateral orbitofrontal cortex (OFC) and BA 10 (Catani, Dell’Acqua, & Thiebaut de Schotten, 2013; Catani & Thiebaut de Schotten, 2008; Von Der Heide, Skipper, Klobusicky, & Olson, 2013).

Evidence for Markowitsch’s (1982) view is complex and varied. The earliest studies of UF function were dissection studies in nonhuman primates. These studies showed that some types of learning are impaired after UF dissection, while others are not. For instance, one type of learning that is consistently impaired after UF dissection in nonhuman primates is conditional rule learning, in which the monkey learns to associate a particular object with a particular choice location that is rewarded (Bussey, Wise, & Murray, 2002; E. A. Gaffan, Gaffan, & Harrison, 1988; Parker & Gaffan, 1998). Similarly, object-in-place learning, which requires the monkey to learn which of two visual objects is associated with a background scene, is also consistently disrupted after damage to the uncinate (Browning, Easton, Buckley, & Gaffan, 2005; Browning & Gaffan, 2008). However, UF disconnection has little to no effect on visual object discrimination learning, configural learning, or delayed matching-to-sample tasks (D. Gaffan & Eacott, 1995; D. Gaffan, Easton, & Parker, 2002; Gutnikov, Ma, & Gaffan, 1997; Parker & Gaffan, 1998).

In humans, one memory deficit consistently found after uncinate dissection is impaired proper name retrieval. Studies conducted on patients during awake neurosurgery for left lateralized gliomas have demonstrated that removal of the UF leads to severe impairment in the ability to retrieve the names of famous faces, both post-surgery and at a 3 month follow-up (Papagno et al., 2011). In a recent extension by the same research group, proper naming deficits remained 12 months post-surgery (Papagno et al., 2014). Similar findings have been reported in other laboratories and replicated across different techniques (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Drane et al., 2008; Grabowski et al., 2001; Nomura et al., 2013; Tranel, Damasio, & Damasio, 1997), suggesting a robust link between proper name retrieval and the UF.

Recent advances in neuroimaging have allowed for the in vivo investigation of white matter pathways using diffusion tensor imaging (DTI) in neurologically normal adults. DTI utilizes diffusion-weighted MR imaging (DW-MRI) to index the degree of diffusion among water molecules within human brain tissue. In myelinated axons, which make up white matter tracts, the direction of diffusion is restricted due to the presence of myelin sheaths. DW-MRI captures the degree of restriction, called anisotropy, and provides measures of the microstructural properties of white matter, such as the orientation and magnitude of diffusion within each voxel of the brain (Alexander et al., 2011; Alexander, Lee, Lazar, & Field, 2007; Jones, 2008; Tournier, Mori, & Leemans, 2011).

Similar to animal studies, a review of the small but growing human DTI literature indicates that only some types of memory are linked to UF function (reviewed in Olson et al. 2015). Several studies have reported that performance on standardized verbal memory tasks, such as the California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 2000) or the auditory immediate and delayed memory subtests from the Wechsler Memory Scale (WMS; Wechsler, 2009), are significantly correlated with UF microstructure across various patient populations, including individuals with temporal lobe epilepsy, schizophrenia, mild traumatic brain injury, or mild cognitive impairment (Hiyoshi-Taniguchi et al., 2014; Mabbott, Rovet, Noseworthy, Smith, & Rockel, 2009; McDonald et al., 2008; Niogi et al., 2008; Wendelken et al., 2014). There are also reports in normal populations that microstructural properties of the UF correlate with auditory recall from the WMS (Charlton, Barrick, Markus, & Morris, 2013) and various paired associates learning tasks (Charlton et al., 2013; Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011; Thomas, Avram, Pierpaoli, & Baker, 2015). In contrast, significant correlations between UF microstructure and performance on standardized visual memory tasks are observed inconsistently (McDonald et al., 2008; Metzler-Baddeley et al., 2011).

We hypothesize that the UF's role in episodic memory is to adjudicate between competing memory representations at retrieval. Going back to the monkey studies, performance in the conditional rule learning task was impaired after UF transection (Bussey et al., 2002; E. A. Gaffan et al., 1988; Parker & Gaffan, 1998). In this task, many similar target objects are presented, and the monkeys are only rewarded if they can correctly recall which one of the four choice locations was paired with a particular object. These locations are repeated each trial so there is a great deal of retrieval competition. Likewise, in many verbal recall tasks, there is a great deal of competition from other word stimuli. In contrast, some of the visual episodic memory tasks commonly tested in this literature, such as the Rey-Osterrieth (Hirni, Kivisaari, Monsch, & Taylor, 2013; Mabbott et al., 2009), rely heavily on mental imagery with little retrieval competition. Interestingly, the visual tasks that have demonstrated relationships with the UF tend to be those that involve some level of retrieval competition. For instance, Metzler-Baddeley and colleagues (2011) subjected participants to a large battery of memory tasks, and the only one to show a significant effect in the uncinate was a paired associates learning task in which memory for learned object-location associations was tested. Likewise, Thomas and colleagues (2015) adapted an object-in-place task from the nonhuman primate literature to examine whether face-place associative learning was related to UF microstructure in healthy adults. During each trial of their task, competition between two face probes had to be resolved in order for participants to learn the correct face-place pairs. Indeed, Thomas et al. (2015) found that learning rate was significantly associated with microstructural properties of the left UF.

The purpose of the present study was to test our hypothesis regarding retrieval competition, and also to extend the findings of Thomas and colleagues (2015), who had participants learn face-place associations. In Experiment 1, we required participants to learn face-name associations which were chosen because there are face-selective cells on the ventral surface of the anterior temporal lobe (Von Der Heide, Skipper, & Olson, 2013), and lesions to this region can affect the ability to recall proper names (Papagno et al., 2011) and discern facial identity (Olson, Ezzyat, Plotzker, & Chatterjee, 2015). Our task was designed to maximize

retrieval competition: the faces were visually similar to one another, the proper names were high-frequency and thus lacked unique qualities that made them salient, and there was a great deal of stimulus repetition from trial to trial. To make a correct memory decision, competition had to be resolved.

We also included two follow-up studies. In Experiment 2 we tested whether uncinate involvement in associative learning would generalize to an associative learning task that used a different learning paradigm and non-face, non-semantic visual stimuli (e.g. fractal-asterisk location associations; see Figure 1). This task was chosen because it closely resembles the design of conditional rule learning tasks, which have exhibited a reliable relationship with UF functionality (e.g. Bussey et al., 2002; E. A. Gaffan et al., 1988; Parker & Gaffan, 1998). In our task, participants learned to associate unique fractal patterns with one of four possible spatial locations, much like conditional rule learning tasks in which primates are rewarded for correctly recalling which of four spatial locations was paired with an object. The nature of our fractal task is also similar to the object-location association task shown by Metzler-Baddeley and colleagues (2011) to correlate with uncinate microstructure, further supporting our rationale to test whether our predicted findings would generalize to the fractal task.

In Experiment 3 we tested whether a relationship would emerge in a memory task with low retrieval competition. The Cambridge Face Memory Test (CFMT; Duchaine & Nakayama, 2006) was chosen as the low retrieval competition task for several reasons. First, the number of faces that participants were required to learn was greatly reduced compared to Experiment 1. Next, the CFMT did not require the added demand of learning to associate a corresponding name with each face. Finally, rather than presenting the faces sequentially as in Experiment 1, all CFMT face stimuli were presented simultaneously, allowing participants to directly compare the faces and search for distinguishing features, thereby decreasing competition among the faces at the time of retrieval.

We used DTI, along with deterministic tractography, in order to examine the microstructural properties of the UF. We predicted that there would be a significant relationship between microstructural properties of the UF and the ability to learn and retrieve face-name pairs over time. We also analyzed a control tract, the *inferior longitudinal fasciculus* (ILF). Both the UF and the ILF terminate in the medial and anterior temporal lobes; however, the ILF has no relationship with the frontal lobe and its function has been strongly linked to high-level vision (Marco Catani, Jones, Donato, & Ffytche, 2003; Pyles, Verstynen, Schneider, & Tarr, 2013). Therefore, we did not expect there to be any relationship between ILF microstructure and associative learning.

2. Materials and Methods

2.1. Participants

A total of 50 healthy individuals (19 male, 31 female) between the ages of 18 and 28 ($M = 21.40$, $SD = 2.30$) participated in one or more of the present experiments. Seven participants were excluded from analyses due to the presence of multivariate outliers (i.e. data exceeded the critical cut-off for Mahalanobis distance, $\chi^2(4) = 9.49$), leaving a sample of 43

participants. All participants were right-handed, native English speakers with normal to corrected-to-normal vision. All participants had no history of psychological or neurological disorders as ascertained by self-report and no MRI contraindications. Informed consent was obtained according to the guidelines of the Institutional Review Board of Temple University, and participants received monetary compensation for participation in the experiments. Twelve individuals participated in all three experiments, 22 participated in two of the experiments, and 9 participated in only one experiment.

2.2. Study Protocol

Study participation occurred in two separate testing sessions, which occurred an average of one week apart. During the behavioral session, participants completed computerized tasks in the laboratory. Participants were tested individually in a well-lit room. Computerized tasks were programmed in E-Prime (Version 2.0 Professional) and presented on Dell computers. During a separate scanning session, diffusion-weighted MRI data, as well as high-resolution anatomical scans, were acquired at Temple University Hospital.

2.3. Behavioral Tasks

2.3.1. Experiment 1: Face-Name Associative Learning Task—Participants ($n = 28$) were instructed to learn face-name pairings to the best of their ability over the course of several learning blocks. On each trial, one face was presented at central fixation on a black background with two name options presented below the face. The task was to make a forced-choice decision about which name was correct within 3 seconds. Choices were made via key press. Importantly, we considered each presentation of a learned face as a retrieval time point, since the correct associative information had to be retrieved in order to make a response. Therefore, we conceptualized retrieval as a part of learning.

On the first presentation of each face-name pair, the correct name choice was not immediately apparent; therefore, participants were told to pay close attention to the feedback given after each trial in order to learn the correct associative pairings. Each face was repeated 5 times per block, thus allowing for the gradual learning of the correct pairs. Presentation order was randomized. The incorrect name choices, as well as the side of the screen on which the correct and incorrect name choices appeared were both randomized. Correct/incorrect feedback was given after each trial by presenting either a large green checkmark or a large red 'X'. The face stimuli consisted of 15 unique female and 15 unique male faces from the Todorov randomly generated faces database (Oosterhof & Todorov, 2008; facegen.com). Faces were free from hair, eyeglasses, or other eye-catching features. Each face had a neutral expression. The name stimuli consisted of 70 common names obtained from the Social Security Administration (SSA, 2014). The task consisted of 30 unique face-name pairs, learned over the course of 4 blocks, each comprised of 150 trials. Each block was separated by a brief 30-second rest period. The task consisted of 600 total trials and lasted approximately 30 minutes. A schematic of the task design is depicted in Figure 1A.

2.3.2. Experiment 2: Fractal-Asterisk Location Learning Task—During this task, participants ($n = 30$) learned to associate unique abstract fractal patterns with the spatial

locations of asterisks. This task was designed to emulate associative learning paradigms often used in nonhuman primate studies. Specifically, four unique fractal patterns were associated with the presentation of an asterisk in one of four spatial locations (represented by the four corners of the computer screen). On each trial, participants were presented with a single fractal pattern and asked to predict, via key press, the location in which the associated asterisk would later appear. Participants were given 4 seconds to make a response. After the allotted decision time, an asterisk appeared in the correct location for the given fractal pattern, and participants received feedback regarding their choice. For each correct response, they earned 10 points, and for each incorrect response, they lost 10 points. Participants were instructed to use the feedback given after each trial in order to learn the correct fractal-asterisk location pairs and accumulate as many points as possible. Presentation order was randomized and each fractal pattern was presented 15 times, yielding a total of 60 trials. This task represented the initial acquisition phase of a larger reversal learning task (reversal data not reported here). A schematic of the task is presented in Figure 1A.

2.3.3. Experiment 3: Cambridge Face Memory Test—Participants ($n = 31$) completed the Cambridge Face Memory Test (CFMT; Duchaine & Nakayama, 2006). This is a standardized test used to assess storage and retrieval of memory for faces. The task consisted of 3 separate blocks that repeatedly exposed participants to 6 distinct male faces. During the first block, each face was encoded and tested separately. Specifically, 3 images of each target face presented from different viewpoints appeared sequentially. Then, participants were asked to identify, via key press, the correct target face from a set of the target and 2 distractor faces. After test, encoding trials were presented for the next target face. The first block was comprised of 18 trials. The second block began with the simultaneous presentation of all 6 target faces for 20 seconds. Next, participants completed a series of 30 3-alternative forced choice test trials in which they identified which of the 3 choices represented a target face. To increase difficulty, target and distractor faces were now presented under different lighting conditions and viewpoints. The final block again began with the simultaneous presentation of the 6 target faces. The procedure was similar to Block 2, such that participants completed 24 3-alternative forced choice test trials; however, to further increase difficulty, visual noise was added to the images presented in the last block. Within each block, trials were presented in a fixed random order. Overall, 12 images of each target face and 46 distractor faces were presented. The task consisted of a total of 72 trials. Given that participants were at ceiling during the first block, only Blocks 2 and 3 are included in the present analyses.

2.4. Image Acquisition

MRI scanning was conducted at Temple University Hospital on a 3.0 T Siemens Verio scanner (Erlangen, Germany) using a Siemens twelve-channel phased-array head coil. DTI data were collected using a diffusion-weighted echo-planar imaging (EPI) sequence covering the whole brain. Salient imaging parameters were as follows: 55 axial slices, 2.5 mm slice thickness, $TR = 9,900$ ms, $TE = 95$ ms, $FOV = 240$ mm², b values of 0 and 1000 s/mm² (one b_0 image acquired), 64 non-collinear directions. These parameters yielded a DTI scan lasting approximately 11 minutes.

In addition to diffusion-weighted images, high-resolution anatomical images (T1-weighted 3D MPRAGE) were also collected for each participant with the following parameters: 160 axial slices, 1 mm slice thickness, TR = 1,900 ms, TE = 2.93 ms, inversion time = 900 ms, flip angle = 9°, FOV = 256 mm². These anatomical images were co-registered to the diffusion images and used to draw regions of interest (ROIs).

2.5. DTI Preprocessing

The diffusion-weighted images were pre-processed using FSL (Smith et al., 2004) to correct for eddy currents and subject motion using an affine registration model. The b-vector matrix was adjusted based on rigid body registration, ensuring a valid computation of the tensor variables. Non-brain tissue was removed using FSL's (Smith et al., 2004) automated brain extraction tool (BET), and a standard least squares diffusion tensor fitting model was then applied to the data. The diffusion tensor fitting provided estimates of fractional anisotropy (FA) and mean diffusivity (MD), as well as three eigenvectors and eigenvalues. FA values

were calculated using the following equation:
$$\sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_3 - \lambda_1)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$
, where λ_1 , λ_2 , and λ_3 represent the three eigenvalues respectively. MD was calculated by averaging the three eigenvalues. Axial diffusivity (AD) was represented by the principal eigenvalue (λ_1). Finally, radial diffusivity (RD) was calculated by averaging the second and third eigenvalues. These estimates were computed on individual voxels using a three-dimensional Gaussian distribution model that yielded a single mean ellipsoid for each voxel.

Tractography was performed in native subject space using the Diffusion Toolkit and TrackVis software packages (Wang, Benner, Sorensen, & Wedeen, 2007). This software uses a fiber assignment continuous tracking (FACT) algorithm (Mori, Crain, Chacko, & Van Zijl, 1999) to determine the branching and curving of the fiber tracts. For a given voxel, this algorithm estimates the orientation of the principal eigenvector in that voxel and then uses nearest-neighbor interpolation to step along that direction. Step length was fixed at 0.1 mm, and an angle threshold of 35 degrees was used to determine the termination point of the fiber tracts. A spline filter was used to smooth the tractography data. A multiple ROI-based axonal tracking approach (Mori et al., 2002; Thomas, Humphreys, Jung, Minshew, & Behrmann, 2011; Wakana et al., 2007) was then used to delineate the UF and ILF bilaterally. This approach, coupled with the brute-force fiber reconstruction technique employed by the FACT algorithm, has been shown to reduce susceptibility to noise and partial volume effects (Huang, Zhang, van Zijl, & Mori, 2004; Thomas et al., 2011; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). ROIs were drawn in subject native space using the high-resolution anatomical T-1 images and the methods outlined by Thomas and colleagues (2011). For the UF, one ROI was drawn in the temporal lobe and included the portion of the temporal cortex that is anterior to the point at which the fornix descends to the mammillary bodies, while the second ROI was comprised of the portion of the frontal cortex located anterior to the rostrum of the callosum. For the ILF, the same anterior temporal lobe ROI was used, along with a ventral occipito-temporal cortex ROI, which included cortex inferior to the lateral ventricles (Thomas et al., 2011). A Boolean AND term was used to select only

the fibers that passed through both of these seed regions of interest. Mean FA, MD, AD, and RD indices were subsequently extracted from the tracts of interest.

2.6. Statistical Analyses

Statistical analyses were performed using SPSS (Version 21.0). Multiple linear regression analyses were used to examine the relationship between microstructure of the UF and performance on the three experimental tasks. Mean values for the microstructural indices of the UF and ILF are presented in Table 1.

First, we asked whether there were hemispheric differences in micro- and macrostructure. Marginal hemispheric differences were found in uncinate AD ($t(84) = 1.80, p = .08$), as well as FA and AD in the ILF ($t(84) = 1.85, p = .07$ and $t(84) = 1.90, p = .06$, respectively). Differences in volume also emerged across right and left hemispheres for both the UF ($t(84) = 2.21, p = .03$) and ILF ($t(84) = 2.25, p = .03$). Thus, analyses were not collapsed across hemispheres.

Next we examined whether there were gender differences because we previously observed gender differences in the microstructural properties of both the UF and ILF (Alm, Rolheiser, Mohamed, & Olson, 2015). These analyses found a number of gender differences in the current sample. Specifically, compared to females, males exhibited increased values for FA in the right UF ($t(41) = 2.41, p = .02$), AD in the left ILF ($t(41) = 2.08, p = .04$), and MD in the left ILF ($t(41) = 2.13, p = .04$). Significant differences were also found in left uncinate MD ($t(41) = 2.26, p = .03$) and left uncinate RD ($t(41) = 2.21, p = .03$), such that females exhibited higher values than males. Because of these differences, gender was controlled for in the regressions.

Separate regression models were constructed for each white matter index of interest. Predictors were entered simultaneously into the regression and each model consisted of three predictors: right and left white matter indices (FA, AD, MD, or RD) and gender. To control for multiple comparisons, family-wise error rate was adjusted using a Bonferroni correction based on the number of simultaneous predictors in each regression model (Mundfrom, Piccone, Perrett, Schaffer, & Roozeboom, 2006). Since each regression consisted of three predictors, the critical p was set at .0167 (i.e. $p = .05/3$). All regression p -values reported are Bonferroni-corrected.

3. Experiment 1

In the first experiment, we tested the hypothesis that individual differences in uncinate microstructure would predict performance on an associative learning task using face-name pairs that were designed to create high levels of retrieval competition.

3.1. Results

3.1.1. Behavioral Data—Behavioral data are presented in Figure 1 B–D. During the first learning block, performance was low (mean accuracy = 64.88%, $SD = 9.67$, range = 48.67% – 78.00%); however, given the trial and error feedback-guided nature of the task, this was to be expected. By the last block, mean accuracy improved to 91.50% ($SD = 6.27$, range =

77.33% – 100.00%). A repeated measures ANOVA revealed a significant main effect of block, $F(3,81) = 138.97$, $p < .001$. Planned post-hoc comparisons revealed that accuracy significantly improved across each learning block (Block 1 vs. Block 2, $t(27) = 13.66$, $p < .001$; Block 2 vs. Block 3, $t(27) = 2.93$, $p = .007$; Block 3 vs. Block 4, $t(27) = 4.57$, $p < .001$). We used performance on Block 4 (B4 accuracy) as an overall measure of learning. Additionally, the steepest increase in performance was observed between Blocks 1 and 2 (see Figure 1B; mean change in accuracy from Block 1 to Block 2 = 18.12%, $SD = 7.02$, range = 3.34% – 30.66%). This is consistent with Thomas and colleagues' (2015) findings; therefore, we chose to also use their measure of learning rate (change in accuracy from Block 1 to Block 2; B2 – B1).

3.1.2. DTI Data—Regression models were constructed to predict overall learning (B4 accuracy), as well as learning rate (B2 – B1). Predictors consisted of bilateral white matter indices (FA, AD, MD, and RD) and gender, which was included as a control variable. Separate regressions were constructed for each white matter index. Results of the regression analyses are presented in Table 2.

3.1.3. Overall Learning—The regression analyses revealed a significant relationship between microstructural properties of the UF and performance at the end of the associative learning task, in Block 4 (B4). Specifically, after controlling for gender, individual differences in both left ($\beta = -0.58$, $t(24) = 3.30$, $p = .009$) and right ($\beta = 0.72$, $t(24) = 3.80$, $p = .003$) uncinate FA significantly predicted B4 accuracy. Additionally, left uncinate AD ($\beta = 0.79$, $t(24) = 3.89$, $p = .003$), left uncinate MD ($\beta = 0.60$, $t(24) = 2.98$, $p = .02$), and left uncinate RD ($\beta = 0.59$, $t(24) = 2.90$, $p = .02$) also significantly predicted B4 accuracy. Initially, right uncinate RD predicted B4 accuracy; however, this effect did not survive correction for multiple comparisons ($p = .04$ uncorrected). Neither right AD nor right MD significantly predicted B4 accuracy (p 's $> .41$).

For the left hemisphere indices, the latter three (left AD, MD, and RD) each exhibited a positive relationship with B4 accuracy, such that higher microstructural values were associated with higher overall learning performance. By contrast, the reverse relationship was demonstrated in left FA; higher FA values were associated with lower overall learning performance. Figure 2 depicts the partial regression plots representing the unique relationship between left uncinate FA and overall learning (Figure 2B), as well as left uncinate AD and overall learning (Figure 2C).

3.1.4. Learning Rate—Here we examined learning rate using the same measure (B2 – B1) as used by Thomas and colleagues (2015). Analogous regression models were constructed, now using the change in accuracy from Block 1 to Block 2 as the dependent measure. After controlling for gender, both left ($\beta = -0.52$, $t(24) = 2.81$, $p = .03$) and right ($\beta = 0.63$, $t(24) = 3.19$, $p = .01$) uncinate FA significantly predicted learning rate. There was also a trending relationship between learning rate and left uncinate RD ($\beta = 0.51$, $t(24) = 2.51$, $p = .06$). No other predictors reached statistical significance after controlling for multiple comparisons (p 's $> .11$). Results of these regression analyses are presented in the supplementary material (Table S1).

3.1.5. Control Tract: The ILF—Regression models were once again constructed to predict overall learning and learning rate. Predictors included gender (control variable) and bilateral ILF white matter indices. Results for the regressions predicting overall learning are presented in Table 2 and Figure 2. No significant relationships were found between ILF FA, AD, or RD microstructure and B4 accuracy (p 's > .11). There was a trending relationship between right ILF MD and B4 accuracy ($\beta = 0.51$, $t(24) = 2.54$, $p = .06$), but no relationship between left ILF MD and B4 accuracy ($\beta = -0.41$, $t(24) = 1.98$, $p = .18$). However, this overall regression model was not significant ($p = .08$); therefore, this finding should be interpreted with caution. Furthermore, none of the ILF indices significantly predicted learning rate (p 's > .08). Learning rate results are presented in the supplementary material (Table S1).

To directly compare the magnitudes of the uncinate and ILF model predictors, z -tests were performed using the respective regression coefficients for the significant findings (Paternoster, Brame, Mazerolle, & Piquero, 1998). The magnitudes of the relationships between overall learning and uncinate predictors were significantly greater than the ILF predictors for right FA ($z = 2.99$, $p = .003$), left AD ($z = 4.04$, $p < .0001$), left MD ($z = 3.42$, $p < .001$) and left RD ($z = 2.95$, $p = .003$); the magnitude was marginally greater for left uncinate FA ($z = 1.84$, $p = .07$). With respect to learning rate, the magnitude of the right FA effect was marginally greater in the uncinate than in the ILF ($z = 1.91$, $p = .06$), but was not significantly different for the left FA predictors ($z = 0.58$, $p = .57$). Taken together, these findings suggest that the ILF does not seem to be critical for associative learning.

3.2. Discussion

In Experiment 1, we found that individual differences in associative learning were predicted by variability in microstructure of the uncinate. We found significant relationships between white matter indices representing the UF and overall learning, as well as learning rate on a face-name associative memory task.

4. Experiment 2

After demonstrating that UF, but not ILF, microstructure significantly predicted learning on the face-name associative memory task, we sought to investigate whether this relationship was specific to associative learning of semantic and facial information, or whether it generalized to other associative stimuli. Therefore, we conducted a follow-up study using non-face, non-semantic associations (e.g. fractal –asterisk location associations). We predicted that a relationship would emerge between the ability to learn visual-visual associations and UF microstructure.

4.1. Results

4.1.1. Behavioral Data—Behavioral data are presented in Figure 1 B–D. Responses were split into 3 blocks of 20 trials each. Performance on the first block was low (mean accuracy = 63.00%, $SD = 20.99$, range = 25.00% – 95.00%); yet, again this was expected given the trial and error nature of the task. By the third block, mean accuracy improved to 89.67% ($SD = 17.17$, range = 40.00% – 100.00%). A repeated measures ANOVA revealed a significant

main effect of block, $F(2,58) = 45.71$, $p < .001$. Planned post-hoc comparisons revealed that accuracy significantly improved from Block 1 to Block 2 ($t(29) = 7.25$, $p < .001$) and from Block 2 to Block 3 ($t(29) = 3.34$, $p = .002$), suggesting that participants did, in fact, learn the correct fractal-asterisk location pairs. We once again used the change in accuracy from Block 1 to Block 2 ($B2 - B1$) as a dependent measure of learning rate. For consistency, we also examined performance on the last block (B3 accuracy) as a measure of overall learning; however, to deal with normality issues, a reflected square root transformation was applied, as is typical for negatively skewed data.

4.1.2. DTI Data—Regression models were constructed to predict learning rate ($B2 - B1$) on the visual associative learning task, as well as transformed B3 accuracy data. Predictors included bilateral white matter indices (FA, AD, MD, and RD) and gender, which again was used as a control variable. Separate regression models were analyzed for each white matter index. Results are presented in Table 3.

Regression analyses revealed a significant relationship between UF microstructure and learning rate on the visual associative learning task. After controlling for gender, both left ($\beta = -0.61$, $t(26) = 2.60$, $p = .045$) and right ($\beta = 0.63$, $t(26) = 2.61$, $p = .045$) uncinate AD significantly predicted the change in performance from B1 to B2. The magnitudes of both effects were significantly greater in the UF than in the ILF (left AD: $z = 2.26$, $p = .02$; right AD: $z = 1.97$, $p = .05$). No other predictors reached statistical significance (p 's $> .60$). None of the UF measures significantly predicted B3 accuracy (p 's $> .38$), potentially due to the fact that many participants were performing at ceiling by this point, so there was insufficient variance in our measure.

Regression models were also constructed to predict both learning rate and B3 accuracy with bilateral ILF indices and gender (control variable) as predictors. Neither learning rate nor overall learning on the visual associative memory task was predicted by ILF microstructure (p 's $> .41$).

4.2. Discussion

Here, we replicated the findings of Experiment 1 by once again demonstrating that microstructural properties of the UF predicted associative learning rate. Furthermore, we extended our previous findings to a visual task with no semantic content. These findings suggest that the overall learning effect from Experiment 1 was not specific to the particular stimuli used in the task.

5. Experiment 3

In Experiment 3, we aimed to further probe our retrieval competition hypothesis. We previously demonstrated that associative learning on two tasks with conditions representing high retrieval competition was related to uncinate microstructure; therefore, we now examined whether there was a relationship under conditions with lower retrieval competition. In line with our hypothesis, we predicted that UF properties would not predict performance on this type of task.

5.1. Results and Discussion

Average performance across Blocks 2 and 3 of the CFMT (mean accuracy = 71.65%, $SD = 15.45$, range = 48.75% – 94.58%) served as the dependent measure for subsequent analyses.

Regression models were constructed to predict mean accuracy on the CFMT. Predictors consisted of bilateral white matter indices and gender, which was entered as a control variable. Results of the regression analyses are presented in supplementary Table S2. None of the UF indices or ILF indices significantly predicted face memory performance ($p's > .17$; $p's > .99$ respectively).

These findings show that uncinate microstructure does not significantly predict performance on a face memory task comprised of lower retrieval competition demands than on our initial face-name task.

6. General Discussion

In this study, we investigated the functional role of a long-range white matter tract, the uncinate fasciculus, in associative learning. The UF connects portions of the anterior and medial temporal lobes to the lateral OFC; therefore, it has long been thought to play an important, albeit undetermined, role in episodic memory (Markowitsch, 1982). Although there is now a small body of research showing that the UF plays some role in episodic memory (and perhaps semantic memory as well), the evidence is inconsistent with respect to which types of memory are linked to UF functionality (reviewed in Olson et al., 2015). Our review of the nonhuman primate literature, as well as the literature on electrical stimulation of the UF in neurosurgical patients, gave rise to our hypothesis that the key factor implicating the UF in certain memory tasks, but not others, is the presence of competing memory representations during retrieval. Studies that boast significant relationships between the UF and memory tend to be those in which competition between stimulus choices must be resolved in order to achieve accurate memory retrieval. In order to test this hypothesis, we designed an associative learning task used in Experiment 1 that consisted of stimuli with similar visual (faces) and verbal (names) information. To perform well on the task, participants had to learn to adjudicate between competing memory representations in order to retrieve the correct face-name pairing on each trial. Thus, retrieval competition was present on all trials following initial exposure. We hypothesized that microstructure of the UF would predict individual differences in the propensity to perform well on the associative learning task. We also designed a follow-up study, Experiment 2, in which participants were required to learn visual-visual associations. The goal of this study was to conceptually replicate and thereby extend our hypothesis beyond facial and semantic information. We included a third task with lower retrieval competition between stimuli to probe our predictions regarding levels of retrieval competition.

Our findings are consistent with our hypothesis. Associative learning was, in fact, predicted by UF variability. On the face-name task, this relationship was found across white matter indices; bilateral uncinate FA, as well as left AD, MD, and RD significantly predicted overall learning at the end of the task. Additionally, both left and right uncinate FA significantly predicted learning rate, as measured by the change in accuracy from Block 1 to

Block 2. The learning rate relationship was replicated in the fractal-asterisk task, such that bilateral uncinate AD significantly predicted the change in accuracy from Block 1 to Block 2. Thus, the effect does not seem specific to facial and semantic stimuli and may extend to visual associations in general.

By contrast, no such relationships were found on the CFMT, a task with lower levels of retrieval competition. Several aspects of the CFMT decreased retrieval competition, as compared to the face-name learning task. First, the CFMT only required participants to learn 6 unique faces, while our face-name learning task consisted of 30 unique faces. Statistically, more stimuli lead to more competition. Second, we created additional retrieval demands in the face-name task by introducing competing name stimuli to be learned with each face. Third, the mode of presentation may modulate retrieval competition. On the CFMT, all 6 faces were presented simultaneously, allowing participants to search for distinguishing features, thereby decreasing the amount of competition between the faces at the time of retrieval. By contrast, each face was presented sequentially on our face-name learning task.

Therefore, our results demonstrating a relationship between UF microstructure and performance on the face-name task, but not on the CFMT, support our hypothesis that the UF is most involved in episodic memory function under conditions of high retrieval competition. Finally, this null finding provides further evidence that the relationship exhibited in Experiment 1 did not rely solely on the presence of facial stimuli.

6.1. Placing our Findings in the Greater Literature

The results of the present study replicate and extend the findings of a recent study by Thomas and colleagues (2015) showing that FA of the left uncinate, but not the right uncinate or ILF, predicted one's ability to learn visual-visual associations. First, we provide a conceptual replication of their visual-visual association findings using different stimuli and different imaging parameters. Next, we extend their findings by showing a similar effect in the UF for visual-semantic associations. Additionally, our findings were more robust than those reported by Thomas and colleagues (2015), as we found this relationship in FA values extracted from both the left and right uncinate, in addition to other white matter indices. These effects remained significant after carefully controlling for gender, as gender differences are known to exist across DTI measures (Gong, He, & Evans, 2011; Kanaan et al., 2012). Finally, our study revealed that the UF-behavior relationship was present under conditions where retrieval competition levels were high, but not when retrieval competition levels were low.

One notable difference between our study and Thomas et al. (2015) is that we tested different hypotheses. While they hypothesized that the UF mediates rapid encoding of associations, we hypothesized that the primary role is in adjudicating between competing representations at retrieval. The present findings, as well as the extant literature, tend to support our view. Performance on tasks with heavy competition between potential memory representations, such as verbal paired associates (Charlton et al., 2013) and object-location associative learning (Metzler-Baddeley et al., 2011) shows a relationship with UF microstructure. In contrast, tasks that do not require adjudication between competing representations, such as the Rey-Osterrieth and many working memory tasks, typically show

no relationship with UF microstructure (reviewed in Olson et al., 2015). Similar dissociations have been found across the nonhuman primate literature. Some tasks, such as object discrimination learning, configural learning, and delayed matching-to-sample tasks are unimpaired after dissection of the UF (D. Gaffan & Eacott, 1995; D. Gaffan et al., 2002; Gutnikov et al., 1997; Parker & Gaffan, 1998). However, other tasks, including conditional rule learning and object-in-place learning are both consistently disrupted after UF dissection (Browning et al., 2005; Browning & Gaffan, 2008; Bussey et al., 2002; E. A. Gaffan et al., 1988; Parker & Gaffan, 1998). Both conditional rule learning and object-in-place learning require the adjudication between competing resources, consistent with our view of UF functionality.

6.2. Specificity and Generality of Findings

The level of neural specificity of any brain-behavior effect is critical for its interpretation. We chose to use an occipital-temporal white matter tract, the ILF, as a control fiber pathway in order to assess the specificity of our findings. This tract was chosen for two reasons. First, like the UF, this tract enters the medial/anterior temporal lobes. Unlike the UF, the ILF has been most closely tied to high-level visual processes (Marco Catani et al., 2003; Pyles et al., 2013), including face recognition (Thomas et al., 2009) and face emotion discrimination (Unger et al., in press). Second, Thomas and colleagues (2015) performed a DTI study using an associative learning task similar to our own and found no relationship between learning rate and ILF microstructure. Our results are consistent with the existing literature on the ILF, since we found no reliable relationship between ILF microstructure and associative learning. Therefore, there seems to be some specificity to our findings.

Conversely, it is also important to consider how the findings of any given study generalize to other tasks and contexts. Given the high degree of concordance between our findings, Thomas and colleagues' (2015) findings, and findings from lesions in nonhuman primates (Browning et al., 2005; Browning & Gaffan, 2008; Bussey et al., 2002; E. A. Gaffan et al., 1988; Parker & Gaffan, 1998), it is tempting to believe that the UF may be involved in all forms of associative memory. However, we do not think this is true. We previously found that there was no relationship between UF microstructure and the learning of simple reward contingencies (e.g. a deck of cards and the probability of a reward or punishment). However, there was a relationship once the retrieval task became challenging, which occurred after the reward and punishment contingencies were reversed (Alm et al., 2015). We argue that this finding fits into the proposed framework as well, since after reversal, participants were faced with competing associations between the deck and two different reward contingencies. In order to perform well on the reversal phase of the task, participants had to learn to resolve the competition between the reward contingency previously associated with the deck and the reward contingency presently associated with the deck.

We can also ask whether the UF's role in memory retrieval generalizes beyond episodic memory to other forms of long-term memory, namely semantic memory. It has been proposed that the UF is an important, but non-essential pathway for semantic memory retrieval (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009). Consistent with this notion, studies examining the UF in the context of semantic memory using tasks such as

object naming have reported inconsistent effects (reviewed in Von Der Heide, Skipper, Klobusicky, & Olson, 2013). Yet, one semantic memory task that is consistently linked to the uncinate is proper name retrieval (e.g. Nomura et al., 2013; Papagno et al., 2010). This can be explained by the fact that retrieving the correct proper name evokes severe retrieval competition, given the arbitrary nature of face-name pairings, such that different people who have little in common, such as Bill Clinton and Bill Nye the Science Guy, can have the same first name. Some theories of semantic memory hold that portions of the anterior temporal lobe store semantic memories, while the inferior frontal gyrus is involved in semantic selection (Barredo, Oztekin, & Badre, 2015). Therefore, the UF may provide an avenue for facilitating interactions between these regions, allowing for near-seamless retrieval of contextually-appropriate words and concepts.

6.3. Relevance to Populations with Memory Complaints

For individuals of all ages, other people's names are difficult to retrieve and prone to tip-of-the-tongue states. As we age, this task becomes increasingly difficult. Indeed, one of the most common memory complaints in older adults is difficulty recalling proper names (Leirer, Morrow, Sheikh, & Pariente, 1990). This is just one example of the difficulty older adults exhibit in forming and retrieving different types of associations (reviewed in Old & Naveh-Benjamin, 2008). It has been proposed that weakening of cortical connectivity may be an important contributor to age-related decline in association formation (MacKay, 1987). As a group, older adults have altered white matter microstructure throughout the brain (Bennett, Madden, Vaidya, Howard, & Howard, 2010). Our findings support the notion that white matter connectivity contributes important variance to the ability – or inability – to retrieve novel associations. Of course, this is speculative, but future research should examine the potential link between age-related alterations in white matter and retrieval of associations.

6.4. Limitations and Future Directions

The UF is a large white matter bundle linking functionally discrete regions of the temporal lobe (e.g. the uncus, entorhinal cortex, amygdala, perirhinal cortex, and temporal pole) to discrete regions of the frontal lobe (the lateral OFC and BA 10), so it is plausible that the UF serves as the information conduit for a family of cognitive processes related to the functions of these regions. This might include social tasks that require the retrieval of information about people's past behaviors, as well as decision making tasks that rely on memory in order to make an optimal decision (Alm et al., 2015). It is also important to note that conditions with increased retrieval competition may also increase the engagement of gray matter regions associated with executive functioning, like the prefrontal cortex. Therefore, enhanced performance on such tasks may also depend on gray matter properties, such as cortical thickness and BOLD activation.

Furthermore, one should be wary of interpreting the directionality of DTI effects. DTI does not lend itself to make claims regarding enhanced or diminished white matter integrity, *per se* (Jones, 2008). We caution against the interpretation that positive correlations between FA and cognitive performance signify “better” connectivity or integrity. Higher values may not always be better, and thicker myelination or increased axonal integrity in general may not

always be equated with better performance (Scholz, Tomassini, & Johansen-Berg, 2009). For example, several studies (Passamonti et al., 2012; Sarkar et al., 2013; Zhang et al., 2014) have reported increased uncinate FA in children with conduct disorder relative to matched controls. Related to this, Sarkar et al. (2013) found a positive correlation between left UF FA and scores on the Antisocial Process Screening Device. Similar effects have been reported in other fiber pathways as well. In a review on concussion-related DTI literature, Shenton and colleagues (2012) reported findings from several studies which revealed increased FA in the corpus callosum at varying time points after patients sustained concussions. Moreover, Hoef and colleagues (2007) demonstrated that patients with Williams syndrome exhibited higher FA than both typically developing and developmentally delayed control groups in the right superior longitudinal fasciculus, and FA was negatively correlated with visuospatial abilities.

Such counterintuitive findings have also emerged in healthy cohorts. For instance, studies have reported lower FA values in expert musicians (Imfeld, Oechslin, Meyer, Loenneker, & Jancke, 2009; Oechslin, Imfeld, Loenneker, Meyer, & Jäncke, 2010) and simultaneous interpreters (Elmer, Hänggi, Meyer, & Jäncke, 2011), compared to non-experts in numerous fiber pathways, suggesting that extensive training is associated with decreased FA in task-relevant tracts. Additionally, Tavor et al. (2014) reported several negative relationships between FA in particular portions of the ILF and performance on scene and face memory tasks. It is possible that certain increases in connectivity may lead to behavioral interference or strategy differences among participants, resulting in the adoption of suboptimal strategies on a given task (Scholz et al., 2009). Therefore, although some of our findings represent negative relationships between UF FA and associative learning measures, we cannot make claims about how this relates to connectivity strength or integrity. Rather, the measures provided by DTI analyses allow us to draw conclusions regarding the presence of relationships between microstructural properties of white matter and task performance differences.

In a similar vein, we must also address the divergent directionality of our reported effects in the right versus left hemisphere. The present experiments were not designed to directly compare the roles of the right and left UF during a competition task, and as such, further examination of the directionality of our DTI results will be the subject of future complementary analysis. Many higher-order cognitive tasks, such as semantic language production and/or comprehension rely on a lateralized system where the left and right hemispheres have distinct roles (Saur et al., 2008). These differing roles are consequently expressed in unique white and gray matter characteristics (Chance, 2014). Along this line, one possible explanation for our results would be that the successful completion of a competition memory task requires simultaneous inhibition of the left UF and excitation of the right UF. Of course, structural connections do not directly cause excitatory or inhibitory signaling. However, the degree of myelination, which is represented in different measures of white matter connectivity, can impact the efficiency of transduction and subsequent functional activation patterns. Since we cannot assume that the left and right hemispheres are used in a similar manner during the competition tasks, different inherent morphological traits in microstructure could predispose some subjects to success. Additionally, the presence or absence of myelination in different locations could feasibly have complementary effects on signal transduction. For example, thicker myelination allows for faster transmission of

neural signals; however, mechanisms like synaptic pruning also improve signaling. Thus, enhanced neural efficiency can be achieved by increasing myelination in some fibers and decreasing myelination in others. The nature of the tasks (one with a verbal component, one that was strictly visual) could also play a fundamental role in determining the directionality of effects, since it is likely that the bilateral UFs operate in a dynamic fashion depending on the nature of the stimuli used. Nevertheless, the magnitude of the effects reported here clearly implicate the uncinate in competitive retrieval tasks, which subsequently warrants further investigation.

It is also important to note the use of tensor based models and deterministic tractography in the present study. These techniques cannot detect crossing fibers within a voxel; therefore, more advanced techniques have recently been developed to deal with this problem. While we do acknowledge this limitation, it is less of an issue when examining large, well-known fiber pathways, such as the UF and ILF. It has been demonstrated that these pathways can be accurately reconstructed using the FACT algorithm (e.g. Catani, Howard, Pajevic, & Jones, 2002) as we have done in the present study. One similar methodological constraint is that our image acquisition sequence only included a single non-diffusion weighted image (b0 image). Future investigations should aim to collect multiple volumes with no diffusion that can be averaged together to increase signal-to-noise ratio and correct potential EPI distortions.

Additionally, some findings in the nonhuman primate literature (e.g. Easton & Gaffan, 2000) have suggested that disconnection of the frontal lobe from the temporal lobe disrupts associative learning post-surgery, but does not impact the retrieval of associations learned prior to surgery. Here, we again emphasize that in the present studies, we focused on retrieval of memory representations that occurred during the learning blocks. Each time a face (or fractal) was presented, retrieval of the associative information was required in order to make an accurate response. Thus, repeated retrievals of memory representations were part of the learning process. The older findings in nonhuman primates may also be interpreted in our retrieval competition framework. It is possible that retrieval competition may be minimized over time by the constant repetition of associations. Once these associations become over-practiced, fluency may be achieved and uncinate involvement may not be as important, thereby accounting for normal performance after resection.

Moreover, Experiment 2 was likely underpowered, given that the task was taken from a larger paradigm and only consisted of 60 trials. Given more trials and more associations, we speculate that findings would have emerged across other white matter indices. However, the fact that bilateral uncinate AD measures significantly predicted learning rate, despite an underpowered design, seems to suggest a robust relationship. Also, although we included the CFMT to demonstrate a differential effect of UF involvement in memory tasks containing retrieval competition, the CFMT is a test of item memory, not associative memory. We cannot exclude the possibility that the UF is only required in episodic memory tasks that are associative in nature.

Last, it will be important for future researchers to extend these findings to populations with memory complaints, such as older adults, individuals with traumatic brain injury or

“chemobrain”, or individuals suffering from mild cognitive impairment. One especially interesting question is whether interventions that enhance the retrieval of associations in older adults, such as non-invasive brain stimulation (see Ross, McCoy, Coslett, Olson, & Wolk, 2011), are accompanied by alterations in UF microstructure.

7. Conclusions

The results of the present study support the hypothesis that variability in UF microstructure predicts learning and memory for associations between faces and names, as well as between distinct visual stimuli. We propose that this effect is specifically driven by a fronto-temporal interaction that assists in retrieval selection, which is especially evident in tasks using items with a high degree of featural or conceptual overlap. Because white matter does not produce behavior – the activity of temporally and spatially defined networks of neurons interconnected by white matter produce behavior – it would be incorrect to say that the UF’s function is associative learning and memory. Rather, our findings indicate that the UF is a critical part of the associative learning and memory connectome.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Hypothesis: the uncinate fasciculus supports resolution of retrieval competition.
- High competition memory tasks: face-name learning; object-location learning.
- Variation in the uncinate predicted performance on high competition tasks.
- No such effect was found in a control tract or low retrieval competition task.
- Thus, this tract facilitates adjudication between competing memory representations.

Figure 1.

(a) Schematics of the associative learning tasks. In Experiment 1 (left), participants learned face-name pairs, while in Experiment 2 (right), they learned fractal-asterisk location pairs. (b) Behavioral performance plotted across learning blocks for each experiment. The blue line depicts mean accuracy (percent correct) for each learning block. Error bars represent standard error of the mean. The green and red lines depict learning curves for the participants with the highest and lowest performance, respectively. (c) Overall learning accuracy (percent correct on the last learning block) is plotted for each participant to display the individual variability among participants. The numbers on the x-axis are a rank for each participant. (d) Learning rate (change in accuracy from Block 1 to Block 2) is plotted for each participant. The x-axis again represents a rank order of participants.

Figure 2.

(a) Tractography delineating the uncinatus fasciculus (UF; red) and inferior longitudinal fasciculus (ILF; purple) in a sample participant. (b) Scatter plots of residuals from the linear regression analyses illustrating the relationship between individual differences in overall learning on the face-name task (y-axis) and mean fractional anisotropy (FA) of the left UF (left) and left ILF (right). A significant effect was observed only in the UF. (c) Scatter plots of the residuals from the linear regression analyses illustrating the relationship between individual differences in overall learning on the face-name task and mean axial diffusivity (AD) of the left UF (left) and the left ILF (right). A significant effect was observed only in the UF. (d) Scatter plots of the residuals from the linear regression analyses illustrating the relationship between individual differences in learning rate on the fractal-asterisk task and mean AD of the right UF (left) and the right ILF (right). A significant effect was observed only in the UF.

Table 1

Mean values for the microstructural white matter indices of the uncinate fasciculus (UF) and inferior longitudinal fasciculus (ILF) collapsed across the study sample (n = 43).

	Left UF	Right UF	Left ILF	Right ILF
FA	0.46 (0.05)	0.46 (0.03)	0.53 (0.04)	0.52 (0.04)
AD ($\times 10^{-3}$ mm ² /s)	1.19 (0.04)	1.17 (0.06)	1.31 (0.09)	1.27 (0.08)
MD ($\times 10^{-3}$ mm ² /s)	0.77 (0.05)	0.75 (0.05)	0.79 (0.06)	0.78 (0.05)
RD ($\times 10^{-3}$ mm ² /s)	0.56 (0.07)	0.55 (0.04)	0.54 (0.06)	0.54 (0.05)

FA: fractional anisotropy, AD: axial diffusivity, MD: mean diffusivity, RD: radial diffusivity, Standard deviations represented in parentheses.

Table 2

Summary of multiple linear regression models predicting individual differences in overall learning (B4 accuracy) on the face-name associative learning task of Experiment 1.

Dependent Variable	Predictor Variables	Uncinate Fasciculus				Inferior Longitudinal Fasciculus			
		β	<i>t</i> -value	<i>F</i>	<i>R</i> ²	β	<i>t</i> -value	<i>F</i>	<i>R</i> ²
Overall Learning									
Gender	Gender	-0.30	1.76	5.98**	0.43	-0.11	0.54	0.10	0.01
	Left FA	-0.58	3.30**			0.01	0.05		
	Right FA	0.72	3.80**			-0.02	0.07		
Gender	Gender	0.16	0.93	5.36**	0.40	0.04	0.20	1.73	0.18
	Left AD	0.79	3.89**			-0.30	1.42		
	Right AD	-0.28	1.47			0.40	2.04	2.59	0.24
Gender	Gender	-0.003	0.02	3.13*	0.28	0.10	0.53		
	Left MD	0.60	3.00*			-0.41	1.98		
	Right MD	-0.30	1.53			0.51	2.54	1.80	0.18
Gender	Gender	-0.10	0.54	3.27*	0.29	0.05	0.26		
	Left RD	0.59	2.90*			-0.33	1.54		
	Right RD	-0.46	2.23			0.48	2.19		

**
 $p < .01$.

*
 $p < .05$ (after controlling for multiple comparisons).

B4: Block 4, FA: fractional anisotropy, AD: axial diffusivity, MD: mean diffusivity, RD: radial diffusivity, β : standardized regression coefficient.

Table 3

Summary of multiple linear regression models predicting individual differences in learning rate (percent change in accuracy from B1 to B2) on the fractal-asterisk associative learning task of Experiment 2.

Dependent Variable	Predictor Variables	Uncinate Fasciculus				Inferior Longitudinal Fasciculus			
		β	t-value	F	R ²	β	t-value	F	R ²
Learning Rate				0.78	0.08			1.53	0.15
	Gender	0.30	1.42			0.23	1.22		
	Left FA	0.04	0.18			-0.06	0.24		
	Right FA	-0.10	0.44			-0.23	0.92		
				3.57 *	0.29			0.79	0.08
	Gender	0.06	0.34			0.30	1.51		
	Left AD	-0.61	2.60 *			-0.11	0.47		
	Right AD	0.63	2.61 *			0.06	0.26		
				1.37	0.14			0.92	0.10
	Gender	0.20	0.97			0.27	1.34		
	Left MD	-0.20	0.89			-0.09	0.37		
	Right MD	0.27	1.32			0.18	0.77		
				1.11	0.11			0.82	0.09
	Gender	0.26	1.30			0.26	1.34		
	Left RD	-0.10	0.46			-0.06	0.24		
	Right RD	0.22	1.06			0.14	0.55		

**
p < .01,

*
p < .05 (after controlling for multiple comparisons).

B1: Block 1, B2: Block 2, FA: fractional anisotropy, AD: axial diffusivity, MD: mean diffusivity, RD: radial diffusivity, β : standardized regression coefficient.