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Diffusion MRI properties of the human uncinate fasciculus correlate with the ability to learn visual associations

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ABSTRACT

The uncinate fasciculus (UF) is a cortico–cortico white matter pathway that links the anterior temporal and the orbitofrontal cortex (OFC). In the monkey, transection of the UF causes significant impairments in learning conditional visual–visual associations, while object discrimination remains intact, suggesting an important role for the UF in mediating the learning of complex visual associations. Whether this functional role extends to the human UF has not been tested directly. Here, we used diffusion tensor magnetic resonance imaging (dMRI) and behavioral experiments to examine the relation between learning visual associations and the structural properties of the human UF. In a group of healthy adults, we segmented the UF and the inferior longitudinal fasciculus (ILF) and derived dMRI measures of the structural properties of the two pathways. We also used a behavioral experiment adapted from the monkey studies to characterize the ability of these individuals to learn to associate a person's face with a group of specific scenes (conditional visual–visual association). We then tested whether the variability in the dMRI measures of the two pathways correlated with variability in the ability to rapidly learn the face–place associations. Our study suggests that in the human, the left UF may be important for mediating the rapid learning of conditional visual–visual associations whereas the right UF may play an important role in the immediate retrieval of visual–visual associations. These results provide preliminary evidence suggesting similarities and differences in the functional role of the UF in monkeys compared to humans. The findings presented here contribute to our understanding of the functional role of the UF in humans and the functional neuroanatomy of the brain networks involved in visual cognition.

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1. Introduction

Visual information processing in the central nervous system is commonly described as a hierarchical process in which information from the retina is primarily transmitted to the primary visual cortex and then propagated to other cortical regions along dorsal and ventral pathways for further processing (Goodale & Milner, 1992; Mishkin, Ungerleider, & Macko, 1983). These two major pathways are composed of a complex network of bidirectional white matter fiber bundles that link the visual cortex with several spatially distant cortical and subcortical regions (Kravitz, Saleem, Baker, & Mishkin, 2011; Kravitz, Saleem, Baker, Ungerleider, & Mishkin, 2013). For example, within the ventral pathway, the occipitotemporal fiber bundle (Tusa & Ungerleider, 2004), also known as the inferior longitudinal fasciculus (ILF), is generally considered as the pathway through which visual information from the occipital cortex is conveyed to regions like the anterior temporal lobe (ATL), where complex information pertaining to social cognition (Simmons & Martin, 2009; Simmons, Reddish, Bellgowan, & Martin, 2010), such as the identity of faces is represented (Kriegeskorte, Formisano, Sorger, & Goebel, 2007; Olson, Plotzker, & Ezzyat, 2007).

The dorsal and ventral pathways are often considered in isolation in the study of vision. However, the projections out of these pathways and interactions with their target regions are critical in supporting adaptive behavior. For example, the ventral visual pathway has at least six major projections to cortical and subcortical structures (Kravitz et al., 2013), including the amygdala, hippocampus, OFC, and the ATL that enable the representation of the stable properties of the visual input and their behavioral relevance. In this paper, we focus on projections from the ATL and, in particular, on the potential role of the uncinate fasciculus (UF), a C-shaped fiber bundle that is thought to link the medial and anterior portions of the temporal cortex with the orbital and medial prefrontal cortex. Although perturbations in the UF have been implicated in several psychiatric and neurological disorders (See Von Der Heide, Skipper, Klobusicky, & Olson, 2013 for a recent review), very little is known about the functional role of this pathway in humans. We first review what is currently known about the UF in human and nonhuman primates and then describe an investigation of the role of the UF in visual cognition using behavioral experiments in conjunction with diffusion tensor MRI (dMRI), which can be used to segment *in vivo* some of the major fasciculi in humans.

1.1. *Structural properties of the UF*

Current understanding of the connectional neuroanatomy of the UF comes primarily from studies that have used fiber degeneration (Chavis & Pandya, 1976; Kuypers, Szwarcbart, Mishkin, & Rosvold, 1965) or autoradiographic techniques (Petrides & Pandya, 1988; Ungerleider, Gaffan, & Pelak, 1989) in nonhuman primates. These studies suggest that the UF is a bidirectional, monosynaptic pathway that connects rostral infero-temporal and rostral superior temporal regions in the temporal lobe, with portions of the OFC and medial prefrontal cortex (Petrides & Pandya, 1988; Ungerleider et al., 1989). Specifically, within the OFC, axonal projections associated with the UF have been labeled with autoradiographic ligands in Brodmann areas (BA) 47/12, 13, 11 and in the medial prefrontal cortex. UF projections have been labeled in BA 9, 10, 14, 25, 32, as well as in BA 24 in the rostral cingulate cortex (Petrides & Pandya, 1988; Schmahmann & Pandya, 2009). In the temporal lobe, fibers associated with the UF have been reported in areas TF, TL, and TH in the parahippocampal cortex, rostral infero-temporal and superior temporal, and amygdala (For a review, see Schmahmann & Pandya, 2009). Selective transection of the UF has been found to disrupt a major proportion of the connections between the prefrontal cortex and inferior and superior portions of the ATL. However, transection of the UF does not appear to impact frontal projections to the amygdala or the banks of the superior temporal sulcus (Ungerleider et al., 1989). Thus, it is important to note that although the UF is a major cortico–cortico pathway that links the temporal lobe with the frontal lobe, there are other direct (Petrides & Pandya, 1988; Rempel-Clower & Barbas, 2000; Saleem, Kondo, & Price, 2008; Ungerleider et al., 1989) and indirect routes that may link the frontal lobe with the temporal lobe via the striatum or the thalamus (Öngür & Price, 2000).

In humans, blunt dissection studies have suggested that the UF consists of a ventromedial aspect that connects the uncus, amygdala, and mesial temporal lobe with the medial frontal lobe (subcallosal gyrus, gyrus rectus) and a dorsomedial aspect that links the superior, middle, and inferior temporal gyri with the medial and lateral orbital gyri in the frontal lobe (Ebeling & Cramon, 1992; Kier, Staib, Davis, & Bronen, 2004; Peuskens et al., 2004). In a postmortem dissection study, an asymmetry in the volume of the UF, with the right UF being larger and containing more fibers than the left UF, was noted (Highley, Walker, Esiri, Crow, & Harrison, 2002). Interestingly, this asymmetry was not observed in a group of individuals with schizophrenia, and consequently it has been hypothesized that structural asymmetry in the UF has some functional relevance.

1.2. *Functional role of the UF*

In nonhuman primates, the functional role of the UF has been explored through studies of the nature of behavioral impairments caused either by transecting the UF bilaterally or by disconnecting the anterior temporal cortex from the prefrontal cortex using crossed unilateral ablations. It is worth noting that transection of the UF only partially disrupts the processing of information propagated between the OFC and the ATL, as other pathways, such as projections from the anterior thalamic radiation, could mediate information processing between the OFC and the ATL. In contrast, crossed unilateral ablation disconnects all intrahemispheric propagation of information between the OFC and the ATL. These two approaches have been used to investigate the monkeys' performance in several types of tasks.

Transection of the UF or complete fronto-temporal disconnection has been found to cause significant impairments in the learning of various types of complex conditional associations such as visual-motor (Bussey, Wise, & Murray, 2001, 2002; Eacott & Gaffan, 1992), visual–visual,

visual–reward (Parker & Gaffan, 1998) (but see Easton & Gaffan, 2002; Gutnikov, Ma, Buckley, & Gaffan, 1997), and visual-strategy implementation (Gaffan, Easton, & Parker, 2002), without producing any significant impairments in the learning of problems involving configural processing (Gutnikov, Ma, & Gaffan, 1997), delayed matching-to-sample (Gaffan & Eacott, 1995a), visual discrimination with an auditory secondary reinforcer (Gaffan & Eacott, 1995b), and visual–time associations (Eacott & Gaffan, 1992). However, a consistent finding across different methods of fronto-temporal disconnection is that monkeys are impaired in an object-in-place task, which requires learning to associate one of two visual items presented in the foreground with a unique, complex, colorful background scene constructed from various geometric shapes (Browning, Easton, Buckley, & Gaffan, 2005; Browning & Gaffan, 2008a). Fronto-temporal disconnections do not appear to impact the monkey's ability to retrieve previously learned associations (Easton & Gaffan, 2000). This finding has led to the proposal that the UF mediates *learning* of complex visual information captured over multiple saccades and integrated over time by interactions between regions of the OFC and ATL (Browning & Gaffan, 2008b).

Whether this functional role extends to the human UF has not been tested directly. Indeed, for obvious reasons, these types of experimental studies cannot be conducted in humans. However, in some rare cases the functional role of UF and adjoining pathways have been investigated in patients undergoing surgical removal of gliomas in the frontal or temporal lobes. In such patients, intraoperative electrical stimulation of the left UF was found to induce phonemic paraphasia (e.g., saying "bastle" when "castle" is meant) in a group of patients with gliomas in the left hemisphere (Papagno et al., 2010). Interestingly, patients who had either the frontal or temporal portion of the left UF removed demonstrated significant impairment in tasks involving naming faces of famous people, object naming, verbal fluency, and verbal long-term memory, while showing normal performance in several nonlexical tasks involving spatial cognition and spatial short-term and long-term memory (Papagno et al., 2010). These findings were partly replicated in a more recent case study that reported impairments in naming pictures and verbal paraphasia following stimulation of the left UF during surgery (Nomura et al., 2013). However, contrary to these findings, another study (Duffau, Gatignol, Moritz-Gasser, & Mandonnet, 2009) found that stimulation of the left UF did not induce any language impairment, whereas stimulation of the inferior fronto-occipito fasciculus and the arcuate fasciculus in the left hemisphere induced distinct language deficits such as semantic paraphasia (e.g., saying "chair" when "table" is meant) and phonemic paraphasia, respectively. While this contradictory finding could be attributed to methodological factors (e.g., precise stimulation of the fasciculi of interest), more evidence based on experimental studies, is needed to explicate the role of the UF in mediating language.

Additional information about the properties of the UF comes from studies that have used dMRI to explore correlations between the structural properties of UF and behavior in clinical populations (for a review, see Von Der Heide et al., 2013). There are several reports of significant correlations between measures of the dMRI properties of the UF and indices of the severity of psychiatric disorders like psychopathy (Craig et al., 2009), antisocial personality disorder (Sundram et al., 2012), schizophrenia (Kubicki et al., 2002) (but see Jones et al., 2006), generalized and social anxiety (Phan et al., 2009), and major depression (A. Zhang et al., 2011). However, given the inconsistencies within the literature, the evidence implicating a dysfunction in the UF in these psychiatric disorders has been suggested to be largely inconclusive (Von Der Heide et al., 2013). In patients with neurological disorders like epilepsy and fronto-temporal dementia, dMRI studies have reported correlations between alterations in the dMRI properties of the UF and deficits in verbal memory and picture naming (Matsuo et al., 2008; McDonald et al., 2008). Similarly, correlations between perturbations in the dMRI properties of the UF and impairments in verbal memory have been reported in patients with traumatic brain injury (Niogi et al., 2008, but see Seo et al., 2012).

In summary, in contrast to the monkey studies that suggest a role in the learning (rather than retrieval) of complex visual associations (Easton & Gaffan, 2000), the data from the human studies suggest that the UF may play an important role in proper name retrieval (Papagno et al., 2010), a role which may be unique to the human. Importantly, the inconsistencies across existing human studies highlight the need for studies with greater experimental control. However, very few published studies (Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan, 2011) have adapted the experimental tasks used in animal studies to probe the function of the human UF. Given that one of the consistent findings from the monkey literature is the impairment in learning rather than retrieval of conditional visual–visual associations, we sought to test this finding directly in a group of healthy volunteers.

1.3. *Motivation for the present study*

The advent of whole-brain quantitative structural MRI techniques has made it possible to explore the relation between individual variability in behavior and variability in measures of brain structure. Although the findings from correlation-based studies should be interpreted with caution, such exploratory studies can offer insights about the relation between behavior and brain structure, which in turn can be tested directly with additional experiments (for a review, see Kanai & Rees, 2011). In the present study, we used dMRI to segment the UF and other white matter pathways and compute quantitative diffusion metrics, mean diffusivity (MD), and fractional anisotropy (FA) in the white matter pathway of interest. We then tested for correlations between the tract properties and the ability to learn conditional visual–visual associations akin to the object-in-place task used in the monkey studies (Browning et al., 2005; Browning & Gaffan, 2008b). However, we modified the task based on current knowledge of the function of the cortical regions associated with the UF in humans. Specifically, since the processing of identity and abstract information about faces has been found to engage human ATL (Simmons et al., 2010), and one of the terminal points of the UF is the ATL, we modified the task from object-in-place to face-in-a-place (Browning et al., 2005; Browning & Gaffan, 2008a). Thus, while recognition of faces may be mediated by the ILF

(Thomas et al., 2008), we predicted that individual variability in learning to associate the identity of faces with other visual information, such as places, will correlate with the variability in the structural properties of the UF.

To test this prediction we segmented the UF and the ILF bilaterally and computed the volume, mean FA, and MD. These dMRI measures are affected by the organizational and structural properties of white matter pathways (Pierpaoli et al., 2001). In addition, we used two different approaches to test our hypothesis. In the first approach, given the specificity of our hypothesis regarding the role of the UF, we computed the structural properties of the bilateral UF and ILF in the native space of each subject and tested for correlations with the behavioral measure. Although the native-space analysis allows for direct testing of a hypothesis, the results do not indicate whether there are other white matter pathways with similar functional roles. Therefore, in the second approach, we used a whole-brain voxelwise search within the white matter skeleton to determine whether the predicted correlations are specific to the UF or if they include white matter pathways other than the UF and the ILF. Thus, the two approaches constitute a comprehensive exploration of the white matter pathways involved in visual cognition.

2. Materials and methods

2.1. Participants

Twenty-six adult volunteers (13 females, age range 21–35 years) participated in the study. All participants were right handed, had normal or corrected-to-normal vision, and gave written informed consent. The consent and protocol were approved by the National Institutes of Health Institutional Review Board (Protocol 93-M-0170, NCT00001360). Participants were scanned on a 3.0 T GE scanner using an eight-channel coil (GE Medical Systems, Milwaukee, WI) before the behavioral training experiment. However, due to technical difficulties the dMRI data from six participants could not be used. Thus the data reported here are from 20 participants (7 females, age range 22–32 years), (average 26 ± 3 years).

2.2. Behavioral experiments

2.2.1. Stimuli

Stimuli for the behavioral experiment consisted of a set of facial images of individuals and a set of scenes. The face stimuli comprised color images of six adult Caucasian females in three different orientations (straight and rotated 30° to the left and right) (Fig. 1a–b). These images of faces were placed in an oval window to remove external features, such as hair, clothing, and accessories. The scene stimuli (see Fig. 1b for a subset) were color images taken from six categories—beaches, deserts, mountains, churches, concert halls, and living rooms. Each scene category contained six exemplar images, and in total, there were 36 unique scenes.

2.2.2. Task

Each female identity was randomly mapped to a specific scene from each of the six categories. Thus participants had to learn a total of 36 unique face–place associations. To make the task engaging, a cover story was provided at the beginning of the training session. Participants were told that they would view a series of photographs taken by six female students (with fictional names) for their photography course. However, due to an administrative error, it was unclear which student had taken which photograph. The participants were told that a software program (i.e., the training experiment) would train them to map each photograph to the person who had taken it.

2.2.3. Training

For each trial (Fig. 1c), one of the 36 scenes was randomly presented along with two faces, each from a different individual (a target and a distractor), positioned on the left and right of the scene. Participants were instructed to report by key press whether the scene should be associated with the woman presented on the right or the left of the scene. Feedback was provided on all trials: a green check mark for correct responses and a red cross with a high-frequency beep for incorrect responses. The trials were balanced such that each target identity and each of the three face-orientations for the target identity appeared an equal number of times on the two sides of a specific scene. In addition, each target face was paired with each of the other five distractor faces. This counter-balancing resulted in a total of 1080 trials, which were split into five blocks of 216 trials each. Thus, each block comprised the full set of face–place associations with three different orientations of each face presented an equal number of times across the two locations of a scene. Participants could take a short break between training blocks. Accuracy and reaction time (RT) were collected as the dependent measures. However, since participants were given unlimited time to respond to each trial, we used accuracy as the primary dependent measure. To characterize each participant's performance in learning the face–place associations, the average accuracy in associating each scene with the target face within each block of trials was calculated. Finally, to assess the improvement in learning the face–place associations across the entire training session we computed the magnitude of improvement (% difference) in accuracy between consecutive blocks (see Fig. 2).

2.2.4. Testing

At the end of the training session, which took approximately 1 h, participants were tested for their ability to retrieve the face–place associations. The motivation for this experiment was twofold: (a) The experiment serves as an independent assessment of the robustness of learning the face–place associations (b) the experiment can be considered as a control experiment for the learning experiment since the monkey literature provides consistent evidence for a relation between UF disruption and learning visual associations, but not for retrieval of previously learnt associations. The stimuli for this experiment consisted of the 36 scene stimuli used in the training session. For each trial, participants were shown images of two scenes consecutively (stimulus duration: 200 ms each, interstimulus interval: 200 ms) and were asked to report whether the two scenes were associated with the same woman or different women from the set of

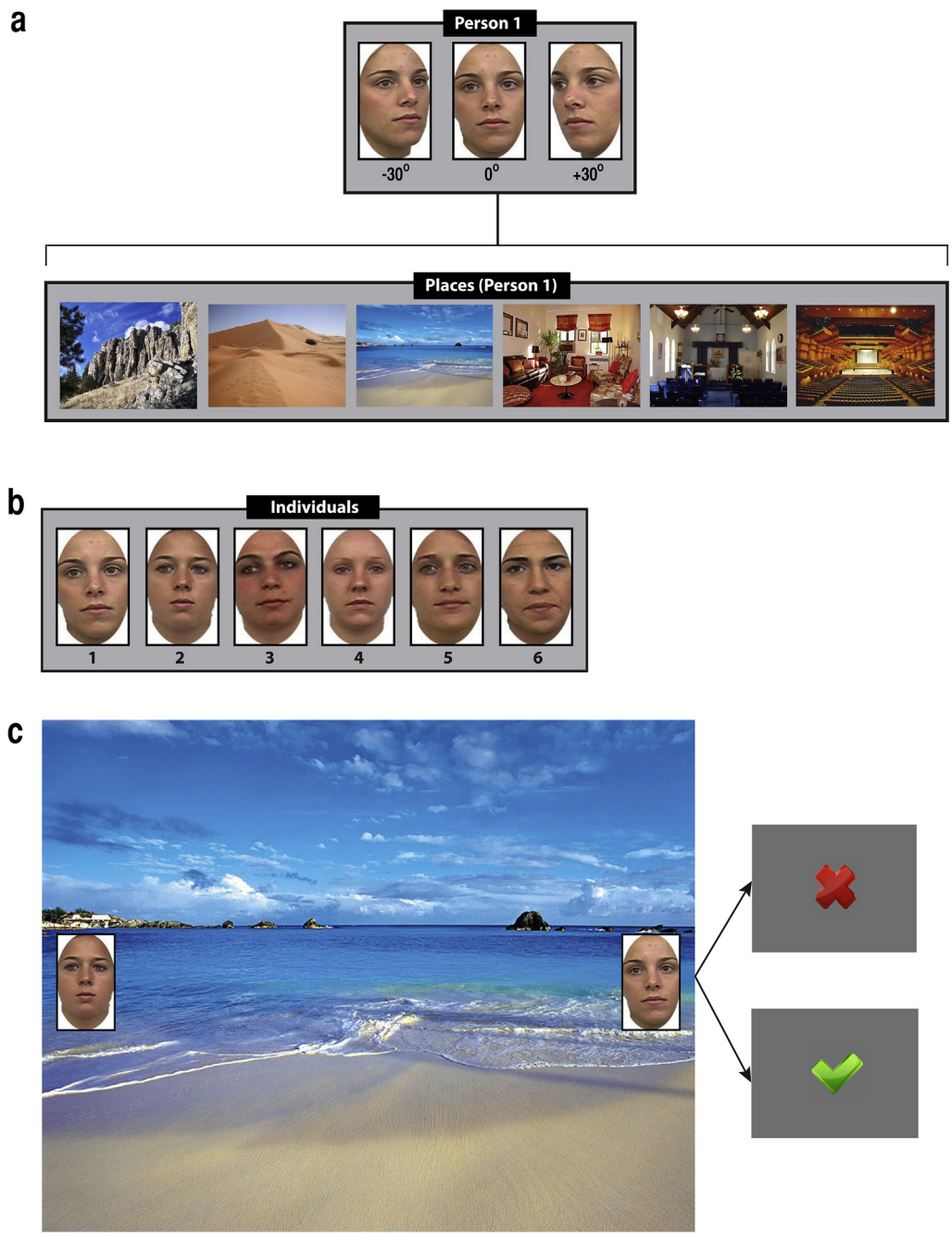

Fig. 1 – The design of the training experiment. (a) Three unique profiles of each face were used to create each identity. These three profiles were mapped to six photographs of places that were unique to that identity. (b) Participants had to learn to associate the identities of six individuals to specific photographs of places. (c) An illustration of a typical training trial. Visual and auditory feedback was provided after each trial.

six identities they had seen in the training session. The presentation of the scene stimuli was pseudo-randomized such that scenes from different categories were always presented. An equal number of same and different trials were presented. Participants were required to respond within three seconds, and no feedback was provided after each trial. Accuracy and RT were collected as the dependent measures. The accuracy data were expressed in d-prime, a bias-free sensitivity index of signal-to-noise derived from the hit-rate and false-alarm rate. The entire session (training and testing) lasted approximately 75 min.

2.3. *MRI data acquisition and processing*

2.3.1. *MRI parameters*

Whole-brain single-shot echo-planar (EPI) diffusion weighted images (DWI) were acquired with the following parameters: TE/TR = 86.9/20996 msec, b values (b = 0, b = 300, and

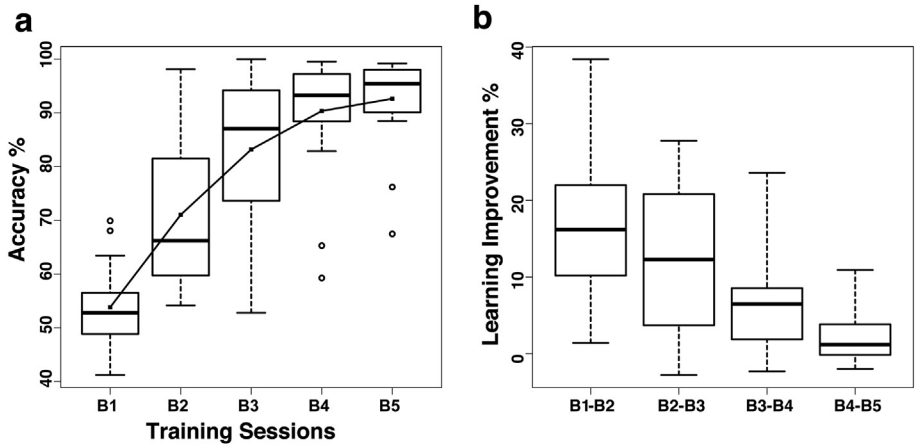

Fig. 2 – The behavioral training profile. (a) Participants showed a steady increase in accuracy over the five training sessions. Each boxplot indicates the upper and lower quartiles, and the thick horizontal line shows the median accuracy for each session. The whiskers show the largest and smallest values within each session. The line linking the boxplots shows the mean accuracy. Circles indicate outliers. (b) The improvement in accuracy between Blocks 1 and 2 and subsequent consecutive training sessions is displayed here. The steepest increase in performance is observed in B1–B2, which also shows the highest interindividual variability in performance.

b = 1100 sec/mm^2), voxel size = 2 mm isotropic, 160 MRI volumes (b_0: 20, b_{300}: 20, b_{1100}: 120), and SENSE acceleration factor (ASSET) = 2. In addition to the DWIs, structural T_2-weighted (T_2W) fast spin-echo images were acquired for each subject with TE/TR = 122/8333 msec, FOV = 240 mm^2, acquisition matrix 512 × 512, and 1.5 mm slice thickness.

2.3.2. *MRI preprocessing*

The T_2-weighted structural images were realigned along the midsagittal plane and the anterior commissure–posterior commissure axis using MIPAV (http://mipav.cit.nih.gov). DWIs were preprocessed with the TORTOISE software package (www.tortoisedti.org) (Pierpaoli et al., 2010). The DWIs were corrected for subject motion and eddy-current distortions, with proper rotation of the b-matrix for each volume (Rohde, Barnett, Basser, Marenco, & Pierpaoli, 2004). In addition, because the DWIs undergo significant geometric distortions along the phase-encoding direction, the distorted DWIs were registered using B-splines (Wu et al., 2008) to the realigned T2-weighted structural images. Then, the DWI from each participant was split in half (Volume A and Volume B) such that each half comprised this set of images: b_0, 10; b_{300}, 10; and b_{1100}, 60. The non-b_0 images were split such that the two halves of the DW data were composed of DWI in orthogonal gradient directions. For each half of the DW data set, nonlinear fitting was used to estimate the diffusion tensor. Thus, for each participant, two sets of tensor volumes were generated.

2.3.3. *In vivo tract segmentation*

The preprocessed tensor volume, Volume A, was imported into Diffusion Toolkit (Wang, Benner, Sorensen, & Wedeen, 2007) and deterministic tractography was performed with the FACT algorithm (Mori & van Zijl, 2002) with standard thresholds for terminating streamline propagation (FA < .20; angular threshold > 45°). The tracks of interest were visualized and extracted using Trackvis (Wang et al., 2007). Streamlines depicting the bilateral UF and the ILF were extracted in native space using the multiple region-of-interest approach proposed by Catani & Thiebaut de Schotten, 2008. Finally, the streamlines generated from tensor Volume A for each tract of interest were used as a mask and applied to tensor Volume B to compute the dMRI measures (mean FA and MD), thereby minimizing any selection bias.

2.3.4. *Whole-brain analysis*

We performed whole-brain analysis using the tract-based spatial statistics (TBSS) (Smith et al., 2006) approach, which constrains the analysis to the white matter skeleton. Prior to the statistical analyses, the individual FA volumes generated from the full DWI data set were co-registered and spatially normalized using the DTI-TK toolkit (Zhang et al., 2007). DTI-TK uses a tensor-based registration algorithm and has been demonstrated to align white matter pathways better than the scalar-based registration methods used in the standard TBSS pipeline, which has limitations (Keihaninejad et al., 2012). The spatially normalized FA volumes were then processed through the TBSS skeletonization pipeline to derive the white matter skeleton.

2.3.5. *Statistical analysis*

The dMRI measures derived from the tract segmentation were subjected to a repeated measure ANOVA with tract (UF/ILF) and hemisphere (left/right) as within-subject factors. Correlations between the dMRI measures and learning performance were tested using the Spearman's rank correlation test (one-tailed). For the whole-brain TBSS analysis, permutation-based nonparametric statistical analysis (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) was performed with threshold-free cluster enhancement (Smith & Nichols, 2009) and corrected for multiple comparisons with familywise error (FWE) correction ($p < .05$, i.e., chance of false positives is not more than 5%) (Hayasaka & Nichols, 2003).

3. Results

We first report the results from the analysis of the behavioral data and follow up with the results of the tract-segmentation analysis. Next, we report the results of the correlation analysis testing for the relation between the behavioral measures and the dMRI properties of the white matter pathways. Finally, we present the results of the whole-brain white matter skeleton analysis.

3.1. *Training phase*

Given that participants were exposed to the full range of face–place associations for the first time in Block 1 (Mean 53.8%; SD 7.22), performance was close to chance during these trials, but improved gradually over the course of the five blocks until average accuracy was above 90% (Mean 92.64%; SD 8.12), As is evident from Fig. 2, participants showed the steepest improvement in accuracy between Blocks 1 and 2, compared with other consecutive blocks. The magnitude of improvement in accuracy diminished in the subsequent blocks, and most participants showed no significant improvement beyond Block 4. Indeed, the wide range in performance gain between Blocks 1 and 2 (Mean 17.22%; SD 9.3), across participants revealed significant individual variability in the ability to learn the full range of face–place associations, the primary focus of the present study. We therefore used the improvement in performance from Blocks 1 to 2 as a measure of the learning rate for each participant.

3.2. *Test phase*

Participants showed high accuracy in the test phase (Mean 82.61%; SD 13.97), suggesting robust learning of the face–place associations. The d-prime analysis revealed a wide range (Mean 2.15; SD .99) in the participant's ability to correctly recall the face–place associations. It is interesting to note that the d-prime measure of post-training performance correlated positively ($\rho = .525$, $p < .009$, one-tailed) with the magnitude of improvement in accuracy between Blocks 1 and 2. Similar significant correlations between d-prime and improvement in accuracy between other training blocks (i.e., B2–B3, B3–B4 and B4–B5) were not observed. This correlation suggests that the learning rate between Blocks 1 and 2 of the training session is predictive of subsequent recall of learning.

3.3. *Tract segmentation*

The bilateral UF and the ILF were extracted in all participants. As is evident from Fig. 3, a qualitative examination of the trajectories of the two pathways reveals considerable inter-individual variability. With tract volume as the dependent measure, the ANOVA revealed significant main effects of both tract [$F(1, 19) = 7.164$, $p < .015$] and hemisphere [$F(1, 19) = 5.032$, $p < .037$)] as well as a significant interaction between these two factors [$F(1, 19) = 25.519$, $p < .001$]. Planned post hoc analysis (paired samples *T*-test, two-tailed) on this interaction confirmed a significantly larger volume of UF fibers in the right hemisphere compared with the left hemisphere ($t_{19} = -4.021$, $p < .001$), whereas the ILF showed the opposite pattern ($t_{19} = 4.543$, $p < .001$).

With mean FA as the dependent measure, the ANOVA again revealed main effects of both tract [$F(1, 19) = 47.86$, $p < .001$] and hemisphere [$F(1, 19) = 15.163$, $p < .001$] with a significant interaction between the two factors [$F(1, 19) = 26.241$, $p < .001$]. Subsequent planned post hoc analysis revealed significantly higher mean FA in the right UF compared with the left UF ($t_{19} = -6.774$, $p < .001$), whereas the difference in mean between the right and left ILF was not significant ($t_{19} = .296$, $p < .77$). Repeating the same analysis with MD as the dependent measure revealed a significant main effect of tract [$F(1, 19) = 21.311$, $p < .001$], although the main effect of hemisphere was not significant [$F(1, 19) = 2.185$, $p < .156$]. However, consistent with the findings from tract volume and FA analysis, the tract-by-hemisphere interaction was also significant [$F(1, 19) = 2.185$, $p < .156$], and subsequent post hoc tests revealed significantly higher MD in the left UF compared with the right UF ($t_{19} = 3.343$, $p < .003$), whereas the difference in MD between the right and left ILF was not significant [$F(1, 19) = -.345$, $p < .734$]. In summary, hemispheric lateralization in the UF (right > left for volume and FA and right < left for MD) was observed across all three dMRI measures, whereas for the ILF, hemispheric lateralization was observed only in terms of tract volume (left > right).

3.4. *Behavior–structure correlation*

To test whether individual variability in the dMRI measures of the bilateral UF and ILF (volume, mean FA, MD) correlated with the variability in learning the face–place associations, we performed correlations between the tract measures and the magnitude of improvement in accuracy between Blocks 1 and 2. The Spearman's correlation test revealed a significant positive correlation between learning rate and the mean FA of the left UF ($\rho = .712$, $p < .001$) and a trend towards significance with the mean FA in the right UF ($\rho = .339$, $p < .072$) (Fig. 4). No other correlations were found to be statistically significant. After correcting for multiple comparisons (i.e., Bonferroni correction for 12 correlations), only the correlation between the mean FA of the left UF and the behavioral measure was found to be statistically significant. However, based on the Williams test (Williams, 1959) for assessing the difference between two nonindependent r-values, the difference between the left and right UF correlations was not statistically significant ($t_{17} = 1.033$, $p > .05$). In contrast, the difference in the correlations between the learning rate and the mean FA of the left UF versus correlations between the learning rate and the mean FA of the right ILF ($t_{17} = 3.021$, $p < .05$) and the left ILF ($t_{17} = 2.007$, $p < .05$) was statistically significant, demonstrating the specificity of the relation between learning of visual–visual associations and microstructural measures of the left UF.

We also explored the relation between FA of the UF and improvement in learning in the training blocks other than B1–B2. The Spearman's correlation test between the bilateral UF and ILF and performance gain in blocks B2–B3, B3–B4 and B4–B5 revealed two statistically significant correlations between FA of the left UF and B3–B4 ($\rho -.444$, $p < .025$), and B4–B5 ($\rho = -.524$, $p < .009$). However, unlike the correlation between B1–B2 and FA of the left UF, these correlations were negative

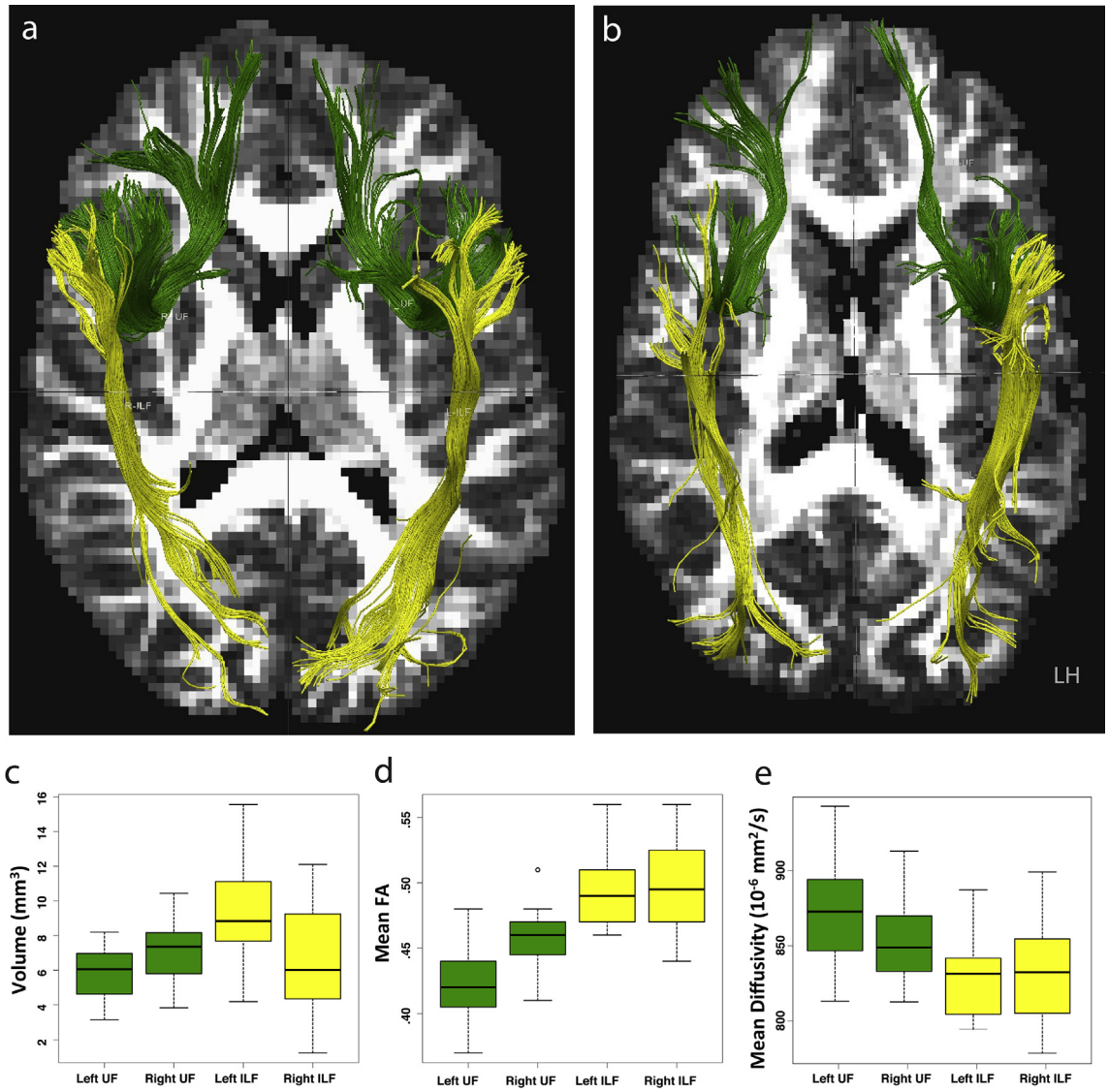

Fig. 3 – A qualitative and quantitative illustration of the individual variability in the macro- and microstructural properties of the two pathways of interest. (a, b) The bilateral UF and ILF extracted in two individuals in native space. (c) Significant hemispheric asymmetry in volume is observed in both the UF (volume higher in right) and the ILF (volume higher in left). However, with regard to the diffusion measures, mean FA (d) and MD (e), a rightward asymmetry is observed only in the UF. The circle in (d) indicates outliers.

because the bulk of the participants who learnt the face–place associations rapidly are at ceiling by Block 4 and Block 5 and thus show very little variability in terms of improvement in performance. However, the few slower learners who begin to show performance gains in Blocks 4 and 5 also have lower mean FA in the left UF, resulting in a negative correlation (Supplementary Fig. S1).

To test whether the correlation between FA of the UF was specific to the ability to rapidly learn visual–visual associations (i.e., performance gains in B1–B2) rather than retrieval of the associations, we performed the same set of correlations between the d-prime measure of post-training performance and the same set of tract measures. This analysis revealed a significant correlation between retrieval of the visual associations and the mean FA of the right UF ($\rho = .476$, $p < .017$), but not the left UF ($\rho = .311$, $p < .091$) (Fig. 5). The difference between these two correlations however was not statistically significant ($t_{17} = .96$, $p > .05$). Finally, we tested whether the hemispheric lateralization observed with regard to the dMRI properties of the UF was related to the learning or retrieval of the face–place associations. A significant negative correlation (Fig. 6) was observed between the lateralization index of the UF (i.e., FA of (right UF − left UF)/(right UF + left UF)) and learning the face–place associations, ($\rho = -.588$, $p < .006$, two-tailed), but not with the ability to retrieve the associations ($\rho = -.16$, $p < .502$).

3.5. *Whole-brain white matter skeleton analysis*

The TBSS analysis did not reveal any significant correlations between the learning rate and mean FA in any of the voxels

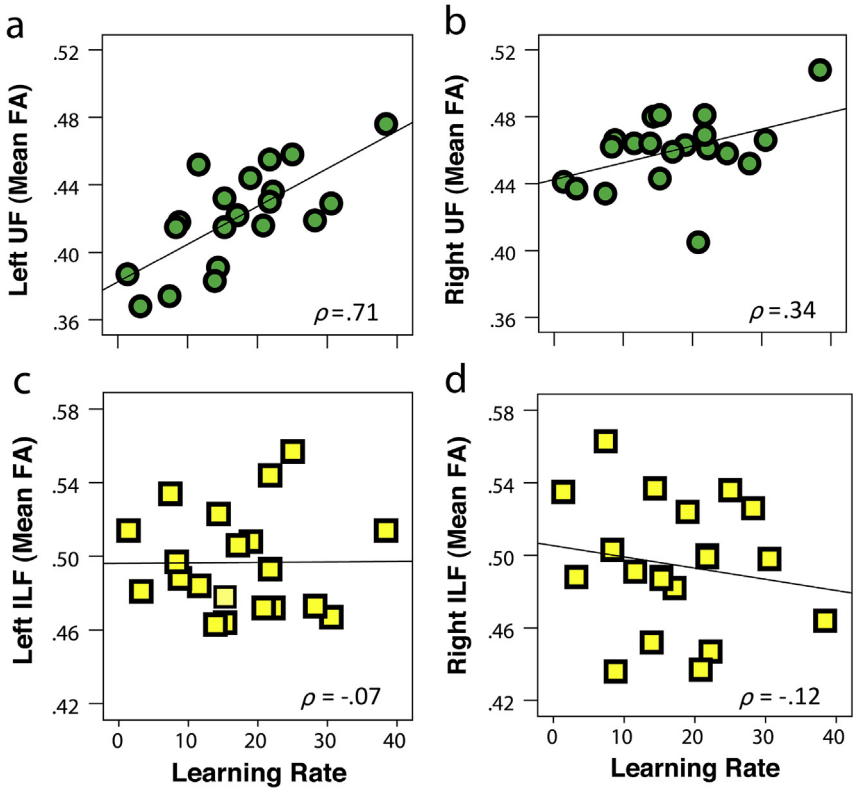

Fig. 4 – Scatter plots show the correlation between learning rate and the mean FA of the two pathways of interest. (a, b) A significant positive correlation is observed in the UF, but not in the ILF (c, d).

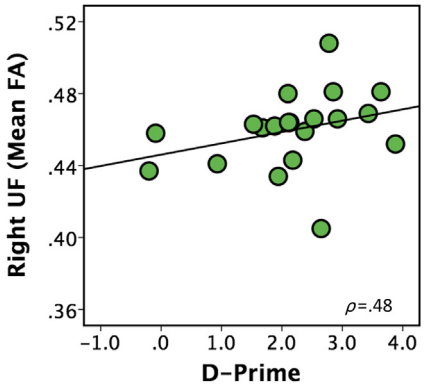

Fig. 5 – Scatter plot shows a significant positive correlation between immediate retrieval of the visual–visual associations and mean FA of the right UF.

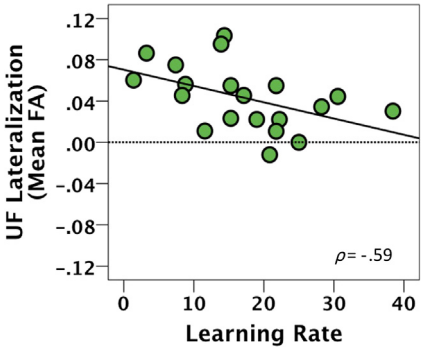

Fig. 6 – Scatter plot shows a significant negative correlation between increased right lateralization of the UF in terms of FA and the learning rate suggesting that increased right lateralization of the UF is related to poor learning of the visual–visual associations.

in the white matter skeleton after correction for familywise error at the recommended threshold of $p < .05$. However, relaxing the p threshold revealed trends in a significant positive correlation between the learning rate and FA in several white matter regions predominantly in the frontal cortex, (including bilateral OFC white matter), consistent with the findings from the native space analysis (see the Supplementary Material for full details).

4. Discussion

In the present study, we sought to examine the functional role of the UF, a major fronto-temporal white matter pathway in the human brain. Specifically, we used DTI tractography to test whether the structural properties of the UF are related to the ability to learn conditional visual–visual associations. Our hypothesis was entirely motivated by prior experimental studies involving monkeys that found significant impairments in learning conditional visual–visual associations

following disconnection of the UF (Browning et al., 2005; Browning & Gaffan, 2008a, 2008b; Eacott & Gaffan, 1992). Our results suggest that the human UF may be important for mediating the rapid learning and immediate retrieval of visual–visual associations. In addition, whereas monkey disconnection studies are constrained by the inability to explore the functional role of multiple anatomical pathways in a single experiment, here, we used the whole-brain DWI data to investigate the possible involvement of other white matter pathways in mediating learning of visual–visual associations. Our findings suggest that in addition to the UF, other white matter pathways may also play an important role in the processing of visual–visual associations. Below, we discuss in detail the importance of the findings from the two analysis approaches we employed in this study.

4.1. *Insights from the native-space analysis*

Because our hypothesis is specific to the UF, we chose a widely used approach for identifying the tract of interest (bilateral UF) and the control tract (bilateral ILF) in native space and for extracting the macro- and microstructural measures of the two pathways for each subject. In contrast to an atlas-based approach in which each individual's volume is registered to create an atlas of the pathways of interest, this approach requires less manipulation of the data and avoids confounds that could be inadvertently introduced during spatial normalization. In our case, as is evident from Fig. 3, there is substantial intersubject variability in the morphology of the white matter pathways under investigation, and therefore, a native-space analysis approach is warranted.

The results from the native-space analysis suggest that the correlation with the behavioral measure (i.e., rapid learning of visual–visual associations) is specific to the UF compared with the ILF. In particular, it is worth noting that although both the right and left UF show a positive correlation with the behavioral measure, and the difference in the two correlations is not statistically significant, only the correlation between the left UF and the behavioral measure survives correction for multiple comparisons. This finding suggests that the left UF may play a greater role in mediating rapid learning of the face–-place associations. Interestingly, contrary to our prediction, interindividual variability in the ability to accurately recall the newly acquired associations correlates with the variability in the FA of the right UF. Thus, in the human, the left and right UF may have complementary roles in supporting learning and retrieval of visual–visual association, respectively. However, the differences in these correlations, in terms of laterality, should be interpreted with caution since the differences in the correlations between right and left UF were not statistically significant and our measures of learning ability and retrieval were also correlated. In summary, our findings reveal similarities and differences in the functional role of the UF in monkeys compared to humans. That the correlation is stronger in the left UF for learning and stronger in the right UF for retrieval may reflect the differences in the functional and structural organization of the human brain emerging from language acquisition. Indeed, the advantage of having language to facilitate rapid learning of complex associations may partly account for the finding that the participants in our study were able to learn 36 unique associations in one hour, while a very similar task typically takes monkeys thousands of trials over several days (Browning, Easton et al. 2005). Future studies could employ the same approach that we have adopted here to directly assess the relation between the microstructure of the UF and retrieval or learning of other associations such as, visual–semantic and visual–motor associations.

4.2. *Structural and functional hemispheric asymmetries*

Our study also found evidence for hemispheric asymmetries in the structural properties of the ILF and the UF. We observed a significantly larger volume of the left ILF compared to the right, but no differences in either the MD or the FA. In contrast, we observed a significantly greater volume and average FA, as well as significantly lower average MD in the right UF compared with the left UF. There is precedence for similar reports of hemispheric asymmetry in the structural properties of the ILF and UF (Park et al., 2004; Wakana et al., 2007). However, in the present study, the hemispheric asymmetry in the UF was observed for both volume and diffusion metrics, while for the ILF no right–left differences in diffusion metrics were found; this finding suggests a structural origin for the UF asymmetry.

That said, a review of the existing literature suggests inconsistencies in the directionality of the structural asymmetry of the UF. Some DWI studies reported that healthy volunteers show a significant increase in the FA in the right UF compared with the left UF (Park et al., 2004; Rodrigo et al., 2007), which is consistent with our findings. Other studies noted the opposite (Diehl et al., 2008; Kubicki et al., 2002), and some did not find any evidence for asymmetries in the UF (Thiebaut de Schotten et al., 2011). However, a noteworthy exception in the literature is a postmortem study that compared the structural properties of the UF in healthy individuals, which served as the control group, with those of a group of individuals with schizophrenia (Highley et al., 2002). The study revealed that in healthy humans, the right UF was larger and contained more axonal fibers than the left UF, a finding consistent with our findings, at least in terms of the hemispheric asymmetry in the volume of the UF. Interestingly, in contrast with the healthy control group, the individuals with schizophrenia did not exhibit the rightward structural asymmetry. Attempts to replicate this finding using DWI have resulted in contradictory findings: some studies found evidence for a lack of asymmetry (Kubicki et al., 2002; Park et al., 2004) and some found no evidence for the asymmetry or any significant difference in the microstructure of the UF in schizophrenia (Jones et al., 2006; Phillips et al., 2009; Shergill et al., 2007).

Hemispheric asymmetries are often attributed to experience-dependent functional specialization of cortical regions during cognitive development (Dundas, Plaut, & Behrmann, 2013), and perturbations in the progression of functional and structural lateralization could be indicative of brain pathology (for a review, see Toga & Thompson, 2003). The results from our study indicate that the right lateralization of the UF in terms of FA is negatively correlated related with individual variability in learning visual–visual associations. This suggests that participants who showed

less right lateralization of the UF tend to perform better in learning the face–place associations. This result is consistent with the findings from Catani et al. (2007) who found that bilateral symmetry in the connectional neuroanatomy correlates with better performance in cognitive tasks. That said, given the inconsistencies in the literature regarding lateralization of the UF, our findings underscore the need for replication of these findings and a systematic exploration of hemispheric asymmetries of the UF and other association pathways.

4.3. *Insights from the whole-brain analysis*

A legitimate concern regarding the use of a native-space approach is that it is not operator independent, and, therefore, there is a possibility of biases in the *in vivo* dissection of the pathways of interest. Moreover, unlike the monkey disconnection studies that, by design, limit exploration to a single pathway, a whole-brain analysis supplements the tract-specific analysis and can potentially reveal the contribution of other white matter pathways that may be involved in subserving the learning of visual–visual associations. Since the present study was largely motivated by the findings from monkey studies involving disconnection of major white matter pathways, we used the TBSS approach, which restricts the voxelwise search to a skeleton of the major white matter pathways. At the recommended statistical threshold of $p < .05$ (FWE corrected), the analysis does not reveal any correlations between FA and the behavioral measure. One could interpret this result as an indication that the significant correlations observed in the native-space analysis are not sufficiently robust. However, it should be noted that the skeleton analysis involves hundreds of voxels, and the corrections employed to reduce the likelihood of false positives may be too conservative. Indeed, when the threshold is relaxed to $p < .09$ (i.e., a false positive rate of 9%), clusters of correlations in the white matter skeleton are revealed overlapping the trajectory of the left UF, whereas when the threshold is further relaxed to $p < .12$, clusters of correlations in the white matter associated with the right UF are revealed, confirming the main result of the native-space analysis (see Supplementary Materials). In addition, clusters indicating significant correlations between the FA and the behavioral measure can be observed along the white matter skeleton associated with the anterior portions of the corpus callosum, the superior aspect of the corona radiate, portions of the fornix, and the splenium of the corpus callosum.

Although interpretation of these correlations is speculative, a few striking features of the topography of these correlations are worth considering. First, within the approximate trajectory of the human UF, the correlations appear to be localized in the orbitofrontal white matter, a region known to be highly involved in the processing of reward features that guide learning and behavior (Schultz, Tremblay, & Hollerman, 2000). Given that the participants in the present study were provided feedback (i.e., high frequency beep) to motivate rapid learning of the face–place associations, a plausible conclusion would be that the orbitofrontal portion of the human UF may be important for learning conditional visual-reward associations, similar to the monkey (Parker & Gaffan, 1998). Second, the clusters of FA–behavior correlations are disproportionately in the left hemisphere and largely localized in prefrontal and frontal lobe white matter, with little or no involvement of occipital or ventral temporal white matter. This finding suggests that multiple white matter pathways involving the prefrontal cortex are probably involved in mediating the learning of the face–place associations. Indeed, the lesion studies involving monkeys have shown that the impairment in object-in-place learning is doubled with crossed unilateral fronto-temporal ablation compared with selective transection of the UF (Browning et al., 2005; Browning & Gaffan, 2008a). Thus, one possible explanation is that the anterior corpus callosum in humans is also an important channel for processing semantic information (Sidtis, Volpe, Holtzman, Wilson, & Gazzaniga, 1981) that may be crucial for creating robust representations of face–place associations. Future studies should systematically explore these correlations further, although, in light of the results from the present study, a larger sample size may be necessary to perform this analysis at a whole-brain level.

4.4. *Challenges in inferring brain–behavior relationship*

The two approaches explored in the present study also highlight an intrinsic limitation in our ability to make inferences about the relation between brain structure and behavior using MRI data. Had we adopted only the native-space approach, we would have concluded that the role of human UF is not very different from that of the UF in the monkey. On the other hand, if we had used only a whole-brain search with the recommended statistical thresholds, the result would have been a null finding. However, adjusting the statistical threshold reveals that pathways other than the UF could have a significant role in mediating the task at hand; although this inference can be potentially less meaningful given the increase in false positives with relaxed statistical thresholds. Since drawing insights from these different approaches is very difficult, we place greater emphasis on the findings from the native space analysis, particularly since they are, in general, consistent with the monkey literature.

Future explorations should strongly consider investing in robust data acquisition, which is crucial to ensure that any structural difference is not driven by an artifact. Indeed, studies have shown that a failure to correct for EPI distortion can produce spurious asymmetries in tractography that can be misinterpreted (İrfanoğlu, Walker, Sarlls, Marenco, & Pierpaoli, 2012). This problem is a major concern for pathways like the UF that are in a region of low signal-to-noise ratio and highly susceptible to EPI susceptibility distortions. Although in the present study we reduced the impact of EPI distortions by using b-spline registration, more accurate corrections can be implemented by using recent advancements such as blip-up–blip-down correction for EPI distortions (Irfanoglu et al., 2014). Likewise, the ability to detect subtle structural properties of white matter pathways can be improved by using dual compartment tensor fitting to remove cerebrospinal fluid contamination from brain parenchyma (Pierpaoli & Jones, 2004).

5. Conclusion

In summary, our study provides preliminary evidence that the human UF plays an important role in the learning and retrieval of conditional visual–visual associations. Although the strength of the correlations appears to be less robust than expected, the evidence from the monkey studies and some recent studies reporting similar results support the present study (Hower, Rolheiser, & Olson, 2014). More importantly, our study adds to the burgeoning literature demonstrating the importance and the benefits of pursuing experimental investigations of the major white matter pathways of the human brain.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2015.01.023.

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