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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.

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 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 et al., 2013; Catani and Thiebaut de Schotten, 2008; Von Der Heide et al., 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 et al., 2002; Gaffan et al., 1988; Parker and 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 et al., 2005; Browning and Gaffan, 2008). However, UF disconnection has little to no effect on visual object discrimination learning, configural learning, or delayed matching-to-sample tasks (Gaffan and Eacott, 1995; Gaffan et al., 2002; Gutnikov et al., 1997; Parker and 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., 2016). Similar findings have been reported in other laboratories and replicated across different techniques (Damasio et al., 1996; Drane et al., 2008; Grabowski et al., 2001;

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Nomura et al., 2013; Tranel et al., 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 et al., 2007; Jones, 2008; Tournier et al., 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., 2015b). Several studies have reported that performance on standardized verbal memory tasks, such as the California Verbal Learning Test (CVLT; Delis et al., 2000) or the auditory immediate and delayed memory subtests from the Weschler 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, and mild cognitive impairment (Hiyoshi-Taniguchi et al., 2015; Mabbott et al., 2009; McDonald et al., 2008; Niogi et al., 2008; Wendelken et al., 2015). There are also reports in normal populations that microstructural properties of the UF correlate with auditory recall from the WMS (Charlton et al., 2013) and various paired associates learning tasks (Charlton et al., 2013; Metzler-Baddeley et al., 2011; Thomas et al., 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; Gaffan et al., 1988; Parker and 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 et al., 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 et al., (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 et al., (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 et al., (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 et al., 2013), and lesions to this region can affect the ability to recall proper names (Papagno et al., 2011) and discern facial identity (Olson et al., 2015a). 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 Fig. 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; Gaffan et al., 1988; Parker and 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 et al., (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 and 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 (Catani et al., 2003; Pyles et al., 2013). Therefore, we did not expect there to be any relationship between ILF microstructure and associative learning.

Materials and methods

Participants

A total of 50 healthy individuals (19 males, 31 females) 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.

Study protocol

Study participation occurred in two separate testing sessions, which occurred an average of one week apart. During the behavioral session,