The role of the pre-commissural fornix in episodic autobiographical memory and simulation

Abbreviated title: Pre-commissural fornix in past and future thinking

Angharad N. Williams[1*], Samuel Ridgeway[1], Mark Postans[1], Kim S. Graham[1+], Andrew, D. Lawrence[1+] & Carl J. Hodgetts[1, 2+]

1. Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University, Maindy Road, Cardiff, CF24 4HQ, United Kingdom
2. Department of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX

* Corresponding author: Dr. Angharad Nia Williams, Cardiff University Brain Research Imaging Centre (CUBRIC), School of Psychology, Cardiff University, Maindy Road, Cardiff, CF24 4HQ, United Kingdom. E-mail: williamsan@cardiff.ac.uk

+ Joint senior authors

Number of pages: 30

Number of figures: 6

Number of tables: 0

Number of words: Abstract (195); Introduction (650); Discussion (1500)

Conflict of interest statement: The authors declare no competing financial and non-financial interests.

Acknowledgments:

This work was supported by funds from the Medical Research Council (MR/N01233X/1) (KG, AL, AW, MP) and a Wellcome Trust Strategic Award (104943/Z/14/Z) (KG, AL, CH). SR is supported via an ESRC Wales Doctoral Training Partnership PhD studentship. We would like to thank Ofer Pasternak and Greg Parker for providing the free water correction pipeline, John Evans for scanning support, and Naomi Warne for assisting with transcription and autobiographical memory task coding.

Abstract

Neuropsychological and functional magnetic resonance imaging (MRI) evidence suggests that the ability to vividly remember our personal past, and imagine future scenarios, involves two closely connected regions: the hippocampus and ventromedial prefrontal cortex (vmPFC). Despite evidence of a direct anatomical connection from hippocampus to vmPFC, it is unknown whether hippocampal-vmPFC structural connectivity supports both past and future-oriented episodic thinking. To address this, we applied diffusion-weighted magnetic resonance imaging (dMRI) and a novel deterministic tractography protocol to reconstruct distinct subdivisions of the fornix previously detected in axonal tracer studies, namely pre-commissural (connecting the hippocampus to vmPFC) and post-commissural (linking the hippocampus and medial diencephalon) fornix, in a group of healthy young adult humans who undertook an adapted past-future autobiographical interview. As predicted, we found that inter-individual differences in pre-commissural - but not post-commissural - fornix microstructure (fractional anisotropy) was significantly correlated with the episodic richness of both past *and* future autobiographical narratives. Notably, these results remained significant when controlling for both non-episodic narrative content and grey matter volumes of the hippocampus and vmPFC. This study provides novel evidence that reconstructing events from one's personal past, and constructing possible future events, involves a distinct, structurally-instantiated hippocampal-vmPFC pathway.

Keywords:

Hippocampus, Episodic memory, Future thinking, Structural connectivity, vmPFC, White matter tractography

Significance Statement

A novel anatomically-guided protocol that allows the pre-commissural and post-commissural fornix fibers to be separately reconstructed *in vivo* (Christiansen et al., 2016) was applied to reconstruct the pre-commissural subdivision of the white matter fornix tract (anatomically linking the hippocampal formation to the vmPFC) and investigate its contribution to episodic memory and future simulation. We demonstrated that the amount of episodic details contained in past and future narratives, collected via an adapted autobiographical interview, was positively correlated with pre-, but not post-, commissural fornix microstructure. These findings highlight how inter-individual variation in the pre-commissural subdivision of the fornix underpins the construction of self-reflective, contextual events – for both the past and future.

Introduction

A key adaptive feature of human cognition is the ability to re-experience our personal histories and imagine the future in vivid detail. According to the constructive episodic simulation hypothesis, the processes and neural machinery that allow us to remember past experiences also allow us to imagine future experiences (Schacter et al., 2012; Addis, 2018). Consistent with this view, remembering past and imagining future events activate a common set of brain regions, including the hippocampus and ventromedial prefrontal cortex (vmPFC) (Addis et al., 2007; Benoit and Schacter, 2015). Furthermore, the ability to retrieve episodically rich autobiographical memories and construct coherent future simulations is diminished following lesions to both the hippocampus and vmPFC (Race et al., 2011; McCormick et al., 2018) (but see Squire et al., 2010). Such findings have led to the suggestion that the hippocampus and vmPFC are critical nodes within a default (Andrews-Hanna et al., 2010; Raichle, 2015) or 'core' network that interact to support autobiographical memory and imagination (Schacter et al., 2012; Schacter et al., 2017) (For related proposals see also Murray et al., 2017; Robin and Moscovitch, 2017; McCormick et al., 2018).

Converging evidence has shifted focus towards this neural network-level approach to support the way we reconstruct our personal past and construct possible future experiences (Schacter et al., 2012; Bellana et al., 2017; Schacter et al., 2017). For instance, studies using functional magnetic resonance imaging (fMRI) have found increased functional connectivity between the hippocampus and vmPFC during both the retrieval of autobiographical memories (McCormick et al., 2015) and the construction of episodic future events (Campbell et al., 2017), and resting state functional connectivity between these regions has been shown to predict the episodic quality of individual's memories (Yang et al., 2013).

The communication of information across networked areas depends on the organization and integrity of the white matter connections between them (Jbabdi and Behrens, 2013). Invasive tract-tracing techniques have revealed direct efferent anatomical connections from the hippocampus to the vmPFC. In rats, the entire longitudinal extent of the subiculum/CA1 is connected - via the pre-commissural fornix - with the vmPFC, with connectivity increasing progressively in strength from

dorsal to ventral hippocampus (Jay and Witter, 1991; Cenquizca and Swanson, 2007). Similarly in primates, the pre-commissural fornix provides the exclusive route for subiculum/CA1 projections to medial and orbitofrontal PFC (Barbas and Blatt, 1995; Aggleton et al., 2015), with relatively more projections arising from the anterior hippocampus. In humans, diffusion-weighted magnetic resonance imaging (dMRI), which can non-invasively delineate the path of major fiber pathways and evaluate their microstructure through indices such as fractional anisotropy (FA) (Jbabdi and Behrens, 2013), has provided initial evidence for hippocampus-PFC connections via the fornix (Croxson et al., 2005). Building on this work, Christiansen et al. (2016) recently developed an anatomically guided dMRI protocol for the selective *in vivo* reconstruction of pre-commissural fornix fibers in humans, allowing investigation of the functions supported by human hippocampus-PFC structural connectivity for the first time.

By application of this novel anatomically-informed tractography protocol, we investigated the role of the pre-commissural fornix in autobiographical past and future thinking using an individual differences design (Palombo et al., 2018a). Participants were asked to recall past experiences and generate future events using word-cues according to a modified Galton-Crovitz cue-word paradigm (Crovitz and Schiffman, 1974). White matter microstructure was assessed in these individuals using high angular resolution diffusion-weighted imaging (HARDI) and constrained spherical deconvolution tractography (Dell'Acqua and Tournier, 2019). Given the directed hippocampus-PFC functional connections identified above in relation to (re)constructing events in episodic memory and episodic simulation (McCormick et al., 2015; Campbell et al., 2017), we hypothesized that individual differences in the episodic richness of past and future thinking would be related to the microstructure of the hippocampus-PFC connections underpinned by the pre-commissural fornix. As a comparison tract, we used the post-commissural fornix, which connects hippocampus to mammillary bodies and anterior thalamic nuclei (Aggleton, 2012; Christiansen et al., 2016; Mathiasen et al., 2019).

Materials and methods

Participants

Participants were 27 healthy Cardiff University undergraduates (aged 18–22 years, mean age = 19, 25 females). Portions of this data have been published previously (Hodgetts et al., 2017a). Here we address a novel and distinct question with unpublished data from a future thinking task and a novel anatomically-informed tractography protocol for reconstructing distinct fornix sub-divisions. Participants completed an adapted autobiographical cue-word paradigm (Crovitz and Schiffman, 1974; Addis et al., 2008) in a separate session from diffusion-weighted magnetic resonance imaging (dMRI). All participants gave written informed consent before participating. Cardiff University School of Psychology Research Ethics Committee reviewed and approved this research.

Experimental Design

Past-future Autobiographical Interview (AI) task procedure

Participants completed an adapted autobiographical cue-word paradigm (Crovitz and Schiffman, 1974; Addis et al., 2008) that probed both past and future events. In each of the two conditions (past, future), ten cue-words (e.g. “holiday”, “birthday”) were provided to each participant, in response to which they were asked to recall or imagine a personal event and to generate as much detail as possible within 1-minute (Cole et al., 2012). Each event was required to be spatiotemporally specific, occurring over a timescale of minutes or hours, but no longer than a day. Future events were required to be plausible given the participant’s current plans and not previously experienced by the participant. Three alternate word lists were used; these were matched for semantic category (i.e., participants either heard the cue-word ‘holiday’, ‘journey’ or ‘vacation’). Prior to commencing, participants were instructed:

“In this test I am going to give you a series of words and ask you to recall an episode from your past, or think of an episode that you might be involved in in the future, related to each of these words. The episode needs to be as specific and detailed as possible. I would like you to give me as much information as you can.”

In cases where the participant either lacked specificity or detail in their description, the experimenter would provide a non-specific prompt for further information (e.g., *“Is*

there anything else you can tell me about this event?"). All trials for one temporal direction (past or future) were completed before beginning the trials for the other condition. Order of presentation of temporal direction (past or future) was counterbalanced, as were the word lists (across the past and future conditions). Participants were tested individually, and responses were recorded using a portable recording device (Zoom H1 Digital Field Recorder) for subsequent transcription and scoring.

Scoring

The standardized AI scoring procedure (Levine et al., 2002) was used. Events (past and future) generated were segmented into distinct chunks of information in order to allow analysis of the levels of episodic or semantic information provided within each. These chunks were typically characterized by grammatical clauses that referenced a unique occurrence, observation or thought (Levine et al., 2002). Two broad categories were used to categorize details: 'internal' details (which described the central event) and 'external' details (decontextualized information, including semantic details and information concerning extended events that are not specific in time and place, and repetitions). In the case that a participant described more than one event, the event that was described in the most detail was coded as 'internal' and the other as 'external'. The central event was required to refer to a specific time and place, thus it can be considered 'episodic' and will be referred to as such henceforth. Episodic details included not only time and place details, but also any other episodic information (sensory details, thoughts and emotions) that were part of the central event (Levine et al., 2002). **Figure 1** contains examples of external and episodic details from past and future narratives. Total score was computed by summing over the 10 event narratives.

Past narrative

External **External** **External**
Vacation um I went to India (.) Saw some elephants (,) my sister got married out there (.) Um (.)
External **External** **External**
We went to the beach (.) Went to Panaji the capital of Goa (.) Um saw the bridge where it was (,)
External **External**
in one of the Bourne Identity films or something (.) Erm that's not for me but the boys liked it (.)
External
Um (.) Yeah went for lots of dinners (.)

Episodic **Episodic** **Episodic**
Um (.) My sister when she got married (,) she looked really nice (,) and we were er on the beach (,)
Episodic **Episodic** **Episodic**
and we had the waves coming in (.) And it was sunset (,) and we had like a white gazebo (.) And
Episodic **Episodic**
her dress was kind of floating around erm in the wind (,) and then we all jumped into the sea (,)
Episodic
and had our pictures taken (.)

Future narrative

External **External** **External**
Erm in a couple of weeks (,) I'm going to go on holiday (,) um to Cyprus (.) My stepsister is getting
Episodic **Episodic**
married out there (,) and so we're um going to have the wedding on um the beach front (.) um a lot
Episodic **Episodic**
of her friends and family are going (.) um and I'm gonna be a bridesmaid (.) Um the weather's
External **External**
supposed to be really nice out there (.) Um and erm mmm yeah there's about 20 people going (.)
External **Episodic**
It's gonna be quite a small wedding (.) Um and um yeah we're gonna have dinner at the hotel (.)

Figure 1. Examples of external and episodic details from past and future narratives.

Consensus scoring was established based on the near perfect inter-rater reliability from two raters who scored the past events (intra-class correlation analysis, two-way random model: episodic r = 0.99; external r = 1.0). The values from one primary coder, who completed both the past and future scoring, were used in the analysis. All raters were blind to dMRI results.

For each event the numbers of episodic and external details were tallied, and the totals were then summed across the 10 events in each condition (past, future) to create episodic and external AI scores for each condition for each participant.

MRI data acquisition

Imaging data were acquired using a General Electric Healthcare (GE) 3-T HDx MRI system with an 8-channel receive-only head coil, at Cardiff University's Brain Research Imaging Centre (CUBRIC). A standard T1-weighted 3D FSPGR sequence (178 axial slices, 1mm isotropic resolution, TR/TE = 7.8/3.0s, FOV = 256 x 256 x 176mm, 256 x 256 x 176 data matrix, 20° flip angle) provided high-resolution anatomical images.

A diffusion weighted single-shot spin-echo Echo-Planar Imaging (EPI) pulse sequence was used to acquire whole-brain High Angular Resolution Diffusion Image (HARDI) data (60 contiguous slices acquired along an oblique-axial plane with 2.4mm thickness and no gap, TE = 87ms; voxel dimensions = 2.4 x 2.4 x 2.4mm^3; FOV = 23 x 23 cm^2; 96 x 96 acquisition matrix). The acquisition was cardiac gated, with 30 isotropic directions at b = 1200 s/mm^2. In addition, three non-diffusion weighted images were acquired with b = 0 s/mm^2.

MRI preprocessing

Diffusion MRI

dMRI data were preprocessed using ExploreDTI version 4.8.3 (Leemans and Jones, 2009). Distortions resulting from eddy currents and participant head motion were corrected. A particular issue for white matter pathways located near the ventricles (e.g., the fornix), is free water contamination from cerebrospinal fluid. This has been shown to significantly affect tract delineation (Concha et al., 2005). Thus, to correct for voxel-wise partial volume artifacts arising from free water contamination, the two-compartment 'Free Water Elimination' (FWE) procedure (Pasternak et al., 2009) was applied – this improves Diffusion Tensor Imaging (DTI)-based tract reconstruction and tissue specificity (Pasternak et al., 2014). Following FWE, corrected diffusion tensor indices were computed. Fractional anisotropy (FA) – a DTI-based index proposed to reflect axonal organization (Pierpaoli et al., 1996), reflects the extent to which diffusion within biological tissue is anisotropic (constrained along a single axis) (Beaulieu, 2002). FA values can range from 0 (fully isotropic) to 1 (fully anisotropic). The resulting free water corrected FA maps were inputs for the tractography analysis.

Tractography

Deterministic tractography was performed from all voxels based on constrained spherical deconvolution (CSD) (Jeurissen et al., 2011; Dell'Acqua and Tournier, 2019). CSD allows for the representation of bending/crossing/kissing fibers in individual voxels, as multiple peaks in the fiber orientation density function (fODF) can be extracted within each voxel (Dell'Acqua and Tournier, 2019). The step size was 1mm, and the fODF amplitude threshold was 0.1. An angle threshold of 30° was used to prevent the reconstruction of anatomically implausible fibers.

To generate 3D fiber reconstructions of each tract segment, waypoint region-of-interest (ROI) gates were drawn manually onto whole-brain free water corrected FA maps. The waypoint ROIs defined the tracts based on a ‘SEED’ point and Boolean logical operations: ‘NOT’ and ‘AND’. The ‘NOT’ and ‘AND’ gates corresponded to whether tracts passing through were omitted from analyses or retained, respectively. These gates were combined to reconstruct the tracts, based on anatomical plausibility. Initially, a multiple ROI approach was applied to reconstruct the fornix (see Metzler-Baddeley et al., 2011; Hodgetts et al., 2017a).

Fornix reconstruction

A ‘SEED’ point ROI was placed on the coronal plane, encompassing the body of the fornix. An ‘AND’ ROI was placed on the axial plane, capturing the crus fornici in both hemispheres at the lower part of the splenium of the corpus callosum. ‘NOT’ ROIs were placed intersecting the corpus callosum on the axial plane, and anterior to the fornix pillars and posterior to the crus fornici on the coronal plane. Further ‘NOT’ way-gates were placed after the initial reconstruction and ensuing visual inspection, to remove anatomically implausible fibers. Subsequently, the anterior body of the fornix was split into the pre- and post- commissural column segments (**Figure 2**).

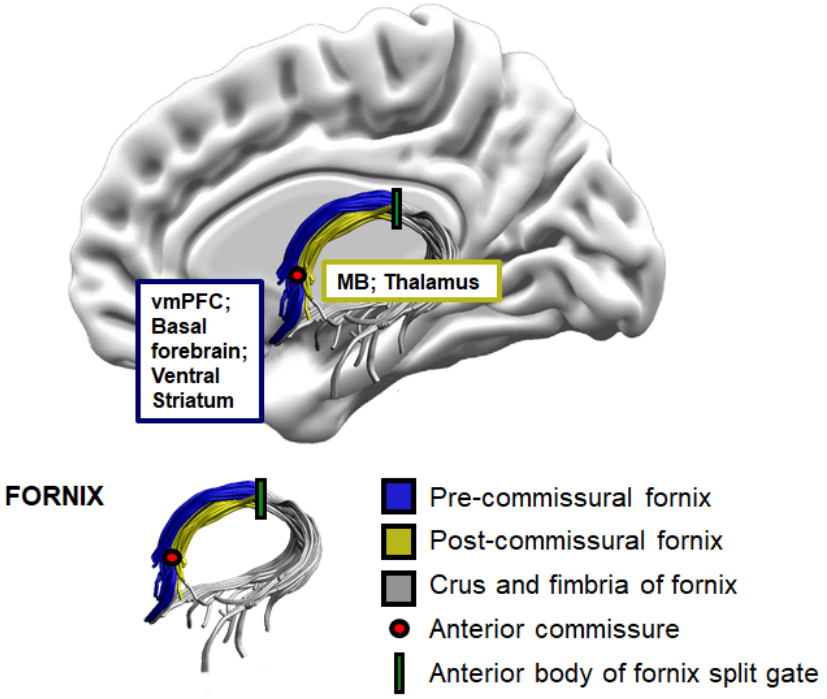

Figure 2. Schematic illustration of the anatomical landmarks for fornix tract sub-division, and the connecting areas of interest. vmPFC = Ventromedial Prefrontal Cortex; MB = Mammillary Bodies.

Waypoint ROIs for the pre-post split (**Figure 3**) were based on the protocol described in Christiansen et al. (2016), and example tract reconstructions are depicted in **Figure 4**. After tract reconstruction for each participant, mean FA values were calculated by averaging the values at each 1mm step along each segment.

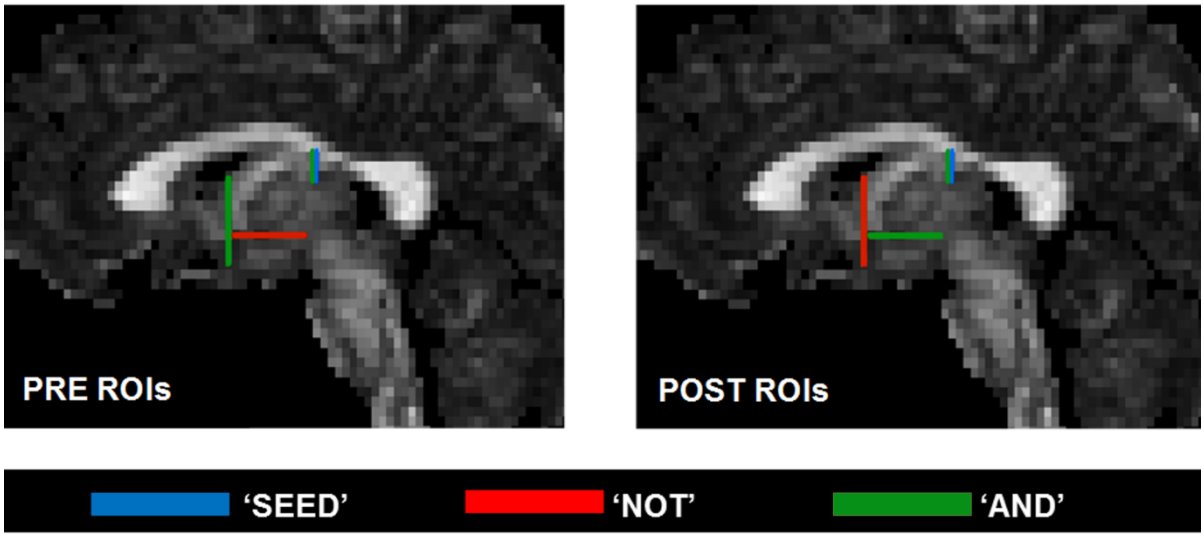

Figure 3. Waypoint region-of-interest (ROI) gates used for reconstructing the pre- and post- commissural fornix tract segments (Blue = SEED, Red = NOT, Green = AND).

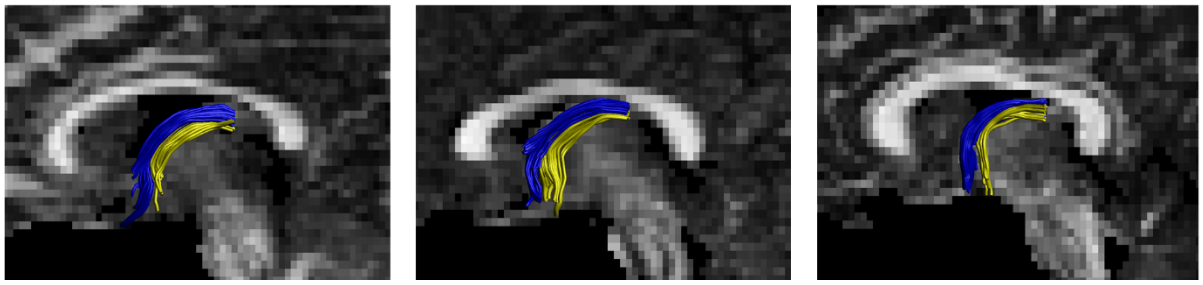

Figure 4. Example reconstructions for the pre- and post- commissural fornix segments (Blue = Pre, Yellow = Post).

Pre- and post- commissural fornix reconstruction

The fornix was split, isolating the anterior-body, by an 'AND' gate positioned at the point of the downward bend to the crus and fimbria of the fornix. In line with Christiansen et al. (2016), fibers of the crus and fimbria of the fornix were excluded from the anterior-body and hence pre- and post- commissural fornix reconstructions. Partial volume effects due to the intermingling of the two fiber populations beyond the crus were, therefore, minimized (Saunders and Aggleton, 2007). In addition, this procedure avoided 'jumping' where tract voxels that pass close to, or across, neighboring tract voxels 'jump' onto them (Jones and Cercignani, 2010). This split was conducted using the tract segmentation tool "splitter" within ExploreDTIv4.8.3.

The anterior-body of the fornix was then divided into the pre- and post-commissural segments. This delineation took advantage of the manner in which the fibers separate at the anterior columns of the fornix. At this level, the segments contain approximately the same number of fibers (Powell et al., 1957). The pre-commissural fornix was delineated by positioning an additional ‘AND’ gate on the coronal plane at the anterior-commissure, as well as an additional ‘NOT’ gate meeting this ‘AND’ gate on the axial plane. For the post-commissural fornix reconstruction, the additional ‘NOT’ and ‘AND’ gates placed for reconstruction of the pre-commissural fornix were swopped (see **Figure 3**). Thus, for the pre-commissural fornix, tracts were included only if they extended anterior to the anterior commissure, and for the post-commissural fornix only tracts running posterior to the anterior commissure were retained (see **Figure 4**) (Christiansen et al., 2016).

Grey matter volumetrics

T1-weighted images were corrected for spatial intensity variations using FMRIB's Automated Segmentation Tool (FAST; Zhang et al., 2001). Bilateral grey matter volumes (expressed as a proportion of estimated total intracranial volume) of the hippocampus were subsequently obtained using FMRIB's Integrated Registration & Segmentation Tool (FIRST; Patenaude et al., 2011). Volumes for the vmPFC ROI were derived using FreeSurfer (surfer.nmr.mgh.harvard.edu: Destrieux et al., 2010), via summing volumes of the medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex (rACC) parcels. One participant was removed from the grey matter analyses due to poor overall data quality on the T1 FSPGR.

Statistical Analysis

As higher values of FA are considered indicative of increased myelination and improved organization, cohesion, and compactness of white matter fiber tracts (Beaulieu, 2002), we predicted a positive association between pre-commissural FA and the episodic richness of past and future constructions. Thus, directional Pearson's correlations were conducted between individual's total scores of episodic and external details produced for the ten past and future narratives; and individual's episodic past and future scores and their FA values for the pre- and post-commissural fornix (Lakens, 2016). Vovk-Sellke Maximum (VS-MPR) *p* –ratios were computed: based on the *p* -value, the maximum possible odds in favor of H_1 over H_0 equals $1/(-e\ p \log(p))$ for $p \leq .37$, where log is the natural logarithm and *e* is its constant base (Benjamin and Berger, 2019). I.e. the VS-MPR represents the largest odds in favor of the alternative hypothesis relative to the null hypothesis that is consistent with the observed data (Benjamin and Berger, 2019). Complementary non-parametric Spearman's rho rank tests were also conducted for the key correlations. These are less sensitive to potential outliers and differences in range (Croux and Dehon, 2010). In addition, partial correlations were conducted for the key episodic-fornix microstructure correlations, to control for the contribution of the number of external details given and regional grey matter volume. All analyses were conducted in JASP (2018, version 0.9.1.0).

Results

Correlations between tract microstructure and past-future AI scores

Number of details produced (episodic and external) for the past and future narratives

Consistent with previous studies (e.g. Addis et al., 2008; Addis et al., 2009; Race et al., 2011), the total number of episodic details (summed across the 10 cue words) an individual recalled for the past (mean = 121.3, median = 114, SD = 40.8, range = 64 - 247) correlated strongly with the number of episodic details imagined for the future (mean = 59.3, median = 54, SD = 23.4, range = 27 - 105) (**Figure 5A**. Pearson's r = 0.69, $p < 0.001$, VS-MPR = 1027.33). Additionally, in line with previous studies, there were significantly more episodic details given for the past in comparison to the future ($t(26) = 10.75$, $p < 0.001$, $d_z = 2.07$, paired t-test). The number of external details an individual recalled for the past (mean = 73.8, median = 71, SD = 39, range = 20 – 182) also correlated significantly with the number of external details imagined for the

future (mean = 86.5, median = 75, SD = 40.8, range = 23 - 198) (**Figure 5B**. Pearson's r = 0.73, p < 0.001, VS-MPR = 3254.64). There were also significantly more external details given for the future in comparison to the past ($t(26) = 2.23$, p = 0.035, $d_z = 0.43$, paired t-test). The number of episodic details an individual recalled for the past also correlated with the number of external details recalled for the past (Pearson's r = 0.35, p = 0.035, VS-MPR = 3.15); this was not the case, however, for the future (Pearson's r = -0.16, p = 0.783, VS-MPR = 1.00).

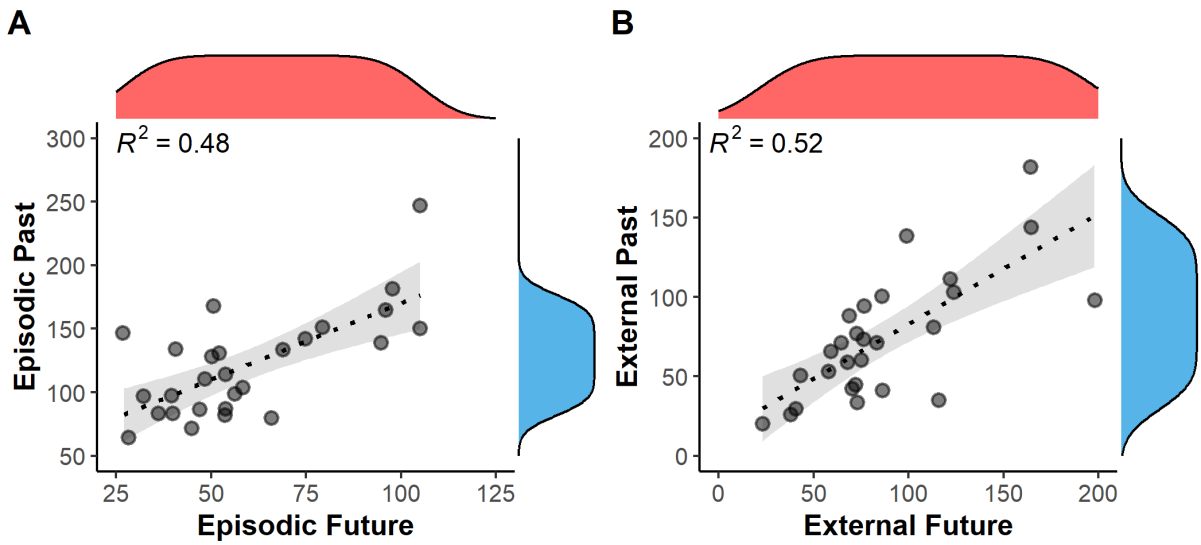

Figure 5 (A, B). Scatterplots depicting correlations between the number of details produced for the past versus the future AI narratives (A. Episodic, B. External) (*N*=27). Marginal density is displayed on the opposite axis. Grey shading equals the 95% CI.

Episodic past details and pre-/post- commissural fornix FA

We found a significant positive correlation between the number of past episodic details and pre-commissural fornix FA (**Figure 6A**. Pearson's r = 0.49, p = 0.005, VS-MPR = 14.49, Spearman's rho = 0.464, p = 0.007, VS-MPR = 10.09). There was no significant correlation between post-commissural fornix FA and episodic past details (**Figure 6B**. Pearson's r = -0.12; p = 0.725, VS-MPR = 1.00, Spearman's rho = 0.02, p = 0.457, VS-MPR = 1.00). The correlation between episodic past details and pre-commissural fornix FA was significantly greater than between episodic past

details and post-commissural fornix FA (Steiger z (27) = 2.29, p = 0.011) (computed using R package 'cocor', Diedenhofen and Musch, 2015).

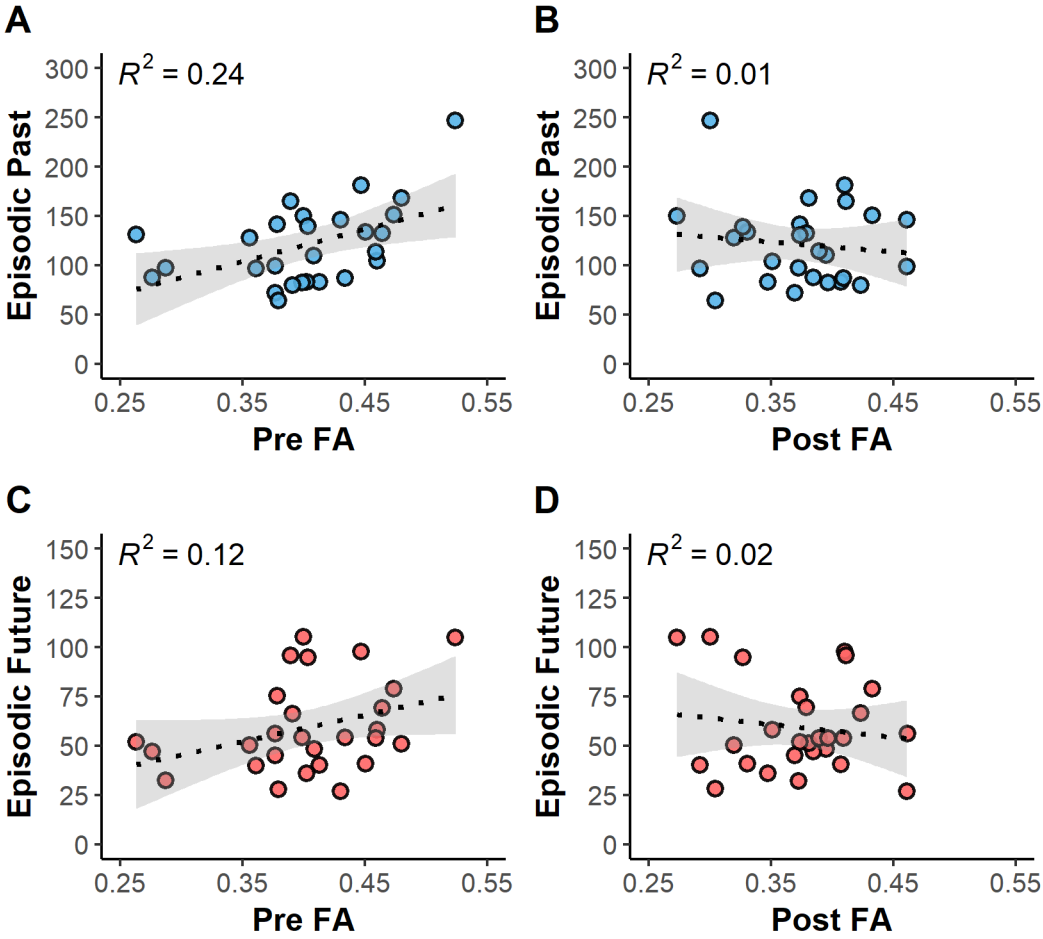

Figure 6 (A-D). Scatterplots depicting the correlations of episodic past (A, B) and future (C, D) AI details with pre-/post- commissural fornix microstructure (fractional anisotropy, FA). Number of episodic past/future details (summed over 10 cue words) is plotted on the y-axis (*N*=27). Grey shading equals the 95% CI.

The correlation between episodic past details and pre-commissural fornix FA was also significantly greater than between external past details and pre-commissural fornix FA (Steiger z (27) = 1.69, p = 0.046). Additionally, when controlling for the number of external details produced by the individual, the correlation between episodic past details and pre-commissural fornix FA remained significant (Pearson's r = 0.48, p = 0.007, Spearman's rho = 0.47, p = 0.007).

Episodic future details and pre-/post- commissural fornix FA

The findings for the episodic future simulation details mirrored those for the episodic past retrieval. There was a significant positive correlation between the total number of future episodic details (summed over the 10 cue words) and pre-commissural fornix FA (**Figure 6C**. Pearson's r = 0.35, p = 0.035, VS-MPR = 3.11, Spearman's rho = 0.33, p = 0.045, VS-MPR = 2.62), and, correspondingly, there was no significant correlation between episodic future details and post-commissural fornix FA (**Figure 6D**. Pearson's r = -0.14, p = 0.752, VS-MPR = 1.00, Spearman's rho = 0.09, p = 0.330, VS-MPR = 1.01). The correlation between episodic future details and pre-commissural fornix FA was also significantly greater than between episodic future details and post-commissural fornix FA (Steiger z (27) = 1.78, p = 0.038). The correlation between episodic future details and pre-commissural fornix FA was not significantly greater than between external future details and pre-commissural fornix FA, however, when controlling for the number of external details given the correlation between episodic future details and pre-commissural fornix FA remained significant (Pearson's r = 0.38, p = 0.028, Spearman's rho = 0.33, p = 0.0499).

Influence of grey matter volume

When hippocampal volume was controlled for, the correlation between past episodic details and pre-commissural fornix FA remained significant (partial correlation: Pearson's r = 0.49, p = 0.006), and there was no significant association between post-commissural fornix FA and episodic past details (partial correlation: Pearson's r = -0.09, p = 0.341). Likewise, the correlation between future episodic details and pre-commissural fornix FA remained significant when controlling for hippocampal volume (partial correlation: Pearson's r = 0.37, p = 0.035), and there was no significant association between post-commissural fornix FA and episodic future details (partial correlation: Pearson's r = 0.04, p = 0.422).

Similarly, when vmPFC volume was controlled for, the correlation between past episodic details and pre-commissural fornix FA remained significant (partial correlation: Pearson's r = 0.54, p = 0.003), and there was no significant correlation between post-commissural fornix FA and past episodic details (partial correlation: Pearson's r = -0.22, p = 0.143). For the future simulations, the correlation between the number of episodic details and pre-commissural fornix FA remained significant

404 when controlling for vmPFC volume (partial correlation: Pearson's r = 0.36, p =
405 0.037), and there was no significant correlation between post-commissural fornix FA
406 and episodic future details (partial correlation: Pearson's r = -0.19, p = 0.178).
407

408 **Discussion**

409 We applied a novel anatomically-guided protocol that allows the pre-commissural
410 and post-commissural fornix fibers to be separately reconstructed *in vivo*
411 (Christiansen et al., 2016). To assess both past- and future-oriented thinking, we
412 used an adapted autobiographical cueing paradigm (Crovitz and Schiffman, 1974;
413 Cole et al., 2012) alongside a validated coding scheme that specifically parses
414 episodic from non-episodic detail within individuals' real-world descriptions (Levine et
415 al., 2002). Using this approach, we found that inter-individual variation in *pre*-
416 commissural, but not *post*-commissural, fornix microstructure was significantly
417 correlated with the amount of episodic detail produced during the construction of
418 both past and future events. Critically, this effect was still seen when controlling for
419 non-episodic content. These findings deepen our understanding of hippocampal-
420 vmPFC interactions in human episodic autobiographical memory and future thinking
421 and provide a 'structural realization' of hippocampal-vmPFC functional connectivity
422 (Kosslyn and Van Kleeck, 1990), that is, a direct relationship between the
423 microstructure of the fiber pathway connecting these distributed regions and
424 individual differences in the episodic content of past and future thinking.
425

426 Our findings highlight the importance of hippocampus-vmPFC structural connectivity
427 mediated by the pre-commissural fornix (Cenquizca and Swanson, 2007; Aggleton et
428 al., 2015), in episodic construction across past and future events. This builds upon
429 previous fMRI studies that have shown that functional coupling between these
430 distributed regions is increased during both the retrieval of autobiographical
431 memories and the construction of future events (McCormick et al., 2015; Campbell et
432 al., 2017). One recent study, which used structural equation modelling of fMRI data,
433 found increased functional connectivity from anterior hippocampus *to* vmPFC when
434 participants retrieved autobiographical memories in response to cue words
435 (McCormick et al., 2015). Similarly, another investigation applied dynamic causal
436 modeling to fMRI data and found that anterior hippocampus *to* vmPFC effective
437 connectivity increased specifically during the initial construction of episodic future

events (Campbell et al., 2017). From this, the authors proposed that 'the hippocampus initiates event construction in response to retrieval cues, which then drives activation in the vmPFC where episodic details may be further integrated'.

This conceptualization is consistent with previous work in both humans and rodents that demonstrated that hippocampal activity precedes medial PFC activity during memory retrieval (McCormick et al., 2015; Place et al., 2016), and with findings in rodents that hippocampus mediates theta drive to vmPFC (O'Neill et al., 2013). Optogenetic studies in mice (e.g. Ciocchi et al., 2015) have also shown that during memory retrieval ventral hippocampal signals carrying contextual information are sent directly to medial PFC, facilitating coordinated activity between these areas.

The differential contributions of the hippocampus and vmPFC to episodic constructive processes are hotly debated (Robin and Moscovitch, 2017; Schacter et al., 2017; McCormick et al., 2018). According to scene construction theory, the hippocampus, and particularly the subiculum, plays a central role in forming representations of spatially coherent scenes across memory, perception and imagination (Zeidman and Maguire, 2016; Hodgetts et al., 2017b), and these conjunctive scene representations have been proposed to provide a scaffold when constructing both past and future events (Murray et al., 2017; Robin, 2018; Barry and Maguire, 2019). In contrast, the constructive episodic simulation hypothesis contends that the construction of spatiotemporal contexts arises out of a more general relational processing mechanism (Eichenbaum and Cohen, 2014) housed in hippocampus, which is also responsible for the integration of other event details into the event representation (Schacter et al., 2012; Schacter et al., 2017; Addis, 2018).
The vmPFC's contribution to episodic construction, by contrast, has been linked to demands on schematic representations (van Kesteren et al., 2012; Gilboa and Marlatte, 2017; Robin and Moscovitch, 2017), in particular the self-schema (Buckner and Carroll, 2007; D'Argembeau, 2013). For instance, Kurczek et al. (2015) (see also Verfaellie et al., 2019) compared the number of references to 'the self' included in autobiographical event narratives from patients with bilateral hippocampal or medial PFC damage as well as healthy controls. Patients with medial PFC damage, despite being able to construct highly detailed episodic events, produced relatively few self-references, and they incorporated themselves in the narratives of their

472 (re)constructions less frequently than the healthy participants. Patients with
473 hippocampal damage showed the opposite pattern: they were impaired in their ability
474 to construct highly detailed episodic events across time periods but not in their
475 incorporation of the self. We have previously suggested (Murray et al., 2017) that
476 hippocampal-vmPFC connectivity serves to (re)create complex conjunctive
477 representations in which one's self is oriented in a particular time, place, and overall
478 situational context (Murray et al., 2017). These conjunctive representations may
479 subsequently constrain further retrieval and construction by the hippocampus
480 (Graham et al., 2010; Preston and Eichenbaum, 2013; Place et al., 2016; Campbell
481 et al., 2017). Thus, recall/imagination of personally relevant episodes involves a
482 prefrontal system that can work in conjunction with the MTL system to help
483 individuals recombine episodic details to construct a *personally relevant* past/future
484 event (but see scene construction theory - McCormick et al., 2018; Barry and
485 Maguire, 2019; Ciaramelli et al., 2019 - for an alternative account of vmPFC
486 contributions that de-emphasizes self-processes).
487
488 Critically, the pre-commissural fornix does not carry reciprocal projections from the
489 vmPFC to the hippocampus (which are indirect via the thalamic nucleus reuniens
490 and entorhinal cortex) (Aggleton et al., 2010; Preston and Eichenbaum, 2013;
491 Murray et al., 2017), but only carries connections to the vmPFC from the
492 hippocampus (subiculum/CA1) (Cenquizca and Swanson, 2007; Aggleton et al.,
493 2015). While several models of episodic memory emphasize the importance of bi-
494 directional interactions between hippocampus and vmPFC (e.g. Preston and
495 Eichenbaum, 2013; Eichenbaum, 2017; Robin and Moscovitch, 2017), with vmPFC
496 playing a regulatory (Preston and Eichenbaum, 2013; Eichenbaum, 2017; Robin and
497 Moscovitch, 2017; Barry and Maguire, 2019) or even initiating (McCormick et al.,
498 2018; Barry et al., 2019) role in episodic construction, our findings reveal that the
499 direct inputs that the hippocampus provides to vmPFC are critical in individual
500 differences for episodic memory and future thinking, and that the pre-commissural
501 fornix is a key link in this broader hippocampal-vmPFC circuit.
502
503 While our findings highlight a key role for hippocampal structural connectivity with
504 medial PFC in constructing self-relevant event representations, previous work in
505 humans, primates and rodents has tended to emphasize the importance of

connectivity between the hippocampus and medial diencephalon (i.e., mammillary bodies and thalamus) in spatial and contextual memory (Parker and Gaffan, 1997; Aggleton and Brown, 1999), connectivity which is mediated by the *post*- but not the *pre*-commissural fornix (Vann and Nelson, 2015; Christiansen et al., 2016; Mathiasen et al., 2019). While the current findings seemingly challenge this account, one caveat is that our post-commissural fornix tract reconstructions principally involve the connections of the hippocampus with the hypothalamus, including the mammillary bodies, and largely exclude the projections to the anterior thalamic nuclei, as these turn towards posterior regions as the fornix columns descend (Poletti and Creswell, 1977; Christiansen et al., 2016). These thalamic fibers do not form a discrete tract, rather they remain diffuse (Mathiasen et al., 2019). Previous work has demonstrated that thalamic degeneration can impair episodic autobiographical memory and future thinking (Irish et al., 2013). Notably, however, Vann and colleagues (Vann et al., 2011; Vann, 2013) have reported that lesions to the descending post-commissural fornix columns in rats have little impact on spatial memory tests that are sensitive to mammillary body, mammillothalamic tract, anterior thalamic, and hippocampal lesions. The implication of this finding is that the hippocampal-mammillary connection may not be important for all forms of episodic memory, including (as here) those that place demand on constructive and self-referential processing (see also Tedder et al., 2016) (but see Christiansen et al., 2016).

Although FA is highly sensitive to the microstructure of fibers, it lacks biological specificity, and may reflect myelination, axon diameter and packing density, axon permeability and fiber geometry (Jones et al., 2013). Concha et al. (2010), using human DTI-histology comparisons, found that FA of the fornix was strongly positively correlated with axonal membranes (cumulative membrane circumference) and axonal density. Variation in such microstructural properties can influence communication efficiency and synchronicity between distal brain regions (Jbabdi and Behrens, 2013; Pajevic et al., 2014). Future studies using multi-shell diffusion MRI and advanced biophysical modeling to estimate specific microstructural properties including axon density (Assaf et al., 2017) will provide further insight into the specific biological attributes underlying these microstructure-cognition associations. Further, while our sample size was comparable to related investigations (e.g. Postans et al.,

2014; Palombo et al., 2018b), and VS-MPRs showed that our findings provide a good level of diagnosticity (Benjamin and Berger, 2019), it will be important to extend our findings to larger lifespan samples.

In summary, we report a novel association between white matter microstructure of the pre-commissural fornix and episodic past and future thinking, thus elucidating a potential anatomical mechanism by which direct hippocampal-to-vmPFC connectivity supports constructive episodic processing. These findings provide important support for the idea of a core-network supporting both the re-construction of past events and the construction of hypothetical events in the future, and that individual differences in structural connectivity may reflect how richly people can reconstruct the past and construct possible futures.

553 **References**

554 Addis DR (2018) Are episodic memories special? On the sameness of remembered
555 and imagined event simulation. Journal of the Royal Society of New Zealand
556 48:64-88.
557 Addis DR, Wong AT, Schacter DL (2007) Remembering the past and imagining the
558 future: common and distinct neural substrates during event construction and
559 elaboration. Neuropsychologia 45:1363-1377.
560 Addis DR, Wong AT, Schacter DL (2008) Age-related changes in the episodic
561 simulation of future events. Psychological Science 19:33-41.
562 Addis DR, Sacchetti DC, Ally BA, Budson AE, Schacter DL (2009) Episodic
563 simulation of future events is impaired in mild Alzheimer's disease.
564 Neuropsychologia 47:2660-2671.
565 Aggleton JP (2012) Multiple anatomical systems embedded within the primate
566 medial temporal lobe: implications for hippocampal function. Neuroscience &
567 Biobehavioral Reviews 36:1579-1596.
568 Aggleton JP, Brown MW (1999) Episodic memory, amnesia, and the hippocampal–
569 anterior thalamic axis. Behavioral and Brain Sciences 22:425-444.
570 Aggleton JP, Wright NF, Rosene DL, Saunders RC (2015) Complementary patterns
571 of direct amygdala and hippocampal projections to the macaque prefrontal
572 cortex. Cerebral Cortex 25:4351-4373.
573 Aggleton JP, O'Mara SM, Vann SD, Wright NF, Tsanov M, Erichsen JT (2010)
574 Hippocampal–anterior thalamic pathways for memory: uncovering a network
575 of direct and indirect actions. European Journal of Neuroscience 31:2292-
576 2307.
577 Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL (2010)
578 Functional-anatomic fractionation of the brain's default network. Neuron
579 65:550-562.
580 Assaf Y, Johansen-Berg H, Thiebaut de Schotten M (2017) The role of diffusion MRI
581 in neuroscience. NMR in Biomedicine 32:1-16.
582 Barbas H, Blatt GJ (1995) Topographically specific hippocampal projections target
583 functionally distinct prefrontal areas in the rhesus monkey. Hippocampus
584 5:511-533.
585 Barry DN, Maguire EA (2019) Remote memory and the hippocampus: a constructive
586 critique. Trends in Cognitive Sciences 23:128-142.

587 Barry DN, Barnes GR, Clark IA, Maguire EA (2019) The neural dynamics of novel
588 scene imagery. Journal of Neuroscience 39:4375-4386.
589 Beaulieu C (2002) The basis of anisotropic water diffusion in the nervous system–a
590 technical review. NMR in Biomedicine 15:435-455.
591 Bellana B, Liu ZX, Diamond N, Grady C, Moscovitch M (2017) Similarities and
592 differences in the default mode network across rest, retrieval, and future
593 imagining. Human Brain Mapping 38:1155-1171.
594 Benjamin DJ, Berger JO (2019) Three Recommendations for Improving the Use of p-
595 Values. The American Statistician 73:186-191.
596 Benoit RG, Schacter DL (2015) Specifying the core network supporting episodic
597 simulation and episodic memory by activation likelihood estimation.
598 Neuropsychologia 75:450-457.
599 Buckner RL, Carroll DC (2007) Self-projection and the brain. Trends in Cognitive
600 Sciences 11:49-57.
601 Campbell KL, Madore KP, Benoit RG, Thakral PP, Schacter DL (2017) Increased
602 hippocampus to ventromedial prefrontal connectivity during the construction of
603 episodic future events. Hippocampus:1-5.
604 Cenquizca LA, Swanson LW (2007) Spatial organization of direct hippocampal field
605 CA1 axonal projections to the rest of the cerebral cortex. Brain Research
606 Reviews 56:1-26.
607 Christiansen K, Aggleton JP, Parker GD, O'sullivan MJ, Vann SD, Metzler-Baddeley
608 C (2016) The status of the precommissural and postcommissural fornix in
609 normal ageing and mild cognitive impairment: an MRI tractography study.
610 NeuroImage 130:35-47.
611 Ciaramelli E, De Luca F, Monk AM, McCormick C, Maguire EA (2019) What" wins" in
612 VMPFC: scenes, situations, or schema? Neuroscience & Biobehavioral
613 Reviews 100:208-210.
614 Ciocchi S, Passecker J, Malagon-Vina H, Mikus N, Klausberger T (2015) Selective
615 information routing by ventral hippocampal CA1 projection neurons. Science
616 348:560-563.
617 Cole SN, Gill NC, Conway MA, Morrison CM (2012) Rapid communication: Mental
618 time travel: Effects of trial duration on episodic and semantic content.
619 Quarterly Journal of Experimental Psychology 65:2288-2296.

620 Concha L, Gross DW, Beaulieu C (2005) Diffusion tensor tractography of the limbic
621 system. American Journal of Neuroradiology 26:2267-2274.
622 Concha L, Livy DJ, Beaulieu C, Wheatley BM, Gross DW (2010) In vivo diffusion
623 tensor imaging and histopathology of the fimbria-fornix in temporal lobe
624 epilepsy. Journal of Neuroscience 30:996-1002.
625 Croux C, Dehon C (2010) Influence functions of the Spearman and Kendall
626 correlation measures. Statistical Methods & Applications 19:497-515.
627 Crovitz HF, Schiffman H (1974) Frequency of episodic memories as a function of
628 their age. Bulletin of the Psychonomic Society 4:517-518.
629 Croxson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinsk MA, Gross CG,
630 Richter W, Richter MC, Kastner S, Rushworth MF (2005) Quantitative
631 investigation of connections of the prefrontal cortex in the human and
632 macaque using probabilistic diffusion tractography. Journal of Neuroscience
633 25:8854-8866.
634 D'Argembeau A (2013) On the role of the ventromedial prefrontal cortex in self-
635 processing: the valuation hypothesis. Frontiers in Human Neuroscience 7:1-
636 13.
637 Dell'Acqua F, Tournier JD (2019) Modelling white matter with spherical
638 deconvolution: how and why? NMR in Biomedicine 32:1-18.
639 Destrieux C, Fischl B, Dale A, Halgren E (2010) Automatic parcellation of human
640 cortical gyri and sulci using standard anatomical nomenclature. NeuroImage
641 53:1-15.
642 Diedenhofen B, Musch J (2015) cocor: a comprehensive solution for the statistical
643 comparison of correlations. PLOS One 10:e0121945.
644 Eichenbaum H (2017) Prefrontal–hippocampal interactions in episodic memory.
645 Nature Reviews Neuroscience 18:547.
646 Eichenbaum H, Cohen NJ (2014) Can we reconcile the declarative memory and
647 spatial navigation views on hippocampal function? Neuron 83:764-770.
648 Gilboa A, Marlatte H (2017) Neurobiology of schemas and schema-mediated
649 memory. Trends in Cognitive Sciences 21:618-631.
650 Graham KS, Barense MD, Lee AC (2010) Going beyond LTM in the MTL: a
651 synthesis of neuropsychological and neuroimaging findings on the role of the
652 medial temporal lobe in memory and perception. Neuropsychologia 48:831-
653 853.

654 Hodgetts CJ, Postans M, Warne N, Varnava A, Lawrence AD, Graham KS (2017a)
655 Distinct contributions of the fornix and inferior longitudinal fasciculus to
656 episodic and semantic autobiographical memory. Cortex 94:1-14.
657 Hodgetts CJ, Voets NL, Thomas AG, Clare S, Lawrence AD, Graham KS (2017b)
658 Ultra-high-field fMRI reveals a role for the subiculum in scene perceptual
659 discrimination. Journal of Neuroscience 37:3150-3159.
660 Irish M, Hodges JR, Piguet O (2013) Episodic future thinking is impaired in the
661 behavioural variant of frontotemporal dementia. Cortex 49:2377-2388.
662 JASP (2018) JASP Team (Version 0.9.1.0) [Computer software]. In.
663 Jay TM, Witter MP (1991) Distribution of hippocampal CA1 and subicular efferents in
664 the prefrontal cortex of the rat studied by means of anterograde transport of
665 Phaseolus vulgaris-leucoagglutinin. Journal of Comparative Neurology
666 313:574-586.
667 Jbabdi S, Behrens TE (2013) Long-range connectomics. Annals of the New York
668 Academy of Sciences 1305:83-93.
669 Jeurissen B, Leemans A, Jones DK, Tournier JD, Sijbers J (2011) Probabilistic fiber
670 tracking using the residual bootstrap with constrained spherical deconvolution.
671 Human Brain Mapping 32:461-479.
672 Jones DK, Cercignani M (2010) Twenty-five pitfalls in the analysis of diffusion MRI
673 data. NMR in Biomedicine 23:803-820.
674 Jones DK, Knösche TR, Turner R (2013) White matter integrity, fiber count, and
675 other fallacies: the do's and don'ts of diffusion MRI. NeuroImage 73:239-254.
676 Kosslyn SM, Van Kleeck M (1990) Broken brains and normal minds: why Humpty-
677 Dumpty needs a skeleton. In: Computational neuroscience (Schwartz E, ed),
678 pp 390-402. Cambridge, MA: MIT Press.
679 Kurczek J, Wechsler E, Ahuja S, Jensen U, Cohen NJ, Tranel D, Duff M (2015)
680 Differential contributions of hippocampus and medial prefrontal cortex to self-
681 projection and self-referential processing. Neuropsychologia 73:116-126.
682 Lakens D (2016) One-sided tests: Efficient and underused [Blog post]. In.
683 Leemans A, Jones DK (2009) The B-matrix must be rotated when correcting for
684 subject motion in DTI data. Magnetic Resonance in Medicine 61:1336-1349.

685 Levine B, Svoboda E, Hay JF, Winocur G, Moscovitch M (2002) Aging and
686 autobiographical memory: dissociating episodic from semantic retrieval.
687 Psychology and Aging 17:677-689.
688 Mathiasen ML, Louch RC, Nelson AD, Dillingham CM, Aggleton JP (2019) Trajectory
689 of hippocampal fibres to the contralateral anterior thalamus and mammillary
690 bodies in rats, mice, and macaque monkeys. Brain and Neuroscience
691 Advances 3:1-18.
692 McCormick C, Ciaramelli E, De Luca F, Maguire EA (2018) Comparing and
693 contrasting the cognitive effects of hippocampal and ventromedial prefrontal
694 cortex damage: a review of human lesion studies. Neuroscience 374:295–
695 318.
696 McCormick C, St-Laurent M, Ty A, Valiante TA, McAndrews MP (2015) Functional
697 and effective hippocampal–neocortical connectivity during construction and
698 elaboration of autobiographical memory retrieval. Cerebral Cortex 25:1297-
699 1305.
700 Metzler-Baddeley C, Jones DK, Belaroussi B, Aggleton JP, O'Sullivan MJ (2011)
701 Frontotemporal connections in episodic memory and aging: a diffusion MRI
702 tractography study. Journal of Neuroscience 31:13236-13245.
703 Murray EA, Wise SP, Graham KS (2017) The evolution of memory systems:
704 ancestors, anatomy, and adaptations. Oxford, UK: Oxford University Press.
705 O'Neill P-K, Gordon JA, Sigurdsson T (2013) Theta oscillations in the medial
706 prefrontal cortex are modulated by spatial working memory and synchronize
707 with the hippocampus through its ventral subregion. Journal of Neuroscience
708 33:14211-14224.
709 Pajevic S, Basser PJ, Fields RD (2014) Role of myelin plasticity in oscillations and
710 synchrony of neuronal activity. Neuroscience 276:135-147.
711 Palombo DJ, Sheldon S, Levine B (2018a) Individual differences in autobiographical
712 memory. Trends in Cognitive Sciences 22:583-597.
713 Palombo DJ, Bacopulos A, Amaral RS, Olsen RK, Todd RM, Anderson AK, Levine B
714 (2018b) Episodic autobiographical memory is associated with variation in the
715 size of hippocampal subregions. Hippocampus 28:69-75.
716 Parker A, Gaffan D (1997) Mamillary body lesions in monkeys impair object-in-place
717 memory: functional unity of the fornix-mamillary system. Journal of cognitive
718 Neuroscience 9:512-521.

719 Pasternak O, Sochen N, Gur Y, Intrator N, Assaf Y (2009) Free water elimination
720 and mapping from diffusion MRI. Magnetic Resonance in Medicine 62:717-
721 730.
722 Pasternak O, Maier-Hein K, Baumgartner C, Shenton ME, Rathi Y, Westin C-F
723 (2014) The estimation of free-water corrected diffusion tensors. In:
724 Visualization and processing of tensors and higher order descriptors for multi-
725 valued data (Westin CF, Vilanova A, Burgeth B, eds), pp 249-270. Berlin,
726 Heidelberg: Springer.
727 Patenaude B, Smith SM, Kennedy DN, Jenkinson M (2011) A Bayesian model of
728 shape and appearance for subcortical brain segmentation. NeuroImage
729 56:907-922.
730 Pierpaoli C, Jezzard P, Basser PJ, Barnett A, Di Chiro G (1996) Diffusion tensor MR
731 imaging of the human brain. Radiology 201:637-648.
732 Place R, Farovik A, Brockmann M, Eichenbaum H (2016) Bidirectional prefrontal-
733 hippocampal interactions support context-guided memory. Nature
734 Neuroscience 19:992-996.
735 Poletti CE, Creswell G (1977) Fornix system efferent projections in the squirrel
736 monkey: an experimental degeneration study. Journal of Comparative
737 Neurology 175:101-127.
738 Postans M, Hodgetts CJ, Mundy ME, Jones DK, Lawrence AD, Graham KS (2014)
739 Interindividual variation in fornix microstructure and macrostructure is related
740 to visual discrimination accuracy for scenes but not faces. Journal of
741 Neuroscience 34:12121-12126.
742 Powell T, Guillery R, Cowan W (1957) A quantitative study of the fornixmamillo-
743 thalamic system. Journal of Anatomy 91:419-437.
744 Preston AR, Eichenbaum H (2013) Interplay of hippocampus and prefrontal cortex in
745 memory. Current Biology 23:R764-R773.
746 Race E, Keane MM, Verfaellie M (2011) Medial temporal lobe damage causes
747 deficits in episodic memory and episodic future thinking not attributable to
748 deficits in narrative construction. Journal of Neuroscience 31:10262-10269.
749 Raichle ME (2015) The brain's default mode network. Annual Review of
750 Neuroscience 38:433-447.
751 Robin J (2018) Spatial scaffold effects in event memory and imagination. Wiley
752 Interdisciplinary Reviews: Cognitive Science 9:1-15.

753 Robin J, Moscovitch M (2017) Details, gist and schema: hippocampal–neocortical
754 interactions underlying recent and remote episodic and spatial memory.
755 Current Opinion in Behavioral Sciences 17:114-123.
756 Saunders RC, Aggleton JP (2007) Origin and topography of fibers contributing to the
757 fornix in macaque monkeys. Hippocampus 17:396-411.
758 Schacter DL, Benoit RG, Szpunar KK (2017) Episodic future thinking: mechanisms
759 and functions. Current Opinion in Behavioral Sciences 17:41-50.
760 Schacter DL, Addis DR, Hassabis D, Martin VC, Spreng RN, Szpunar KK (2012) The
761 future of memory: remembering, imagining, and the brain. Neuron 76:677-
762 694.
763 Squire LR, van der Horst AS, McDuff SG, Frascino JC, Hopkins RO, Mauldin KN
764 (2010) Role of the hippocampus in remembering the past and imagining the
765 future. Proceedings of the National Academy of Sciences 107:19044-19048.
766 Tedder J, Miller L, Tu S, Hornberger M, Lah S (2016) Into the future with little past:
767 exploring mental time travel in a patient with damage to the mammillary
768 bodies/fornix. The Clinical Neuropsychologist 30:334-349.
769 van Kesteren MT, Ruiter DJ, Fernández G, Henson RN (2012) How schema and
770 novelty augment memory formation. Trends in Neurosciences 35:211-219.
771 Vann SD (2013) Dismantling the Papez circuit for memory in rats. Elife 2:1-21.
772 Vann SD, Nelson AJ (2015) The mammillary bodies and memory: more than a
773 hippocampal relay. Progress in Brain Research 219:163-185.
774 Vann SD, Erichsen JT, O'Mara SM, Aggleton JP (2011) Selective disconnection of
775 the hippocampal formation projections to the mammillary bodies produces
776 only mild deficits on spatial memory tasks: implications for fornix function.
777 Hippocampus 21:945-957.
778 Verfaellie M, Wank AA, Reid AG, Race E, Keane MM (2019) Self-related processing
779 and future thinking: distinct contributions of ventromedial prefrontal cortex and
780 the medial temporal lobes. Cortex 115:159-171.
781 Yang X-F, Bossmann J, Schiffhauer B, Jordan M, Immordino-Yang MH (2013)
782 Intrinsic default mode network connectivity predicts spontaneous verbal
783 descriptions of autobiographical memories during social processing. Frontiers
784 in Psychology 3:1-10.
785 Zeidman P, Maguire EA (2016) Anterior hippocampus: the anatomy of perception,
786 imagination and episodic memory. Nature Reviews Neuroscience 17:173-182.

787 Zhang Y, Brady M, Smith S (2001) Segmentation of brain MR images through a
788 hidden Markov random field model and the expectation-maximization
789 algorithm. IEEE Transactions on Medical Imaging 20:45-57.
790