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

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

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1 **Abstract**

2 Neuropsychological and functional magnetic resonance imaging (MRI) evidence

3 suggests that the ability to vividly remember our personal past, and imagine future

4 scenarios, involves two closely connected regions: the hippocampus and

5 ventromedial prefrontal cortex (vmPFC). Despite evidence of a direct anatomical

6 connection from hippocampus to vmPFC, it is unknown whether hippocampal-

7 vmPFC structural connectivity supports both past and future-oriented episodic

8 thinking. To address this, we applied diffusion-weighted magnetic resonance imaging

9 (dMRI) and a novel deterministic tractography protocol to reconstruct distinct

10 subdivisions of the fornix previously detected in axonal tracer studies, namely pre-

11 commissural (connecting the hippocampus to vmPFC) and post-commissural (linking

12 the hippocampus and medial diencephalon) fornix, in a group of healthy young adult

13 humans who undertook an adapted past-future autobiographical interview. As

14 predicted, we found that inter-individual differences in pre-commissural - but not

15 post-commissural - fornix microstructure (fractional anisotropy) was significantly

16 correlated with the episodic richness of both past *and* future autobiographical

17 narratives. Notably, these results remained significant when controlling for both non-

18 episodic narrative content and grey matter volumes of the hippocampus and vmPFC.

19 This study provides novel evidence that reconstructing events from one's personal

20 past, and constructing possible future events, involves a distinct, structurally-

21 instantiated hippocampal-vmPFC pathway.

22

26

27 **Significance Statement**

28 A novel anatomically-guided protocol that allows the pre-commissural and post-

29 commissural fornix fibers to be separately reconstructed *in vivo* (Christiansen et al.,

30 2016) was applied to reconstruct the pre-commissural subdivision of the white

31 matter fornix tract (anatomically linking the hippocampal formation to the vmPFC)

32 and investigate its contribution to episodic memory and future simulation. We

33 demonstrated that the amount of episodic details contained in past and future

34 narratives, collected via an adapted autobiographical interview, was positively

35 correlated with pre-, but not post-, commissural fornix microstructure. These findings

36 highlight how inter-individual variation in the pre-commissural subdivision of the

37 fornix underpins the construction of self-reflective, contextual events – for both the

38 past and future.

39

Introduction

40

41 A key adaptive feature of human cognition is the ability to re-experience our personal

42 histories and imagine the future in vivid detail. According to the constructive episodic

43 simulation hypothesis, the processes and neural machinery that allow us to

44 remember past experiences also allow us to imagine future experiences (Schacter et

45 al., 2012; Addis, 2018). Consistent with this view, remembering past and imagining

46 future events activate a common set of brain regions, including the hippocampus and

47 ventromedial prefrontal cortex (vmPFC) (Addis et al., 2007; Benoit and Schacter,

48 2015). Furthermore, the ability to retrieve episodically rich autobiographical

49 memories and construct coherent future simulations is diminished following lesions

50 to both the hippocampus and vmPFC (Race et al., 2011; McCormick et al., 2018)

51 (but see Squire et al., 2010). Such findings have led to the suggestion that the

52 hippocampus and vmPFC are critical nodes within a default (Andrews-Hanna et al.,

53 2010; Raichle, 2015) or 'core' network that interact to support autobiographical

54 memory and imagination (Schacter et al., 2012; Schacter et al., 2017) (For related

55 proposals see also Murray et al., 2017; Robin and Moscovitch, 2017; McCormick et

56 al., 2018).

57

58 Converging evidence has shifted focus towards this neural network-level approach to

59 support the way we reconstruct our personal past and construct possible future

60 experiences (Schacter et al., 2012; Bellana et al., 2017; Schacter et al., 2017). For

61 instance, studies using functional magnetic resonance imaging (fMRI) have found

62 increased functional connectivity between the hippocampus and vmPFC during both

63 the retrieval of autobiographical memories (McCormick et al., 2015) and the

64 construction of episodic future events (Campbell et al., 2017), and resting state

65 functional connectivity between these regions has been shown to predict the

66 episodic quality of individual's memories (Yang et al., 2013).

67

68 The communication of information across networked areas depends on the

69 organization and integrity of the white matter connections between them (Jbabdi and

70 Behrens, 2013). Invasive tract-tracing techniques have revealed direct efferent

71 anatomical connections from the hippocampus to the vmPFC. In rats, the entire

72 longitudinal extent of the subiculum/CA1 is connected - via the pre-commissural

73 fornix - with the vmPFC, with connectivity increasing progressively in strength from

74 dorsal to ventral hippocampus (Jay and Witter, 1991; Cenquizca and Swanson,
75 2007). Similarly in primates, the pre-commissural fornix provides the exclusive route
76 for subiculum/CA1 projections to medial and orbitofrontal PFC (Barbas and Blatt,
77 1995; Aggleton et al., 2015), with relatively more projections arising from the anterior
78 hippocampus. In humans, diffusion-weighted magnetic resonance imaging (dMRI),
79 which can non-invasively delineate the path of major fiber pathways and evaluate
80 their microstructure through indices such as fractional anisotropy (FA) (Jbabdi and
81 Behrens, 2013), has provided initial evidence for hippocampus-PFC connections via
82 the fornix (Croxson et al., 2005). Building on this work, Christiansen et al. (2016)
83 recently developed an anatomically guided dMRI protocol for the selective *in vivo*
84 reconstruction of pre-commissural fornix fibers in humans, allowing investigation of
85 the functions supported by human hippocampus-PFC structural connectivity for the
86 first time.

87

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

104

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*

139   *there anything else you can tell me about this event?").* All trials for one temporal

140   direction (past or future) were completed before beginning the trials for the other

141   condition. Order of presentation of temporal direction (past or future) was

142   counterbalanced, as were the word lists (across the past and future conditions).

143   Participants were tested individually, and responses were recorded using a portable

144   recording device (Zoom H1 Digital Field Recorder) for subsequent transcription and

145   scoring.

146

147   **Scoring**

148   The standardized AI scoring procedure (Levine et al., 2002) was used. Events (past

149   and future) generated were segmented into distinct chunks of information in order to

150   allow analysis of the levels of episodic or semantic information provided within each.

151   These chunks were typically characterized by grammatical clauses that referenced a

152   unique occurrence, observation or thought (Levine et al., 2002). Two broad

153   categories were used to categorize details: 'internal' details (which described the

154   central event) and 'external' details (decontextualized information, including semantic

155   details and information concerning extended events that are not specific in time and

156   place, and repetitions). In the case that a participant described more than one event,

157   the event that was described in the most detail was coded as 'internal' and the other

158   as 'external'. The central event was required to refer to a specific time and place,

159   thus it can be considered 'episodic' and will be referred to as such henceforth.

160   Episodic details included not only time and place details, but also any other episodic

161   information (sensory details, thoughts and emotions) that were part of the central

162   event (Levine et al., 2002). **Figure 1** contains examples of external and episodic

163   details from past and future narratives. Total score was computed by summing over

164   the 10 event narratives.

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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

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215   Deterministic tractography was performed from all voxels based on constrained

216   spherical deconvolution (CSD) (Jeurissen et al., 2011; Dell'Acqua and Tournier,

217   2019). CSD allows for the representation of bending/crossing/kissing fibers in

218   individual voxels, as multiple peaks in the fiber orientation density function (fODF)

219   can be extracted within each voxel (Dell'Acqua and Tournier, 2019). The step size

220   was 1mm, and the fODF amplitude threshold was 0.1. An angle threshold of 30° was

221   used to prevent the reconstruction of anatomically implausible fibers.

222

223   To generate 3D fiber reconstructions of each tract segment, waypoint region-of-

224   interest (ROI) gates were drawn manually onto whole-brain free water corrected FA

225   maps. The waypoint ROIs defined the tracts based on a 'SEED' point and Boolean

226   logical operations: 'NOT' and 'AND'. The 'NOT' and 'AND' gates corresponded to

227   whether tracts passing through were omitted from analyses or retained, respectively.

228   These gates were combined to reconstruct the tracts, based on anatomical

229   plausibility. Initially, a multiple ROI approach was applied to reconstruct the fornix

230   (see Metzler-Baddeley et al., 2011; Hodgetts et al., 2017a).

231

Fornix reconstruction

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233   A 'SEED' point ROI was placed on the coronal plane, encompassing the body of the

234   fornix. An 'AND' ROI was placed on the axial plane, capturing the crus fornici in both

235   hemispheres at the lower part of the splenium of the corpus callosum. 'NOT' ROIs

236   were placed intersecting the corpus callosum on the axial plane, and anterior to the

237   fornix pillars and posterior to the crus fornici on the coronal plane. Further 'NOT'

238   way-gates were placed after the initial reconstruction and ensuing visual inspection,

239   to remove anatomically implausible fibers. Subsequently, the anterior body of the

240   fornix was split into the pre- and post- commissural column segments (**Figure 2**).

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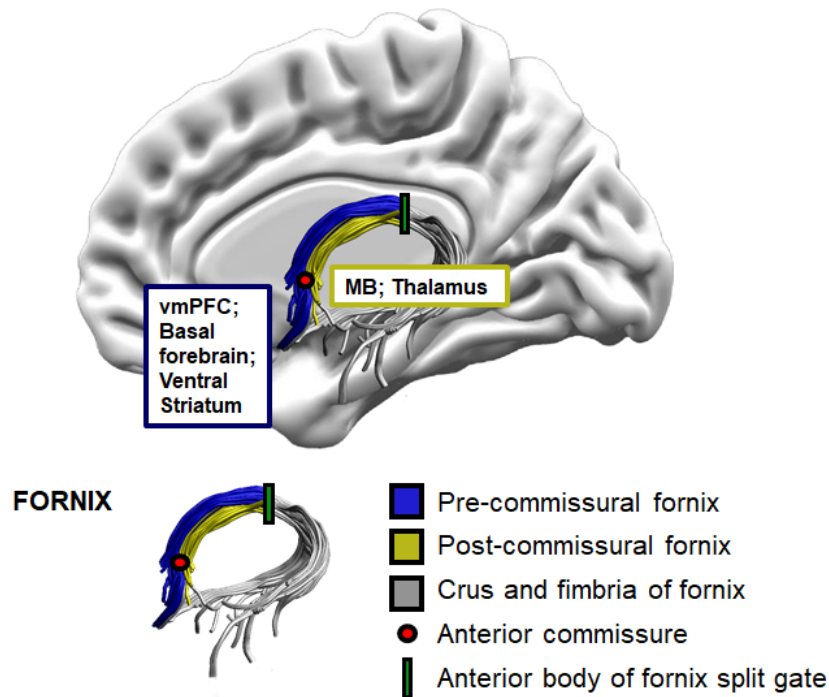
Figure 2. Schematic illustration of the anatomical landmarks for fornix tract sub-division, and the connecting areas of interest. vmPFC = Ventromedial Prefrontal Cortex; MB = Mammillary Bodies.

246

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.
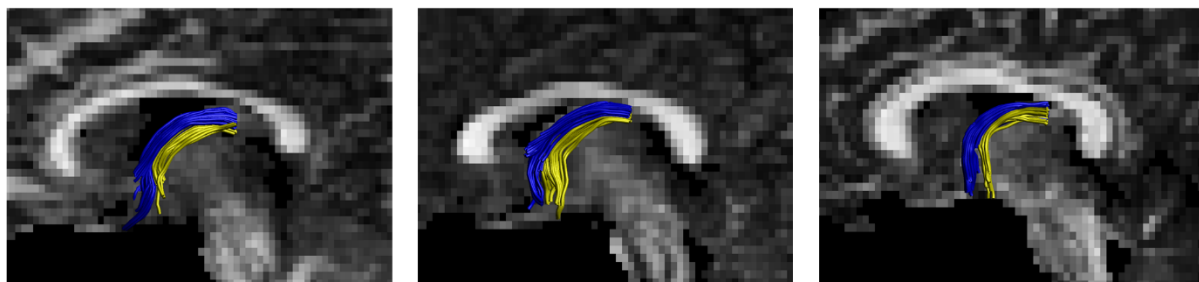
251
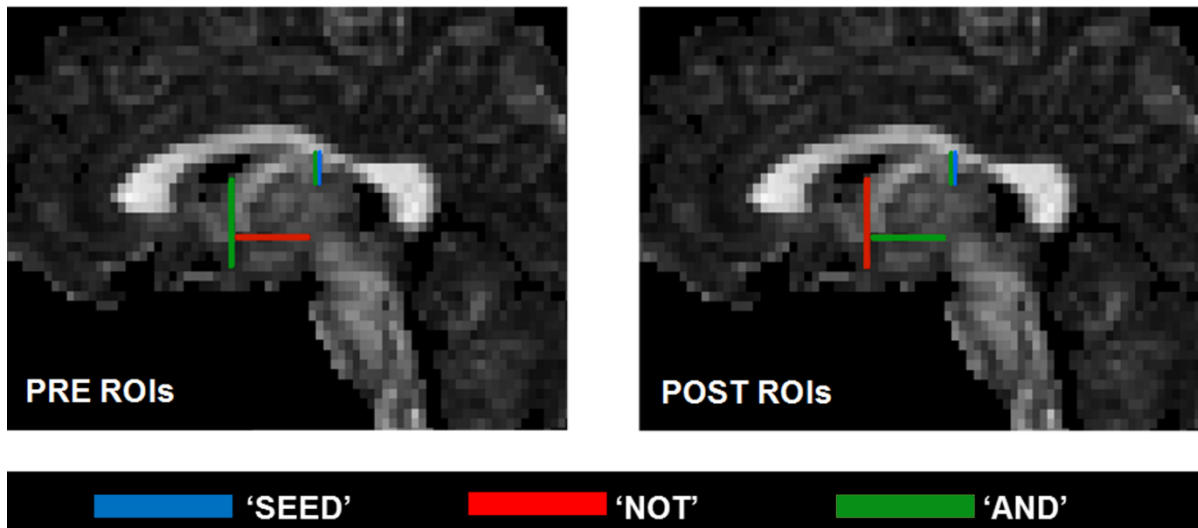
Figure 3. Waypoint region-of-interest (ROI) gates used for reconstructing the pre- and post- commissural fornix tract segments (Blue = SEED, Red = NOT, Green = AND).

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.

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272   The anterior-body of the fornix was then divided into the pre- and post-commissural

273   segments. This delineation took advantage of the manner in which the fibers

274   separate at the anterior columns of the fornix. At this level, the segments contain

275   approximately the same number of fibers (Powell et al., 1957). The pre-commissural

276   fornix was delineated by positioning an additional 'AND' gate on the coronal plane at

277   the anterior-commissure, as well as an additional 'NOT' gate meeting this 'AND' gate

278   on the axial plane. For the post-commissural fornix reconstruction, the additional

279   'NOT' and 'AND' gates placed for reconstruction of the pre-commissural fornix were

280   swopped (see **Figure 3**). Thus, for the pre-commissural fornix, tracts were included

281   only if they extended anterior to the anterior commissure, and for the post-

282   commissural fornix only tracts running posterior to the anterior commissure were

283   retained (see **Figure 4**) (Christiansen et al., 2016).

284

285   **Grey matter volumetrics**

286   T1-weighted images were corrected for spatial intensity variations using FMRIB's

287   Automated Segmentation Tool (FAST; Zhang et al., 2001). Bilateral grey matter

288   volumes (expressed as a proportion of estimated total intracranial volume) of the

289   hippocampus were subsequently obtained using FMRIB's Integrated Registration &

290   Segmentation Tool (FIRST; Patenaude et al., 2011). Volumes for the vmPFC ROI

291   were derived using FreeSurfer (surfer.nmr.mgh.harvard.edu: Destrieux et al., 2010),

292   via summing volumes of the medial orbitofrontal cortex (mOFC) and rostral anterior

293   cingulate cortex (rACC) parcels. One participant was removed from the grey matter

294   analyses due to poor overall data quality on the T1 FSPGR.

295

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

14

330   future (mean = 86.5, median = 75, SD = 40.8, range = 23 - 198) (**Figure 5B**.

331   Pearson's r = 0.73, p < 0.001, VS-MPR = 3254.64). There were also significantly

332   more external details given for the future in comparison to the past (t(26) = 2.23, p =

333   0.035, d_z = 0.43, paired t-test). The number of episodic details an individual recalled

334   for the past also correlated with the number of external details recalled for the past

335   (Pearson's r = 0.35, p = 0.035, VS-MPR = 3.15); this was not the case, however, for

336   the future (Pearson's r = -0.16, p = 0.783, VS-MPR = 1.00).

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338

A   **B**
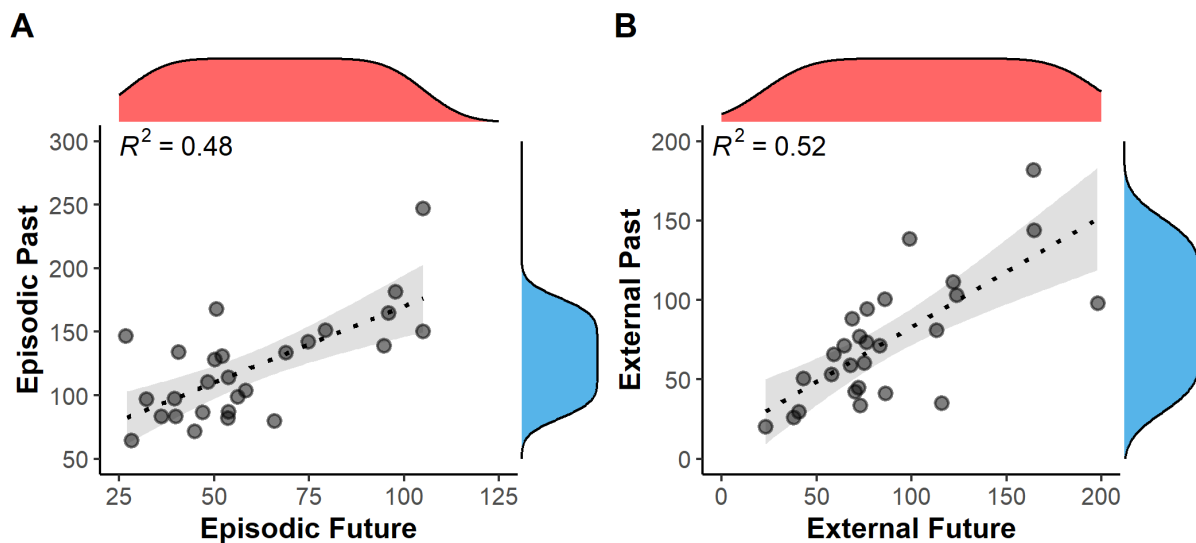
339

340   **Figure 5 (A, B)**. Scatterplots depicting correlations between the number of details

341   produced for the past versus the future AI narratives (A. Episodic, B. External)

342   (*N*=27). Marginal density is displayed on the opposite axis. Grey shading equals the

343   95% CI.

344

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

346   We found a significant positive correlation between the number of past episodic

347   details and pre-commissural fornix FA (**Figure 6A**. Pearson's r = 0.49, p = 0.005,

348   VS-MPR = 14.49, Spearman's rho = 0.464, p = 0.007, VS-MPR = 10.09). There was

349   no significant correlation between post-commissural fornix FA and episodic past

350   details (**Figure 6B**. Pearson's r = -0.12; p = 0.725, VS-MPR = 1.00, Spearman's rho

351   = 0.02, p = 0.457, VS-MPR = 1.00). The correlation between episodic past details

352   and pre-commissural fornix FA was significantly greater than between episodic past

353   details and post-commissural fornix FA (Steiger z (27) = 2.29, p = 0.011) (computed

354   using R package 'cocor', Diedenhofen and Musch, 2015).

355
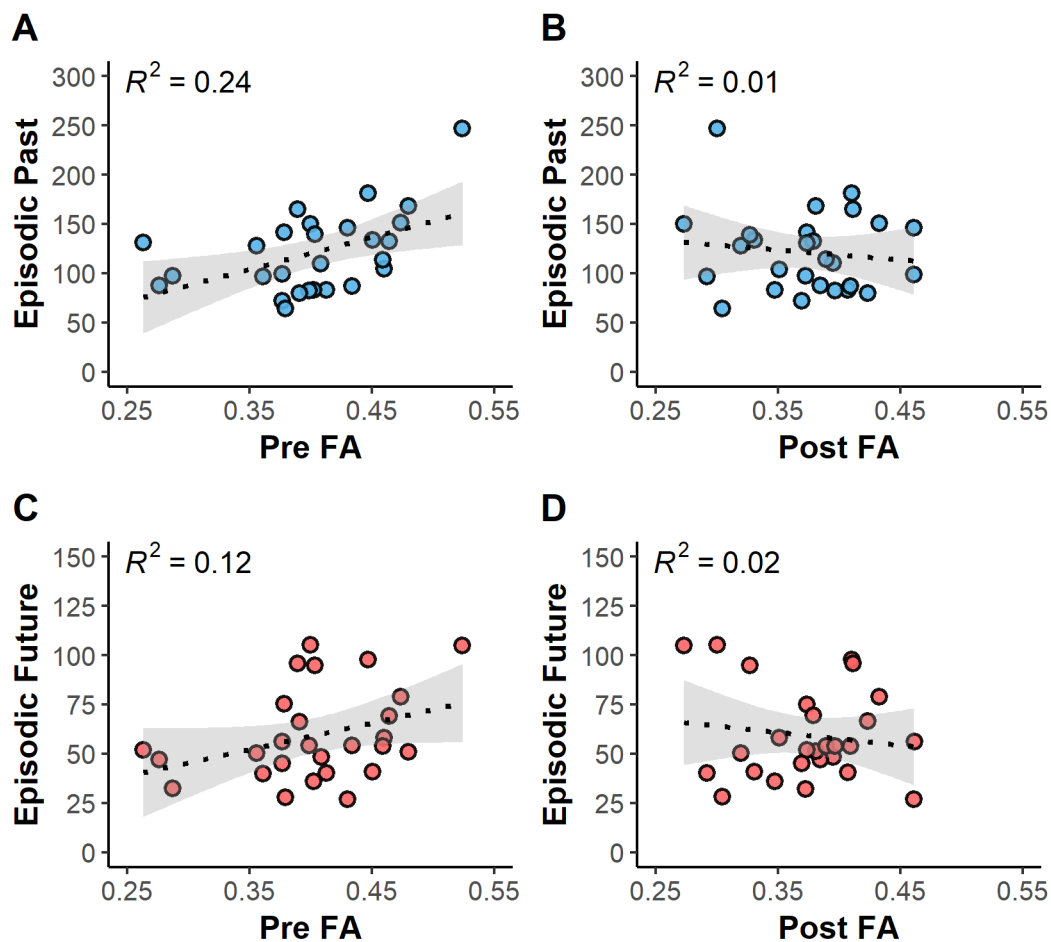
Figure 6 (A-D). Scatterplots depicting the correlations of episodic past (A, B) and future (C, D) AI details with pre-/post- commissural fornix microstructure (fractional anisotropy, FA). Number of episodic past/future details (summed over 10 cue words) is plotted on the y-axis (*N*=27). Grey shading equals the 95% CI.

361

362   The correlation between episodic past details and pre-commissural fornix FA was

363   also significantly greater than between external past details and pre-commissural

364   fornix FA (Steiger z (27) = 1.69, p = 0.046). Additionally, when controlling for the

365   number of external details produced by the individual, the correlation between

366   episodic past details and pre-commissural fornix FA remained significant (Pearson's

367   r = 0.48, p = 0.007, Spearman's rho = 0.47, p = 0.007).

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369

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

371 The findings for the episodic future simulation details mirrored those for the episodic

372 past retrieval. There was a significant positive correlation between the total number

373 of future episodic details (summed over the 10 cue words) and pre-commissural

374 fornix FA (**Figure 6C**. Pearson's r = 0.35, p = 0.035, VS-MPR = 3.11, Spearman's

375 rho = 0.33, p = 0.045, VS-MPR = 2.62), and, correspondingly, there was no

376 significant correlation between episodic future details and post-commissural fornix

377 FA (**Figure 6D**. Pearson's r = -0.14, p = 0.752, VS-MPR = 1.00, Spearman's rho =

378 0.09, p = 0.330, VS-MPR = 1.01). The correlation between episodic future details

379 and pre-commissural fornix FA was also significantly greater than between episodic

380 future details and post-commissural fornix FA (Steiger z (27) = 1.78, p = 0.038). The

381 correlation between episodic future details and pre-commissural fornix FA was not

382 significantly greater than between external future details and pre-commissural fornix

383 FA, however, when controlling for the number of external details given the correlation

384 between episodic future details and pre-commissural fornix FA remained significant

385 (Pearson's r = 0.38, p = 0.028, Spearman's rho = 0.33, p = 0.0499).

386

387 **Influence of grey matter volume**

388 When hippocampal volume was controlled for, the correlation between past episodic

389 details and pre-commissural fornix FA remained significant (partial correlation:

390 Pearson's r = 0.49, p = 0.006), and there was no significant association between

391 post-commissural fornix FA and episodic past details (partial correlation: Pearson's r

392 = -0.09, p = 0.341). Likewise, the correlation between future episodic details and pre-

393 commissural fornix FA remained significant when controlling for hippocampal volume

394 (partial correlation: Pearson's r = 0.37, p = 0.035), and there was no significant

395 association between post-commissural fornix FA and episodic future details (partial

396 correlation: Pearson's r = 0.04, p = 0.422).

397

398 Similarly, when vmPFC volume was controlled for, the correlation between past

399 episodic details and pre-commissural fornix FA remained significant (partial

400 correlation: Pearson's r = 0.54, p = 0.003), and there was no significant correlation

401 between post-commissural fornix FA and past episodic details (partial correlation:

402 Pearson's r = -0.22, p = 0.143). For the future simulations, the correlation between

403 the number of episodic details and pre-commissural fornix FA remained significant

17

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

18

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

441

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

449

450   The differential contributions of the hippocampus and vmPFC to episodic
451   constructive processes are hotly debated (Robin and Moscovitch, 2017; Schacter et
452   al., 2017; McCormick et al., 2018). According to scene construction theory, the
453   hippocampus, and particularly the subiculum, plays a central role in forming
454   representations of spatially coherent scenes across memory, perception and
455   imagination (Zeidman and Maguire, 2016; Hodgetts et al., 2017b), and these
456   conjunctive scene representations have been proposed to provide a scaffold when
457   constructing both past and future events (Murray et al., 2017; Robin, 2018; Barry and
458   Maguire, 2019). In contrast, the constructive episodic simulation hypothesis
459   contends that the construction of spatiotemporal contexts arises out of a more
460   general relational processing mechanism (Eichenbaum and Cohen, 2014) housed in
461   hippocampus, which is also responsible for the integration of other event details into
462   the event representation (Schacter et al., 2012; Schacter et al., 2017; Addis, 2018).
463   The vmPFC's contribution to episodic construction, by contrast, has been linked to
464   demands on schematic representations (van Kesteren et al., 2012; Gilboa and
465   Marlatte, 2017; Robin and Moscovitch, 2017), in particular the self-schema (Buckner
466   and Carroll, 2007; D'Argembeau, 2013). For instance, Kurczek et al. (2015) (see also
467   Verfaellie et al., 2019) compared the number of references to 'the self' included in
468   autobiographical event narratives from patients with bilateral hippocampal or medial
469   PFC damage as well as healthy controls. Patients with medial PFC damage, despite
470   being able to construct highly detailed episodic events, produced relatively few self-
471   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

506 connectivity between the hippocampus and medial diencephalon (i.e., mammillary
507 bodies and thalamus) in spatial and contextual memory (Parker and Gaffan, 1997;
508 Aggleton and Brown, 1999), connectivity which is mediated by the *post*- but not the
509 *pre*-commissural fornix (Vann and Nelson, 2015; Christiansen et al., 2016;
510 Mathiasen et al., 2019). While the current findings seemingly challenge this account,
511 one caveat is that our post-commissural fornix tract reconstructions principally
512 involve the connections of the hippocampus with the hypothalamus, including the
513 mammillary bodies, and largely exclude the projections to the anterior thalamic
514 nuclei, as these turn towards posterior regions as the fornix columns descend
515 (Poletti and Creswell, 1977; Christiansen et al., 2016). These thalamic fibers do not
516 form a discrete tract, rather they remain diffuse (Mathiasen et al., 2019). Previous
517 work has demonstrated that thalamic degeneration can impair episodic
518 autobiographical memory and future thinking (Irish et al., 2013). Notably, however,
519 Vann and colleagues (Vann et al., 2011; Vann, 2013) have reported that lesions to
520 the descending post-commissural fornix columns in rats have little impact on spatial
521 memory tests that are sensitive to mammillary body, mammillothalamic tract, anterior
522 thalamic, and hippocampal lesions. The implication of this finding is that the
523 hippocampal-mammillary connection may not be important for all forms of episodic
524 memory, including (as here) those that place demand on constructive and self-
525 referential processing (see also Tedder et al., 2016) (but see Christiansen et al.,
526 2016).

527

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

540 2014; Palombo et al., 2018b), and VS-MPRs showed that our findings provide a

541 good level of diagnosticity (Benjamin and Berger, 2019), it will be important to extend

542 our findings to larger lifespan samples.

543

544 In summary, we report a novel association between white matter microstructure of

545 the pre-commissural fornix and episodic past and future thinking, thus elucidating a

546 potential anatomical mechanism by which direct hippocampal-to-vmPFC connectivity

547 supports constructive episodic processing. These findings provide important support

548 for the idea of a core-network supporting both the re-construction of past events and

549 the construction of hypothetical events in the future, and that individual differences in

550 structural connectivity may reflect how richly people can reconstruct the past and

551 construct possible futures.

552

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