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   The ability to vividly remember the past, and imagine the future, involves two key

3   regions: the hippocampus and ventromedial prefrontal cortex (vmPFC). Despite

4   evidence of a direct anatomical connection between these structures, it is unknown

5   whether hippocampal-vmPFC structural connectivity supports both past and future-

6   oriented episodic thinking. We applied diffusion-weighted magnetic resonance

7   imaging (dMRI) and a novel tractography protocol to reconstruct distinct fornix

8   subdivisions previously detected in axonal tracer studies, namely pre-commissural

9   (connecting anterior hippocampus to vmPFC) and post-commissural (linking posterior

10 hippocampus and medial diencephalon) fornix, in a group of healthy humans who

11 undertook a past-future autobiographical interview. Inter-individual differences in pre-

12 but not post-commissural fornix microstructure significantly correlated with the

13 episodic richness of both past *and* future autobiographical narratives. These results

14 remained significant when controlling for both non-episodic narrative content and

15 regional volumes. Reconstructing events from one's past, and constructing possible

16 future events, thus involves a distinct, structurally-instantiated hippocampal-vmPFC

17 pathway.

18

19 ***Keywords:***

20 Hippocampus, Episodic memory, Future thinking, Structural connectivity, vmPFC,

21 White matter tractography

22

23 **Significance Statement**

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

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

26 2016) was applied to reconstruct the pre-commissural subdivision of the white matter

27 fornix tract (anatomically linking the hippocampal formation to the vmPFC) and

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

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

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

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

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

33 underpins the construction of self-reflective, contextual events – for both the past and

34 future.

35

Introduction

36 **Introduction**

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

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

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

40 past experiences also allow us to imagine future experiences (Addis, 2018; Schacter

41 et al., 2012). Consistent with this view, remembering past and imagining future events

42 activate a common set of brain regions, including the hippocampus and ventromedial

43 prefrontal cortex (vmPFC) (Addis, Wong, & Schacter, 2007; Benoit & Schacter, 2015).

44 Furthermore, the ability to retrieve episodically rich autobiographical memories and

45 construct coherent future simulations is diminished following lesions to both the

46 hippocampus and vmPFC (McCormick, Ciaramelli, De Luca, & Maguire, 2018; Race,

47 Keane, & Verfaellie, 2011; but see Squire et al., 2010). Such findings have led to the

48 suggestion that the hippocampus and vmPFC are critical nodes within a default

49 (Raichle, 2015) or 'core' network that interact to support autobiographical memory and

50 imagination (Addis, 2018; Schacter et al., 2012; Schacter, Benoit, & Szpunar, 2017)

51 (see Behrens et al., 2018; McCormick et al., 2018; Murray, Wise, & Graham, 2017;

52 Robin & Moscovitch, 2017, for related proposals).

53

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

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

56 experiences (Bellana, Liu, Diamond, Grady, & Moscovitch, 2017; Schacter et al., 2012;

57 Schacter et al., 2017). For instance, studies using functional magnetic resonance

58 imaging (fMRI) have found increased functional connectivity between the

59 hippocampus and vmPFC during both the retrieval of autobiographical memories

60 (McCormick, St-Laurent, Ty, Valiante, & McAndrews, 2015) and the construction of

61 episodic future events (Campbell, Madore, Benoit, Thakral, & Schacter, 2017), and

62 resting state functional connectivity between these regions has been shown to predict

63 the episodic quality of individual's memories (Yang, Bossmann, Schiffhauer, Jordan,

64 & Immordino-Yang, 2013).

65

66 The communication of information across networked areas depends on the

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

68 Behrens, 2013). Invasive tract-tracing techniques have revealed a direct

69 hippocampus-to-PFC pathway comprising the major efferent anatomical connection

70 from the hippocampus to the PFC (Jin & Maren, 2015). In rats, the hippocampus-PFC

71 pathway projects, via the pre-commissural fornix, from ventral CA1 and ventral

72 subiculum to medial PFC (Cenquizca & Swanson, 2007). Similarly in primates, the

73 pre-commissural fornix provides the route for anterior CA1 and subiculum projections

74 to medial and orbitofrontal PFC (Aggleton, Wright, Rosene, & Saunders, 2015). In

75 humans, diffusion-weighted imaging (dWI), which can non-invasively delineate the

76 path of major fiber pathways and evaluate their microstructure through indices such

77 as fractional anisotropy (FA) (Jbabdi & Behrens, 2013), has provided initial evidence

78 for hippocampus-PFC connections via the fornix (Croxson et al., 2005). Building on

79 this work, Christiansen et al. (2016) recently developed an anatomically guided dWI

80 protocol for the selective *in vivo* reconstruction of pre-commissural fornix fibers in

81 humans, allowing investigation of the functions of the human hippocampus-PFC

82 pathway for the first time.

83

84 By application of this novel protocol, we investigated the role of the pre-commissural

85 fornix in autobiographical past and future thinking using an individual differences

86 design (Palombo, Sheldon, & Levine, 2018). Participants were asked to recall past

87 experiences and generate future events using word cues according to a modified

88 Galton-Crovitz cue-word paradigm (Crovitz & Schiffman, 1974). White matter

89 microstructure was assessed in these individuals using high angular resolution

90 diffusion-weighted imaging (HARDI) and constrained spherical deconvolution

91 tractography (Dell'Acqua & Tournier, 2019). Given the directed hippocampus-PFC

92 functional connections identified above in relation to (re)constructing events in

93 episodic memory and episodic simulation (Campbell et al., 2017; McCormick et al.,

94 2015), we hypothesized that individual differences in the episodic richness of past and

95 future thinking would be related to the microstructure (FA) of the hippocampus-PFC

96 pathway underpinned by the pre-commissural fornix. As a comparison tract, we used

97 the post-commissural fornix, which connects posterior hippocampus to mammillary

98 bodies and anterior thalamic nuclei (Aggleton, 2012; Christiansen et al., 2016). Since

99 higher values of FA are considered indicative of increased myelination and improved

100 organization, cohesion, and compactness of white matter fiber tracts (Beaulieu, 2002),

101 we predicted a positive association between pre-commissural FA and the episodic

102 richness of past and future constructions.

103

Materials and methods

Participants

Participants were 27 healthy Cardiff University undergraduates (aged 18–22 years, mean age = 19, 25 females). They completed an adapted Galton-Crovitz cue word paradigm (Crovitz & Schiffman, 1974) 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 AI task procedure

Participants completed an adapted version of the Autobiographical Interview (AI) (Addis, Wong, & Schacter, 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 a 1-min time-limit. 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

6

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

139   scoring.

140

Scoring

142   The standardized AI scoring procedure (Levine, Svoboda, Hay, Winocur, &

143   Moscovitch, 2002) was used. Events (past and future) generated were segmented into

144   distinct chunks of information in order to allow analysis of the levels of episodic or

145   semantic information provided within each. These chunks were typically characterized

146   by grammatical clauses that referenced a unique occurrence, observation or thought

147   (Levine et al., 2002). Two broad categories were used to categorize details: 'internal'

148   details (which described the central event) and 'external' details (decontextualized

149   information, including semantic details and information concerning extended events

150   that are not specific in time and place, and repetitions). In the case that a participant

151   described more than one event, the event that was described in the most detail was

152   coded as 'internal' and the other as 'external'. The central event was required to refer

153   to a specific time and place, thus it can be considered 'episodic' and will be referred

154   to as such henceforth. Episodic details included not only time and place details, but

155   also any other episodic information (sensory details, thoughts and emotions) that were

156   part of the central event (Levine et al., 2002). **Figure 1** contains examples of external

157   and episodic details from past and future narratives. Total score was computed by

158   summing over the 10 event narratives.

159

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 (.)

161

162 **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 (.)

163

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

165

166 Consensus scoring was established based on the near perfect inter-rater reliability

167 from two raters who scored the past events (intra-class correlation analysis, two-way

168 random model: episodic r = 0.99; external r = 1.0). The values from one primary coder,

169 who completed both the past and future scoring, were used in the analysis. All raters

170 were blind to dMRI results.

171

172 For each event the numbers of episodic and external details were tallied, and the totals

173 were then summed across the 10 events in each condition (past, future) to create

174 episodic and external AI scores for each condition for each participant.

175

176 **MRI data acquisition**

177 Imaging data were acquired using a General Electric Healthcare (GE) 3-T HDx MRI

178 system with an 8-channel receive-only head coil, at Cardiff University's Brain

179 Research Imaging Centre (CUBRIC). A standard T1-weighted 3D FSPGR sequence

180 (178 axial slices, 1mm isotropic resolution, TR/TE = 7.8/3.0s, FOV = 256 x 256 x

181 176mm, 256 x 256 x 176 data matrix, 20° flip angle) provided high-resolution

182 anatomical images.

183

184 A diffusion weighted single-shot spin-echo Echo-Planar Imaging (EPI) pulse sequence

185 was used to acquire whole-brain High Angular Resolution Diffusion Image (HARDI)

186 data (60 contiguous slices acquired along an oblique-axial plane with 2.4mm thickness

187 and no gap, TE = 87ms; voxel dimensions = 2.4 x 2.4 x 2.4mm^3; FOV = 23 x 23 cm^2;

188 96 x 96 acquisition matrix). The acquisition was cardiac gated, with 30 isotropic

8

189   directions at b = 1200 s/mm^2. In addition, three non-diffusion weighted images were

190   acquired with b = 0 s/mm^2.

191

MRI preprocessing

Diffusion MRI

194   Diffusion MRI (dMRI) data were preprocessed using ExploreDTIv4.8.3 (Leemans &

195   Jones, 2009). Distortions resulting from eddy currents and participant head motion

196   were corrected. A particular issue for white matter pathways located near the

197   ventricles (e.g., the fornix), is free water contamination from cerebrospinal fluid. This

198   has been shown to significantly affect tract delineation (Concha, Gross, & Beaulieu,

199   2005). Thus, to correct for voxel-wise partial volume artifacts arising from free water

200   contamination, the two-compartment 'Free Water Elimination' (FWE) procedure

201   (Pasternak, Sochen, Gur, Intrator, & Assaf, 2009) was applied – this improves

202   Diffusion Tensor Imaging (DTI)-based tract reconstruction and tissue specificity

203   (Pasternak et al., 2014). Following FWE, corrected diffusion tensor indices were

204   computed. Fractional anisotropy (FA) – a DTI-based index proposed to reflect axonal

205   organization (Pierpaoli, Jezzard, Basser, Barnett, & Di Chiro, 1996), reflects the extent

206   to which diffusion within biological tissue is anisotropic (constrained along a single

207   axis) (Beaulieu, 2002). FA values can range from 0 (fully isotropic) to 1 (fully

208   anisotropic). The resulting free water corrected FA maps were inputs for the

209   tractography analysis.

210

Tractography

212   Deterministic tractography was performed from all voxels based on constrained

213   spherical deconvolution (CSD) (Dell'Acqua & Tournier, 2019; Jeurissen, Leemans,

214   Jones, Tournier, & Sijbers, 2011). CSD allows for the representation of

215   bending/crossing/kissing fibers in individual voxels, as multiple peaks in the fiber

216   orientation density function (fODF) can be extracted within each voxel (Dell'Acqua &

217   Tournier, 2019). The step size was 1mm, and the fODF amplitude threshold was 0.1.

218   An angle threshold of 30° was used to prevent the reconstruction of anatomically

219   implausible fibers.

220

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

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

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

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

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

226   These gates were combined to reconstruct the tracts, based on anatomical plausibility.

227   Initially, a multiple ROI approach was applied to reconstruct the fornix (see Hodgetts,

228   Postans, et al., 2017; Metzler-Baddeley, Jones, Belaroussi, Aggleton, & O'Sullivan,

229   2011).

230

231   **Fornix reconstruction**

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

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

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

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

236   fornix pillars and posterior to the crus fornici on the coronal plane. Further 'NOT' way-

237   gates were placed after the initial reconstruction and ensuing visual inspection, to

238   remove anatomically implausible fibers. Subsequently, the anterior body of the fornix

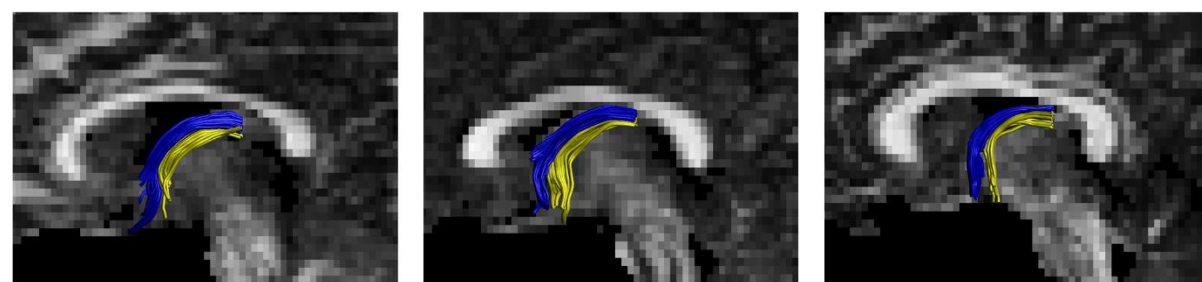239   was split into the pre- and post- commissural column segments (**Figure 2**).

240

241
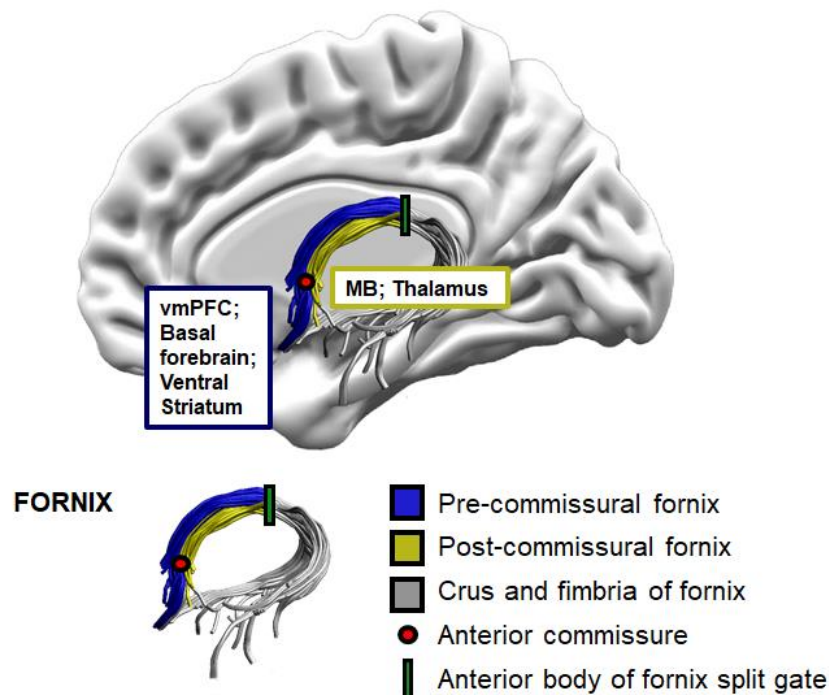
242 **Figure 2**. Schematic illustration of the anatomical landmarks for fornix tract sub-
243 division, and the connecting areas of interest. vmPFC = Ventromedial Prefrontal
244 Cortex; MB = Mammillary Bodies.

245

246 Waypoint ROIs for the pre-post split (**Figure 3**) were based on the protocol described
247 in Christiansen et al. (2016), and example tract reconstructions are depicted in **Figure**
248 **4**. After tract reconstruction for each participant, mean FA values were calculated by
249 averaging the values at each 1mm step along each segment.

250

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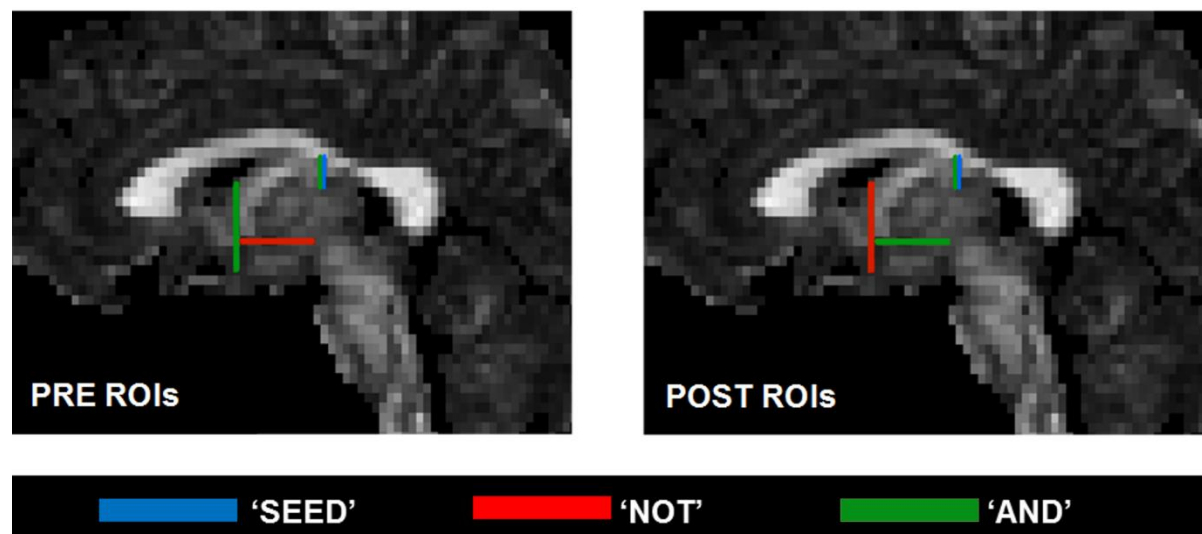
252 **Figure 3**. Waypoint region-of-interest (ROI) gates used for reconstructing the pre- and
253 post- commissural fornix tract segments (Blue = SEED, Red = NOT, Green = AND).

254

255

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

258

259 **Pre- and post- commissural fornix reconstruction**
260 The fornix was split, isolating the anterior-body, by an 'AND' gate positioned at the
261 point of the downward bend to the crus and fimbria of the fornix. In line with

262   Christiansen et al. (2016), fibers of the crus and fimbria of the fornix were excluded

263   from the anterior-body and hence pre- and post- commissural fornix reconstructions.

264   Partial volume effects due to the intermingling of the two fiber populations beyond the

265   crus were, therefore, minimized (Saunders & Aggleton, 2007). In addition, this

266   procedure avoided 'jumping' where tract voxels that pass close to, or across,

267   neighboring tract voxels 'jump' onto them (Jones & Cercignani, 2010). This split was

268   conducted using the tract segmentation tool "splitter" within ExploreDTIv4.8.3.

269

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

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

272   at the anterior columns of the fornix. At this level, the segments contain approximately

273   the same number of fibers (Powell, Guillery, & Cowan, 1957). The pre-commissural

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

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

276   on the axial plane. For the post-commissural fornix reconstruction, the additional 'NOT'

277   and 'AND' gates placed for reconstruction of the pre-commissural fornix were swopped

278   (see **Figure 3**). Thus, for the pre-commissural fornix, tracts were included only if they

279   extended anterior to the anterior commissure, and for the post-commissural fornix only

280   tracts running posterior to the anterior commissure were retained (see **Figure 4**)

281   (Christiansen et al., 2016).

282

283   **Grey matter volumetrics**

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

285   Automated Segmentation Tool (FAST; Zhang, Brady, & Smith, 2001). Bilateral grey

286   matter volumes (expressed as a proportion of estimated total intracranial volume) of

287   the hippocampus were subsequently obtained using FMRIB's Integrated Registration

288   & Segmentation Tool (FIRST; Patenaude, Smith, Kennedy, & Jenkinson, 2011).

289   Volumes   for   the   vmPFC   ROI   were   derived   using   FreeSurfer

290   (surfer.nmr.mgh.harvard.edu: Destrieux, Fischl, Dale, & Halgren, 2010), via summing

291   volumes of the medial orbitofrontal cortex (mOFC) and rostral anterior cingulate cortex

292   (rACC) parcels. One participant was removed from the grey matter analyses due to

293   poor overall data quality on the T1 FSPGR.

294

295 **Statistical Analysis**

296 Directional Pearson's correlations were conducted between individual's total scores of

297 episodic and external details produced for the ten past and future narratives; and

298 individual's episodic past and future scores and their FA values for the pre- and post-

299 commissural fornix. Vovk-Sellke Maximum (VS-MPR) p–ratios were computed: based

300 on the p -value, the maximum possible odds in favor of H_1 over H_0 equals 1/(-e p

301 log(p)) for $p \leq .37$ (Sellke, Bayarri, & Berger, 2001). Complementary non-parametric

302 Spearman's rho rank tests were also conducted for the key correlations. These are

303 less sensitive to potential outliers and differences in range (Croux & Dehon, 2010). In

304 addition, partial correlations were conducted for the key episodic-fornix microstructure

305 correlations, to control for the contribution of the number of external details given and

306 regional grey matter volume. All analyses were conducted in JASP (2018, version

307 0.9.1.0).

308

309 **Results**

310 **Correlations between tract microstructure and past-future AI scores**

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

312 Consistent with previous studies (e.g. Addis, Sacchetti, Ally, Budson, & Schacter,

313 2009; Addis et al., 2008; Race et al., 2011), the total number of episodic details

314 (summed across the 10 cue words) an individual recalled for the past (mean = 121.3,

315 median = 114, SD = 40.8, range = 64 - 247) correlated strongly with the number of

316 episodic details imagined for the future (mean = 59.3, median = 54, SD = 23.4, range

317 = 27 - 105) (**Figure 5A**. Pearson's r = 0.69, p < 0.001, VS-MPR = 1027.33).

318 Additionally, in line with previous studies, there were significantly more episodic details

319 given for the past in comparison to the future (t(26) = 10.75, p < 0.001, d_z = 2.07,

320 paired t-test). The number of external details an individual recalled for the past (mean

321 = 73.8, median = 71, SD = 39, range = 20 – 182) also correlated significantly with the

322 number of external details imagined for the future (mean = 86.5, median = 75, SD =

323 40.8, range = 23 - 198) (**Figure 5B**. Pearson's r = 0.73, p < 0.001, VS-MPR = 3254.64).

324 There were also significantly more external details given for the future in comparison

325 to the past (t(26) = 2.23, p = 0.035, d_z = 0.43, paired t-test). The number of episodic

326 details an individual recalled for the past also correlated with the number of external

327 details recalled for the past (Pearson's r = 0.35, p = 0.035, VS-MPR = 3.15); this was

328 not the case, however, for the future (Pearson's r = -0.16, p = 0.783, VS-MPR = 1.00).

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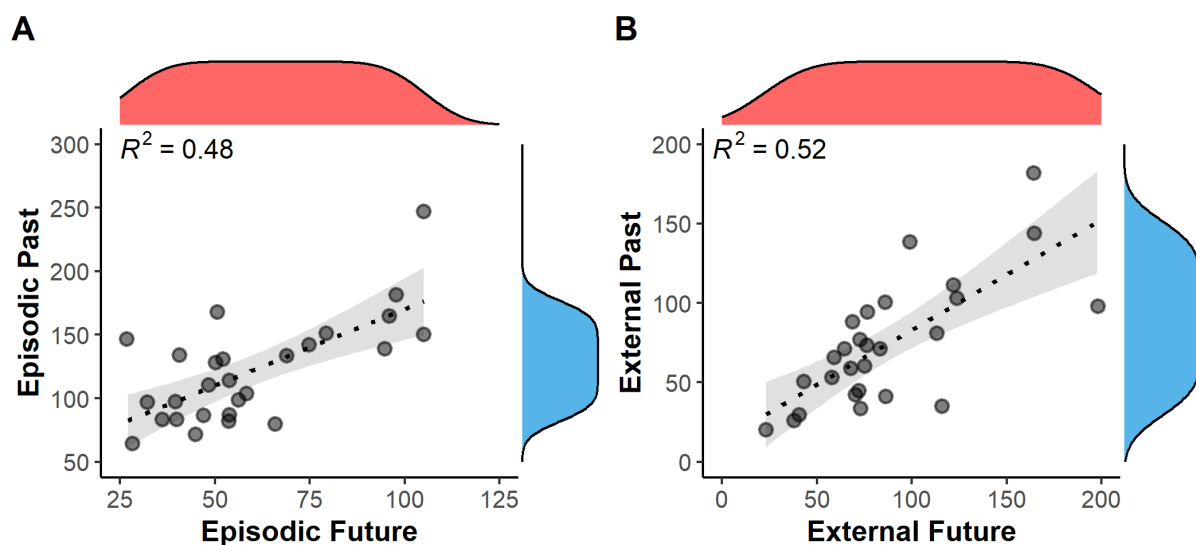
331 **Figure 5 (A, B)**. Scatterplots depicting correlations between the number of details

332 produced for the past versus the future AI narratives (A. Episodic, B. External) (*N*=27).

333 Marginal density is displayed on the opposite axis. Grey shading equals the 95% CI.

334

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

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

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

338 14.49, Spearman's rho = 0.464, p = 0.007, VS-MPR = 10.09). There was no significant

339 correlation between post-commissural fornix FA and episodic past details (**Figure 6B**.

340 Pearson's r = -0.12; p = 0.725, VS-MPR = 1.00, Spearman's rho = 0.02, p = 0.457,

341 VS-MPR = 1.00). The correlation between episodic past details and pre-commissural

342 fornix FA was significantly greater than between episodic past details and post-

343 commissural fornix FA (Steiger z (27) = 2.29, p = 0.011) (computed using R package

344 cocor, Diedenhofen & Musch, 2015).

345
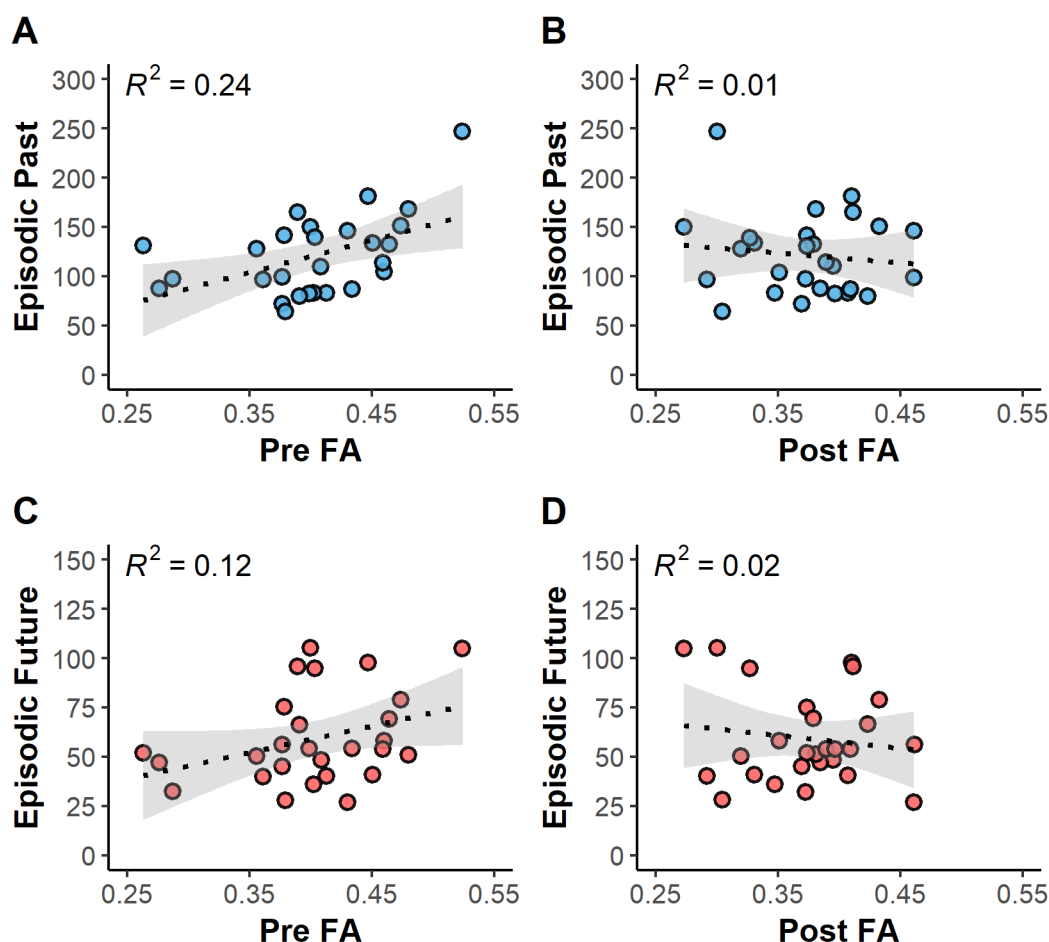
Figure 6 (A-D). Scatterplots depicting the correlations of episodic past (A, B) and future (C, D) AI details with pre-/post- commissural fornix microstructure (fractional anisotropy, FA). Number of episodic past/future details (summed over 10 cue words) is plotted on the y-axis (N=27). Grey shading equals 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

363   FA (**Figure 6C**. Pearson's r = 0.35, p = 0.035, VS-MPR = 3.11, Spearman's rho = 0.33,

364   p = 0.045, VS-MPR = 2.62), and, correspondingly, there was no significant correlation

365   between episodic future details and post-commissural fornix FA (**Figure 6D**. Pearson's

366   r = -0.14, p = 0.752, VS-MPR = 1.00, Spearman's rho = 0.09, p = 0.330, VS-MPR =

367   1.01). The correlation between episodic future details and pre-commissural fornix FA

368   was also significantly greater than between episodic future details and post-

369   commissural fornix FA (Steiger z (27) = 1.78, p = 0.038). The correlation between

370   episodic future details and pre-commissural fornix FA was not significantly greater

371   than between external future details and pre-commissural fornix FA, however, when

372   controlling for the number of external details given the correlation between episodic

373   future details and pre-commissural fornix FA remained significant (Pearson's r = 0.38,

374   p = 0.028, Spearman's rho = 0.33, p = 0.0499).

375

376   **Influence of grey matter volume**

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

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

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

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

381   0.09, p = 0.341). Likewise, the correlation between future episodic details and pre-

382   commissural fornix FA remained significant when controlling for hippocampal volume

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

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

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

386

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

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

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

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

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

392   number of episodic details and pre-commissural fornix FA remained significant when

393   controlling for vmPFC volume (partial correlation: Pearson's r = 0.36, p = 0.037), and

394   there was no significant correlation between post-commissural fornix FA and episodic

395   future details (partial correlation: Pearson's r = -0.19, p = 0.178).

396

Discussion

397
398 The goal of this study was to investigate the role of the direct hippocampal-vmPFC
399 pathway, formed by the pre-commissural fornix, in autobiographical past and future
400 thinking. We applied a novel anatomically-guided protocol that allows the pre-
401 commissural and post-commissural fornix fibers to be separately reconstructed *in vivo*
402 (Christiansen et al., 2016). To assess both past- and future-oriented thinking, we used
403 an adapted autobiographical cueing paradigm (Addis et al., 2008; Crovitz & Schiffman,
404 1974) alongside a validated coding scheme that specifically parses episodic from non-
405 episodic detail within individuals' real-world descriptions (Hodgetts, Postans, et al.,
406 2017; Levine et al., 2002). Using this approach, we found that inter-individual variation
407 in *pre*-commissural, but not *post*-commissural, fornix microstructure was significantly
408 correlated with the amount of episodic detail produced during the construction of both
409 past and future events. Critically, this effect was still seen when controlling non-
410 episodic content. These findings deepen our understanding of hippocampal-vmPFC
411 interactions in human episodic autobiographical memory and future thinking and
412 provide a 'structural realization' of hippocampal-vmPFC functional connectivity
413 (Kosslyn & Van Kleeck, 1990), that is, a direct relationship between the microstructure
414 of the fiber pathway connecting these distributed regions and individual differences in
415 episodic past and future thinking.
416

417 Our findings highlight the importance of direct hippocampus-PFC connectivity
418 mediated by the pre-commissural fornix (Aggleton et al., 2015; Cenquizca & Swanson,
419 2007; Jin & Maren, 2015), in episodic construction across past and future events. This
420 builds upon previous fMRI studies that have shown that functional coupling between
421 these distributed regions is increased during both the retrieval of autobiographical
422 memories and the construction of future events (Campbell et al., 2017; McCormick et
423 al., 2015). One recent study, which used structural equation modelling of fMRI data,
424 found increased functional connectivity from anterior hippocampus *to* vmPFC when
425 participants retrieved autobiographical memories in response to cue words
426 (McCormick et al., 2015). Similarly, another investigation applied dynamic causal
427 modeling to fMRI data and found that anterior hippocampus *to* vmPFC effective
428 connectivity increased specifically during the initial construction of episodic future
429 events (Campbell et al., 2017). From this, the authors proposed that 'the hippocampus

17

430   initiates event construction in response to retrieval cues, which then drives activation

431   in the vmPFC where episodic details may be further integrated'.

432

433   This conceptualization is consistent with previous work in both humans and rodents

434   that demonstrated that hippocampal activity precedes medial PFC activity during

435   memory retrieval (McCormick et al., 2015; Place, Farovik, Brockmann, & Eichenbaum,

436   2016), and with findings in rodents that ventral hippocampus mediates theta drive to

437   vmPFC (O'Neill, Gordon, & Sigurdsson, 2013). Optogenetic studies in mice (e.g.

438   Ciocchi, Passecker, Malagon-Vina, Mikus, & Klausberger, 2015) have also shown that

439   during memory retrieval ventral hippocampal signals carrying contextual information

440   are sent directly to medial PFC, facilitating coordinated activity between these areas.

441

442   The precise contributions of the hippocampus and vmPFC to episodic memory and

443   future thinking are hotly debated. As noted earlier, the pre-commissural fornix

444   originates primarily from the ventral (rodent) or anterior (primate) hippocampus,

445   particularly the subiculum and CA1 (Aggleton et al., 2015; Cenquizca & Swanson,

446   2007), whereas the post-commissural fornix arises from the posterior hippocampus

447   (Aggleton et al., 2015). Thus, our findings have implications for understanding

448   functional specializations or gradients within the hippocampus itself, and how these

449   are reflected in its extrinsic connectivity (Poppenk & Moscovitch, 2011; Strange,

450   Witter, Lein, & Moser, 2014). According to scene construction theory, the anterior

451   hippocampus, and particularly the subiculum, plays a central role in forming

452   representations of spatially coherent scenes across memory, perception and

453   imagination (Hodgetts, Voets, et al., 2017; Zeidman & Maguire, 2016), and these

454   conjunctive scene representations have been proposed to provide a scaffold when

455   constructing both past and future events (Barry & Maguire, 2019; Murray et al., 2017;

456   Robin, 2018). In contrast, the constructive episodic simulation hypothesis contends

457   that the construction of spatial contexts arises out of a general relational processing

458   mechanism housed in anterior hippocampus, which is also responsible for the

459   integration of other event details into the event representation (Addis, 2018; Schacter

460   et al., 2012; Schacter et al., 2017).

461

462   Other accounts emphasize graded representations along the hippocampal long-axis.

463   In particular, both human neuroimaging and electrophysiological studies in rodents

464   suggest an anterior–posterior gradient in the 'scale' of spatial/event representations in
465   the hippocampus (Brunec et al., 2018; Buzsáki & Moser, 2013; Komorowski et al.,
466   2013; Nielson, Smith, Sreekumar, Dennis, & Sederberg, 2015; Sheldon & Levine,
467   2016), in which the anterior hippocampus forms coarser, 'gist-like' generalized
468   representations of extended events or contexts and the posterior hippocampus
469   represents finer-grained perceptual and spatiotemporal detail (Addis, 2018). As we
470   used broad retrieval cues, featuring extended events like 'holiday', our experiment may
471   have emphasized construction processes mediated by anterior hippocampus. More
472   specific cues leading directly to detailed representations may entail earlier posterior
473   hippocampal activity. This is an important area for future studies to explore.

474

475   The vmPFC's contribution to episodic construction, by contrast, has been linked to
476   demands on schematic representations (Campbell et al., 2017; Robin & Moscovitch,
477   2017), in particular the self-schema (Buckner & Carroll, 2007; D'Argembeau, 2013).
478   For instance, Kurczek et al. (2015) (see also Verfaellie, Wank, Reid, Race, & Keane,
479   2019) compared the number of references to 'the self' included in autobiographical
480   event narratives from patients with bilateral hippocampal or medial PFC damage as
481   well as healthy controls. Patients with medial PFC damage, despite being able to
482   construct highly detailed episodic events, produced relatively few self-references, and
483   they incorporated themselves in the narratives of their (re)constructions less frequently
484   than the healthy participants. Patients with hippocampal damage showed the opposite
485   pattern: they were impaired in their ability to construct highly detailed episodic events
486   across time periods but not in their incorporation of the self. We have previously
487   suggested (Murray et al., 2017) that hippocampal-vmPFC connectivity serves to
488   (re)create complex conjunctive representations in which one's self is oriented in a
489   particular time, place, and overall situational context (Murray et al., 2017). These
490   conjunctive representations may subsequently constrain further retrieval and
491   construction by the hippocampus (Campbell et al., 2017; Graham, Barense, & Lee,
492   2010; Place et al., 2016; Preston & Eichenbaum, 2013). Thus, recall/imagination of
493   personally relevant episodes involves a prefrontal system which can work in
494   conjunction with the MTL system to help individuals recombine episodic details to
495   construct a *personally relevant* past/future event (but see Barry & Maguire, 2019;
496   Ciaramelli, De Luca, Monk, McCormick, & Maguire, 2019; McCormick et al., 2018,
497   scene construction theory, for a view which de-emphasizes self-processes).

498

499   Critically, the pre-commissural fornix does not carry reciprocal projections from the

500   vmPFC to the hippocampus (which are indirect via the thalamic nucleus reuniens and

501   entorhinal cortex) (Murray et al., 2017; Preston & Eichenbaum, 2013), but only carries

502   connections to the vmPFC from the anterior hippocampus. While several models of

503   episodic memory emphasize the importance of bi-directional interactions between

504   hippocampus and vmPFC (e.g. Manns, Howard, & Eichenbaum, 2007; Preston &

505   Eichenbaum, 2013; Robin & Moscovitch, 2017), with vmPFC playing a regulatory

506   (Barry & Maguire, 2019; Manns et al., 2007; Preston & Eichenbaum, 2013; Robin &

507   Moscovitch, 2017) or even initiating (Barry, Barnes, Clark, & Maguire, 2019;

508   McCormick et al., 2018) role in episodic construction, our findings reveal that the direct

509   inputs that the hippocampus provides to vmPFC are a critical source of individual

510   differences in episodic memory and future thinking, and that the pre-commissural

511   fornix is a key link in this broader hippocampal-vmPFC circuit.

512

513   While these findings highlight a key role for anterior hippocampal connectivity with

514   medial PFC in constructing self-relevant event representations, previous work in both

515   humans and rodents have emphasized the importance of connections between the

516   hippocampus and medial diencephalon (i.e., mammillary bodies and thalamus) in

517   spatial and contextual memory (Aggleton & Brown, 1999), which is mediated by the

518   *post*-commissural fornix (Christiansen et al., 2016). While the current findings

519   seemingly challenge this account, it is important to note that the post-commissural

520   fornix tract reconstructions principally involve the connections of the hippocampus with

521   the hypothalamus, including the mammillary bodies, and largely exclude the

522   projections to the anterior thalamic nuclei, as these turn towards posterior regions as

523   the fornix columns descend (Christiansen et al., 2016; Poletti & Creswell, 1977).

524   Indeed, previous work has demonstrated that thalamic degeneration can impair

525   episodic autobiographical memory and future thinking (Irish, Hodges, & Piguet, 2013).

526   Notably, however, Vann (2013) found that lesions to the descending post-commissural

527   fornix columns in rats did not impact on spatial memory tests that are sensitive to

528   mammillary body, mammillothalamic tract, anterior thalamic, and hippocampal lesions.

529   The implication of this finding is that the hippocampal-mammillary connection may not

530   be important for all classes of episodic memory, particularly those that place demand

531   on constructive and self-referential processing.

532

533   Although FA is highly sensitive to the microstructure of fibers, it lacks biological
534   specificity, and may reflect myelination, axon diameter and packing density, axon
535   permeability and fiber geometry (Concha, Livy, Beaulieu, Wheatley, & Gross, 2010;
536   Jones, Knösche, & Turner, 2013). Each of these may differently affect communication
537   efficiency and synchronicity between distal brain regions (Jbabdi & Behrens, 2013)
538   and be influenced by distinct genetic and environmental factors (Budisavljevic et al.,
539   2015). Future studies using novel approaches to estimate specific microstructural
540   properties including axon density (Assaf, Johansen-Berg, & Thiebaut de Schotten,
541   2017) will provide further insight into the specific biological attributes underlying these
542   brain-cognition associations. Further, while our sample size was comparable to related
543   investigations (Hodgetts, Postans, et al., 2017; Palombo, Bacopulos, et al., 2018), and
544   VS-MPRs showed that our findings provide a good level of diagnosticity, it will be
545   important to replicate these effects in larger samples.

546

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

555

Acknowledgments

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