

1 **Increased posterior default mode network activity and structural**
2 **connectivity in young adult *APOE*- ϵ 4 carriers: a multi-modal imaging**
3 **investigation**

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27 **Abstract**

28 Young adult *APOE*- ϵ 4 carriers show increased activity in posterior regions of
29 the default mode network (pDMN), but how this is related to structural
30 connectivity is unknown. Thirty young adults (half *APOE*- ϵ 4 carriers, the other
31 half *APOE*- ϵ 3/ ϵ 2 ϵ 3; mean age 20 years) were scanned using both diffusion
32 and functional magnetic resonance imaging. Diffusion tractography was used
33 to quantify the microstructure (mean diffusivity, MD; fractional anisotropy, FA)
34 of the parahippocampal cingulum bundle (PHCB), which links pDMN and the
35 medial temporal lobe. *APOE*- ϵ 4 carriers had lower MD and higher FA relative
36 to non-carriers in PHCB. Further, PHCB microstructure was selectively
37 associated with pDMN activity during a scene discrimination task known to be
38 sensitive to Alzheimer's disease (AD). These findings are consistent with a
39 lifespan view of AD risk, where early-life structural and functional brain
40 changes in specific, vulnerable networks leads to increased neural activity
41 that may ultimately trigger amyloid- β deposition.

42

43 **Key Words**

44 Alzheimer's disease; *APOE*; Default mode network; Diffusion MRI; Functional
45 MRI; Individual differences; Scene processing; Parahippocampal cingulum
46 bundle

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52 **1. Background**

53 The default mode network (DMN) is a large-scale brain system displaying
54 continuously high levels of coordinated activity in the resting-state (Raichle,
55 2015). DMN activity is maintained or enhanced during internally directed
56 cognition (e.g., autobiographical memory, mind-wandering), and is attenuated
57 during many cognitive tasks demanding external perceptual attention (e.g.
58 episodic memory encoding) (Raichle, 2015).

59

60 Rather than constituting a single, unitary brain network, the DMN can be
61 divided into several functionally dissociable subsystems (Andrews-Hanna et
62 al., 2010; Raichle, 2015), which are affected differently by Alzheimer's
63 disease (AD) progression (Myers et al., 2014). Notably, the posterior DMN
64 (pDMN), comprising posterior cingulate, precuneus and retrosplenial cortex
65 (Cauda et al., 2010), is one of the earliest brain areas to undergo amyloid- β
66 accumulation and reduced metabolism in AD (Gonneaud et al., 2016;
67 Palmqvist et al., 2017). The pDMN also constitutes the brain's structural
68 "core" and is characterized both by high levels of baseline activity/metabolism
69 and dense functional and structural inter-connectivity (Bero et al., 2012;
70 Buckner et al., 2009; Hagmann et al., 2008).

71

72 The striking spatial overlap between the pDMN and regions that show early
73 amyloid- β accumulation has led to a 'lifespan systems vulnerability' (LSV)
74 account of AD, where increased activity and connectivity - over the *lifetime* -
75 may predispose this region to later-life amyloid- β (Buckner et al., 2009; de
76 Haan et al., 2012; Jagust and Mormino, 2012). Providing strong evidence for

77 a link between neural activity/connectivity and amyloid- β , a study in
78 transgenic mice (Bero et al., 2011) reported that interstitial amyloid- β levels
79 were associated with increased markers of neural activity, and this, in turn,
80 predicted amyloid- β deposition, particularly in pDMN ((Bero et al., 2011); see
81 also (Yamamoto et al., 2015)). A further study showed that region-specific
82 levels of functional connectivity in young A β - mice was proportional to the
83 degree of amyloid- β burden in older animals (Bero et al., 2012). Similarly,
84 human neuroimaging studies have reported associations, within-subjects,
85 between the degree of baseline pDMN functional connectivity and subsequent
86 amyloid- β load in both mild cognitive impairment (MCI) (Myers et al., 2014)
87 and cognitively-normal older adults (Jack and Holtzman, 2013). While these
88 studies suggest that functional properties may drive pathological markers, it
89 could reflect a later-life compensatory response induced by early amyloid- β
90 burden in key networks (Jagust and Mormino, 2012; Jones et al., 2016).

91
92 If later-life amyloid- β deposition in pDMN is associated with increased
93 functional activity/connectivity across the lifespan, then alterations may be
94 evident in younger individuals at elevated risk of AD. Further, as amyloid- β
95 deposition is highly unlikely in young adults (de Haan et al., 2012; Mormino,
96 2014), this approach addresses a key limitation of studies in elderly
97 individuals where compensatory functional activity may reflect early pathology
98 (Jagust and Mormino, 2012).

99
100 The *APOE*- ϵ 4 allele is the strongest genetic risk factor for both sporadic early
101 and late-onset AD (Liu et al., 2013) and is strongly linked to amyloid- β

102 accumulation in later life (Gonneaud et al., 2016). Functional magnetic
103 resonance imaging (fMRI) studies have typically found that young *APOE-ε4*
104 carriers show increased activity, relative to non-carriers, in pDMN and inter-
105 connected medial temporal lobe (MTL) regions (Dennis et al., 2010; Filippini
106 et al., 2009; Shine et al., 2015). *APOE-ε4* carriers have also been shown to
107 have greater intrinsic functional connectivity in the DMN during “rest” (Filippini
108 et al., 2009).

109

110 Given the view that pDMN vulnerability to amyloid-β accumulation is linked to
111 its role as a large-scale connectivity hub (Jagust and Mormino, 2012; Jones et
112 al., 2016), the heightened pDMN activity in young *APOE-ε4* carriers may itself
113 be linked to variation in structural connectivity (Brown et al., 2011; de Haan et
114 al., 2012) - particularly those connections linking pDMN with other regions
115 affected early in AD.

116

117 The major white matter connection linking pDMN with MTL (particularly
118 parahippocampal cortex) (Greicius et al., 2009; Heilbronner and Haber, 2014)
119 is the parahippocampal cingulum bundle (PHCB). Studies applying diffusion
120 magnetic resonance imaging (dMRI) – a method allowing *in vivo* quantification
121 of white matter microstructure – have reported greater mean diffusivity (MD)
122 and lower fractional anisotropy (FA) in the PHCB of cognitively-normal older
123 *APOE-ε4* carriers compared to non-carriers (Heise et al., 2014). One cross-
124 sectional dMRI study found that young adult *APOE-ε4* carriers had higher
125 PHCB FA but showed a steeper decline across life, leading to relative FA
126 reduction relative to non-carriers from mid-life onwards ((Felsky, 2013); see

127 also (Brown et al., 2011)). Disruption of this pathway is also seen in both MCI
128 and AD (Mito et al., 2018; Rieckmann et al., 2016), and has been linked to
129 pDMN activity/metabolism in AD (Villain et al., 2008) and amyloid- β burden in
130 preclinical AD (Racine et al., 2014). Overall, these studies point toward the
131 potential early-life vulnerability of a broader posterior network that is
132 structurally underpinned by the PHCB (Greicius et al., 2009). Further, they
133 support the view that increased brain activity over the lifespan – driven by
134 structural connectivity - leads to amyloid- β deposition, and ultimately results in
135 decreased activity/connectivity in later life due to “wear and tear” (Jagust and
136 Mormino, 2012).

137

138 It is unclear, however, whether these PHCB microstructural alterations are
139 evident earlier in life when amyloid- β deposition is unlikely, concomitant with
140 the identified functional changes in college-aged adults (Dennis et al., 2010;
141 Filippini et al., 2009; Shine et al., 2015). Moreover, if increased activity in
142 pDMN stems from its role as a large-scale connectivity hub (Brown et al.,
143 2011; de Haan et al., 2012), then those individuals who show elevated pDMN
144 activity (Filippini et al., 2009; Shine et al., 2015) should also have “increased”
145 structural connectivity (de Haan et al., 2012). To address these questions we
146 applied high angular resolution dMRI (HARDI (Tuch et al., 2002)), alongside
147 constrained spherical deconvolution (CSD) tractography (Jeurissen et al.,
148 2011), to test whether the presence of an *APOE*- ϵ 4 allele in young adults,
149 who are unlikely to harbor amyloid burden, influences PHCB tissue
150 microstructure. Given evidence that young *APOE*- ϵ 4 carriers show elevated
151 pDMN activity at rest and during tasks (Shine et al., 2015), we predicted that

152 *APOE*- ϵ 4 carriers would show greater FA and lower MD in the PHCB,
153 compared to non-carriers. Finally, to demonstrate a link between activity and
154 connectivity, as predicted by an LSV view of AD risk, we examined whether
155 inter-individual variation in PHCB tissue microstructure was associated with
156 pDMN activity during a scene discrimination task that is sensitive to early AD
157 (Lee, 2006).

158

159 **2. Material and Methods**

160 **2.1. Participants**

161 Full details regarding DNA extraction and genotypic distribution can be found
162 in a previous article (Shine et al., 2015). The available sample for this analysis
163 was 30 participants (15 per group; 14 females per group) - a sample size
164 similar to other structural/functional studies of *APOE*- ϵ 4 (Dennis et al., 2010;
165 Filippini et al., 2009; Oh and Jagust, 2013). The non-carrier *APOE* allele
166 distribution was 10 *APOE*- ϵ 3 ϵ 3 and 5 *APOE*- ϵ 2 ϵ 3 individuals. The carrier
167 *APOE* allele distribution was 14 *APOE*- ϵ 3 ϵ 4 and 1 *APOE*- ϵ 2 ϵ 4. Both groups
168 were matched for age (carriers: 19.7 years, S.D. = 0.84; non-carriers: 19.7
169 years, S.D. = 0.89) and education level. Family history was matched across
170 the groups, with two reports of a positive family history in each. All participants
171 were right-handed, native English speakers with normal or corrected-to-
172 normal vision, and had no self-reported history of neurological/psychiatric
173 disorders. Groups were well matched on standard neuropsychological tests
174 (Shine et al., 2015). All experimental procedures were conducted in
175 accordance with, and were approved by, the Cardiff University School of

176 Psychology Research Ethics Committee. Informed consent was obtained from
177 all participants, and research was conducted in a double-blind manner.

178

179 **2.2. MRI scan parameters**

180 Imaging data were collected at the Cardiff University Brain Research Imaging
181 Centre (CUBRIC) using a GE 3-T HDx MRI system (General Electric
182 Healthcare, Milwaukee, WI) with an 8-channel receive-only head coil. Whole
183 brain HARDI (Tuch et al., 2002) data were acquired using a diffusion-
184 weighted single-shot spin-echo echo-planar imaging (EPI) pulse sequence
185 with the following parameters: TE = 87ms; voxel dimensions = 2.4 x 2.4 x 2.4
186 mm³; field of view = 23 x 23 cm²; 96 x 96 acquisition matrix; 60 slices
187 (oblique-axial with 2.4 mm thickness). Acquisitions were cardiac gated using a
188 peripheral pulse oximeter. Gradients were applied along 30 isotropic
189 directions with $b = 1200 \text{ s/mm}^2$. Three non-diffusion weighted images were
190 acquired with $b = 0 \text{ s/mm}^2$.

191

192 **2.3. Diffusion MRI preprocessing**

193 Motion and eddy current correction was conducted using ExploreDTI
194 (Leemans and Jones, 2009). Partial volume corrected maps of tissue FA and
195 MD were generated by applying the bi-tensor 'Free Water Elimination' (FWE)
196 procedure (Pasternak et al., 2009). FA reflects the extent to which diffusion is
197 anisotropic, or constrained along a single axis, and can range from 0 (fully
198 isotropic) to 1 (fully anisotropic). MD ($10^{-3} \text{ mm}^2 \text{ s}^{-1}$) reflects a combined average
199 of axial (diffusion along the principal axis) and radial diffusion (diffusion along
200 the orthogonal direction).

201 **2.4. Tractography**

202 Deterministic whole-brain tractography was conducted in ExploreDTI
203 (Leemans and Jones, 2009) using the CSD model (Jeurissen et al., 2011),
204 which extracts multiple peaks in the fiber orientation density function (fODF)
205 (Vettel et al., 2017). Streamlines were reconstructed using the following
206 parameters: fODF amplitude threshold = 0.1; step size = 0.5 mm; angle
207 threshold = 60°.

208

209 Three-dimensional reconstructions of the PHCB (Figure 1A) were obtained
210 from individual subjects using a Boolean, way-point region of interest (ROI)
211 approach, where “AND” and “NOT” ROIs were applied and combined to
212 isolate PHCB streamlines in each subject’s whole-brain tractography data.
213 These ROIs were drawn manually on the direction-encoded FA maps in
214 native space by one experimenter (HW) who was blind to *APOE-ε4* carrier
215 status and quality-assessed by a second experimenter (CJH).

216

217 *2.4.1. Parahippocampal cingulum reconstruction*

218 Reconstruction of the PHCB followed a previously published and reliable
219 protocol (termed “restricted parahippocampal cingulum”; see (Jones et al.,
220 2013)). Following tract reconstruction in both hemispheres, the partial volume
221 corrected maps for FA and MD were intersected with the PHCB tract masks to
222 obtain mean bilateral measures of tract microstructure (MD, FA).

223

224 *2.4.2. Analysis of tractography data*

225 MD and FA values of the bilateral PHCB in *APOE-ε4* carriers and non-carriers

226 were compared directly using directional Welch t-tests in R. We also report
227 Default JZS Bayes Factors for our key analyses, computed using JASP
228 (<https://jasp-stats.org>). The Bayes factor, expressed as BF_{10} , reflects the
229 strength of evidence that the data provide for the alternative hypothesis (H1)
230 relative the null (H0). A BF_{10} much greater than 1 allows us to conclude that
231 there is substantial evidence for the alternative versus the null hypothesis
232 (Wagenmakers et al., 2017).

233

234 **2.5 Tract-Based Spatial Statistics (TBSS)**

235 Voxel-wise statistical analysis of the dMRI data was carried out using TBSS
236 (Smith et al., 2006). This method involves non-linearly projecting subjects'
237 free water corrected statistical maps (both MD & FA) onto a mean tract
238 skeleton and then applying voxel-wise cross-subject statistics. We applied a
239 general linear model (GLM) contrasting *APOE*- ϵ 4 carriers and non-carriers for
240 each dMRI metric. To restrict our analysis to the PHCB, we extracted the
241 PHCB mask from the Johns Hopkins University ICBM-DTI-81 white-matter
242 atlas using FSLview (e.g., (Heise et al., 2014)). Significant clusters were
243 extracted using Threshold-Free Cluster Enhancement (Smith and Nichols,
244 2009) with a corrected alpha of $p = 0.05$. Additional exploratory whole brain
245 analyses were conducted using the same TFCE-corrected statistical
246 threshold. All reported coordinates are in Montreal Neurological Institute (MNI-
247 152) space.

248

249 **2.6. Functional MRI methods**

250 Further information regarding fMRI acquisition, preprocessing and analysis

251 can be found in Shine et al. (Shine et al., 2015). Five participants were
252 excluded from the fMRI analysis due to subject motion (4 subjects) and
253 scanner error (1 subject) resulting in a final sample of 25 participants (13
254 carriers & 12 non-carriers). The fMRI measure-of-interest was the BOLD
255 response (percent signal change) in the pDMN during a perceptual ‘odd-one-
256 out’ discrimination task for scenes and faces (Figure 1A). The pDMN ROI was
257 defined independently using a different cognitive task (short-term memory);
258 this analysis confirmed a significant group difference (carriers > non-carriers)
259 during scene short-term memory in pDMN (Shine et al., 2015). Individual
260 percent signal change values for scenes and faces (each against a “size”
261 oddity baseline condition) were calculated from this ROI using FSL and
262 correlated with diffusion metrics using directional Pearson’s r correlations.
263 Directional Bayes factors and 95% Bayesian credibility intervals (BCI) are
264 reported for all correlations. BCIs inform us that, given our observed data,
265 there is a 95% probability that the true value of our effect (Pearson’s r) lies
266 within this interval. Correlations between each fMRI task condition and PHCB
267 microstructure were compared using a one-tailed Steiger Z test of dependent
268 correlations in ‘cocor’ (<http://comparingcorrelations.org/>) (Diedenhofen and
269 Musch, 2015).

270

271 **3. Results**

272 **3. 1. Comparing PHCB microstructure using tractography**

273 *APOE*- ϵ 4 allele carriers had significantly lower MD compared to non-carriers (t
274 (28) = 2.3 p = 0.015, d = 0.84, BF_{10} = 4.55; Figure 1B). While there was a
275 strong trend for PHCB FA in the predicted direction, the between-group

276 difference just failed to reach significance ($t(28) = 1.69$, $p = 0.051$, $d = 0.62$,
277 $BF_{10} = 1.83$; Figure 1B).

278

279 Given suggested gender differences associated with *APOE-ε4* (Heise et al.,
280 2014; Ungar et al., 2014), we also conducted this analysis without male
281 participants (removal of one individual from each group). A significant
282 difference was found between carriers and non-carriers for PHCB MD, though
283 with a slightly larger effect size ($t(26) = 2.42$, $p = 0.012$, $d = 0.92$, $BF_{10} = 5.5$).
284 A significant difference was also found for PHCB FA ($t(26) = 2$, $p = 0.03$, $d =$
285 0.75 , $BF_{10} = 2.82$).

286

287 **3.2. Voxel-wise approach**

288 TBSS analyses identified a significant cluster in right posterior PHCB for FA (p
289 $= 0.02$; 29, -49, -1), reflecting higher FA in *APOE-ε4* carriers (Figure 2) -
290 consistent with the tractography analysis. We found no TFCE-corrected
291 clusters for MD. Using an uncorrected threshold of $p = 0.005$ (Postans et al.,
292 2014), we identified a significant cluster in left posterior PHCB reflecting lower
293 MD in carriers ($p < 0.001$; -28, -58, 0). An exploratory whole brain analysis
294 (TFCE-corrected) revealed no significant clusters for either metric.

295

296 **3.3. The relationship between pDMN activity and PHCB microstructure**

297 To examine the functional relevance of these structural connectivity metrics,
298 we tested whether inter-individual variation in PHCB microstructure (MD, FA)
299 was associated with fMRI response in the pDMN during an 'odd-one-out'
300 discrimination task for scenes and faces (Shine et al., 2015). Across all

301 subjects, we found a significant negative association between PHCB MD and
302 scene activity (vs. “size” baseline) in the pDMN ($r = -0.51$, $p = 0.01$, $BF_{10} =$
303 12.1 , 95% BCI $[-0.73, -0.13]$; Figure 1C). There was no significant association
304 between MD and face activity ($r = -0.03$, $p = 0.01$, $BF_{10} = 0.29$, 95% BCI $[-$
305 $0.45, -0.01]$). A one-tailed Steiger Z test revealed a significant difference
306 between these coefficients ($z = 2.5$, $p < 0.01$). For PHCB FA, we likewise
307 observed a significant association with scene, but not face, pDMN BOLD
308 response (scene: $r = 0.49$, $p = 0.01$, $BF_{10} = 8.87$, 95% BCI $[0.12, 0.72]$); face:
309 $r = 0.12$, $p = 0.01$, $BF_{10} = 0.41$, 95% BCI $[-0.45, -0.01]$; Figure 1C). The
310 correlation between PHCB FA and scene activity was significantly greater
311 than the correlation with face activity ($z = 2$, $p = 0.02$).

312

313 **4. General discussion**

314 Based on the view that pDMN vulnerability to amyloid- β arises from its role as
315 a large-scale connectivity hub (Bero et al., 2012; Brown et al., 2011; Buckner
316 et al., 2009; de Haan et al., 2012; Jagust and Mormino, 2012), we asked
317 whether young adults at heightened genetic risk for AD (via presence of the
318 *APOE*- $\epsilon 4$ allele) would show increased pDMN structural connectivity (Greicius
319 et al., 2009). Supporting this hypothesis, we found that *APOE*- $\epsilon 4$ carriers,
320 relative to non-carriers, had microstructural differences in the PHCB – a white
321 matter tract linking the pDMN with the MTL, particularly parahippocampal
322 regions (Heilbronner and Haber, 2014). Moreover, inter-individual variation in
323 PHCB microstructure was selectively associated with pDMN activity during a
324 scene discrimination task that is sensitive to early AD (Lee, 2006).

325

326 The pDMN has been labelled the brain's epicenter (Hagmann et al., 2008),
327 given its disproportionately high structural/functional connectivity (Buckner et
328 al., 2009; Hagmann et al., 2008). This region is also one of the first brain
329 areas to undergo amyloid- β deposition in AD (Gonneaud et al., 2016;
330 Palmqvist et al., 2017). The early deposition of amyloid- β in pDMN suggests
331 that the high connectivity/activity demands on this region may, over the
332 lifespan, lead to amyloid- β accumulation and ultimately atrophy and cognitive
333 decline (Bero et al., 2011). In human neuroimaging studies, strong within-
334 subject correspondence has been found between pDMN functional
335 connectivity strength and subsequent amyloid- β load in individuals MCI
336 (Myers et al., 2014). Elevated pDMN connectivity in low-amyloid individuals
337 (A β -) has also been associated with increased amyloid- β deposition at follow-
338 up (Jack et al., 2013). These increases in functional connectivity in older
339 individuals, however, could reflect a compensatory response induced by early
340 pathology (Jagust and Mormino, 2012; Jones et al., 2016; Schultz et al.,
341 2017).

342

343 In young adult *APOE*- ϵ 4 carriers, who are highly unlikely to harbor amyloid- β ,
344 increased functional activity in pDMN and MTL has been seen across AD-
345 relevant cognitive tasks (Dennis et al., 2010; Filippini et al., 2009; Shine et al.,
346 2015). Young *APOE*- ϵ 4 carriers also display greater intrinsic functional
347 connectivity in the DMN compared to non-carriers (Filippini et al., 2009) -
348 consistent with the view that functional activity differences may reflect
349 increased connectivity. This contrasts with studies in older, cognitively-normal
350 *APOE*- ϵ 4 carriers, which report decreased functional connectivity (and also

351 activity) in pDMN regions (Sheline et al., 2010).

352

353 Extending these studies, we found that college-aged *APOE-ε4* carriers had
354 increased *structural* connectivity (see below) in the PHCB – the main white
355 matter pathway of the pDMN (Greicius et al., 2009). Specifically, young adult
356 *APOE-ε4* carriers had lower MD and higher FA compared to non-carriers. The
357 direction of this effect contrasts with studies in older, cognitively-normal
358 *APOE-ε4* carriers and MCI, where decreased FA (and increased MD) is
359 typically seen (Heise et al., 2014; Villain et al., 2008). Further, to demonstrate
360 that these differences in structural connectivity are linked to difficulties
361 modulating pDMN activity in *APOE-ε4*, we correlated inter-individual variation
362 in PHCB microstructure with pDMN BOLD response during a scene
363 discrimination task that is sensitive to early cognitive changes in AD [37]. This
364 multi-modal, individual differences approach demonstrated that individuals
365 with the highest pDMN activity during scene discrimination had the highest
366 structural connectivity in the PHCB (lower MD/higher FA), suggesting that
367 individual variation in structural connectivity in the PHCB may impact activity
368 in pDMN, and subsequent vulnerability to amyloid-β in later life (Jagust and
369 Mormino, 2012). While group differences in MD and FA most likely reflect an
370 impact of *APOE-e4* on some aspect(s) of structural connectivity, we cannot
371 readily determine what these are; variation in these diffusion metrics could
372 arise from multiple, functionally-relevant biological properties (e.g.,
373 myelination, membrane permeability and/or axon number, diameter and
374 voxel-wise configuration (D K Jones et al., 2013)).

375

376 One interpretation of these white matter differences is that they reflect early
377 neuropathology, such as axonal loss or demyelination. Studies in
378 asymptomatic adult carriers of a disease-causing *PSEN1* mutation (Ryan et
379 al., 2013), and also in older adults with a parental history of AD (Melah et al.,
380 2016), have reported, like here, greater FA (and lower MD) in a wide range of
381 tracts, including the cingulum. Greater FA has also been observed in
382 individuals with A β + versus A β - MCI (Racine et al., 2014). Such differences
383 have been attributed to axonal loss within specific fiber sub-populations of
384 complex crossing-fiber areas (Douaud et al., 2011). This would lead to a
385 reduction in fiber complexity and a concomitant increase in local anisotropy.
386 Given that these *APOE*- ϵ 4 carriers will not harbor amyloid- β (Mormino, 2014),
387 however, this neuropathological interpretation seems highly unlikely. Further,
388 the pattern reported here is opposite to that seen typically in older individuals,
389 where studies have shown reported lower FA/higher MD in individuals with
390 AD and MCI ((Mito et al., 2018; Rieckmann et al., 2016) but see (Racine et
391 al., 2014)). Rather, these findings support a LSV view of AD risk, where early-
392 life, non-pathologically driven structural and functional alterations in specific
393 brain networks may confer risk for later-life AD neuropathology (Jagust and
394 Mormino, 2012).

395

396 Given this, one possible explanation for these white matter differences is that
397 *APOE*- ϵ 4 carriers and non-carriers undergo different patterns of white matter
398 maturation. Previous studies suggest that efficient communication between
399 distributed brain regions may emerge across development via overgrowth and
400 then pruning of redundant axons (Yeatman et al., 2012). *APOE*- ϵ 4 carriers,

401 therefore, may show somewhat delayed axonal pruning of the late-maturing
402 cingulum (Yeatman et al., 2014) during a critical period, such as adolescence
403 (Yeatman et al., 2012), which leads to an overshoot in tissue microstructure
404 and relative increases in pDMN neural activity (Figure 4). This increased
405 pDMN activity in young adult *APOE*- ϵ 4 carriers (as seen here during scene
406 discrimination) may thus reflect some form of lifelong reduced network
407 efficiency (Jagust and Mormino, 2012) or flexibility (Westlye et al., 2011),
408 which impacts the ability of the pDMN to modulate activity (or state-dependent
409 connectivity with MTL (Harrison et al., 2016; Westlye et al., 2011)) required to
410 accommodate the need of a particular task.

411

412 Critically, these early life increases in pDMN structural connectivity (i.e.,
413 higher FA/lower MD), and concomitant changes in functional activity (Shine et
414 al., 2015), may portend a faster decline in connectivity over the lifespan
415 (Brown et al., 2011; Felsky, 2013), which ultimately leads to early amyloid- β
416 deposition and neurodegeneration (de Haan et al., 2012) (depicted in Figure
417 4). For instance, a cross-sectional study, which applied graph theory to
418 measure the network characteristics of dMRI data, found that younger *APOE*-
419 ϵ 4 carriers had greater 'local interconnectivity' relative to non-carriers but
420 exhibited a steeper age-related reduction ((Brown et al., 2011); see also
421 (Felsky, 2013)). A potential compensatory increase in connectivity/activity, in
422 response to accumulating amyloid- β pathology (Schultz et al., 2017), will
423 result in nodal stress and ultimately network failure (Jones et al., 2016), as
424 reflected by a second steep decline in network integrity (activity/connectivity;
425 Figure 3). A recent study, for instance, found that amyloid- β contributes to the

426 spreading of tau pathology via the PHCB (Jacobs et al., 2018). Future multi-
427 modal imaging studies, conducted longitudinally across the lifespan, would
428 provide further insights into how *APOE-ε4* influences white matter
429 microstructure and task-related activity across the lifespan.

430

431 While comparable to previous studies (Dennis et al., 2010; Filippini et al.,
432 2009; Oh and Jagust, 2013), the sample size in the current study is relatively
433 modest. This issue is partly mitigated by a clear hypothesis-driven approach
434 (Button et al., 2013) and Bayesian analyses showing that our findings have
435 high evidential value (Dienes, 2014).

436

437 While we observed significant differences for both FA and MD, our reported
438 effects were somewhat stronger for MD, particularly for the tractography
439 analysis. This is consistent with reports that FA shows greater intra-tract
440 variability than MD – i.e. tracts do not have a signature FA value that is
441 consistent along the tract length (Yeatman et al., 2012). Future dMRI studies
442 using advanced tract profiling and biophysical modelling would shed further
443 insight into the relation between *APOE-ε4* and PHCB microstructure (Assaf et
444 al., 2017; Yeatman et al., 2012).

445

446 **Conclusion**

447 To conclude, we have shown that *APOE-ε4*-related increases in pDMN
448 activity (Shine et al., 2015) are linked to structural connectivity in the PHCB -
449 the main white matter conduit linking pDMN with the MTL (Heilbronner and
450 Haber, 2014). Specifically, *APOE-ε4* carriers had significantly lower MD, and

451 higher FA, in this pathway – the opposite effect to that seen in cognitively-
452 normal older *APOE*- ϵ 4 carriers (Felsky, 2013). By combining dMRI and BOLD
453 fMRI measures, we showed that inter-individual variation in PHCB
454 microstructure (increased FA/decreased MD) was linked to increased pDMN
455 activity during a scene discrimination task that is affected in AD (Lee, 2006).
456 These findings support a LSV model of AD risk, whereby connectivity-
457 associated increases in pDMN activity across the lifespan may confer risk for
458 amyloid- β accumulation in later life – one of the earliest biomarkers of AD
459 pathology.

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476 **Author contributions**

477 CJH, ADL and KSG designed research; CJH collected the data; CJH, JPS,
478 HW and MP analyzed the neuroimaging data; RS and JW analyzed the
479 genetic data; CJH wrote the paper with support from all other authors; CJH
480 and JPS are joint first authors.

481

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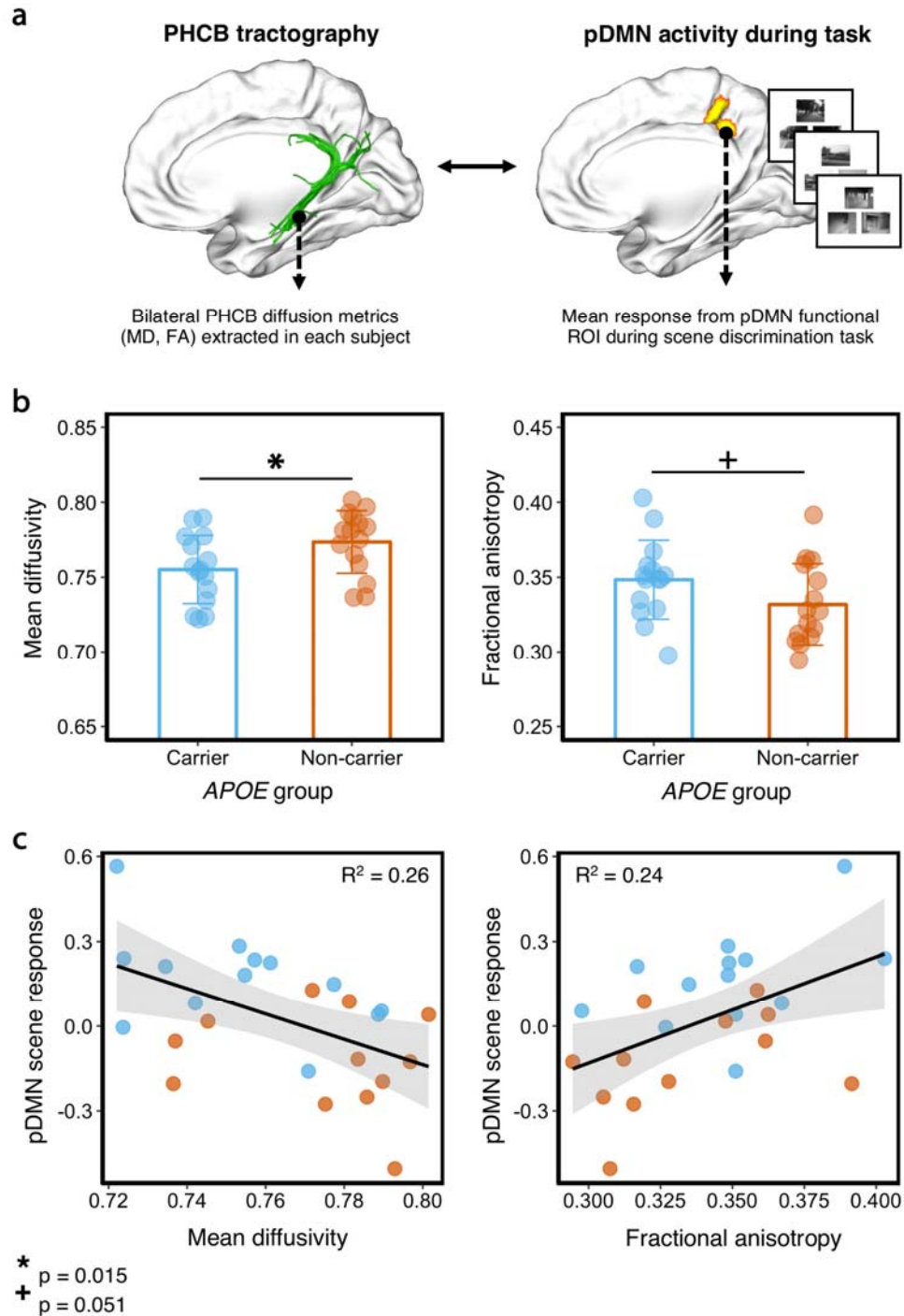
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751 **Figures**



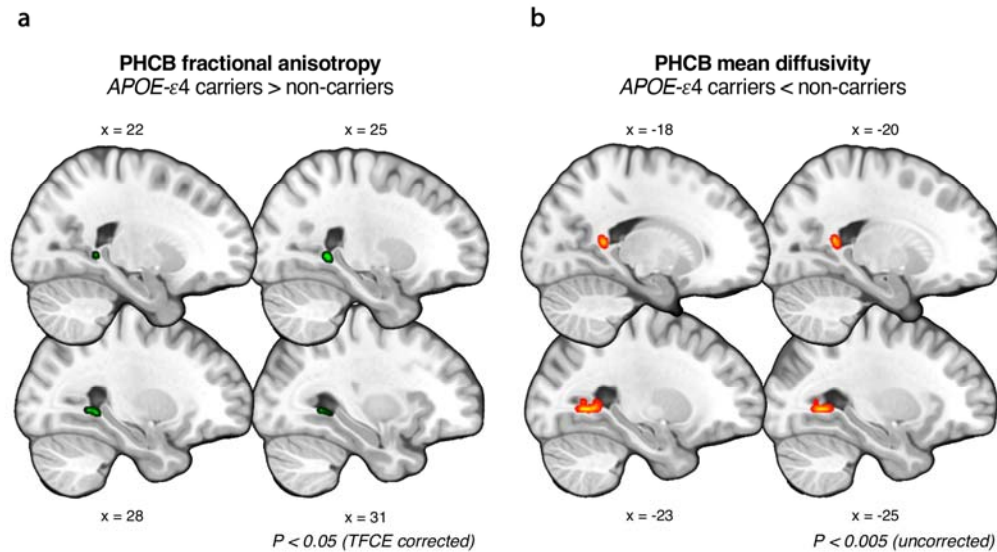
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756 **Figure 1. Comparing parahippocampal cingulum bundle (PCHB) tissue**
757 **microstructure between *APOE-ε4* carriers and non-carriers.** (a) Left:
758 Deterministic tractography was conducted in each subject and free water
759 corrected indices of bilateral PHCB microstructure (MD, FA) were extracted
760 (left). Right: To examine associations with functional activity, these metrics
761 were correlated with BOLD activity from an independently-defined posterior
762 default mode network (pDMN) functional region-of-interest during a perceptual
763 discrimination task (Shine et al., 2015). Example scene trials for the
764 perceptual ‘odd-one-out’ discrimination task are shown. (b) Plots comparing
765 mean bilateral PHCB MD and FA for *APOE-ε4* carriers and non-carriers.
766 Individual data points are displayed jittered on each bar. (c) Scatter plots
767 showing the association between scene (vs. “size” baseline) activity in pDMN
768 and MD (left) and FA (right) in the PHCB. A total of 25 data points are shown
769 on each scatter plot (13 carriers, blue markers; 12 non-carriers, orange
770 markers; see Section 2.6).
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774 **Figure 2. Comparing parahippocampal cingulum bundle (PHCB)**
775 **microstructure in *APOE-ε4* carriers and non-carriers using tract-based**
776 **spatial statistics.** (a) A significant cluster (shown in green) was found
777 showing greater FA in *APOE-ε4* carriers versus non-carriers in posterior
778 PHCB ($p < 0.05$, TFCE-corrected). (b) A sub-threshold cluster (shown in red-
779 yellow) reflecting lower MD in *APOE-ε4* carriers versus non-carriers was
780 identified in posterior PHCB ($p < 0.005$, uncorrected). For visualization
781 purposes, clusters have been 'thickened' using 'TBSS fill' in FSL. There were
782 no voxel-wise differences for MD that survived stringent correction.

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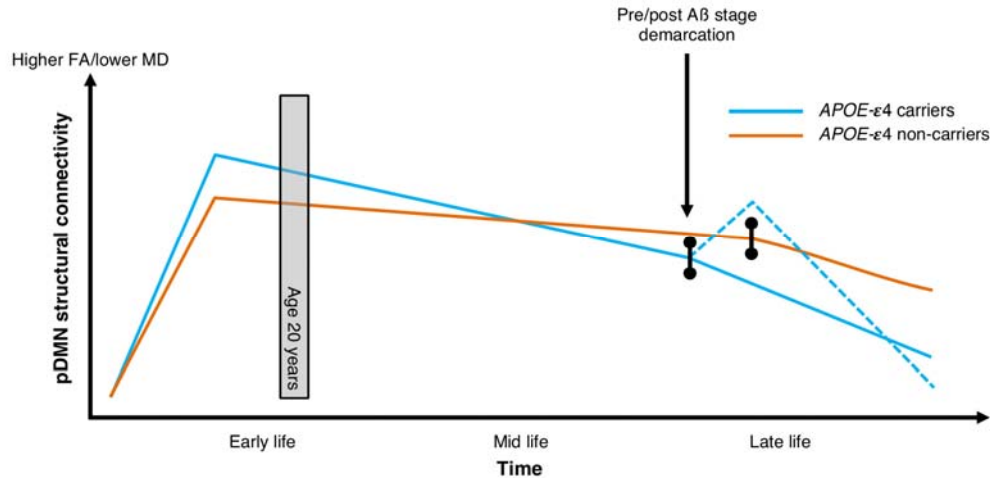
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790 **Figure 3. Posterior DMN structural connectivity and amyloid deposition**

791 **across the lifetime.** Figure depicts hypothetical trajectories of pDMN

792 structural connectivity in *APOE-ε4* carriers and non-carriers (as can be

793 quantified using microstructural metrics derived from dMRI – i.e., FA and MD).

794 Increased structural connectivity in young adult *APOE-ε4* carriers (the age of

795 our sample indicated by a grey box at 20 years) - which emerges over

796 development – is proposed to lead to steeper decline across the lifespan

797 (Brown et al., 2011; Felsky, 2013). Variation in structural connectivity across

798 the lifespan leads to different demarcation points for amyloid-β aggregation,

799 with *APOE-ε4* carriers showing earlier accumulation. The dashed blue

800 indicates a hypothesized increase in connectivity in response to initial

801 amyloid-β burden – which may be mirrored in activity changes (Jagust and

802 Mormino, 2012). Amyloid-β deposition leads to “wear and tear” in the pDMN

803 and a steep later-life decline in network structural connectivity, and eventual

804 network failure (Jones et al., 2016).