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Age-Related Changes in Diffusion Tensor Imaging Metrics of Fornix Subregions in Healthy Humans

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Key Words
Forniceal diffusivity · Diffusion tensor imaging · Magnetic resonance imaging · Brain · Microstructure · Aging

Abstract
Objective: White matter diffusivity measures of the fornix change with aging, which likely relates to changes in memory and cognition in older adults. Subregional variations in forniceal diffusivity may exist, given its heterogeneous anatomy and connectivity; however, these have not been closely examined in vivo. We examined diffusivity parameters (fractional anisotropy, FA; radial diffusivity, RD; axial diffusivity, AD) in forniceal subregions of healthy subjects and correlated them with age and hippocampal volume. ***Methods:*** Diffusion-weighted imaging and streamline tractography of the fornix were performed on 20 healthy, right-handed females (23–66 years). Six anatomical subregions were defined: midline (body, column, precommissural fornix) or lateral (fimbria, crura, postcommissural fornix). Regression analysis was performed comparing diffusivities against age. Hippocampal and ventricular volumes were also compared. ***Results:*** Diffusivity values revealed statistical changes with age in both midline and lateralized subregions. The fornix body and left crus showed age-related alterations in all metrics (FA, RD, AD), whereas only right crus FA was altered. There was no significant change in hippocampal volumes, suggesting that forniceal changes may precede hippocampal age-related changes. ***Conclusions:*** Age-related changes in fornix diffusivity measures appear subregion dependent and asymmetrical. Specific subregion diffusivity measures may be a more sensitive aging marker than hippocampal volume change.

Introduction

In humans, relatively little is known about how the fornix, which is estimated to have 5.8–7.2 million axons arranged in uniform bundles [1], changes over time. Anatomically, the fornix can be described in terms of subregions which extend from the hippocampal region (fimbria), curve around the thalami (crura) and join together at the midline (body), from which they project anteriorly until dividing laterally again near the anterior commissure (columns) and anteriorly/posteriorly (pre-/post-

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commissural fibers) to terminate in the septal nuclei and nucleus accumbens and the mammillary bodies, respectively [2]. Thus, the subregions are either located along the midline (body, columns) or more laterally (fimbria, crura, postcommissural fibers) [3].

The role of medial temporal structures has been the subject of intense study, particularly related to memory impairment in both normal aging and neurodegenerative disorders. There is ample evidence that reduced memory performance is related to hippocampal dysfunction and atrophy [4–6] and also appears a consequence of forniceal injury. The importance of the role of the fornix in memory function is well known, with lesions in both animals [7–9] and humans [10–14] producing many memory deficits, with particular impairments in memory formation [for reviews, see 15, 16]. Moreover, neuroimaging research suggests that loss of fornix integrity is an early event in Alzheimer's disease and precedes hippocampal volume loss [17]. Deep brain stimulation of the fornix can elicit memory recollection [18], and these findings have driven promising studies aimed at improving memory function in those with early stage Alzheimer's disease [19]. Nonetheless, as most studies in humans have imaged or stimulated large areas of the fornix, it is currently unclear which subregions of the fornix might be involved in these effects.

For instance, a study by Tsivilis et al. [14] in patients with surgically treated colloid cysts found that mammillary body volume (an indirect measure of fornix fiber integrity), but not whole forniceal volume, was correlated with changes in memory formation. The authors suggested that given the frequent distortion of forniceal tracts, whole volume measures themselves were unlikely to be consistent and comparable. Moreover, as the impact on memory performance seen in their study was due to forniceal damage, which likely resulted in localized network disconnections, they suggested that local measures which better quantify the damage subregionally are more likely to be reliable and interpretable compared to measures of overall volume. Additionally, while no human studies have looked at differential subregional connectivity of the fornix using diffusion tensor imaging (DTI), a recent study by Jang and Kwon [20] showed that the posterior body of the fornix has widespread connectivity to cortical and subcortical regions, such as the pre- and postcentral gyri and posterior parietal cortex, via the splenium of the corpus callosum, posterior limb of the internal capsule, forniceal crura and thalamus. Together, these results further support a subregional approach when investigating the structure and function of the fornix.

Beyond connectivity, DTI also permits in vivo assessment of neural microstructure by utilizing the diffusion properties of water in constrained compartments [21, 22]. Therefore, DTI diffusivities can potentially provide information about the human fornix in health and disease. The kind of diffusivity metrics which are typically drawn from DTI are described based on the primary eigenvector involved, with each kind believed to preferentially provide information on different processes. The commonly studied diffusivities include fractional anisotropy (FA) – which describes the directional diffusivity of water along tracts, reflects a broad measure of fiber integrity, and is sensitive to various parameters such as regional myelination, fiber crossing, axonal density and diameter [23] – and radial diffusivity (RD) and axial diffusivity (AD) which have been correlated with myelin and axonal integrity, respectively [24–26].

Several studies of diffusivity within the human fornix have identified changes which occur with normal aging [27, 28] and in neurodegenerative disease [17, 29]. For instance, FA has been reported to decrease with aging while mean diffusivity (a combined measure of RD and AD) increases, possibly reflecting degradation, breakdown or deterioration in fiber integrity [27, 28]. However, since the fornix is a large and heterogeneous structure, diffusivities measured for its entire volume may not be accurate or reveal highly localized changes. Assessment of diffusivity at the subregional level is not commonly performed due to technical constraints, which have included a limited ability to image fornix anatomy and accurate subregional identification. Here, we use a readily available single-tensor tractography model to identify differences in the subregions of the fornix. Specifically, the aim of the study was to determine (i) the ability for DTI tractography to delineate the anatomical structure of the fornix and (ii) identify age-related differences in subregions of the fornix in a cross-section of healthy adults.

Methods

Data Acquisition

All subjects were healthy volunteers, imaged using a General Electric 3-tesla Signa HDx MRI scanner with an 8-channel head coil. T1-weighted anatomical and diffusion-weighted images were acquired from 20 healthy right-handed females, aged 23–66 years (mean 43.9, standard deviation 13.8). T1-weighted scans were acquired using axial fast spoiled gradient echo sequences with slice thickness = 1 mm. Diffusion-weighted images were acquired with 60 gradient directions with spin echo planar imaging sequence, slice thickness = 3 mm, in-plane voxel size = 0.97 × 0.97, TE = 86.6, TR = 12,000, NEX = 1, matrix = 128 × 128, b-value = 1,000 s/mm^2,

slice number = 55, asset = ON, parallel factor = 2. Institutional research ethics board approval was obtained for this study, and all subjects gave their written informed consent.

Region of Interest Definition

The fornix was subdivided into 6 anatomical subregions as follows: (i) fimbria – the short segment between the end of the hippocampal region until the coalescing of the fimbrial fibers into the bundle of the crura; this also corresponds to the point that is furthest away from the anterior commissure (AC) position; (ii) crura – from the end point of the fimbria until the joining of the crura to form the body; (iii) body – midline structure that continues anteriorly and rostrally following the roof of the third ventricle; (iv) column – short midline structure located between the edge of the roof of the third ventricle to the position of the AC; it is characterized by its vertical course towards the AC; (v) precommissural columns – bilateral structures which travel anteriorly to the AC, and (vi) postcommissural columns – also bilateral, travel posterior to the AC. The subregions of the fornix can be further classified into 2 groups: midline structures, where the left/right components cannot be visually discerned from MRI images (i.e. body, column and precommissural fibers) and clearly discernable lateralized subregions (i.e. fimbriae, precommissural and postcommissural columns).

For the purposes of intersubject comparison of subregional diffusivities, the regions of interest (ROIs) were identified in unique points where the location of the subregion is most consistent and therefore least likely to be erroneously placed in a different subregion. The following criteria were used to help further guide ROI placement: fimbria – inflection point of the fibers and point furthest away from the position of the AC; crura – immediately posterior to the body of the fornix, where the bilateral structure can be clearly distinguished; body – midpoint, along the roof of the third ventricle; column – along the vertical course, above the position of the AC; precommissural fibers – anterior to the AC; postcommissural fibers – posterior to the AC.

Image Processing and Tractography

All image processing and tractography analyses were completed using 3D Slicer software [30]. Diffusion data were corrected for eddy current and motion distortions using FSL software [31] and imported into 3D Slicer, where the DTI tensor volume was calculated. The T1-weighted anatomical scan was also imported and registered to the DTI baseline using linear registration. A seeding ROI was placed at the column of the fornix superior to the AC, where the location of the fornix is the most universally recognizable across all the subjects' scans to reduce tract inconsistency. Another seeding ROI was placed at the center of the AC to delineate the AC tracts (fig. 1). A single-tensor tractography model was generated with initial seed spacing = 0.5 mm, initial seeding FA threshold = 0.2, stopping FA threshold = 0.1, curvature threshold = 0.8 and integration distance = 0.1. Erroneous tracts were filtered out using the ROI Select Boolean operation.

Diffusion Statistics

Scalar DTI metrics were extracted, using 3D Slicer, from ROIs placed at the precommissural column, left and right postcommissural columns, column of the fornix superior to the AC, posterior fornix body directly anterior of the hippocampal commissure, left and right crura, and left and right fimbria (fig. 2 and as described

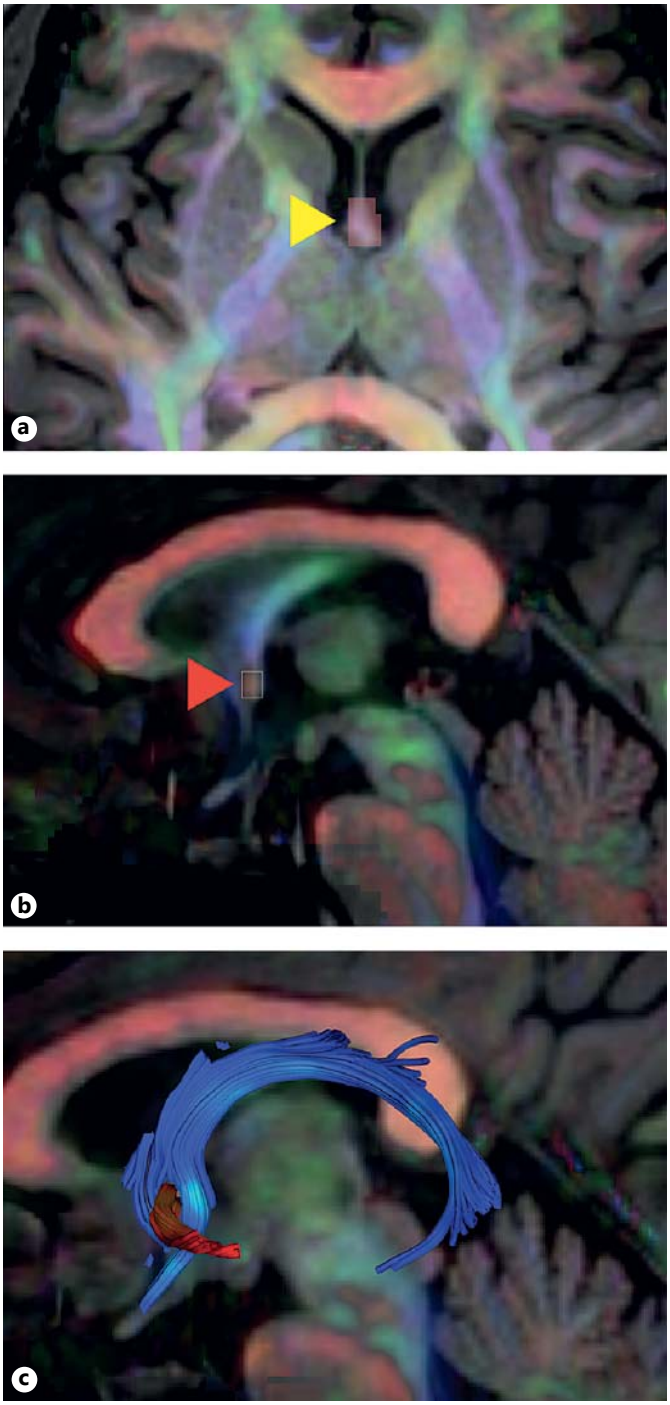

Fig. 1. DTI model reconstruction using deterministic tractography. **a** Axial slice of a sample brain with the T1-weighted anatomical scan superimposed onto the DTI image of the same subject. The DTI image is shown in color-by-orientation (red: left-right; green: anterior-posterior; blue: superior-inferior). The yellow arrowhead denotes the seeding ROI. **b** Midsagittal slice; the red arrowhead denotes the ROI for AC seeding. **c** Sagittal representative fornix tractography reconstruction overlaid onto the combined DTI tensor/anatomical image.

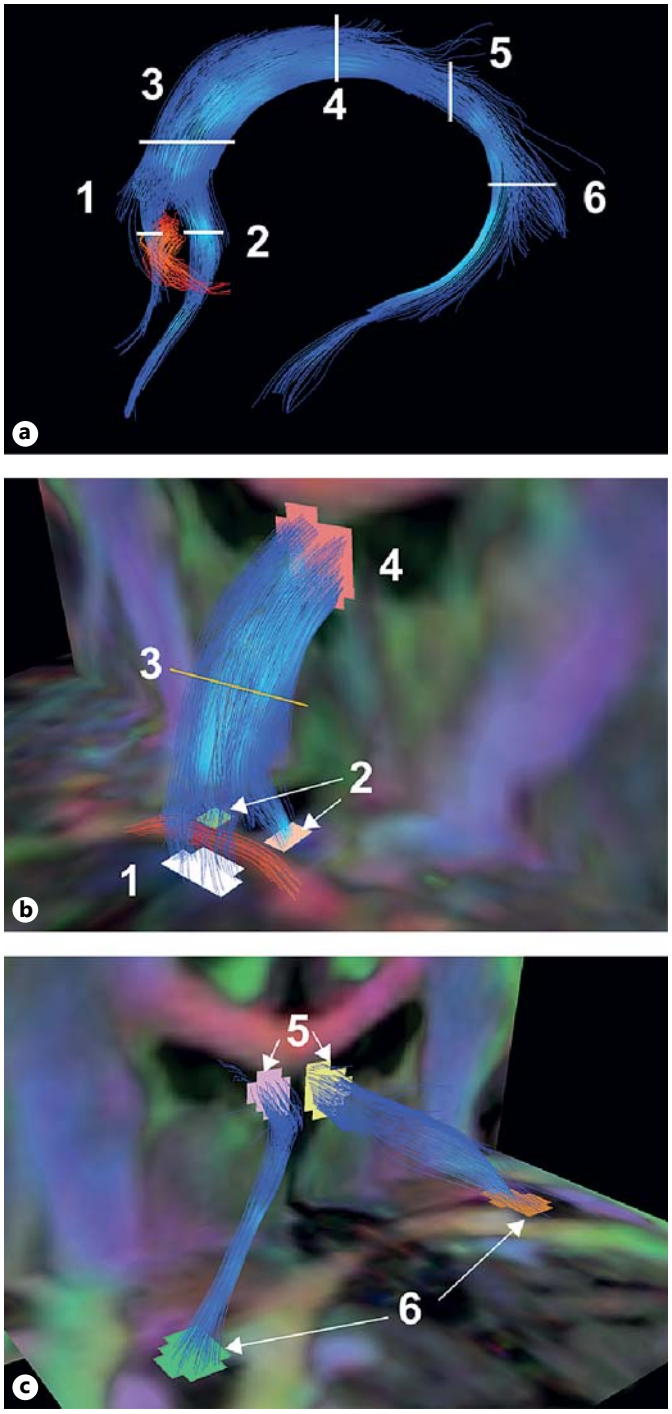

Fig. 2. ROI placement within the forniceal subregions. **a** Regions of the fornix that are of interest: 1 = precommissural column; 2 = postcommissural column; 3 = column of fornix; 4 = body of fornix; 5 = crura; 6 = fimbriae. The red fiber delineates the position of the AC as anatomical reference. **b**, **c** The specific cross-sections where the respective ROIs were measured.

above). ROI locations were selected to be near the AC and hippocampal commissure to minimize spatial variability between subjects. ROI volumes were based on automatically generated masks from the tracts to minimize user bias.

Subcortical Volume Measurements

Freesurfer image analysis suite was used for volumetric segmentation of the hippocampi and lateral ventricles. The processing steps included intensity normalization of the T1-weighted MRI scans, skull stripping of nonbrain tissue, automated Talairach transformation, mapping the subcortical regions onto an averaged brain template and stochastically labeling the subcortical regions [32]. The segmentation maps were imported into 3D Slicer and registered onto the DTI scan to visualize the hippocampus and amygdala. Hippocampal volume statistics were corrected against intracranial volume.

Linear regression and analysis of variance calculations were computed using the R statistics package to determine the relationship between diffusivity parameters in different regions of the fornix and age. False discovery rate multiple comparison correction was applied to the correlation statistics. Ordinal linear regression, weighted linear regression and quadratic regression were computed and compared using analysis of variance to determine the effect of model selection. Left and right lateral ventricular volumes were compared with the pairwise Student t test.

Results

Reconstruction of the Tracts of the Fornix

3D tract reconstructions of all subregions of the fornix were achieved in all subjects (fig. 1a). The position of the AC was also assessed in detail for each case, since it serves as reference point for the pre- and postcommissural fibers (fig. 1b). The reconstructed tracts were overlaid onto anatomical images to ensure that there is accurate correspondence between the two modalities of imaging (fig. 1c). Each subregion was defined based on these reconstructions and a priori determined anatomical criteria, allowing for accurate positioning of the ROIs for diffusivity calculations (fig. 2, 3). The overall 3D structure of the fornix was examined within and across subjects. While some variation in shape was visible, all forniceal subregions were clearly visible in every subject.

Age-Related Diffusivity Changes in the Subregions of the Fornix Are Not Uniform

Forniceal subregional diffusivity metrics were correlated with age (fig. 4). Midline subregions (precommissural fornix, body and column) and lateralized subregions (postcommissural fornix, crura) were examined separately. In midline subregions, the body of the fornix showed FA, RD and AD changes with age ($p < 0.05$). The

column showed an increase in RD with age, but no changes in FA and AD. The pre- and postcommissural column diffusivities were not significant across time.

Asymmetry of the Crura

When the diffusivity values were compared for each crus, we observed that the left crus changed across time for all 3 measures of diffusivity while the right crus only demonstrated change in FA. By comparison, the fimbriae did not show significant correlations with age. Analysis of variance for the different regression models showed no significant differences as a result of different model-fitting methods. Hippocampal volume was both linearly and quadratically regressed with age; however, no significant correlations were found. Pairwise comparisons of left to right lateral ventricular volume showed no statistically significant differences ($t = -0.08$, $p = 0.93$).

Discussion

Our study demonstrates the feasibility of independently measuring the DTI properties of the forniceal subregions. By carrying out subregional analysis, we observed previously unidentified asymmetrical diffusivities that were subregion, side and age related. Assessment of hippocampal volumes in this cohort of healthy subjects did not reveal significant age-related volumetric changes, suggesting that diffusivity changes in the fornix may precede changes in the hippocampus. This fact may be of relevance in the development of better markers for the process of healthy aging and possibly in the prediction of cognitive decline which is a hallmark of many neurodegenerative disorders, although future studies must be done to further explore such a relationship.

Asymmetric Diffusivities in Lateralized Subregions of the Fornix

We observed decreased FA and increased RD and AD in the left crus associated with aging, and a decrease in FA only on the right side. We investigated the possibility that ventricular asymmetry might result in such differences. While there is evidence of ventricular asymmetry in the schizotypical population [33], and instances of trapped ventricular horns can affect forniceal anatomy, analysis of left and right lateral ventricular volume showed no significant differences in our subject group. Therefore forniceal diffusivity asymmetry is not the result of lateral ventricular asymmetry. This right-left forniceal discrepancy may be an indication of hemisphere dominance, since in this case all

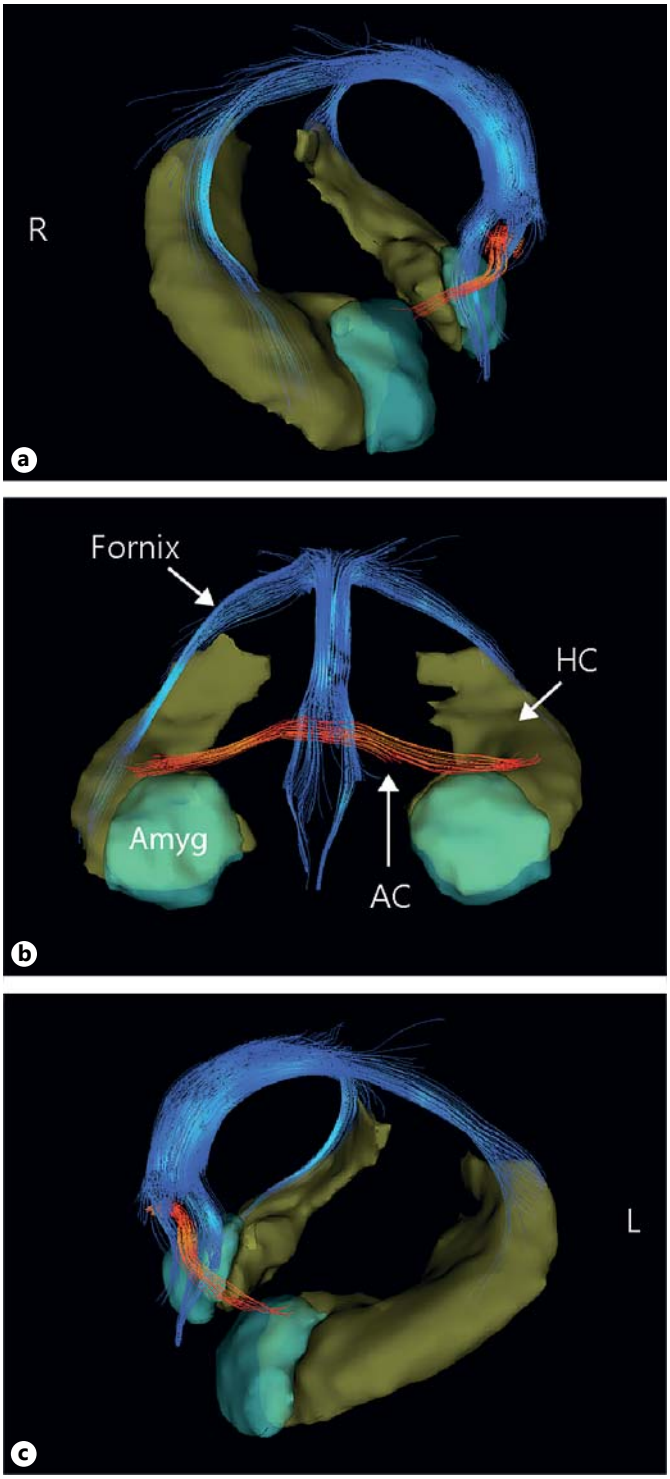

Fig. 3. Tractography model of the fornix highlighting asymmetry (blue). **b** Identified for visualization purposes are the AC, hippocampal area (HC) and amygdala (Amyg). The models are generated from Freesurfer segmentations of the same subject. Note that **a** shows a solid bundle of fimbria tract extending into the left hippocampus while the right fimbria tract in **c** does not show the same extension. This asymmetry in tract propagation is most prevalent in older subjects.

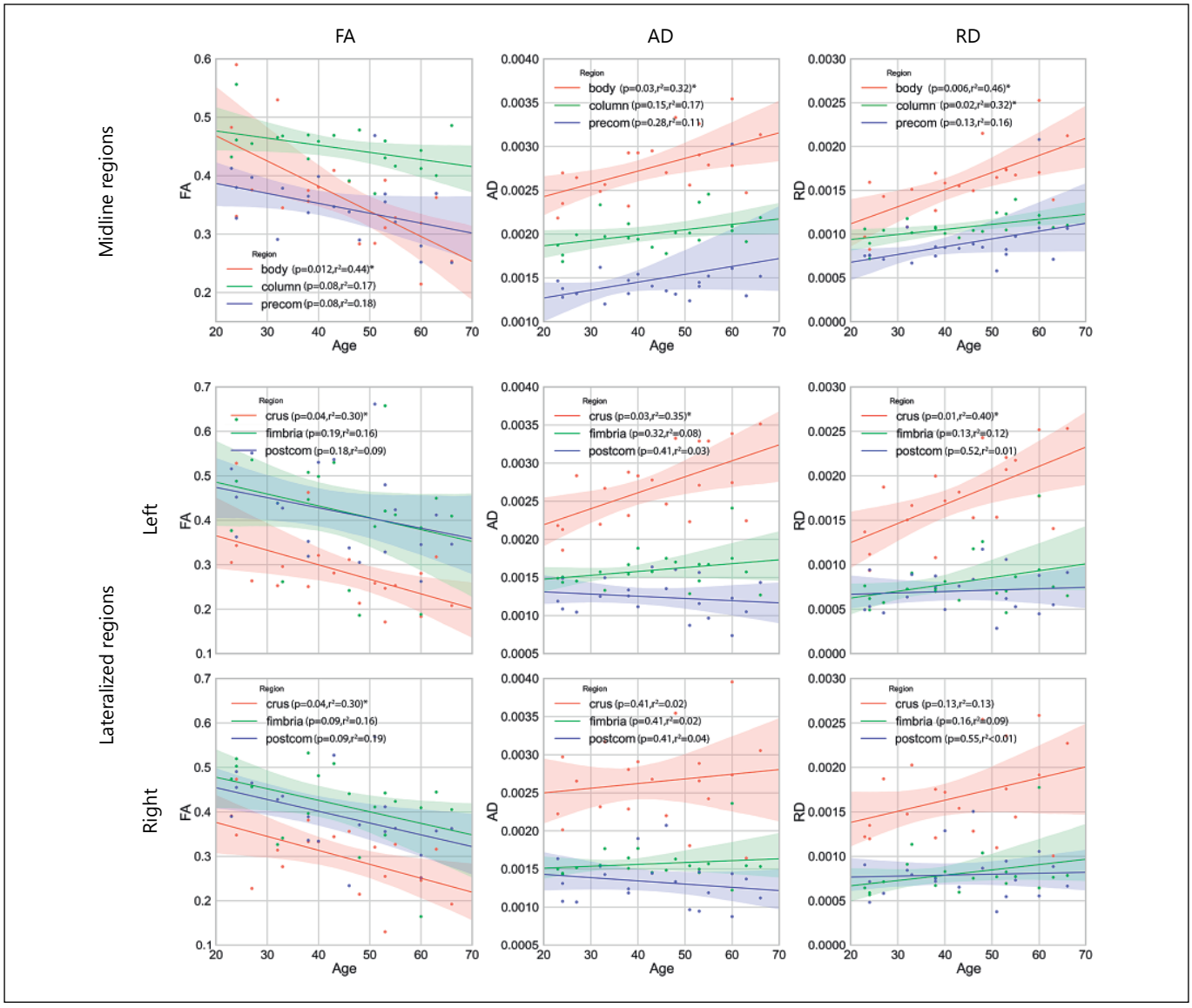

Fig. 4. Linear regression plot of diffusivity metrics versus age. Columns show FA, AD and RD, respectively; the first row shows diffusivities in midline forniceal subregions (precommissural column, column and body); second and third rows show diffusivities of left and right lateralized subregions (postcommissural column, crura and fimbriae), respectively. Shaded areas represent 95% confidence intervals.

subjects were right handed. As the crus is the subregion most proximal to the hippocampus, it is possible that its diffusivity changes are a reflection of hippocampal changes relating to age, particularly as some studies of the hippocampal areas have also noted a left-side asymmetrical decrease in volume related to aging [34, 35]. Longitudinal diffusivity and cognitive correlation with cohorts older than the present population may clarify this finding further. Interestingly, a recent study has shown a positive correlation between cerebrospinal fluid concentrations of the Alzheimer-related marker proteins (Aβ42 and Aβ42/p-Tau181 ratios) and FA values in the left crus – independent of total fornix volume, and this is not seen in the hippocampus – in healthy older adults at risk for developing Alzheimer's disease [36].

Diffusivities in Midline Subregions of the Fornix

The body and column of the fornix clearly demonstrated changes with age. While the forniceal body showed decreased FA, and increased RD and AD over time, only

RD values in the column showed significant increases over time. Although the reason for this result is currently unclear, given the slight trend in decreased FA also seen in this region, it is possible that the inclusion of additional subjects or older adults might reveal significant column changes in FA. Nonetheless, the present results suggest that the fornix body is especially susceptible to age-related degradation. Similarly, the precommissural and postcommissural columns demonstrated no significance but showed a similar weak decreasing trend in FA values. These results suggest that, even within a clearly labeled tract such as the anterior fornix, its diffusivity changes can be highly heterogeneous. Our results are consistent with other literature which reports decreased FA values in the fornix with age [37, 38]. While studies have shown that age-independent demyelination or axonal injury strongly correlates with specific DTI metrics such as RD or AD, respectively [39–41], it is unsurprising to see changes in FA, AD and RD in our current study sample given that multiple events involving different aspects of white matter integrity are involved in aging.

The literature investigating the effects of age-related hippocampal atrophy has demonstrated that decreased hippocampal volume follows a nonlinear trend [42]. Therefore both linear and quadratic regressions were performed to examine age-related diffusivity changes in our cohort, which was younger (mean age of 44 years) compared to typical studies in older adults (e.g. see Ezzati et al. [43]; mean age of 80 years). Nonetheless, our analysis revealed no difference in the resulting model selection, suggesting that age-related forniceal diffusivity changes in healthy younger adults do not follow a nonlinear trend – again, supporting the notion that these forniceal changes may precede those seen in the hippocampus.

Correlation of Hippocampal Volume with Age

While it is known that the volume of the hippocampus decreases with age [38, 44, 45], we did not observe a significant decline in hippocampal volume in our group of healthy subjects. Longitudinal studies have demonstrated that there is whole-brain, and especially hippocampal, atrophy with age which correlates with a decline in cognition [46]. That we did not observe a correlation between hippocampal volume and age is likely a reflection of the overall younger age group of subjects and lack of obvious cognitive impairments. It is also consistent with findings in a much larger cohort which revealed a pattern of increasing hippocampal volume over the first 30 years of life, followed by a slow decrease across the ages of 30–60 and a more rapid decrease from the ages of 60 to 90 [47]. Moreover, that study showed an even slower rate of decreasing gray matter volume in the parahippocampal area across time – a region which is included in our mask of the hippocampal area. Although the present results from the fornix suggest that this region may be a better early predictor of age-related changes, when compared to the decreases in hippocampal volume, this claim needs to be explicitly examined in longitudinal studies. In particular, future studies should look for clear evidence that these early changes in the fornix are strongly tied to later volumetric changes in the hippocampal area. One study along these lines has shown that whole-fornix FA values correlate strongly with hippocampal volumes, and that each measure was a good predictor of the transition from mild cognitive impairment to a diagnosis of Alzheimer's disease [17]. Analyses with a subregional approach will aid in our understanding of neuroanatomical changes in these disorders.

Limitations

The crura and fimbriae have traditionally been the most difficult regions to resolve by DTI tractography because of the divergence of the forniceal tract and its proximity to the hippocampus. The precommissural and postcommissural fibers have also been difficult to image due to their proximity to the many crossing pathways near the mammillary bodies and hypothalamus. Previous papers focusing on tractography of the fornix have been limited by their inability to resolve these structures [48–51]. Jang et al. [27] examined the FA values in the forniceal column, body and crura with a 1.5-tesla MRI magnet, which is a lower field strength than used in our work (3-tesla MRI) and results in lower resolution images. Moreover, they did not examine RD and AD in these regions. Together, these issues may help explain why these authors failed to find the asymmetry noted in the present study.

We have used a single-tensor model that is widely available and relatively easy to use (e.g. 3D Slicer) to demonstrate that differences can be found along a structure as robust as the fornix, and suggest that these differences should be routinely considered in clinical studies. Although the fornix is known to be a distinctively uniform white-matter bundle across most of its subregions, it is important to note that regions with many crossing fibers which lie anteriorly in the regions of the pre- and postcolumns are typically problematic for the DTI algorithm, as the fornix splits anteriorly/posteriorly to connect to the septal nuclei, nucleus accumbens and mammillary bodies. Thus, although our focus was not on these anatomically transitional structures per se, and despite the fact that the single-tensor approach appeared to outline these

structures relatively well, future studies should utilize more advanced strategies to investigate these regions. For instance, multitensor tractography models are better at delineating fine-grained anatomical details and in imaging structures with heavy crossing fibers [52, 53].

The placements of the ROIs used for diffusion metric extraction may be prone to user bias in visual selection. Therefore care has been taken to use the tractography model as a template, and consistent anatomical landmarks were used to minimize such biases. More detailed studies may be possible in the future by using nongaussian diffusion imaging methods with high angular resolution diffusion imaging [54], as well as automated tractography quantification tools to allow full examination of the fornix structural diffusion metrics. While these tools are still highly experimental and are in the process of development at the time of writing, with the improvement in technology, additional insight may be gained.

Conclusions

We have demonstrated differential significant changes in diffusivity across forniceal subregions in aging healthy adults. Our results support asymmetrical changes of the crura despite an absence of hippocampal volume changes. Diffusivity metrics may be a more sensitive marker in detecting forniceal changes in early aging, and more detailed studies may shed light on the relationship of fornix and hippocampal changes in the younger aging population.

References

1 Daitz H: Note on the fibre content of the fornix system in man. Brain 1953;76:509–512.
2 Morgane PJ, Galler JR, Mokler DJ: A review of systems and networks of the limbic forebrain/limbic midbrain. Prog Neurobiol 2005;75:143–160.
3 Thomas AG, Koumellis P, Dineen RA: The fornix in health and disease: an imaging review. Radiographics 2011;31:1107–1121.
4 Small SA, Perera GM, De La Paz R, Mayeux R, Stern Y: Differential regional dysfunction of the hippocampal formation among elderly with memory decline and Alzheimer's disease. Ann Neurol 1999;45:466–472.
5 Apostolova LG, Thompson PM, Green AE, Hwang KS, Zoumalan C, Jack CR, et al: 3D comparison of low, intermediate, and advanced hippocampal atrophy in MCI. Hum Brain Mapp 2010;31:786–797.
6 Stoub TR, Rogalski EJ, Leurgans S, Bennett DA, deToledo-Morrell L: Rate of entorhinal and hippocampal atrophy in incipient and mild AD: relation to memory function. Neurobiol Aging 2010;31:1089–1098.
7 Rawlins JN, Lyford GL, Seferiades A, Deacon RM, Cassaday HJ: Critical determinants of nonspatial working memory deficits in rats with conventional lesions of the hippocampus or fornix. Behav Neurosci 1993;107:420–433.
8 Galani R, Obis S, Coutureau E, Jarrard L, Cassel J-C: A comparison of the effects of fimbria-fornix, hippocampal, or entorhinal cortex lesions on spatial reference and working memory in rats: short versus long postsurgical recovery period. Neurobiol Learn Mem 2002;77:1–16.
9 White NM, Holahan MR, Goffaux P: Involuntary, unreinforced (pure) spatial learning is impaired by fimbria-fornix but not by dorsal hippocampus lesions. Hippocampus 2003;13:324–333.
10 Hodges JR, Carpenter K: Anterograde amnesia with fornix damage following removal of IIIrd ventricle colloid cyst. J Neurol Neurosurg Psychiatry 1991;54:633–638.
11 D'Esposito M, Verfaellie M, Alexander MP, Katz DI: Amnesia following traumatic bilateral fornix transection. Neurology 1995;45:1546–1550.
12 McMackin D, Cockburn J, Anslow P, Gaffan D: Correlation of fornix damage with memory impairment in six cases of colloid cyst removal. Acta Neurochir (Wien) 1995;135:12–18.
13 Poreh A, Winocur G, Moscovitch M, Backon M, Goshen E, Ram Z, et al: Anterograde and retrograde amnesia in a person with bilateral fornix lesions following removal of a colloid cyst. Neuropsychologia 2006;44:2241–2248.
14 Tsivilis D, Vann SD, Denby C, Roberts N, Mayes AR, Montaldi D, et al: A disproportionate role for the fornix and mammillary bodies in recall versus recognition memory. Nat Neurosci 2008;11:834–842.
15 Aggleton JP, Brown MW: Episodic memory, amnesia, and the hippocampal-anterior thalamic axis. Behav Brain Sci 1999;22:425–444; discussion 444–489.
16 Spiers HJ, Maguire EA, Burgess N: Hippocampal amnesia. Neurocase 2001;7:357–382.
17 Mielke MM, Okonkwo OC, Oishi K, Mori S, Tighe S, Miller MI, et al: Fornix integrity and hippocampal volume predict memory decline and progression to Alzheimer's disease. Alzheimers Dement 2012;8:105–113.
18 Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, et al: Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 2008;63:119–123.
19 Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al: A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010;68:521–534.
20 Jang SH, Kwon HG: Neural connectivity of the posterior body of the fornix in the human brain: diffusion tensor imaging study. Neurosci Lett 2013;549:116–119.
21 Basser PJ, Jones DK: Diffusion-tensor MRI: theory, experimental design and data analysis – a technical review. NMR Biomed 2002;15:456–467.
22 Descoteaux M, Deriche R, Knösche TR, Anwander A: Deterministic and probabilistic tractography based on complex fibre orientation distributions. IEEE Trans Med Imaging 2009;28:269–286.
23 Beaulieu C: The basis of anisotropic water diffusion in the nervous system – a technical review. NMR Biomed 2002;15:435–455.
24 Werring DJ, Clark CA, Barker GJ, Thompson AJ, Miller DH: Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. Neurology 1999;52:1626–1632.
25 Cercignani M, Inglese M, Pagani E, Comi G, Filippi M: Mean diffusivity and fractional anisotropy histograms of patients with multiple sclerosis. AJNR Am J Neuroradiol 2001;22:952–958.
26 Horsfield MA, Jones DK: Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases – a review. NMR Biomed 2002;15:570–577.
27 Jang SH, Cho S-H, Chang MC: Age-related degeneration of the fornix in the human brain: a diffusion tensor imaging study. Int J Neurosci 2011;121:94–100.
28 Lebel C, Gee M, Camicioli R, Wieler M, Martin W, Beaulieu C: Diffusion tensor imaging of white matter tract evolution over the lifespan. Neuroimage 2012;60:340–352.

29 Oishi K, Mielke MM, Albert M, Lyketsos CG, Mori S: The fornix sign: a potential sign for Alzheimer's disease based on diffusion tensor imaging. J Neuroimaging 2012;22:365–374.
30 Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, et al: 3D Slicer as an image computing platform for the Quantitative Imaging Network. Magn Reson Imaging 2012;30:1323–1341.
31 Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM: FSL. Neuroimage 2012;62:782–790.
32 Fischl B, Salat DH, Busa E, Albert M, Dieterich M, Haselgrove C, et al: Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 2002;33:341–355.
33 Buchsbaum MS, Yang S, Hazlett E, Siegel BV, Germans M, Haznedar M, et al: Ventricular volume and asymmetry in schizotypal personality disorder and schizophrenia assessed with magnetic resonance imaging. Schizophr Res 1997;27:45–53.
34 Simic G, Bexheti S, Kelovic Z, Kos M, Grbic K, Hof PR, et al: Hemispheric asymmetry, modular variability and age-related changes in the human entorhinal cortex. Neuroscience 2005;130:911–925.
35 Wenger E, Mårtensson J, Noack H, Bodammer NC, Kühn S, Schaefer S, et al: Comparing manual and automatic segmentation of hippocampal volumes: reliability and validity issues in younger and older brains. Hum Brain Mapp 2014;35:4236–4248.
36 Gold BT, Zhu Z, Brown CA, Andersen AH, LaDu MJ, Tai L, et al: White matter integrity is associated with cerebrospinal fluid markers of Alzheimer's disease in normal adults. Neurobiol Aging 2014;35:2263–2271.
37 Sala S, Agosta F, Pagani E, Copetti M, Comi G, Filippi M: Microstructural changes and atrophy in brain white matter tracts with aging. Neurobiol Aging 2012;33:488–498.
38 Tohno Y, Tohno S, Ongkana N, Suwannahoy P, Azuma C, Minami T, et al: Age-related changes of elements and relationships among elements in human hippocampus, dentate gyrus, and fornix. Biol Trace Elem Res 2010;138:42–52.
39 Janve VA, Zu Z, Yao S-Y, Li K, Zhang FL, Wilson K, et al: The radial diffusivity and magnetization transfer pool size ratio are sensitive markers for demyelination in a rat model of type III multiple sclerosis (MS) lesions. Neuroimage 2013;74:298–305.
40 Song SK, Sun SW, Ju WK, Lin SJ, Cross AH, Neufeld AH: Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. Neuroimage 2003;20:1714–1722.
41 Budde MD, Xie M, Cross AH, Song S-KK: Axial diffusivity is the primary correlate of axonal injury in the experimental autoimmune encephalomyelitis spinal cord: a quantitative pixelwise analysis. J Neurosci 2009;29:2805–2813.
42 Uematsu A, Matsui M, Tanaka C, Takahashi T, Noguchi K, Suzuki M, et al: Developmental trajectories of amygdala and hippocampus from infancy to early adulthood in healthy individuals. PLoS One 2012;7:e46970.
43 Ezzati A, Zimmerman ME, Katz MJ, Sundermann EE, Smith JL, Lipton ML, et al: Hippocampal subfields differentially correlate with chronic pain in older adults. Brain Res 2014;1573:54–62.
44 Bigler ED, Blatter DD, Anderson CV, Johnson SC, Gale SD, Hopkins RO, et al: Hippocampal volume in normal aging and traumatic brain injury. AJNR Am J Neuroradiol 1997;18:11–23.
45 Maheswaran S, Barjat H, Rueckert D, Bate ST, Howlett DR, Tilling L, et al: Longitudinal regional brain volume changes quantified in normal aging and Alzheimer's APP × PS1 mice using MRI. Brain Res 2009;1270:19–32.
46 Kramer JH, Mungas D, Reed BR, Wetzel ME, Burnett MM, Miller BL, et al: Longitudinal MRI and cognitive change in healthy elderly. Neuropsychology 2007;21:412–418.
47 Grieve SM, Korgaonkar MS, Clark CR, Williams LM: Regional heterogeneity in limbic maturational changes: evidence from integrating cortical thickness, volumetric and diffusion tensor imaging measures. Neuroimage 2011;55:868–879.
48 Concha L, Gross DW, Beaulieu C: Diffusion tensor tractography of the limbic system. AJNR Am J Neuroradiol 2005;26:2267–2274.
49 Fujiwara S, Sasaki M, Kanbara Y, Inoue T, Hirooka R, Ogawa A: Feasibility of 1.6-mm isotropic voxel diffusion tensor tractography in depicting limbic fibers. Neuroradiology 2008;50:131–136.
50 Malykhin N, Concha L, Seres P, Beaulieu C, Coupland NJ: Diffusion tensor imaging tractography and reliability analysis for limbic and paralimbic white matter tracts. Psychiatry Res 2008;164:132–142.
51 Zahr NM, Rohlfing T, Pfefferbaum A, Sullivan EV: Problem solving, working memory, and motor correlates of association and commissural fiber bundles in normal aging: a quantitative fiber tracking study. Neuroimage 2009;44:1050–1062.
52 Akter M, Hirai T, Sasao A, Nishimura S, Uetani H, Iwashita K, et al: Multi-tensor tractography of the motor pathway at 3T: a volunteer study. Magn Reson Med Sci 2011;10:59–63.
53 Qazi AA, Radmanesh A, O'Donnell L, Kindlmann G, Peled S, Whalen S, et al: Resolving crossings in the corticospinal tract by two-tensor streamline tractography: method and clinical assessment using fMRI. Neuroimage 2009;47(suppl 2):T98–T106.
54 Farquharson S, Tournier J-D, Calamante F, Fabinyi G, Schneider-Kolsky M, Jackson GD, et al: White matter fiber tractography: why we need to move beyond DTI. J Neurosurg 2013;118:1367–1377.