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The status of the precommissural and postcommissural fornix in normal ageing and mild cognitive impairment: An MRI tractography study

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ABSTRACT

The fornix connects the hippocampal formation with structures beyond the temporal lobe. Previous tractography studies have typically reconstructed the fornix as one unified bundle. However, the fornix contains two rostral divisions: the precommissural fornix and the postcommissural fornix. Each division has distinct anatomical connections and, hence, potentially distinct functions. Diffusion weighted MRI and spherical deconvolution based tractography were employed to reconstruct these separate fornix divisions and to examine their microstructural properties in both healthy ageing and Mild Cognitive Impairment (MCI). Reliable reconstructions of precommissural and postcommissural fibres were achieved in both groups, with their fibres retaining largely separate locations within the anterior body of the fornix. Ageing and MCI had comparable effects on the two segments. Ageing was associated with changes in mean, axial and radial diffusivity but not with alterations of fibre population-specific diffusion properties, estimated with the hindrance modulated orientational anisotropy (HMOA). Individual HMOA variation in postcommissural, but not precommissural, fibres correlated positively (and unrelated to age) with visual recall performance. This provides novel evidence for a role of postcommissural fibres, which connect structures of the extended hippocampal network, in episodic memory function. Separating the fornix into its two principal divisions brings new opportunities for distinguishing different hippocampal networks.

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Introduction

The fornix is the principal tract linking the hippocampal formation with sites beyond the temporal lobe. Numerous clinical studies have shown how fornix damage disrupts episodic memory, confirming the importance of these hippocampal connections for cognition (Gaffan and Gaffan, 1991; Hodges and Carpenter, 1991; D'Esposito et al., 1995; McMackin et al., 1995; Aggleton et al., 2000; Tsivilis et al., 2008; Vann et al., 2008). This same association is reinforced by MRI-based tractography studies of young (Rudebeck et al., 2009) and older (Metzler-Baddeley et al., 2011) healthy participants. In these MRI studies, indices of fornix microstructure were correlated with episodic memory performance (Rudebeck et al., 2009; Metzler-Baddeley et al., 2011). It is unsurprising, therefore, that amnestic Mild Cognitive Impairment (MCI), which disproportionately affects episodic memory (Albert et al., 2011), should consistently compromise the fornix according to diffusion tensor MRI tractography (Metzler-Baddeley et al., 2012a; Oishi et al., 2012; Zhuang et al., 2012).

The majority of previous studies into age and disease related changes in fornix microstructure, including their relationships with episodic memory, have treated the fornix as a unified tract. Anatomical studies show, however, that the rostral fornix separates into two main branches, split by the anterior commissure (Poletti and Creswell, 1977; Fig. 1). The precommissural fornix principally innervates the basal forebrain (including the septum), ventral striatum and prefrontal cortex, as well as containing fibres projecting from the septum to the hippocampus. Meanwhile, the postcommissural fornix principally innervates the anterior thalamus and the mammillary bodies (Poletti and Creswell, 1977; Aggleton, 2012) and, hence, provides crucial connections between structures of an extended hippocampal network thought to be critical for episodic memory (Aggleton and Brown, 1999).

In response to the evidence for this tract division, the first aim of the present research was to develop an anatomically guided protocol for the *in vivo* reconstruction of precommissural and postcommissural fornix fibres in humans. Separating the reconstructions of precommissural and postcommissural fornix fibres should provide a useful tool for investigating any functional dissociations between these different hippocampal networks, as well as for studying age and disease related effects on these distinct systems. By reconstructing precommissural and

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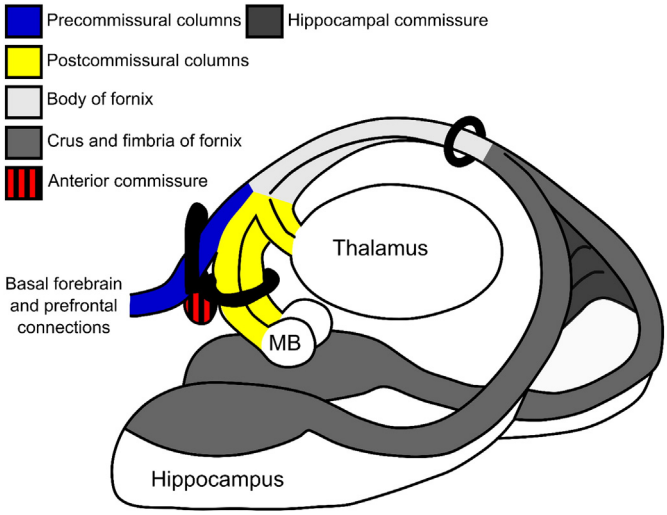

Fig. 1. Schematic of the principal components of the fornix and the main areas to which it connects. The black rings represent the placement of the various AND and NOT gates used for the tract reconstructions, as well as the seed ring around the body of the fornix. Abbreviations: MB, mammillary bodies.

postcommissural fibres, it also becomes possible to examine whether these different fibre populations intermingle within the body of the fornix or whether they retain distinct topographies.

Two previous diffusion tensor imaging (DTI) studies have distinguished the precommissural from the postcommissural fornix (Yeo et al., 2013; Chen et al., 2015). The first study used probabilistic tractography to reconstruct the two segments in a group of young, healthy participants (Yeo et al., 2013). The authors reported larger levels of fractional anisotropy (FA), an index of white matter coherence and diffusion directionality, and reduced levels of mean diffusivity (MD) (average diffusion in all directions) in the postcommissural compared to the precommissural fornix (Yeo et al., 2013). The second study divided the fornix into six subregions of interest (precommissural and postcommisural fornices, column, body, crus and fimbria) and found age-related changes in radial diffusivity (RD), i.e., the diffusion perpendicular to the fibres, and axial diffusivity (AD), i.e., the diffusion along the fibres, in all subregions (Chen et al., 2015).

The present study extended these previous findings by investigating the effects of both ageing and neurodegeneration on precommissural and postcommissural white matter microstructure in the fornix of healthy older adults (53–93 years of age) and a group of individuals with MCI. We employed deterministic tractography based on the modified damped Richardson–Lucy (dRL) algorithm for spherical deconvolution that allows, in contrast to conventional DTI, tracking through areas of complex fibre architecture and regions affected by isotropic partial volume (Dell'Acqua et al., 2010). Cerebrospinal fluid (CSF) based partial volume artefacts are of concern for the fornix since this tract is surrounded by the lateral and third ventricles **and volume artefacts may be accentuated** by age- and disease-related atrophy (Metzler-Baddeley et al., 2012b). Based on dRL it was also possible to calculate the hindrance modulated orientational anisotropy (HMOA), a novel index of white matter microstructural organization, defined as the absolute amplitude of the fibre orientation distribution (Dell'Acqua et al., 2013). The HMOA provides a fibre population-specific index of the diffusion properties along the reconstructed fibres that has been shown to be sensitive to individual variation in white matter microstructural organization (Chechlacz et al., 2015) and has been proposed to be more sensitive to changes in diffusion than conventional DTI metrics (Dell'Acqua et al., 2013).

In the present study we excluded fibres of the crus and the fimbria of the fornix from our precommissural and postcommissural fornix reconstructions. The intention was to minimise partial volume effects between the two fibre populations given the fibre crossing and intermingling that must occur between the columns of the fornix and the crus and fimbria of the fornix (Saunders and Aggleton, 2007).

To isolate the two divisions of the fornix, it was necessary to seed different groups of fibres as they descend close to the anterior commissure in the columns of the fornix. At this level, the precommissural and postcommissural divisions contain roughly similar numbers of fibres (Daitz, 1953; Powell et al., 1957). It can be anticipated that the postcommissural reconstructions predominantly involved the connections of the hippocampus with the hypothalamus, including the mammillary bodies (Poletti and Creswell, 1977; Aggleton et al., 2005; Fig. 1). Although the postcommissural fornix also contains many hippocampal projections to the anterior thalamic nuclei (Aggleton et al,. 1986), these fibres were largely excluded from the present study as they turn caudally into the rostral thalamus, just as the columns of the fornix begin to descend (Poletti and Creswell, 1977; Fig. 1).

White matter microstructure in the precommissural and postcommissural fornix segments was investigated with the tract-specific average HMOA index and DTI-based indices of FA, MD, RD and AD (Pierpaoli and Basser, 1996). All DTI-based indices were corrected for CSF-based, partial volume artefacts with the Free Water Elimination (FWE) method (Pasternak et al., 2009). The FWE method also generates a measure of tissue volume fraction (f), an index that reflects the volume remaining in each voxel attributable to tissue after the elimination of free water (Pasternak et al., 2009; Metzler-Baddeley et al., 2012b).

The first aim of our study was to demonstrate that it was possible to separate the precommissural fornix from the postcommissural fornix. Secondly, we investigated correlations between the microstructural indices for the two fornix segmentations in a group of healthy older adults, allowing us to investigate age-related effects on microstructure. Thirdly, we studied potential MCI related effects on white matter microstructure in the two segments. Fourthly, we studied whether individual differences in the microstructure of the postcommissural and precommissural fornix fibres were related to differences in episodic memory performance.

Methods

Participants

The MRI and cognitive data comprised part of a project into healthy and pathological ageing (MCI) (see Metzler-Baddeley et al., 2011, 2012a).

Healthy ageing cohort

A total of 44 control participants were recruited through advertisements in the local community, GP waiting rooms, newsletters, mail, and via the School of Psychology Community Panel at Cardiff University (Metzler-Baddeley et al., 2011). Participants were between 53 and 93 years of age (mean age 67.7, standard deviation 8.6) and 22 were females. Exclusion criteria were: a history of neurological disease or mental disorder [Clinical Disorders or Acute Medical Conditions/Physical Disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)], including a past history of moderate to severe head injury, prior or current alcohol and/or drug abuse, symptomatic memory or other cognitive function decline, previous stroke or cerebral hemorrhage, significant vascular disease elsewhere (peripheral vascular disease, carotid or vertebral artery stenosis or previous coronary intervention), structural heart disease or heart failure, and contra-indications to MRI. Five participants were later excluded due to ill health, motion artefacts, white matter hyper-intensities, or incomplete scan data. These exclusions left 39 control participants in the present study.

MCI group and their matched controls

Patients in the MCI group were recruited through the Cardiff Memory Clinic. All patients underwent a standard memory clinic

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