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Development, validation and application of a new fornix template for studies of aging and preclinical Alzheimer's disease

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ABSTRACT

We developed a merged younger-older adult template of the fornix and demonstrated its utility for studies of aging and preclinical Alzheimer's disease (AD). In Experiment 1, probabilistic tractography was used to reconstruct the fornix in younger and older adults and successful streamlines were then averaged to create a merged template in standard space. The new template includes the majority of the fornix from the hippocampal formation to the subcallosal region and the thalamus/hypothalamus. In Experiment 2, the merged template was validated as an appropriate measure for studies of aging, with comparisons against manual tracing measures indicating identical spatial coverage in younger and older adult groups. In Experiment 3, the merged template was found to outperform age-specific templates in measures of sensitivity and specificity computed on diffusion tensor imaging data of an independent participant cohort. In Experiment 4, relevance to preclinical AD was demonstrated via associations between fractional anisotropy within the new fornix template and cerebrospinal fluid markers of AD pathology ($A\beta_{42}$ and the t-tau/$A\beta_{42}$ ratio) in a third independent cohort of cognitively normal older adults. Our new template provides an appropriate measure for use in future studies seeking to characterize microstructural alterations in the fornix associated with aging and preclinical AD.

1. Introduction

The fornix is a key associative tract of the limbic system, interconnecting the hippocampal formation with subcortical structures in the basal forebrain and diencephalon. The fornix forms a core portion of the Papez circuit, described in 1937 (Papez, 1937), and its course has been extensively studied in animal tracer experiments (Daitz and Powell, 1954; Aggleton and Brown, 1999). Anatomically, the fornix is an arched, C-shaped structure divided into four bilateral sections. Left and right fornices connect with their ipsilateral hippocampal formation as the fimbria, sweep toward the midline as the crura, arch dorsally under the corpus callosum as the body, and curve ventrally as the columns. The postcommissural columns principally connect the hippocampal formation with the thalamus and hypothalamic nuclei (Aggleton, 2012). The precommissural columns principally connect the hippocampal formation with deep septal nuclei (Poletti and Creswell, 1977).

The advent of diffusion tensor imaging (DTI) (Basser et al., 1994; Le Bihan et al., 2001) has allowed for in vivo study of the fornix in aging and age-related neurodegenerative conditions. A body of DTI studies have shown that microstructural properties of the fornix are negatively affected by aging (Lebel et al., 2012; Michielse et al., 2010; Salat et al., 2005; Sullivan et al., 2010). Additional, more pronounced, declines in fornix microstructure have been reported in Alzheimer's disease (AD) and amnestic mild cognitive impairment (aMCI) (Bozzali, 2002; Kantarci et al., 2001; Rose et al., 2006).

More recent findings suggest that measures of fornix microstructure may be useful in detecting early/preclinical AD stages (Nowrangi and Rosenberg, 2015). First, there is evidence of altered WM microstructure in the fornix in cognitively normal older adults at high AD-risk compared to their low risk peers (Gold et al., 2010, 2012; Nierenberg et al., 2005; Persson et al., 2006; Ringman et al., 2007). Second, poorer WM microstructure in the fornix is associated with more AD pathology (as

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reflected by in vivo measures) in cognitively normal older adults (Gold et al., 2014; Molinuevo et al., 2014).

The increasing interest in understanding age- and disease-related alterations in fornix microstructure calls for a standardized template to allow for direct comparison of results across studies. An important feature of a template intended for comparisons between groups with morphological differences is that it be representative of the 'average' anatomy of these groups. At present, most fornix templates were developed solely on younger adult samples (Lawes et al., 2008; Thiebaut de Schotten et al., 2011; Wassermann et al., 2010). Limitations associated with the use of younger-only templates in studies of aging are well known and have motivated calls for the use of merged younger-older or study-specific reference data which can improve registration, better control for volumetric differences and thus improve measurement accuracy (Ashburner and Friston, 2000; Good et al., 2001; Smith et al., 2006; Thompson et al., 2001).

At present, DTI studies of aging focusing on specific tracts such as the fornix can use custom regions of interest (ROIs, e.g. Ringman et al., 2007; Gold et al., 2014), computationally intensive labeling algorithms (Jin et al., 2014, 2015), or voxel-wise analyses (Gold et al., 2010; Lebel et al., 2012; Salat et al., 2005). While valuable, these methods are not relevant to the goal of creating a standardized template that can be used across studies for the purpose of comparison of results. Currently, the most widely used fornix template is that developed as part of the ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008). The ICBM-DTI-81 white-matter labels atlas was created by hand segmentation of an average DTI map from 81 adults ranging from young to middle-aged (range 18–59 years old, Mean = 39 years old). Though highly useful, the ICBM-DTI-81 white-matter labels templates include only small discontinuous sections of the fornix and include non-fornix fibers from the stria terminalis.

Here we sought to develop a single, continuous DTI template of the fornix appropriate for future studies seeking to characterize WM microstructure alterations associated with aging and preclinical AD. Four experiments were conducted. In Experiment 1, a merged younger-older adult template of the fornix was developed. Probabilistic tractography was used as the fornix follows a complex, spiral trajectory that lacks clear anatomical boundaries in most sections. In Experiment 2, the new template was validated against manual tracings of the fornix body. In Experiment 3, the merged younger-older fornix template was qualitatively and quantitatively compared to age-specific fornix templates in a new participant cohort. In Experiment 4, potential associations between fractional anisotropy (FA) in the new merged fornix template and cerebrospinal fluid (CSF) measures of AD pathology were explored.

2. Methods

2.1. General methods

Methods common to all studies are reported first, followed by a description of experiment-specific procedures.

2.1.1. Participants

A total of 221 adults between the ages of 18–92 years old participated. All participants provided written informed consent in a manner approved by the University of Kentucky Medical Institutional Review Board and were financially compensated for their time. Exclusion criteria were a major head injury, stroke, a neurological or psychiatric disorder, high blood pressure, diabetes, claustrophobia, pacemakers, the use of psychotropic drugs, or presence of metal fragments and/or metallic implants contraindicated for MRI. All participants were recruited as part of multiple fMRI studies that had inclusion criteria that individuals have normal or corrected-to-normal vision and not be color-blind.

Three distinct participant samples were involved in the present study. Data from sample 1 (55 younger adults aged 25–40 years old, 65 older adults aged 57–83 years old) was used for template generation and anatomic validation (Experiments 1 and 2). Data from sample 2 (29 younger adults aged 18–34 years old, 30 older adults aged 61–77 years old) was used for comparison of the merged and age-specific templates in a new cohort (Experiment 3). Data from sample 3 (42 older adults aged 65–92 years old) was used for assessing relationships between the merged and age-specific templates with CSF markers of AD pathology (Experiment 4). Final characteristics of each sample are provided in the experiment-specific sections below.

2.1.2. DTI acquisition and processing

All imaging data were collected on a 3 T Siemens Trio TIM scanner at the University of Kentucky Magnetic Resonance Imaging and Spectroscopy Center. FMRIB's Diffusion Toolbox (FDT) v3.0 was used for all DTI processing. Raw images underwent eddy current correction, brain extraction, and motion correction using a 12-parameter affine transformation to the b0 images. DTIFIT was used to compute a tensor model and eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) within each voxel, which were then used to calculate FA images. Each participant's FA image was co-registered to the FMRIB58 FA 1 mm standard space template using tract-based spatial statistics [TBSS (Smith et al., 2006)], as described in detail in our previous work (Johnson et al., 2012). Briefly, non-linear voxel-wise registration was used to transform FA images into MNI space, where they were averaged to generate a mean FA image. The mean FA image was subsequently used to create a common white matter (WM) tract skeleton. The skeleton was thresholded at FA > 0.2 in order to minimize partial volume effects after warping across all participants. Finally, each participant's FA image was projected onto the FA skeleton to account for residual misalignments between participants after initial registration. TBSS_fill was used for visualization purposes of DTI data.

2.2. Experiment 1: creation of a combined younger-older fornix template using probabilistic tractography

The purpose of Experiment 1 was to develop a fornix template on a combined sample of younger and older adults. Probabilistic tractography was first used to reconstruct a fornix pathway for each individual participant on a voxel-to-voxel basis. Individual participants' tractography-derived fornix masks were then registered into standard space and merged to create a group template reflecting the average anatomical features of younger and older adults.

2.2.1. Participants

DTI data from 120 participants (sample 1) were initially screened for use in the creation of a fornix template. Inclusion criteria were the availability of: (1) DTI and T1-weighted images collected on the same scanner and head coil, using the same MRI sequence, and (2) cognitive test results (for the purpose of between-group matching). Some of the participants included in the present DTI experiment also took part in functional magnetic resonance imaging (fMRI) experiments requiring decisions about colored stimuli, the results of which have been reported elsewhere (Hakun et al., 2015a, 2015b; Zhu et al., 2015).

From the original pool of 120 participants, 10 were excluded for motion or other artifacts and 15 participants were excluded for insufficient coverage of the fornix (i.e. data did not include the entire hippocampal seed mask used in tractography). Intelligence was estimated using the Cattell Culture Fair Intelligence Test (Cattell and Baggaley, 1960), and digit spans were measured using the digits forward (DF) and backward (DB) subtests of the Wechsler Memory Scale (WMS III, Wechsler, 1997).

2.2.2. MRI acquisition

DT imaging used a double spin-echo echo-planar imaging (EPI) sequence [repetition time (TR) = 6900 ms, echo time (TE) = 105 ms, flip angle = 90°, field of view (FOV) = 224 mm^2, in-plane resolution =