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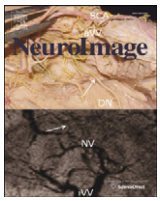

Full Length Articles

Measuring longitudinal change in the hippocampal formation from in vivo high-resolution T2-weighted MRI

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ABSTRACT

The hippocampal formation (HF) is a brain structure of great interest because of its central role in learning and memory, and its associated vulnerability to several neurological disorders. In vivo oblique coronal T2-weighted MRI with high in-plane resolution (~0.5 mm × 0.5 mm), thick slices (~2.0 mm), and a field of view tailored to imaging the hippocampal formation (denoted HF-MRI in this paper) has been advanced as a useful imaging modality for detailed hippocampal morphometry. Cross-sectional analysis of volume measurements derived from HF-MRI has shown the modality's promise to yield sensitive imaging-based biomarker for neurological disorders such as Alzheimer's disease. However, the utility of this modality for making measurements of longitudinal change has not yet been demonstrated. In this paper, using an unbiased deformation-based morphometry (DBM) pipeline, we examine the suitability of HF-MRI for estimating longitudinal change by comparing atrophy rates measured in the whole hippocampus from this modality with those measured from more common isotropic (~1 mm^3) T1-weighted MRI in the same set of individuals, in a cohort of healthy controls and patients with cognitive impairment. While measurements obtained from HF-MRI were largely consistent with those obtained from T1-MRI, HF-MRI yielded slightly larger group effect of greater atrophy rates in patients than in controls. The estimated minimum sample size required for detecting a 25% change in patients' atrophy rate in the hippocampus compared to the control group with a statistical power $\beta = 0.8$ was $N = 269$. For T1-MRI, the equivalent sample size was $N = 325$. Using a dataset of test–retest scans, we show that the measurements were free of additive bias. We also demonstrate that these results were not a confound of certain methodological choices made in the DBM pipeline to address the challenges of making longitudinal measurements from HF-MRI, using a region of interest (ROI) around the HF to globally align serial images, followed by slice-by-slice deformable registration to measure local volume change. Additionally, we present a preliminary study of atrophy rate measurements within hippocampal subfields using HF-MRI. Cross-sectional differences in atrophy rates were detected in several subfields.

Introduction

The hippocampal formation (HF) is widely studied by clinicians and neuroscientists alike, owing to its central role in cognitive processing, particularly in processes mediating learning and memory (Squire et al., 2004). Structural as well as functional measurements in the hippocampal region of interest (ROI) and its neighboring medial temporal lobe (MTL) structures have been successfully used as imaging-based biomarkers of brain pathology in several neurological disorders. Hippocampal volume, measured using structural MRI, is significantly reduced in Alzheimer's Disease (AD) (Jack et al., 1992) and in its prodromal stages (de Leon et al., 1997), in other neurodegenerative disorders such as semantic dementia (Chan et al., 2001), as well as in psychiatric disorders such as schizophrenia (Bogerts et al., 1993), and other neurological conditions (a review can be found in (Geuze et al., 2005)).

While such cross-sectional volumetry studies provide useful clinical information, a great deal of emphasis has been placed in the recent literature on MRI-based measurements of longitudinal change in the hippocampal volume. It has been hypothesized that the estimates of hippocampal atrophy rate derived from such measures will play a key role in reducing the cost and duration of clinical trials for disease-modifying pharmaceutical treatments in AD and other neurodegenerative diseases (Jack et al., 2010). Among the various biomarkers proposed for such clinical trials, MRI-based hippocampal atrophy estimates are thought to offer the best combination of sensitivity to disease progression in the early symptomatic stages of the disease and robustness to repeat measurement errors (Caroli et al., 2010).

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Longitudinal change in the hippocampus measured from MRI has been studied for more than a decade (Du et al., 2004; Fox et al., 1996; Fox et al., 2005; Fuerst et al., 2003; Hashimoto et al., 2005; Jack et al., 1998; Jack et al., 2003; Kaye et al., 2005; Leung et al., 2010; Ridha et al., 2006; Rohrer et al., 2008; Schuff et al., 2009; Steffens et al., 2011; Thompson et al., 2004; Wang et al., 2003). Atrophy rates in the hippocampus have been measured in clinical populations such as Alzheimer's disease (AD) (Fox et al., 1996; Jack et al., 1998; Ridha et al., 2006), depression (Steffens et al., 2011), epilepsy Fuerst et al., 2003 and non-AD dementia (Rohrer et al., 2008). Typically, such studies use one of a few well-established longitudinal measurement techniques, such as deformation-based morphometry (DBM) (Chung et al., 2001; Leow et al., 2006; Studholme et al., 2004), brainboundary shift integral (BSI) (Barnes et al., 2004; Freeborough and Fox, 1997; Leung et al., 2010), anatomical surface-based shape modeling (Csernansky et al., 2000; Thompson et al., 1996; Thompson et al., 2004; Wang et al., 2003) or manual labeling of serial images (Fox et al., 2005; Jack et al., 2003; Kaye et al., 2005). In particular, large studies using the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset (Schuff et al., 2009; Schott et al., 2010; Wolz et al., 2010; Yushkevich et al., 2010a) that employed some of these techniques have characterized the hippocampal longitudinal atrophy patterns in the AD and mild cognitive impairment (MCI) extensively. A more complete review of hippocampal atrophy rate measurements reported in the literature can be found in Barnes et al. (2009). Group effects between elderly controls and individuals with MCI, which is frequently a preclinical stage of AD, have been found (Jack et al., 2000; Apostolova et al., 2010; Leung et al., 2010; Schott et al., 2010; Wolz et al., 2010). Many recent studies have provided estimates of sample sizes required to detect a given amount of change in the HF and other MTL regions during a clinical trial (Holland et al., 2011). This extensive body of work underscores the importance of longitudinal change measurements in the HF.

Prior studies of longitudinal change in the HF have typically used the same approaches as whole-brain longitudinal studies, and thus relied almost exclusively on T1-weighted MRI (T1-MRI), usually with nearly isotropic ~1 mm^3 resolution. By contrast, in cross-sectional studies of the HF, much attention has recently been placed on alternative MRI protocols that are more tailored for imaging the HF and other medial temporal lobe (MTL) structures (Kerchner et al., 2010; La Joie et al., 2010; Mueller et al., 2008; Malykhin et al., 2010; Prudent et al., 2010; Small et al., 2000; Thomas et al., 2008; Theysohn et al., 2009; Van Leemput et al., 2009; Zeineh et al., 2003). In particular, superior intensity contrast in the HF can be obtained using T2-weighted MRI (Fig. 1) with high in-plane spatial resolution, oblique slice orientation perpendicular to the long axis of the hippocampus (Fig. 1), and high slice thickness. We use the term HF-MRI to describe this type of MRI scan, both for brevity, and to emphasize that unlike most clinical T2-weighted MRI scans, the field of view, resolution, and orientation are chosen with the specific goal of imaging the HF and nearby MTL structures. A particular appeal of HF-MRI is the improved visibility of anatomical landmarks in the hippocampal region, specifically, of a hypointense band thought represent myelinated fibers in the stratummoleculare/lacunosum (Eriksson et al., 2008). This property has led researchers to label the subfields of the HF in HF-MRI, and estimate their volume (Mueller et al., 2007; Malykhin et al., 2010). It has been hypothesized that such subfield-specific hippocampal volume measures will prove more sensitive to disease effects than whole hippocampus volume measures. This hypothesis stems from the selective vulnerability of these subregions to pathological processes (Huesgen et al., 1993; Sass et al., 1991; Saravia et al., 2006). Indeed, cross-sectional studies that used HF-MRI have found patterns of disease-related atrophy in the HF in various neurological disorders (Mueller et al., 2009; Mueller et al., 2010), largely consistent with pathological findings in these diseases.

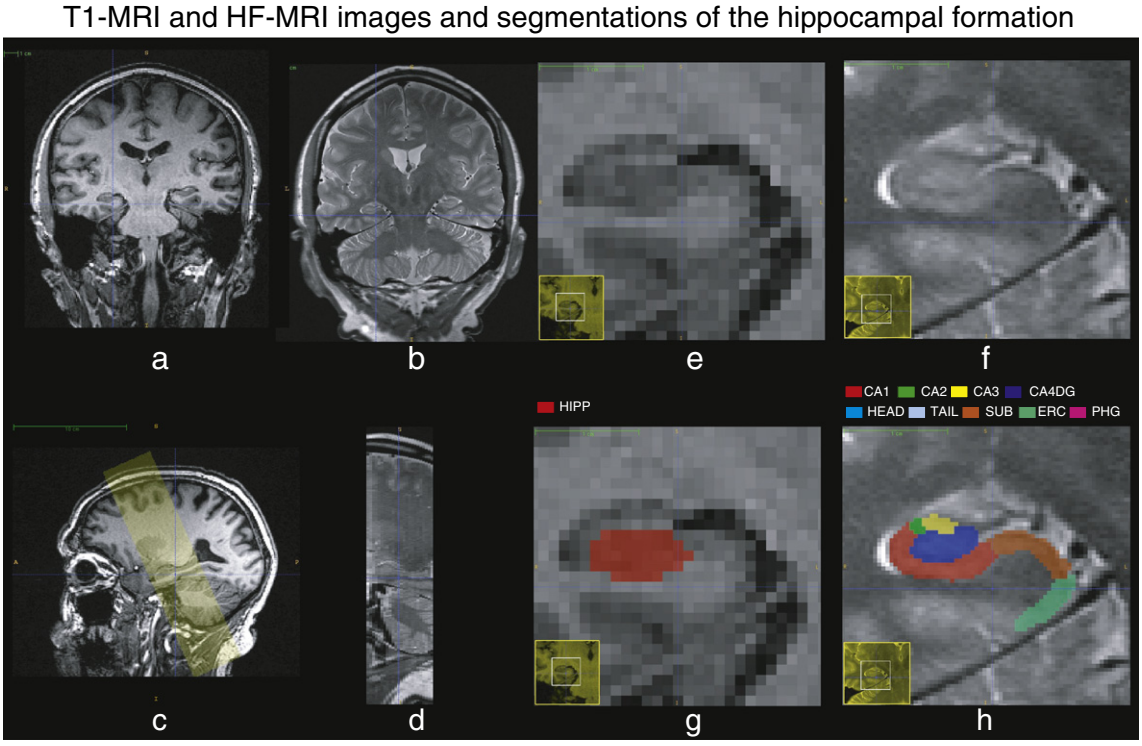

Fig. 1. Example of T1-MRI and HF-MRI images for a subject. (a)–(d): Whole brain images. (a) Coronal view of T1-MRI, (b) oblique coronal slice from HF-MRI of the same subject as in (a) (0.4×0.4 mm resolution), (c) sagittal view of T1-MRI with the field of view of the obliquely oriented T2-weighted HF-MRI overlaid in light yellow, (d) sagittal cross-section of the HF-MRI, illustrating the anisotropy of the voxels. The voxel size is 2.0 mm along the anterior–posterior direction. (e)–(h) Enlarged view of the region around the right hippocampal formation in the coronal slice. (e) T1-MRI image, (f) HF-MRI image, (g) T1-MRI whole hippocampus label, (h) HF-MRI subfield labels. Insets in (e)–(h) show the extent of the ROI image used in the ROI-RIGID approach.