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High resolution in-vivo diffusion imaging of the human hippocampus

Sarah Treit [a], Trevor Steve [b], Donald W. Gross [b], Christian Beaulieu [a,*]

[a] Department of Biomedical Engineering, Faculty of Medicine & Dentistry, University of Alberta, Canada
[b] Division of Neurology, Faculty of Medicine & Dentistry, University of Alberta, Canada

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ABSTRACT

The human hippocampus is a key target of many imaging studies given its capacity for neurogenesis, role in long term potentiation and memory, and nearly ubiquitous involvement in neurological and psychiatric conditions. Diffusion tensor imaging (DTI) has detected microstructural abnormalities of the human hippocampus associated with various disorders, but acquisitions have typically been limited to low spatial resolution protocols designed for whole brain (e.g. >2 mm isotropic, >8 mm^3 voxels), limiting regional specificity and worsening partial volume effects. The purpose here was to develop a simple DTI protocol using readily available standard single-shot EPI at 3T, capable of yielding much higher spatial resolution images (1 x 1 x 1 mm^3) of the human hippocampus in a 'clinically feasible' scan time of ~6 min. A thin slab of twenty 1 mm slices oriented along the long axis of the hippocampus enabled efficient coverage and a shorter repetition time, allowing more diffusion weighted images (DWIs) per slice per unit time. In combination with this strategy, a low b value of 500 s/mm^2 was chosen to help overcome the very low SNR of a 1 x 1 x 1 mm^3 EPI acquisition. 1 mm isotropic mean DWIs (averaged over 120–128 DWIs) showed excellent detail of the hippocampal architecture (e.g. morphology and digitations, subregions, stratum lacunosum moleculare - SLM) that was not readily visible on 2 mm isotropic diffusion images. Diffusion parameters within the hippocampus were consistent across subjects and fairly homogenous across subregions of the hippocampus (with the exception of the SLM and tail). However, it is expected that DTI parameters will be sensitive to microstructural changes associated with a number of clinical disorders (e.g. epilepsy, dementia) and that this practical, translatable approach for high resolution acquisition will facilitate localized detection of hippocampal pathology.

Introduction

Ultra-high resolution *ex-vivo* diffusion tensor imaging (DTI) of the 'healthy' human hippocampus yields diffusion-weighted images and colour anisotropy maps which enable visualization of internal architecture variations of fractional anisotropy (FA) and mean diffusivity (MD) reflecting known microstructural heterogeneity identified with histology (Shepherd et al., 2007). Further, e*x-vivo* DTI of hippocampal sclerosis in temporal lobe epilepsy patients (i.e. samples from hippocampal resection aimed to control seizures) has demonstrated aberrant intra-hippocampal connections (Modo et al., 2016), reduced layers (Coras et al., 2014), and microstructural variation reflecting changes in neuronal cell bodies, dendritic fields, and axonal projection systems (Colon-Perez et al., 2015) confirmed with histology in these same samples. The ultra-high spatial resolution (60–220 μm in-plane with 0.1–0.7 mm thick slices; 0.001–0.011 mm^3 voxel volumes) of these *ex-vivo* datasets is made possible by high field strengths (7–17.6 T), small RF coils with increased sensitivity, and very long scan times (5–15 h).

Given its demonstrated utility *ex-vivo*, there is significant interest in *in-vivo* diffusion imaging of the hippocampus, which may provide unique information about regional microstructural pathology that precedes or coincides with macrostructural changes such as volume loss typically quantified on conventional high-resolution relaxation-weighted scans in a variety of disorders. A number of previous studies have demonstrated DTI changes in the hippocampus associated with aging (e.g. Cherubini et al., 2009; Yassa et al., 2011), mild cognitive impairment and dementia (e.g. Li et al., 2013; Tang et al., 2016; van Uden et al., 2016), epilepsy (Nazem-Zadeh et al., 2014), ALS (Barbagallo et al., 2014), multiple sclerosis (Cappellani et al., 2014; Planche et al., 2017), stroke (Kliper et al., 2016), schizophrenia (Chiapponi et al., 2014; Nazeri et al., 2017) and others. Interestingly, diffusion parameters have also been shown to be sensitive to transient, short-time scale changes in hippocampal microstructure correlating with various processes in healthy adults, including learning and memory (Sagi et al., 2012) and sex hormone

* Corresponding author. 1098 Research Transition Facility, Department of Biomedical Engineering, University of Alberta, Edmonton T6G-2V2, AB, Canada.
E-mail address: christian.beaulieu@ualberta.ca (C. Beaulieu).

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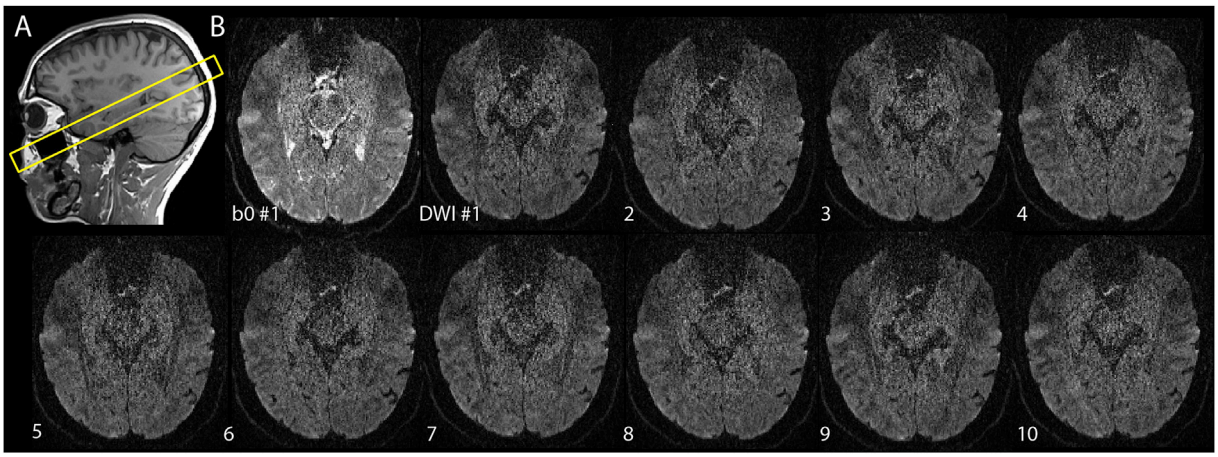

Fig. 1. (A) A slab of twenty 1 mm axial oblique slices aligned along the long axis of the hippocampus was acquired to reduce scan time and limit coverage to just the hippocampus, as prescribed on a sagittal slice of the 3D T1-weighted MPRAGE. (B) Examples of individual images, including 1 b = 0 s/mm^2 and 10 unique gradient directions at 500 s/mm^2. It is visually evident that despite signal boosting strategies, acquisition of 1 x 1 x 1 mm^3 resolution produces very low signal-to-noise images (~3–5 in the hippocampus). Note that pre-scan normalize was used to minimize B1 sensitivity variations across the slice and improve visualization of the hippocampus.

fluctuations in the female menstrual cycle (Barth et al., 2016). This work collectively suggests that diffusion tensor parameters are sensitive, albeit not specific, to microstructural change in the hippocampus over a wide range of conditions and disorders. However, these studies have almost exclusively used whole-brain diffusion protocols with poor spatial resolution (i.e. $\geq$ 2 mm isotropic) and have extracted diffusion values either from a manually drawn single-slice region of interest, or averaged across the whole hippocampus as delineated on co-registered anatomical images such as T1.

Down-sampling of *ex-vivo* DTI acquisitions demonstrates that despite the obvious increase in partial volume effects relative to 0.1 or even 0.5 mm^3, 1 mm^3 resolution provides marked improvement in delineation of hippocampal structures relative to the 8 mm^3 typical of most currently published *in-vivo* studies (see MD maps in Fig. 4 of Modo et al., 2016). Although another *ex-vivo* study conversely concluded that down-sampling of 220 μm ex-vivo images to 1 mm^3 was insufficient to delineate internal structures (Colon-Perez et al., 2015), it should be noted that this study examined tissue samples from hippocampal sclerosis, which is itself characterized by a loss of internal architecture (Jackson et al., 1993). The utility of 1 mm isotropic resolution in the healthy human hippocampus should therefore be evaluated *in vivo* in order to determine any advantage over a standard DTI acquisition of ~2 mm isotropic (8 mm^3 voxel volume). Specifically, in addition to allowing for visual discrimination of structure on diffusion images, this resolution could potentially mitigate the need for co-registration to anatomical images, thus greatly improving accuracy and reducing partial volume effects on diffusion parameters.

Beyond whole hippocampus measurements, there is also significant interest in imaging hippocampal sub-fields, which play unique roles in human memory (Neunuebel and Knierim, 2014) and the pathophysiology of several diseases (e.g. Epilepsy, Steve et al., 2014; and Alzheimer's Disease, West et al., 1994). A few papers have reported diffusion parameters within hippocampal subfields by delineating on T1 or T2 and then co-registering with DTI maps. While this work has suggested sub-field specific associations between diffusion parameters and aging (Pereira et al., 2014), epilepsy sub-types (Bernhardt et al., 2016), anxiety and depression (Cha et al., 2016), and memory (Kobe et al., 2016), these DTI acquisitions used low spatial resolutions of 2–2.5 mm isotropic or $1.7 \times 1.7 \times 3$ mm^3 (8–15.6 mm^3 voxels), leading to concerns with accuracy and partial volume effects which may be mitigated at higher spatial resolutions. Multi-shot EPI with a spatial resolution of 1.4 mm isotropic has demonstrated the potential for high resolution diffusion imaging of the human hippocampus and its white matter circuitry *in vivo*, but the method required a clinically infeasible scan time of 60 min (8.5 min x 7 repetitions for 70 directions at 1500 s/mm^2) even for limited coverage of 27 slices at 3T with an 8 channel RF coil (Zeineh et al., 2012).

The purpose of this study was to develop and test a practical acquisition using single-shot 2D EPI that could yield high quality 1 mm isotropic resolution *in-vivo* diffusion tensor images of the human hippocampus within a 'clinically feasible' scan time of ~6 min at 3T. The protocol proposed here can be readily translated to other sites given its use of standard methodology and efficient scan time allowing it to be incorporated with other key scan acquisitions for application to a wide range of disorders affecting the hippocampus.

Materials and methods

MRI acquisition

Several protocol manipulations were required to use a readily available standard single-shot 2D EPI sequence at 3T to produce high spatial resolution images (1 x 1 x 1 mm^3) of the human hippocampus in a short scan time. Rather than whole-brain coverage, a thin slab of twenty 1 mm axial-oblique slices oriented along the long axis of the hippocampus (Fig. 1A) was acquired to yield efficient coverage of bilateral hippocampus with far fewer slices (and thus a significant savings in scan time) than would otherwise be required for whole brain coverage or coverage of the hippocampus using coronal slices as is typical of T2-weighted imaging. Twenty slices was estimated to provide adequate coverage of the bilateral hippocampi in a range of subjects with varying hippocampal volumes while allowing for some asymmetry of bilateral orientation. In addition to providing efficient coverage of the anatomy of interest, fewer total slices enabled a shorter repetition time (TR) that allows for acquisition of more diffusion images per slice per unit time to help overcome the very low signal-to-noise ratio (SNR) (Fig. 1B). A lower than typical b-value of 500 s/mm^2 (versus 1000–1500 s/mm^2) was chosen to further mitigate SNR loss from diffusion weighting (i.e. 67% of b0 signal with b500 relative to 45% at b1000 or 30% at b1500 for a typical brain diffusion coefficient of 0.8×10^{-3} mm^2/s), while still yielding sufficient diffusion contrast (e.g. nulled CSF). The shorter gradient pulses needed for b = 500 s/mm^2 also yielded a shorter echo time (TE), limiting T2 signal loss.

Experiments were performed with a 64 channel RF coil on a 3T Siemens Prisma with 80 mT/m gradient strength per axis which further enable a much shorter TE for a given b value. Diffusion scans were aligned along the long-axis of the hippocampus on high resolution T1-