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Original contribution

T_1, diffusion tensor, and quantitative magnetization transfer imaging of the hippocampus in an Alzheimer's disease mouse model

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ABSTRACT

Alzheimer's disease (AD) pathology causes microstructural changes in the brain. These changes, if quantified with magnetic resonance imaging (MRI), could be studied for use as an early biomarker for AD. The aim of our study was to determine if T_1 relaxation, diffusion tensor imaging (DTI), and quantitative magnetization transfer imaging (qMTI) metrics could reveal changes within the hippocampus and surrounding white matter structures in *ex vivo* transgenic mouse brains overexpressing human amyloid precursor protein with the Swedish mutation. Delineation of hippocampal cell layers using DTI color maps allows more detailed analysis of T_1-weighted imaging, DTI, and qMTI metrics, compared with segmentation of gross anatomy based on relaxation images, and with analysis of DTI or qMTI metrics alone. These alterations are observed in the absence of robust intracellular Aβ accumulation or plaque deposition as revealed by histology. This work demonstrates that multiparametric quantitative MRI methods are useful for characterizing changes within the hippocampal substructures and surrounding white matter tracts of mouse models of AD.

1. Introduction

As the global population ages and faces an increasing prevalence of Alzheimer's disease (AD), the most common cause of dementia, the need for more powerful diagnostic tools becomes ever more urgent. A definitive diagnosis of AD is presently obtained by an autopsy that confirms the presence of β-amyloid (Aβ) peptide plaques and tau protein tangles in brain tissue, but criteria have emerged over the past decade that incorporate molecular imaging and fluid analytes for a differential diagnosis in preclinical stages [1,2]. Identifying early biomarkers of AD is essential to diagnose and stratify patients for research into effective treatment options, and can aid in the preparation for disease management before debilitating symptoms are present. Magnetic resonance imaging (MRI) is a non-invasive diagnostic technique that can readily detect gross features of brain tissue in order to exclude neurosurgical causes of declining cognition, such as tumor or stroke; mounting evidence indicates its utility in quantifying brain atrophy to assess the severity of AD (see Pini et al. [68] for review).

It is well established that pathology in AD originates in the region of the hippocampus [3] and that decreases in the gray matter volume of this region predict the onset of AD [4]. More recently, parahippocampal white matter volume has also been shown to be a sensitive predictor of AD in cognitively normal people [5]. Although hippocampal volumetry is one of the most important imaging MRI biomarkers currently available to assist in AD diagnoses [6], it lacks the specificity to stand alone as an accurate diagnostic test [7], and indicates an advanced stage of neurodegeneration. Development of MR methods that reveal more subtle microstructural pathologies is an active and promising area of research, because these pathologies might be indicative of progression to AD. Previous studies have demonstrated that certain subregions within the complex internal structure of the hippocampus are differentially implicated in memory function and cognitive impairment [8,9].

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The application of multiparametric quantitative MRI protocols can provide different types of contrast within the hippocampus [10–12] and might prove useful to provide specific biomarkers for AD [13].

Diffusion tensor imaging (DTI) is one such quantitative MRI method [14], which has been used extensively to study white matter integrity [15–20]. Numerous DTI studies of AD have reported an increased mean diffusivity (MD) and decreased fractional anisotropy (FA) in white matter serving as promising indicators of AD (see [21] for review). Given that MD and FA are influenced by water diffusion in both radial and axial planes, the radial ($\lambda_\perp$) and axial ($\lambda_\parallel$) diffusivity themselves could give a more precise representation of white matter tissue damage in AD [22] and may be useful for disease staging by describing different white matter pathologies [23]. However, the precise nature of white matter damage in AD has not been characterized, and it remains unknown whether it occurs before or after gray matter damage [24]. Correlations between DTI changes in gray matter and tissue pathologies are under study, but gray matter diffusivity has been shown to have superior predictive power for AD over conventional volumetry (see Weston et al. [69] for review).

A growing body of literature has successfully utilized magnetization transfer imaging (MTI) to characterize neurodegenerative disorders including AD (see Tambasco et al. [70] for review). Several studies have examined the magnetization transfer ratio (MTR) [25], and have found it to decrease in early phases of AD [26–28] and map disease progression [29]. However, a conflicting finding has been reported in transgenic mouse models of AD, where an increased MTR value appeared to be primarily driven by Aβ load [30], and even preceded plaque formation and memory deficits [31]. Because the MTR is dependent upon the imaging parameters and field strength chosen by the experimenter, quantitative MTI (qMTI) methods are necessary for an effective comparison between studies. Metrics derived from the two-pool model of magnetization transfer offer more complete information on the macromolecular structures in brain tissue than does the MTR [32] and several qMTI metrics have been suggested to be useful biomarkers in prodromal stages of AD [33–35].

In the present study, a single transgenic mouse model of AD is utilized (Tg2576; [36]), harboring the Swedish mutation (K670N/M671L) of the gene that codes for human amyloid precursor protein (hAPP695) under the control of mouse prion protein promoter elements. This mutation leads to an abundance of Aβ in the central nervous system and the formation of Aβ plaques by 11 to 13 months of age [36]. There appears to be a loss of synapses in the hippocampus and compromised integrity of hippocampal circuitry in animals as young as 4.5 months [37–39]. In the absence of tau pathology, this model acts as a powerful reductionist tool for extracting the contribution of amyloid-related pathological changes to the alteration of MR properties.

With a need for understanding and detecting early gray matter changes in AD, this study uses T_1 relaxometry, DTI, and qMTI to study the hippocampus in mice with and without amyloid accumulation. The use of directionally encoded color (DEC) maps from DTI reveals cytoarchitectural details within the hippocampus and allows the identification of cell layers (strata) with characteristic fibre orientations. This produces a richer data set from which to analyze changes in quantitative MR metrics within these otherwise indistinguishable strata. We compare gray matter of the hippocampus and surrounding white mater tracts between the Tg2576 mouse model of AD and control mice using these multiple quantitative MRI metrics and interpret the results based on immunohistochemical staining for Aβ. To our knowledge, this is the first study to examine qMTI metrics in a mouse model of AD, and the first to examine multiple quantitative MR metrics within the strata of the hippocampus. We aim to determine if the combination of metrics examined in hippocampal strata can provide novel insight into the pathological changes that occur in the hippocampus early in the AD process.

2. Methods

2.1. Mouse model

Six male 7.5 month-old $APP_{K670N/M67L}$ [36] mice originally obtained from AstraZeneca R&D and derived from B6SJL F1 background were used in this study. Six male 7.5 month-old wild-type mice from the same genetic background served as controls, and allowed for comparative analysis between transgenic and healthy strains. The mice were genotyped by PCR using genomic DNA isolated from tail biopsies at weaning (21 days of age). Unique six-digit numbers were assigned to each mouse and used to identify mice in all experiments so that investigators were blinded to mouse genotype. All mice were provided with food and water *ad libitum* and maintained on a 12-hour light/dark cycle in accordance with the University of Manitoba Animal Care Committees who adhere to the guidelines and principles created by the Canadian Council on Animal Care.

2.2. Euthanasia

All 12 mice were sacrificed for *ex vivo* study at 7.5 months of age. Under deep anesthesia (5% isoflurane in oxygen), the mice were intracardially perfused with 0.1 M phosphate buffered saline (PBS) followed by a fixative solution of 4% paraformaldehyde (PFA). The mouse brains in skulls were removed from the bodies and all external tissue was cleaned off prior to storage in 4% PFA at 4 °C. Euthanasia procedures were carried out as per the guidelines and principles of the Canadian Council on Animal Care and were approved by the local Institutional Animal Care Committees at University of Manitoba and University of Winnipeg.

2.3. MRI

Imaging was done on most brains within one month of perfusion with PBS and PFA, with the maximum time spent in PFA being eight weeks. The mouse brains in skulls were transferred to PBS 48 h before imaging to wash the sample of any fixative. For imaging, the brains in skulls were secured in a custom-built acrylic sample holder and immersed in room temperature Fomblin Perfluoropolyether Y04 grade fluid (Solvay Solexis, Milan, Italy) to maintain hydration, and eliminate external proton signal and susceptibility artifacts. This sample tube was then inserted to a custom-built 24 mm internal diameter, 300 MHz inductively coupled quadrature radiofrequency (RF) volume coil (NRC Institute for Biodiagnostics, Winnipeg, Canada). The coil was loaded inside a Bruker BGA 12-S actively shielded gradient system with integrated shim coils (Bruker BioSpin, Milton, Canada). The experiments were performed on a 7 T 21 cm Bruker AVANCE III NMR system running Paravision 5.0 (Bruker BioSpin).

To image the hippocampus and surrounding white matter structures, three coronal slices labelled rostral, middle, and caudal, were selected at a position centered at 2.50 mm caudal to the anterior commissure (Fig. 1). The same slice geometry was used for all images to minimize differences in the slice alignment along the rostral-caudal plane when comparing data between mice. Images had a $(2\ cm)^2$ field of view and (256 × 256) matrix size, a 0.5 mm slice thickness, and were spaced with 1.0 mm interslice distance, resulting in images with a 78 μm × 78 μm × 500 μm resolution.

Relaxation images, DT images, and qMT images were collected during an overnight imaging session for each mouse brain, throughout which time 18 °C water-cooled gradients were used to maintain ambient bore temperature.

T_1 data were acquired using a rapid acquisition with refocused echoes (RARE) sequence, with a repetition time (T_R) = (4895.5, 2895.5, 1395.5, 695.5, 295.5, 95.5) ms, effective echo time (T_E) = 11 ms, RARE factor = 2, and 4 averages, for a total experiment time of 71 min.

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