Cortical atrophy and hypoperfusion in a transgenic mouse model of Alzheimer's disease

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ABSTRACT

Magnetic resonance imaging studies have revealed distinct patterns of cortical atrophy and hypoperfusion in patients with Alzheimer's disease. The relationship between these in vivo imaging measures and the corresponding underlying pathophysiological changes, however, remains elusive. Recently, attention has turned to neuroimaging of mouse models of Alzheimer's disease in which imaging-pathological correlations can be readily performed. In this study, anatomical and arterial spin labeling perfusion magnetic resonance imaging scans of amyloid precursor protein transgenic and age-matched wild-type mice were acquired at 3, 12, and 18 months of age. Fully-automated image processing methods were used to derive quantitative measures of cortical thickness and perfusion. These studies revealed increased regional cortical thickness in young transgenic mice relative to age-matched wild-type mice. However, the transgenic mice generally demonstrated a greater rate of cortical thinning over 15 months. Cortical perfusion was significantly reduced in young transgenic mice in comparison with wild-type mice across most brain regions. Previously unreported regional genotype differences and age-related changes in cortical thickness and cerebral perfusion were identified in amyloid precursor protein transgenic and wild-type mice.

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1. Introduction

Noninvasive neuroimaging-based measures of regional cerebral perfusion, metabolism, and structure are increasingly used to improve our understanding of the natural evolution of Alzheimer's disease (AD) and to evaluate response to therapeutic intervention. [18F]2-Fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) has been extensively used in AD studies, and characteristic patterns of AD-associated glucose hypometabolism have emerged (Mosconi et al., 2010; Mosconi and McHugh, 2011). Given the wider availability of magnetic resonance imaging (MRI) compared with PET scanners, it is highly desirable to identify similar MRI-based measures of brain function. Strong concordance between regional hypoperfusion and glucose hypometabolism measured by arterial

spin labeling (ASL) perfusion MRI and FDG PET, respectively, has recently been demonstrated in patients with AD (Chen et al., 2011b). Regional cerebral hypoperfusion has been suggested to be an early imaging biomarker for AD (Alsop et al., 2010; Chao et al., 2010), and large-scale studies using ASL MRI, such as the Alzheimer's Disease Neuroimaging Initiative (ADNI-2) (Jack et al., 2010), are currently underway. These cerebral blood flow (CBF) and metabolism measures are complemented by quantitative, structural information derived from anatomical MR images. Volume- and surface-based morphometry measures have revealed well-defined patterns of brain atrophy across the spectrum of AD progression (reviewed by Lin et al., 2012).

Recent studies have demonstrated that structural and functional brain alterations have distinct spatial patterns. Chen et al. (2011a) found that the regional effects of age on CBF, which were most prominent in the superior frontal, orbitofrontal, superior parietal, middle and inferior temporal, insular, precuneus, supramarginal, lateral occipital, and cingulate regions, differed from that of gray matter atrophy in normal aging. Tosun et al. (2010) performed a joint analysis of structural and perfusion MRI data in AD, and

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determined that structural and physiological brain changes in AD provide complementary information. The analysis performed in this study also indicated that cortical thinning had a greater association with the variability of AD severity than the CBF measures. Based on these studies, an apparent dissociation between structural and cerebral perfusion measures in normal aging and AD exists, but the biological underpinnings of this counterintuitive imaging data remain elusive.

The routine clinical use of quantitative MRI and PET biomarkers for diagnosis, staging, and therapeutic efficacy monitoring in AD has been hampered by a relatively poor understanding of the pathophysiological processes underlying these measures. The ability to tightly link noninvasive imaging measures with microscopic and molecular processes in human subjects is challenging and often impossible to achieve. Alternatively, studies of animal models of AD allow for tight correlation of in vivo imaging and invasive and/or post-mortem data. Transgenic (Tg) murine models with targeted expression of mutant human amyloid precursor protein (APP) genes recapitulate many of the cognitive and neuropathological features of AD, and high-resolution images from the brains of these mice can be obtained with dedicated, high-field, small animal MRI systems.

Several recent studies have identified differences in whole or regional brain volumes between APP Tg and wild-type (WT) mice (Badea et al., 2010; Delatour et al., 2006; Lau et al., 2008; Maheswaran et al., 2009; Oberg et al., 2008). Cortical hypoperfusion has also been observed in mutant APP Tg mice by ASL MRI (Faure et al., 2011; Massaad et al., 2010; Poisnel et al., 2012; Weidensteiner et al., 2009). However, a detailed examination of the relationship between regional cortical surface morphometry and perfusion across the lifespan of APP Tg mice has not been performed.

This study examined the spatiotemporal pattern of altered cortical structure and blood flow over a 15-month period in a well-established mouse model of AD pathology by MRI. Noninvasive, whole brain, three-dimensional (3D) MRI acquisition and sophisticated, fully-automated image processing and analysis methods were used to interrogate the relationship between cortical thickness and perfusion in Tg and age-matched WT mice. The unique observations from this study provide a basis for further investigation of the complex interplay between macroscale (imaging) and microscale (cellular) processes in AD.

2. Materials and methods

2.1. Animals

Heterozygous Tg mice with neuronal overexpression of the Swedish ($670/671_{KM \to NL}$) and Indiana ($717_{V \to F}$) mutations of human APP driven by the platelet-derived growth factor β (PDGF-β) promoter on a C57BL/6J background (line J20) (Mucke et al., 2000; Tong et al., 2005) were used for these studies. This model has been well characterized for amyloidosis (Mucke et al., 2000), cognitive/behavioral impairments (Palop et al., 2003), and cerebrovascular dysfunction (Tong et al., 2005).

Separate cohorts of mice at three ages were evaluated in a cross-sectional study design, specifically young (age = 3.3 ± 0.2 months; n = 19 Tg [9 male, 10 female], 20 WT [10 male, 10 female]), middle-aged (age = 12.7 ± 1.3 months; n = 20 Tg [10 male, 10 female], 20 WT [10 male, 10 female]), old (age = 18.7 ± 0.5 months; n = 17 Tg [9 male, 8 female], 19 WT [9 male, 10 female]). Mice were housed using a 12-hour light/12-hour dark schedule and fed standard laboratory chow and water ad libitum. Experiments were approved by the Animal Ethics Committee of the Montreal Neurological Institute and McGill University, and were conducted in accordance with the guidelines of the Canadian Council on Animal Care.

2.2. In vivo MRI acquisition

Mice were anesthetized with an induction dose of 4%–5% sevoflurane and secured in an MRI-compatible bed. All MRI studies were performed under ~2.5%–3% sevoflurane in medical air and animals were allowed to breathe spontaneously without mechanical ventilation. Respiration rate and body temperature were continuously monitored using an MR-compatible system (Small Animal Instruments Inc, Stony Brook, NY, USA) and the temperature was maintained at 37 ± 0.2 °C throughout the study using a feedback-regulated warming system (Small Animal Instruments Inc, Stony Brook, NY, USA).

All MR images were obtained from a 7T Bruker Pharmascan system (Bruker Biospin, Ettlingen, Germany) using a quadrature volume resonator (RAPID MR International, Columbus, OH, USA), with an inner diameter of 28 mm. Following the acquisition of scout images, region-of-interest (ROI)-based shimming (MAPSHIM, Bruker Biospin) was performed to increase the magnetic field homogeneity within the brain. Anatomical images were acquired using a 3D balanced steady-state free precession (b-SSFP) sequence with the following parameters: matrix size, 128 × 128 × 64; field of view, 1.8 × 1.8 × 0.9 cm; spatial resolution, 140 × 140 × 140 μm; number of phase cycles, 4; and number of averages, 4. The phase-cycled images were combined using the sum-of-squares reconstruction method to minimize banding artifacts (Bangerter et al., 2004). Perfusion images were acquired with a customized, 3D pseudocontinuous ASL sequence using the following parameters: matrix size, 64 × 64 × 32; field of view, 1.8 × 1.8 × 0.9 cm; spatial resolution, 280 × 280 × 280 μm; and 48 averages. Perfusion labeling was achieved by positioning a 2-mm thick inversion slab in the neck region (~7 mm inferior to the level of the brainstem) and inverting inflowing blood within this slab every 14 milliseconds using spatially-selective sinc radiofrequency pulses. The entire scanning session lasted approximately 2.5 hours per animal.

2.3. MRI processing

An unbiased, symmetric, customized template was generated from anatomical scans from the 115 mice using an iterative process (Fonov et al., 2011; Lau et al., 2008). Before template generation, each reconstructed image volume underwent image nonuniformity correction using the N3 algorithm (Sled et al., 1998), brain masking, and linear spatial normalization using a 12-parameter affine transformation (Collins et al., 1994) to map individual images from native coordinate space to reference space. Briefly, the template generation process involved an iterative (coarse-to-fine resolution) estimation of the nonlinear transformation to match each MRI scan to the evolving average of the population. The final anatomical template (population average) was generated with an isotropic voxel resolution of 0.06 mm (Fig. 1A). This customized template was parcellated into an atlas (Fig. 1B) consisting of 14 cerebral cortical regions per hemisphere, specifically anterior cingulate cortex, auditory cortex, barrel cortex, entorhinal cortex, frontal cortex, insula, motor cortex, perirhinal cortex, piriform cortex, posterior cingulate cortex, retrosplenial cortex, somatosensory cortex 1, somatosensory cortex 2, and visual cortex, using the Montreal Neurological Institute (MNI) McConnell Brain Imaging Centre DISPLAY software package (http://www.bic.mni.mcgill.ca). The masks for the 14 cerebral cortical regions were projected onto a standardized cortical surface template for surface-based ROI analysis (Fig. 2).

For cortical thickness measurements, the cortical mask with inside, outside, interhemispheric, and resistive boundaries (Fig. 1B) was nonlinearly registered from the atlas to each subject. Streamlines running from the inner to outer boundaries of the cortex were