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

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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.

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 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., 2010b). Regional cerebral hypoperfusion has been suggested to be an early imaging biomarker for AD (Alsup 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...
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; Maheshwaran 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 morphology 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 (670/671K<sup>M</sup>→<sup>N</sup>L) and Indiana (717V<sup>I</sup>→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/dysfunction (Tong et al., 2005), and cerebrovascular 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]), and 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 (Bangert 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
defined using Laplace’s equation and their length was used as the measure of cortical thickness (Lerch et al., 2008). The mean cortical thickness was computed from an intermediate surface for each of the 14 predefined ROIs from the spatially normalized thickness maps.

The control perfusion images were linearly registered to the anatomical images for each mouse to compensate for potential slight movement during the scanning session. Parametric perfusion maps based on the fractional ASL signal, defined as the ratio between the difference [control elabeled and control images (Borogovac and Asllani, 2012; Lu et al., 2010), were calculated on a voxel-by-voxel basis. The perfusion maps were spatially normalized to reference space using the transformations derived from the anatomical image registration. To directly compare cortical thickness and perfusion measures, the perfusion data was projected to the cortical surface by averaging the image intensity along each streamline passing through each vertex. The individual, spatially normalized perfusion maps were averaged to produce group mean parametric maps. ROI-based perfusion measures were derived using the surface MRI atlas in reference space.

2.4. Statistical analysis

Statistical analysis was performed using Matlab (Mathworks, Natick, MA, USA) and the SurfStat toolbox (http://www.math.mcgill.ca/keith/surfstat) (Worsley et al., 2009). Linear mixed-effects models using the restricted maximum likelihood (REML) estimation method were used to assess group differences and cross-sectional changes (Pinheiro and Bates, 2000). Specifically, a one-way analysis of variance (ANOVA) was used to assess between-group differences (Tg vs. WT) at each age level (young, middle-aged, old). For each genotype, a one-way ANOVA was also used to assess across-age (within-groups, cross-sectional) differences. A two-way ANOVA was used to assess the genotype-by-age interaction. Quantitative results of the vertexwise analysis are expressed as statistical parametric maps resulting from post hoc Student's two-tailed t-tests. The statistical parametric maps are presented without thresholding to demonstrate the overall pattern of group differences. For the ROI-based analysis, measures from the left and right hemispheres were combined to maximize statistical power, and quantitative results are expressed as mean ± standard deviation of the effect of interest (between-groups and cross-sectional within-groups differences). The ROI-based data was adjusted for multiple comparisons using the Bonferroni correction.

3. Results

3.1. APP Tg and WT mice exhibit age-related differences in regional cortical thickness

A globally increased mean cortical thickness was identified in the young Tg mice compared with young WT mice (Fig. 3). The ROI-based analysis (Fig. 3) demonstrated that the difference in cortical thickness (Tg > WT) in the young Tg mice was significant (p < 0.05) in all regions examined, except for the barrel cortex, motor cortex, and somatosensory cortex 1, which did not survive correction for multiple comparisons. This difference was greatest in the perirhinal cortex (t = 6.2, p < 0.001), posterior cingulate cortex (t = 5.1, p < 0.001), insula (t = 4.9, p < 0.001), and entorhinal cortex (t = 4.4, p < 0.001). The vertexwise t-statistic maps (Fig. 4) revealed the
spatial heterogeneity of cortical thickness differences between young Tg and WT mice. The Tg mice showed greater thinning across the entire cortex over 15 months than the WT mice (Fig. 5A). For both Tg and WT groups, minimal change in cortical thickness was observed over the 15-month timeframe in the anterior/posterior cingulate and retrosplenial cortical regions (Figs. 6 and 7A). The remaining cortical regions demonstrated cortical thinning in both groups with greater...
reduction in cortical thickness (i.e., atrophy) in the Tg mice relative to WT mice (Figs. 6 and 7A). Although most of these regions demonstrated significant differences in the age-by-genotype interaction at 15 months without Bonferroni correction (entorhinal cortex, \( p_{\text{uncorrected}} = 0.004 \); perirhinal cortex, \( p_{\text{uncorrected}} = 0.016 \); motor cortex, \( p_{\text{uncorrected}} = 0.008 \); piriform cortex, \( p_{\text{uncorrected}} = 0.024 \)), the significance did not survive multiple comparisons. The Tg group had a higher variability than

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**Fig. 5.** Cortical thickness (A) and cortical perfusion (B) change (% change relative to young mouse group) of whole cortex over 15 months in transgenic and wild-type mice. The whole cortex showed an increased cortical thinning rate in transgenic mice relative to wild-type mice, which was statistically significant over 15 months. There was no significant difference in the rate of whole cortex perfusion change across genotypes. \( * p < 0.05 \).

**Fig. 6.** Cortical thickness change (% change relative to young mouse group) over 15 months in transgenic and wild-type mice. The anterior/posterior cingulate and retrosplenial cortical regions did not show appreciable change over time. In contrast, a greater rate of cortical thinning was seen in transgenic mice than in age-matched wild-type mice in the remaining regions. For the sake of clarity, not all regions-of-interest (ROIs) have been included. The following behavior was seen in the remaining ROIs: auditory, barrel, and somatosensory 2 cortices were similar to somatosensory cortex 1; the visual cortex was similar to the motor cortex; and the frontal cortex was similar to the entorhinal cortex. \( * p < 0.05 \).
regions along the rhinal mice (Figs. 7B and 9), indicating the importance of examining loco-regional changes revealed striking differences between Tg and WT genotypes (Fig. 5B). However, analysis of the vertexwise and significance did not survive multiple comparisons. Although several studies support potential mechanisms for this finding. Plaschke et al. (1997) demonstrated that long-term cerebral hypoperfusion resulted in increased regional concentrations of APP in a rat model. Oh et al. (2009) demonstrated that overexpression of mutant (APPsw) or WT APP in Tg mice can induce hypertext of cortical neurons. Iacono et al. (2009) identified hypertrophic cortical neurons in human autopsy material from the Nun Study and postulated that neuronal hypertrophy may constitute an early cellular response to AD pathology and/or reflect compensatory mechanisms that prevent cognitive impairment despite substantial AD-associated pathological changes. Astrogliosis is also prominent in AD and has been associated with a specific cortical laminar pattern (Beach et al., 1989). Hence, APP β-amyloid–driven neuronal hypertrophy and/or astrogliosis could potentially explain the apparent increase in cortical thickness in Tg mice. Future studies could assess cortical structure in even younger (e.g., 1 month-old) mice to investigate the age-of-onset of these pathological processes.

The regions along the interhemispheric and rhinal fissures demonstrated the most significant differences in cortical thickness between young Tg and WT mice. These areas are associated with limbic, memory, and human default-mode network–type functions, which are affected in AD. It is possible that the high constitutive activity of these regions may result in early pathological changes (Bero et al., 2011; Buckner et al., 2009). Although all of these spatially remote regions demonstrated increased thickness in young Tg mice, the regions along the interhemispheric fissure did not seem to atrophy appreciably over time, whereas the areas along the rhinal fissure displayed the greatest rate of cortical thinning. It is possible that the midline regions are more resilient than other brain regions (Driscoll and Troncoso, 2011).

Our cortical perfusion data also demonstrated heterogeneous spatial and temporal patterns. Most areas of the brain were hypoperfused in the young Tg mice. Our data from in vivo ASL MRI is consistent with the observations of Niwa et al. (2002) who identified reduced CBF in young (2–3 months old) APP Tg2123 and 2576 mice by quantitative autoradiography. Given that mice in the Niwa study and our study do not yet exhibit amyloid plaques, soluble β-amyloid may be responsible for altered blood flow. Han et al. (2008) used digital video microscopy to demonstrate that soluble β-amyloid is a major contributor to age-dependent cerebrovascular dysfunction in Tg2576 mice. BACE1 or γ-secretase inhibitors could be used in future studies to support the role of soluble β-amyloid in the perfusion deficits observed in the young mice (without plaques and cerebral amyloid angiopathy) in our study.

3.2. Tg mice demonstrate profound regional cortical hypoperfusion and distinct spatiotemporal patterns relative to WT mice

The young Tg mice demonstrated statistically significant (p < 0.05) hypoperfusion in all cortical regions (Figs. 4B and 8). The most significant differences were observed in perirhinal cortex (t = 6.8, p < 0.001), retrosplenial cortex (t = 6.0, p < 0.001), entorhinal cortex (t = 5.8, p < 0.001), and posterior cingulate cortex (t = 5.7, p < 0.001), which are the same regions that had the greatest differences in cortical thickness. All cortical regions remained significantly hypoperfused in the middle-aged and old Tg mice relative to the age-matched WT mice.

The change in cortical perfusion over 15 months across the whole cortex did not demonstrate a significant difference between genotypes (Fig. 5B). However, analysis of the vertexwise and regional changes revealed striking differences between Tg and WT mice (Figs. 7B and 9), indicating the importance of examining loco-regional changes, which are often obscured in global measures. The regions along the rhinal fissure, including insula (Puncorrected = 0.007), perirhinal cortex (Puncorrected = 0.004), and entorhinal cortex (Puncorrected = 0.036), displayed an increasing level of perfusion over 15 months in the Tg mice, whereas stable or decreasing perfusion was observed in the WT mice. While these regions demonstrated significant differences before Bonferroni correction, this significance did not survive multiple comparisons. Although significant group differences were not identified in the other ROIs, regional heterogeneity was readily apparent.

4. Discussion

This study examined the spatiotemporal patterns of cortical thickness and resting perfusion derived from in vivo MRI scans of APP Tg and age-matched WT mice and represents the first demonstration of the regional effects of APP overexpression on both cortical structure and cerebrovascular physiology across the mouse lifespan derived from noninvasive MRI data. A striking feature of our data is the spatial and temporal heterogeneity of morphometric and functional alterations. Regional differences in cortical thickness and CBF are well documented in human MRI studies of patients with AD (Chen et al., 2011a; Lerch et al., 2005; Tosun et al., 2010), which motivated our approach to explore pathological alterations in mouse brain using fully-automated processing with vertexwise and ROI-based analysis.

The observation of increased cortical thickness in the young Tg mice was unexpected and seemingly counterintuitive. However, several studies support potential mechanisms for this finding. Plaschke et al. (1997) demonstrated that long-term cerebral hypoperfusion resulted in increased regional concentrations of APP in a rat model. Oh et al. (2009) demonstrated that overexpression of mutant (APPsw) or WT APP in Tg mice can induce hypertrophy of cortical neurons. Iacono et al. (2009) identified hypertrophic cortical neurons in human autopsy material from the Nun Study and postulated that neuronal hypertrophy may constitute an early cellular response to AD pathology and/or reflect compensatory mechanisms that prevent cognitive impairment despite substantial AD-associated pathological changes. Astrogliosis is also prominent in AD and has been associated with a specific cortical laminar pattern (Beach et al., 1989). Hence, APP β-amyloid–driven neuronal hypertrophy and/or astrogliosis could potentially explain the apparent increase in cortical thickness in Tg mice. Future studies could assess cortical structure in even younger (e.g., 1 month-old) mice to investigate the age-of-onset of these pathological processes.

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In addition to differences in the temporal evolution of changes in cortical thickness between the regions along the interhemispheric and rhinal fissures, these two groups of structures also demonstrated distinct patterns of age-related perfusion changes. Although the anterior/posterior cingulate and retrosplenial cortical areas showed perfusion changes (decreases) similar to WT mice, the insula and perirhinal/entorhinal regions demonstrated increased perfusion over time in Tg mice. A potential mechanism that would explain this observation includes increased local vascular density resulting from long-term angiogenesis (Desai et al., 2009). Dai et al. (2009) observed increases in regional CBF in portions of the limbic system in mild cognitive impairment (MCI) and patients with AD using ASL MRI, and suggested a compensatory cellular and/or vascular process. The apparent inverse relationship between temporal changes in cortical thickness and perfusion in these regions is particularly intriguing and it warrants further investigation into the mediators of these processes. As suggested by Dai et al. (2009), brain structural and functional changes may be asynchronous during disease evolution. Thus, animal model studies should provide new insights into findings in human AD multimodality neuroimaging studies.

A potential confounding effect of the perfusion data in this study is the use of anesthesia during MRI scanning. Inhaled anesthetic agents are known vasodilators and increased CBF has been demonstrated in rats under isoflurane (Sicard et al., 2003). Lenz et al. (1998) demonstrated that sevoflurane produces a smaller increase in CBF than isoflurane, and Flores et al. (2008) found that sevoflurane is preferred for physiological imaging in mice. Based on the literature and our own experience, these studies were performed under sevoflurane. To date, all ASL MRI and the majority of other, non-terminal, cerebrovascular physiology studies (e.g., laser Doppler flowmetry) in mice have been performed under anesthesia and it is unknown if our observed genotype- and age-related group differences in cortical perfusion are influenced by the anesthetic agent. Although imaging of awake animals may be preferable from a physiological perspective, minimizing the effects of motion is a primary concern for these sensitive MRI scans. Although Desai et al. (2010) recently reported the feasibility of optogenetic functional MRI studies in awake mice and Mizuma et al. (2010) described PET studies in conscious mice, the use of a head post for immobilization is impractical for long-term studies and the requirements for customized surface radiofrequency coils may limit accurate assessment of subcortical structures. Our group is currently investigating noninvasive methods for head restraint that will facilitate perfusion and functional MRI studies of conscious mice.

A limitation of this study is the cross-sectional design. This particular strategy was used given that the ultimate objective of our work is correlation between temporally-matched neuroimaging and neuropathology data. Longitudinal studies, which may potentially reveal more subtle group (genotype, age) differences, are being initiated in our laboratory. This study, like most AD mouse model studies, also focused on a single mouse line. Future studies should examine other APP Tg mouse models to better assess the generalizability of our results.

Substantial insight into the pathophysiological processes driving the distinct patterns of abnormal neuroanatomical structure and cerebrovascular physiology can potentially be gained by intervention with putative disease-modifying therapeutic agents.
with different mechanisms of action (e.g., amyloid-clearing biologics, amyloid-lowering secretase inhibitors, neuroprotective agents, neuroinflammation modulators). The noninvasive nature of 3D MRI scanning provides a distinct advantage over other techniques (e.g., autoradiography, laser Doppler flowmetry) for therapeutic studies, as it allows for longitudinal assessment of structural and physiological changes across the entire brain. Effective translation of knowledge gleaned from such preclinical imaging studies should facilitate the development of effective treatments to delay, slow, halt, and/or reverse the progression of AD.

Disclosure statement

The authors have no conflicts of interest relevant to the subject of this manuscript, including no institutional contracts relating to this research or any other agreements of the authors or their institutions that could be seen as involving a financial interest in this work.

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