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Gray and white matter degeneration revealed by diffusion in an Alzheimer mouse model

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ABSTRACT

In patients with Alzheimer's disease (AD) the severity of white matter degeneration correlates with the clinical symptoms of the disease. In this study, we performed diffusion-tensor magnetic resonance imaging at ultra-high field in a mouse model for AD ($APP_{swe}/PS1_{dE9}$) in combination with a voxel-based approach and tractography to detect changes in water diffusivity in white and gray matter, because these reflect structural alterations in neural tissue. We found substantial changes in water diffusion parallel and perpendicular to axonal tracts in several white matter regions like corpus callosum and fimbria of the hippocampus, that match with previous findings of axonal disconnection and myelin degradation in AD patients. Moreover, we found a significant increase in diffusivity in specific hippocampal subregions, which is supported by neuronal loss as visualized with Klüver-Barrera staining. This work demonstrates the potential of ultra-high field diffusion-tensor magnetic resonance imaging as a noninvasive modality to describe white and gray matter structural changes in mouse models for neurodegenerative disorders, and provides valuable knowledge to assess future AD prevention strategies in translational research.
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1. Introduction

Alzheimer's disease (AD) is the most common type of dementia and is characterized by a progressive loss of neuronal function, leading to gradual memory impairment, confusion, and general withdrawal. Pathologic hallmarks are the accumulation of extracellular amyloid plaques, caused by amyloid-β protein (Aβ) aggregation, and the presence of intracellular neurofibrillary tangles, formed by aggregates of the hyperphosphorylated tau protein. These pathologic changes originate in the medial temporal lobe, especially the entorhinal cortex and hippocampus, spreading further across the limbic cortex and neocortex (Arnold et al., 1991; Braak and Braak, 1995). Along with Aβ- and neurofibrillary tangle gray matter pathology, histological studies identified several changes in white matter structures. More than 50% of confirmed cases of AD show white matter disease in neuropathologic examinations, with a widespread distribution in patients with moderate- to late-stage dementia (Englund and Brun, 1990). Several studies reported a correlation of the incidence of white matter lesions with severity of the underlying AD pathology (Bozzali et al., 2002; Bronge et al., 2002; de Groot et al., 2000). The etiology of AD-related white matter pathology remains to be fully elucidated, although some underlying processes have been proposed, including (1) interhemispheric disconnection through Wallerian degeneration (Tomimoto et al., 2004); (2) axonal damage and gliosis after vascular disease (Englund, 1998); and (3) primary myelin degradation resulting in axonal disconnection (Medina et al., 2006; Xie et al., 2006).

Magnetic resonance imaging (MRI) offers tools to measure white and gray matter architecture in vivo. Diffusion weighted MRI measures the incoherent motion of water molecules for every imaged voxel and provides complementary information to conventional MRI on tissue microstructure (Le Bihan et al., 1986). Since its first description (Basser et al., 1994), diffusion tensor MRI (DT-MRI) has been widely used to investigate white matter because of the relatively coherent organization of axons in fiber bundles that results in

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a marked diffusion anisotropy, with greater diffusivity occurring along the axonal direction. By measurement of the diffusivity in multiple directions, DT-MRI can reconstruct an ellipsoid to model the diffusion in every voxel. The diffusion tensor is characterized by the magnitude of the diffusivity over its 3 axes (eigenvectors). The mean diffusivity (MD) is the average of these diffusivities and captures the size of the tensor. Other informative measures include the axial diffusivity (λ_1) aligned to the primary diffusion direction and the radial diffusivity (RD) that represent the diffusivity perpendicular to this main direction. The shape of the diffusion tensor is often quantified by the fractional anisotropy (FA), which is an index between 0 and 1 that indicates the degree to which diffusivity is different over the 3 axes of the tensor.

DT-MRI is particular well suited for studies of neurological disorders, like AD, because structural changes in neural tissue, like neuronal cell death and white matter microstructural pathology, are reflected in shape and size of the diffusion tensor (Kantarci, 2011). In AD patients changes in DT-MRI parameters are particularly consistent, showing increased diffusivity with loss of directionality—decreased FA—in white matter and increased MD in gray matter regions (Hanyu et al., 1998; Kantarci, 2011; Song et al., 2004). Histologic examinations in brains of AD mice models suggested that myelin loss, decrease in axonal density, and axonal disconnection contribute to the diffusion changes in white matter (Chen et al., 2011; Song et al., 2004). In gray matter, the increased diffusivity has been attributed to neuronal loss, because the diffusivity of water molecules increases when fewer cell membranes restrict their random motion (Sykova et al., 2005). Interestingly, changes in gray matter diffusion (e.g., elevated hippocampal MD) predicted the conversion from mild cognitive impairment to AD similarly or even better than hippocampal volumetric changes in 2 independent studies (Fellgiebel et al., 2006; Kantarci et al., 2005). These results highlight the importance of characterizing the diffusion properties not only in white, but also in gray matter structures, because these contain unique and complementary information about the progression of the disease.

For translational research in AD it is important to perform similar DT-MRI studies in animal models of the disease, but only recently the availability of new dedicated hardware and methods for acquisition and data analysis enabled the study of brain water diffusion in small animals. The results reported in mouse models of cerebral amyloidosis showed white matter diffusion changes similar to those in human studies, but no further investigation on diffusion in gray matter substructures has yet been performed (Song et al., 2004; Sun et al., 2005).

In this study, we aimed to assess water diffusion changes in white and gray matter in a double transgenic mouse model for AD (APP_{swe}/$PS1_{dE9}$) (Jankowsky et al., 2001, 2004). We used state-of-the-art methodology for in vivo DT-MRI data acquisition (Harsan et al., 2010) at ultra-high field (11.7 T) with respiratory and cardiac motion correction and robust tensor estimation (Harsan et al., 2010; Zwiers, 2010). Thereafter, we employed region of interest (ROI)-based and whole-brain voxel-based approaches in combination with tractography algorithm to describe genotype differences with the highest possible spatial resolution. This enables an innovative and accurate description of diffusion changes, for a comprehensive spatial characterization of the underlying pathology in our AD mouse model.

2. Methods

2.1. Animals

The APP_{swe}/$PS1_{dE9}$ founders were obtained from Johns Hopkins University, Baltimore, MD, USA (D. Borchelt and J. Jankowsky, Department of Pathology). A colony was bred and established at the Central Animal Facility at the Radboud University Nijmegen Medical Centre, The Netherlands. The transgenic mice were created by cotransfection with chimeric mouse/human amyloid precursor protein APP_{swe} (mouse APP695 harboring a human Aβ domain and mutations K595N and M596L linked to Swedish familial AD pedigrees) and human presenilin 1 with deletion of exon 9 ($PS1_{dE9}$) vectors controlled by independent mouse prion protein promoter element (Jankowsky et al., 2001, 2004). These 2 genes cointegrate and cosegregate as a single locus. Breeder mice were backcrossed to C57BL6/J for 12 generations to obtain the animals for this study. Throughout the duration of the experiment the mice were housed in groups. Room temperature was kept at 21 °C with an artificial 12-hour light:dark cycle. Food and water were available ad libitum. The experiments were performed according to Dutch federal regulations for animal protection and were approved by the Veterinary Authority of the Radboud University Nijmegen Medical Centre.

2.2. Magnetic resonance imaging

Twelve-month-old male APP_{swe}/$PS1_{dE9}$ transgenic mice ($n = 9$) and age-matched wild type (WT) littermates (C57BL6/J $n = 15$) were used for DT-MRI. Isoflurane (3.5% for induction and approximately 2% for maintenance) was used for anesthesia. The anesthetic concentration was adjusted during the experiment in order to maintain the breathing frequency at 65–85 per minute. The mice were placed in a stereotactic device to immobilize the head. Body temperature was measured using a rectal thermometer and maintained at 37 °C using a heated air flow device.

Magnetic resonance (MR) measurements were performed on a 11.7 T BioSpec Avance III small animal MR system (Bruker BioSpin, Ettlingen, Germany) equipped with an actively shielded gradient set of 600 mT/m. We used a circular polarized volume resonator for signal transmission and an actively decoupled mouse brain quadrature surface coil for signal reception (Bruker BioSpin).

Gradient echo images in the axial, sagittal, and coronal orientation were acquired to visualize the anatomy and the morphology of the mouse brain structures. Imaging parameters were: echo time = 5 ms, repetition time = 630 ms, flip angle = 12°, field of view = 40 × 40 mm, matrix size = 512 × 512, slice thickness = 0.345 mm.

Diffusion MRI was performed following a modified protocol of Harsan et al. (2010). In short, 31 axial slices covering the whole brain were acquired with a spin-echo planar imaging protocol. B0 shift compensation, navigator echoes, and automatic ghost correction algorithm were implemented to limit the occurrence of ghosts and artifacts. Encoding b-factors of 0 s/mm^2 (b0 images; 5×) and 1000 s/mm^2 were used, and diffusion-sensitizing gradients were applied along 30 noncollinear directions of 3-dimensional space. Other imaging parameters were: echo time = 21.4 ms, repetition time = 7750 ms, time between the application of diffusion gradient pulses $\Delta = 10$ ms, diffusion gradient duration $\delta = 4$ ms, number of segments = 4, total resolution 156 × 156 × 500 μm. This results in a total scan time of 18 minutes for each mouse.

2.3. Data preprocessing

For spatial normalization, a study-specific template was created of all WT and transgenic animals using Advanced Normalization Tools (ANTs. V1.9.x, http://picsl.upenn.edu/ANTS/). A group-wise normalization procedure (SyGN, as implemented in the buildtemplateparallel.sh script V0.0.13) was employed on the realigned mean diffusion image of each mouse (Avants et al., 2008). The default implementation was followed with 4 iterations using mutual information as the initial affine similarity metric and cross-correlation as 'greedy SyN' diffeomorphic transformation metric. A mask that included the entire brain was manually defined in the

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