Is Myelin Content Altered in Alzheimer's Disease?

S. C. Deoni[1], S. Correia[2], T. Su[2], J. Man[2], P. Malloy[3], and S. Salloway[3]
[1]School of Engineering, Brown University, Providence, RI, United States, [2]Psychiatry and Human Behavior, Brown University, Providence, RI, United States, [3]Alpert Medical School, Brown University, Providence, RI, United States

INTRODUCTION: Alzheimer's disease (AD) is a degenerative neurological disease characterized by the progressive loss of memory, attention, language and other cognitive functions. The most common form of dementia, there is currently no effective treatment for AD. Further, there remains no robust diagnostic test for AD in the earliest pre-symptomatic stages of the disease, when treatment therapies are likely to be most successful. Alongside the classic neuropathological hallmarks of AD, i.e., amyloid deposits and neurofibrillary tangle formation, white matter (WM) damage is also commonly observed. An emerging white matter hypothesis of AD posits the disorder is associated with marked myelin alteration and reduction[1,2], potentially preceding amyloid and tau pathology[3]. This hypothesis stems from transgenic animal studies[3], the established toxicity of amyloid and tau pathology on myelin microstructure[4], and observation of myelin loss, split or balloon myelin sheaths, and oligodendroglial cell loss[5]. Combined, these results suggest a more central role of WM and, specifically, myelin, alteration in AD than typically thought. To date, however, direct assessment of myelin change in AD has been difficult. In this work, we report on our initial findings investigating changes in myelin content in early mild AD. Using the rapid mcDESPOT[6] multicomponent relaxation time technique, myelin content (quantified through the myelin water fraction, MWF) was directly measured throughout the brains of AD patients and healthy age and sex matched controls. Our results reveal altered myelin content differences between healthy controls and AD patients in distinct brain regions, as well as associations between MWF and degree of disability (measured through the Mini Mental State Exam, MMSE).

METHODS: MRI Whole-brain, voxel-wise myelin water fraction (MWF) maps were acquired on 18 participants; 9 healthy controls with MMSE scores greater than 25 and Clinical Dementia Rating (CDR) score of 0 (mean age = 58, age range = 46-64); and 9 patients with mild AD with MMSE scores between 18 and 25 and CDR scores less than 1 (mean age = 61, age range = 52-66). All data were acquired on a Siemens Tim Trio scanner equipped with a 32-channel head array coil. mcDESPOT sequence specifics were: a common (22x22x16)cm^3 sagittal FOV, 128x128x96 matrix, SPGR: TE/TR/ = 2.4ms/5.4ms/(3,4,5,6,7,9,13, and 18) degrees, BW=350Hz/pixel; SSFP: TE/TR/ = 5.7ms/11.4ms/(10,14,19,24,29,35,45, and 60) degrees, BW=560Hz/pixel. Two SSFP phase-cycling patterns (0 and 180 degrees) were acquired to correct for off-resonance effects[7]. A reduced resolution IR-SPGR image was also acquired (TE/TR/TI/=2.4ms/5.4ms/(450ms/5 degrees, BW=380Hz/pixel) to correct for flip angle heterogeneity[8]. Following acquisition and normal mcDESPOT post-processing to derive the MWF maps[6], a study-specific template image, in MNI space, was created by first co-registering and averaging all participants' data to the MNI template. The high flip angle SPGR image from each participant was subsequently non-linearly co-registered to this study template, and the transformation matrix applied to the participant's myelin fraction map.

Non-parametric group comparisons and correlation analysis was performed voxel-wise using the Randomise tool, part of the FSL library (www.fmrib.ox.ac.uk/fsl). Control-mild AD group comparisons (groups based on CDR rating) were calculated to determine brain regions of significant (p<0.05 FDR) difference. Further, correlation analysis between MWF and MMSE score was performed to identify brain regions with significant (p<0.05 FDR) correlation. Correction for multiple comparisons was performed using threshold-free cluster enhancement. For all analysis, subject age was included as an additional covariate.

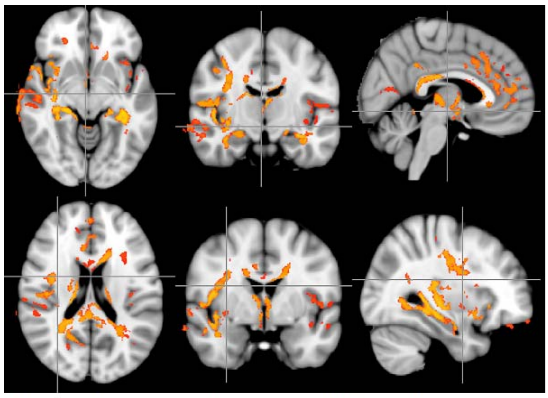

Figure 1: Areas of significant group difference between healthy controls and mild AD patients. R=R.

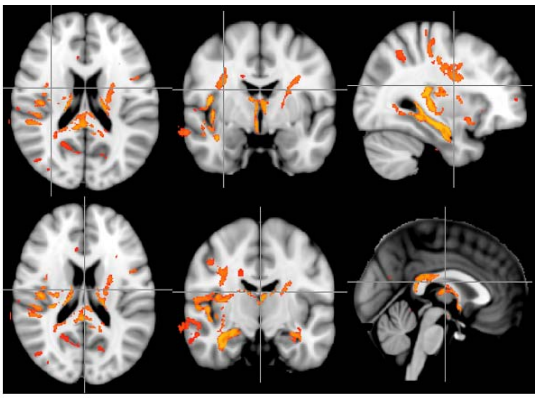

Figure 2: Areas showing significant correlation between myelin content and MMSE score. R=R.

RESULTS: Figure 1 displays brain regions found to differ significantly in MWF between the healthy controls and mild AD patients. Images are shown in radiological format; R=R. Regions of difference included left temporal lobe WM, portions of the genu, splenium and body of the corpus callosum, bilateral cingulate bundles, and WM adjacent and superior to the amygdala and hippocampus bilaterally. In Fig. 2, regions displaying significant MWF vs. MMSE correlation are shown (in radiological format, n=18). Similar areas as highlighted by the group comparison results are observed, including left temporal lobe WM, portions of the splenium and body of the corpus callosum, and WM adjacent and superior to the amygdala and hippocampus. While bilateral, this result does appear to be greater in extent in the left hemisphere.

DISCUSSION: Our results present the first direct investigation of myelin content alteration in AD, revealing areas of difference corresponding to brain regions previously implicated in the disorder, including the corpus callosum, left temporal lobe, cingulate bundles, amygdalae, and hippocampi. Despite our relatively small but homogeneous sample size, robust alterations are observed even in the mild stages of the disorder. Results from our correlation analysis further suggest the utility in identifying change in early stages of the disease. Our results could offer new insights into the mechanisms underlying early structural brain changes associated with AD. Further work in pre-symptomatic participants is required to elucidate the ability of myelin content imaging as an early diagnostic marker of the disease.

REFERENCES: [1] Bartzokis G. (2004). Neurobiol Aging. 25, 5-18. [2] Benes FM. (2004). Neurobiol Aging. 25, 41-43. [3] Desai MK, Sudol KL, Janelsins MC, et al. (2009). Glia. 57, 54-65. [4] Malone MJ, Szoke MC. (1985). Arch. Neurol. 42, 1063-1066. [5] Englund E, Brun A. (1981). In: Biological Psychiatry 1981. Ed. C Perris, G. Struwe, B. Jansson. Amsterdam: Elsevier/North-Holland. Pp. 951-956. [6] Deoni SCL, Rutt BK, Arun T, et al. (2008). Magn. Reson. Med. 60, 1372-1387. [7] Deoni SCL et al. ISMRM pp 4609. (2009). [8] Deoni SCL et al. (2007) JMRI. 26; 1106-1111.