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Widespread white matter degeneration preceding the onset of dementia

Klaus H. Maier-Hein[a,b,c,*], Carl-Fredrik Westin[a], Martha E. Shenton[a,d,e], Michael W. Weiner[f], Ashish Raj[g], Philipp Thomann[h], Ron Kikinis[a], Bram Stieltjes[c], Ofer Pasternak[a,d]

[a]*Department of Radiology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[b]*Junior Group Medical Image Computing, German Cancer Research Center, Heidelberg, Germany*
[c]*Junior Group Quantitative Image-based Disease Characterization, German Cancer Research Center, Heidelberg, Germany*
[d]*Department of Psychiatry, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA*
[e]*Health Scientist, Veterans Affairs Boston Healthcare System, Brockton Division, Brockton, MA, USA*
[f]*Center for Imaging of Neurodegenerative Disease, San Francisco VA Medical Center, University of California, San Francisco, USA*
[g]*Image Data Evaluation and Analytics Lab (IDEAL), Weill Cornell Medical College, New York, NY, USA*
[h]*Department of General Psychiatry, Section of Geriatric Psychiatry, Ruprecht-Karls-University, Heidelberg, Germany*

Abstract

Background: Brain atrophy in subjects with mild cognitive impairment (MCI) introduces partial volume effects, limiting the sensitivity of diffusion tensor imaging to white matter microstructural degeneration. Appropriate correction isolates microstructural effects in MCI that might be precursors of Alzheimer's disease (AD).

Methods: Forty-eight participants (18 MCI, 15 AD, and 15 healthy controls) had magnetic resonance imaging scans and clinical evaluations at baseline and follow-up after 36 months. Ten MCI subjects were diagnosed with AD at follow-up and eight remained MCI. Free-water (FW) corrected measures on the white matter skeleton were compared between groups.

Results: FW corrected radial diffusivity, but not uncorrected radial diffusivity, was increased across the brain of the converted group compared with the nonconverted group ($P < .05$). The extent of increases was similar to that found comparing AD with controls.

Conclusion: Partial volume elimination reveals microstructural alterations preceding dementia. These alterations may prove to be an effective and feasible early biomarker of AD.

Keywords: Alzheimer's disease; Mild cognitive impairment; Diffusion tensor imaging; Partial volume elimination; Free-water imaging

1. Background

Magnetic resonance imaging (MRI) can identify pathological brain alterations associated with Alzheimer's disease (AD) [1]. These include macrostructural effects such as gray matter (GM) and white matter (WM) atrophy, and microstructural WM alterations, such as Wallerian degeneration and compromised myelin integrity. GM atrophy can be identified using volumetric measures based on anatomical MRI, whereas microstructural alterations can be identified using diffusion MRI (dMRI), a method that is sensitive to micron scale tissue architecture [2].

Mild cognitive impairment (MCI) is often a prestage of AD with a tenfold higher risk of developing dementia compared with healthy subjects [3]. Therefore, the detection of imaging abnormalities in MCI may increase our understanding of the pathogenesis of AD, as it may lead to improved early detection of patients at risk, and may thus provide an objective means for the assessment of medication(s) in early stage clinical trials. MRI studies have not yet been able to provide a robust diagnostic measure for the early stages of the disease [4]. Specifically, dMRI studies report inconsistent findings when comparing patients with

*Corresponding author. Tel.: +49-6221/42-3545; Fax: +49-6221/42-2345.
E-mail address: k.maier-hein@dkfz.de

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MCI and controls, even when using similar analysis methods (e.g., see tract-based spatial statistics [TBSS] studies in Supplementary Table 1).

The inconsistent findings in MCI might stem from the fact that the cognitive deficits of some patients may stabilize, improve, or progress to other dementias [5]. Patients with MCI are also likely to have different underlying pathology, as for example some subjects have AD pathology in the form of neurofibrillary tangles of hyperphosphorylated tau (p-tau) and beta amyloid (Aβ) neuritic plaques [6], which may be responsible for the MCI, whereas others may not have AD pathology, and their MCI is due to other pathologies [5]. Therefore, patients with MCI do not comprise one clinical entity, which limits the predictive validity of MCI imaging abnormalities as a predementia syndrome and/or as biomarkers of AD pathology [7–10].

Another limiting factor in the study of patients with MCI and AD is the influence of brain atrophy on the sensitivity of dMRI to microstructural changes. Part of the atrophy is likely age associated, because atrophy also appears in normal aging [11]. Moreover, many structural MRI studies have demonstrated increased GM atrophy (e.g., hippocampi, entorhinal cortex, amygdala) and WM atrophy (e.g., corpus callosum) in patients with AD or MCI in comparison with age-matched controls [12,13]. Atrophy in subjects with MCI might be an early manifestation of AD pathology [14]. Nevertheless, atrophy has limited specificity as a precurser of AD, as it may appear both in subjects with MCI who will develop AD and also appear in those who will not, as well as in patients with other brain disorders. Atrophy introduces macroscopic morphologic changes in WM, such as loss of volume, reduced cellular density, and increased extracellular space [15], which due to the limited resolution of dMRI, increases the influence of partial volume between different tissues [16]. Unless these macroscopic morphologic changes are accounted for, they decrease dMRI specificity and lead to difficulties in the interpretation of derived measurements. Thus, the partial volume effects associated with variable amounts of atrophy may have affected the interpretation of previous data [16]. This, in conjunction with the group heterogeneity, might explain the diversity of previous findings regarding dMRI alterations in MCI.

Our aim is to decouple macroscopic and microscopic effects and obtain dMRI derived microstructural precursors of dementia by studying a sample of subjects diagnosed with MCI who were followed for 3 years after an initial MRI scan. Within this period, some subjects developed dementia and were diagnosed with AD, whereas others did not. By comparing these two subsets of MCI subjects, we were able to identify abnormalities that may constitute an early precursor of AD. These abnormalities were revealed only when controlling for partial-volume effects by applying the free-water (FW) imaging method [17], which corrects each image voxel for contamination from freely diffusing extracellular water molecules. The method separately models the contribution of such molecules from water molecules that are in the vicinity of cellular membranes such as axonal membrane and myelin sheath [18]. By eliminating the extracellular contribution, the method accounts for partial-volume that could be introduced by atrophy, and makes it possible to identify whether microstructural changes, such as WM degeneration occur [16].

2. Methods

2.1. Study populations

This study comprised 48 subjects including 18 patients diagnosed with MCI, 15 patients diagnosed with AD, and 15 age-matched healthy control subjects (HC). A demographic and clinical characterization of the groups can be found in Table 1. Group effects were evaluated using analysis of deviance for the generalized linear model implemented in MathWorks Matlab (R2012a, 7.14.0.739). Global cognitive deficits were assessed using the mini-mental state examination (MMSE). Cognitive performance was investigated with a standardized extensive neuropsychological test battery (CERAD). Subjects were classified

Table 1
Demographic and clinical characterization of subject groups

	HC	MCI	AD	MCI-c	MCI-nc	Group effect
N	15	18	15	10	8	
Age	63.0 ± 9.4	71.9 ± 6.5	73.6 ± 7.7	72.3 ± 7.5	71.4 ± 5.5	–
Sex (m/f)	8/7	7/11	5/10	4/6	3/5	–
MMSE	29.3 ± 0.7	26.4 ± 1.5	19.2 ± 4.9	26.1 ± 1.8	26.8 ± 0.9	†
Verbal fluency	.746 ± .946	−.133 ± 1.21	−1.19 ± 1.09	−.300 ± 1.30	.055 ± 1.15	†
Boston naming test	.653 ± .312	−.686 ± 1.91	−2.4 ± 1.93	−1.00 ± 2.32	−.330 ± 1.37	†
Word list learning	−.020 ± .651	−1.48 ± 1.18	−4.15 ± 3.2	−1.61 ± 1.18	−1.32 ± 1.25	†
Word list delayed recall	.0287 ± .739	−1.60 ± 1.49	−3.31 ± .681	−1.70 ± 1.46	−1.50 ± 1.61	†
Word list recognition	.317 ± .411	−1.92 ± 2.40	−4.73 ± 2.91	−2.91 ± 2.75	−.801 ± 1.37	†
Constructional praxis	.287 ± 1.33	.195 ± 1.18	−1.32 ± 2.47	−.0667 ± 1.5	.490 ± .638	*
Delayed constructional praxis	.733 ± .769	−.268 ± 1.43	−2.73 ± 1.32	-.553 ± 1.18	.0537 ± 1.69	†

Abbreviations: AD, Alzheimer's disease; MCI-c, mild cognitive impairment, later diagnosed with AD; MCI-nc, mild cognitive impairment, did not develop with dementia; MMSE, Mini-Mental State Examination; HC, healthy controls; m/f, male/female.

*Group effect $P < .05$.

†Group effect with $P < 10^{-3}$.