White Matter Involvement in Mild Cognitive Impairment and Mild Alzheimer's Disease Using Whole-Brain Probabilistic Tractography Normalization

Oranan Tritanon[1], Jiraporn Laothamatas[1], Chewarat Wirojtananugoon[1], Witaya Sungkarat[1], Chakrit Sukying[2], and Sirintorn Chansirikarnjana[3]

[1]Advanced Diagnostic Imaging and Image-Guided Minimal Invasive Therapy Center and Radiology Dept., Ramathibodi Hospital Faculty of Medicine, Mahidol University, Rajataewe, Bangkok, Thailand, [2]Department of Psychiatry, Ramathibodi Hospital Faculty of Medicine, Mahidol University, Rajataewe, Bangkok, Thailand, [3]Department of Medicine, Ramathibodi Hospital Faculty of Medicine, Mahidol University, Rajataewe, Bangkok, Thailand

Introduction:

Alzheimer's disease (AD) is the most common form of dementia, while mild cognitive impairment (MCI) refers to the transitional stage between normal aging and dementia, which is a risk factor for AD [1]. A pathological study showed extensive white matter involvement in AD and MCI occurring before clinical symptoms. Most analyses of white matter changes in AD and MCI measuring mean diffusivity (MD) and fractional anisotrophy (FA) were based on regions of interest (ROI), which showed varieties in MD and/or FA values [2-7]**.** ROI approach can be subjective in determining anatomical borders, resulting in poor reproducibility. A quantitative voxel-wise DTI analysis based on a new whole-brain probabilistic tractography normalization is used for comparing FA and MD between groups in this study. The method is not subject to the issues of human-based tracing reliability and reproducibility**.** It is based on normalizing FA and MD based on normalizing individual whole-brain probabilistic tractography map with an age-matched whole-brain probabilistic tractography template of a control group. This method is very robust, and has been developed to normalize dog's brain images. The most difficulty to conduct a voxel-based group analysis on elder people brain images is that it is very difficult to find an image modality for a normalization process giving accurate coregistration and warping results.

Materials and Methods:

Three groups of subjects (15 mild AD, 10 MCI, and 20 age-matched controls) underwent diffusion tensor imaging (DTI) scanning by a 3-Tesla MRI scanner (Achieva, Philips Healthcare, Best, the Netherlands) with a DTI sequence (SSEPI with TR/TE=10430/71ms, FOV=240x240mm, 128x128 matrix, 80 contiguous slices at 2-mm thick, one b=0s/mm^2 and 32 isotropic gradient directions with b=800s/mm^2). Axial 3DTFE T1-weighted images were also acquired for anatomical mapping (TR/TE=212/4.6ms, FOV=240x240mm, 80 contiguous slices at 2-mm thick). Upon individual DTI data, FSL (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain -- FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl) was utilized to correct eddy current artifacts, calculate FA, MD, and whole-brain probabilistic tractography maps. A customized probabilistic tractography template was constructed by averaging 20 registered whole-brain probabilistic tractography maps of the normal control group using SPM2 (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm). Then, to the probabilistic tractography template, FA, MD, and whole-brain probabilistic tractography maps of the two patient groups and age-matched control group were anatomically normalized. Finally, group analyses of FA and MD differences were performed using the ANOVA module in SPM2. For the comparisons of the AD versus control groups and MCI versus control groups, the results were obtained with statistically significant thresholds at $p < 0.00001$ and $p < 0.001$ for FA and MD group analyses respectively, while those of AD versus MCI, they were $p < 0.001$ and $p < 0.05$ respectively.

Results and Discussion:

Compared to the age-matched controls, mild AD patients had significantly decreased FA in the right superior-middle frontal gyri, cingulum bundle, limbic lobes, insular cortices, genu of the corpus callosum, deep grey nuclei, internal capsules, midbrain, cerebellum, bilateral parietal, temporal/occipital white matters, and increased MD in bilateral limbic/temporal lobes, posterior cingulate, bilateral thalami, right frontal, left parietal, and left occipital lobes (**Fig. 1**). In MCI versus age-matched control results, the number and size of areas with significantly decreased FA were smaller than those of AD group; however, the major areas located in the same area as AD. In AD vs. MCI, there were significantly decreased FA in the anterior cingulate, right posterior cingulate, bilateral temporal, bilateral occipital, left frontal lobe, left parietal lobe, and left thalamus, and increased MD in right anterior cingulate, bilateral temporal, right frontal, left parietal, right insular, and bilateral internal capsules (**Fig. 2**).

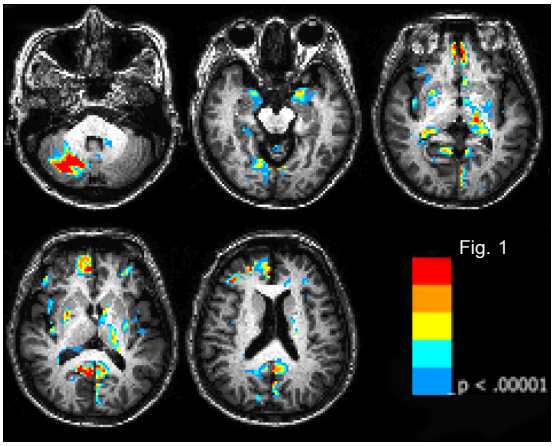

Fig. 1: Clusters of significant decreased FA in AD group compared to age matched control group, p <.00001

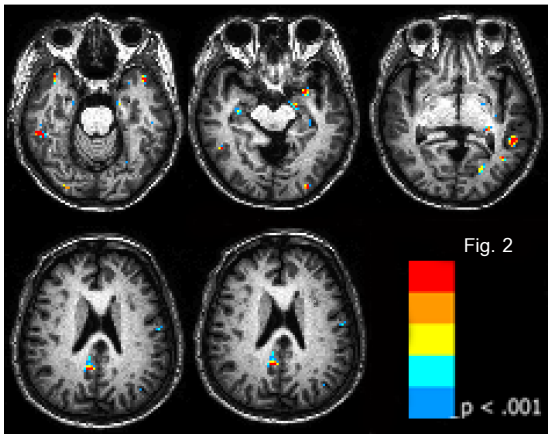

Fig. 2: Cluster of significant decreased FA in AD groups compared to MCI group, p < .001

The axonal damage in microtubule and neurofilament affects integrity of the myelin sheath and axonal transportation, which can be measured in term of fractional anisotrophy [8]. There is significantly decreased FA and increased MD in many regions of the brain in this study. Some areas, e.g., insular lobe, had never been reported in previous literatures. Decreased FA values in frontal lobe are supported by neuropathologic studies, possibly caused by early frontal-temporal disconnection [9-11]. Decreased FA areas at the cingulum bundle, bilateral rectus gyri, and bilateral occipital lobes, may reflect lateral cholinergic pathway damage [12]. Decreased FA at the left thalamus and the left internal capsule may affect the integrity of corticospinal tract, corticothalamic and thalamocortical fibers [13]. There were decreased FA areas in cerebella. Still its etiology is unknown. However, a pathological study on the cerebella in AD showed, pronounced on the molecular layer, a regionally marked loss of neurons, gliosis, few neuritic plaques, and neurofibrillary tangles [14]. From the good results in this study, the quantitative voxel-wise DTI analysis based on whole-brain probabilistic tractography normalization seems to be a very sensitive method to detect white matter involvement in mild AD and MCI.

References:

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