Evaluation of Distribution of Cross-Correlation Coefficients of Spontaneous Low Frequency in Alzheimer's Disease Patients

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Introduction: Alzheimer's disease (AD)-related neurofibrillary tangles and neurotic plaques are thought to first occur in the hippocampus formation. Li *et al* introduced a functional MR imaging index called COSLOF index as a marker to measure changes in functional synchrony in the hippocampus, and found that AD patients had a significant lower COSLOF index value than controls (1). COSLOF index was defined and quantified as the mean of the cross-correlation coefficients of spontaneous low frequency (0.015-0.08Hz) (SLF) components between possible pairs of voxel time courses in a specific brain region. In this study we carefully examined the distribution of cross-correlation coefficients of SLFs to clearly understand the intrinsic power of COSLOF index for distinguishing AD patients from control subjects.

Methods: Fourteen AD patients (age: 72±6 yrs) and 13 cognitively healthy controls (age: 68±4 yrs) were recruited from the Memory Disorders Clinic participated in the study. Informed consents were obtained from all subjects for this IRB-approved study. All fMRI data acquisition was conducted on a GE Signa 1.5T scanner using a local gradient coil and an end-capped birdcage RF coil. A single-shot, gradient echo EPI sequence was used with the imaging parameters: TR of 2s, TE of 40ms, FOV of 24cm, slice thickness of 7mm, and matrix of 64×64. A total of 15 sagittal slices and 180 images per slice were obtained in 6 min. The corresponding 256×256 T_1-weighted anatomic images were also acquired. During scanning, all the subjects were in resting status. All functional datasets were preprocessed to detect motion and remove linear trends. Four AD patients and 4 controls were excluded to further process due to excessive motion. The entire hippocampal region was masked on T_1-weighted images according to the brain atlas. The voxel time courses in the hippocampus were selected by mapping the high-resolution masks to the low-resolution fMRI datasets and were numbered from 1 to K, where K is the number of selected voxels. To extract the SLF components, the selected original time courses were filtered with a 9-point Hamming band-pass filter with the pass-band 0.015-0.08Hz. Cross-correlation coefficients cc_{ij}, $i > j$, were calculated between SLFs of i and j voxel time courses. There were $K(K\text{-}1)/2$ of cross-coefficients for each subject. The range of cc_{ij} is between -1 and 1 with zero indicating that two voxel time courses are not correlated. We divided the range from -1 to 1 into 3 segments, that is, $cc_{ij} < -0.20$ meaning that two SLFs have a strong negative correlation, $-0.20 \le cc_{ij} \le 0.20$ a weak correlation, and $cc_{ij} > 0.20$ a strong positive correlation. For each subject, we calculated the histogram (percentage) of correlation coefficients that was denoted as a 3-dimensional vector $\mathbf{C}_{k,l}$, where k is the group index (AD or Control) and l is the subject index. The distribution of $\mathbf{C}_{k,l}$ approximately has a 3-dimensional Gaussian. The average vectors were calculated for each group.

Results and Discussion: The average percentage of strong negative correlation, weak correlation and strong positive correlation were (33%, 24%, 43%) for the AD group and (11%, 22%, 67%) for the control group. Fig. 1 shows the coefficient histograms. The percentage of correlation coefficients for the AD group is significantly larger than the control group ($p<0.0001$) for strong negative correlation, no significant difference for weak correlation, and significantly smaller ($p<0.0001$) for strong positive correlation. This finding supports our previous study that COSLOF index, the mean of the cross-correlation coefficients of SLF components between possible pairs of voxel time courses in hippocampus, is smaller for AD group than control group. Cross-correlation coefficient between two time courses can be interpreted as a measurement of signal synchronization or phase shift between them, so our results indicate that the SLFs of AD patients are significantly less synchronized among voxels than controls. It is suggested that the neurofibrillary tangles or neurotic plaques in human brain occurring in AD patients may disrupt neural signal transmission or reception, resulting in dis-synchronization of voxel time courses.

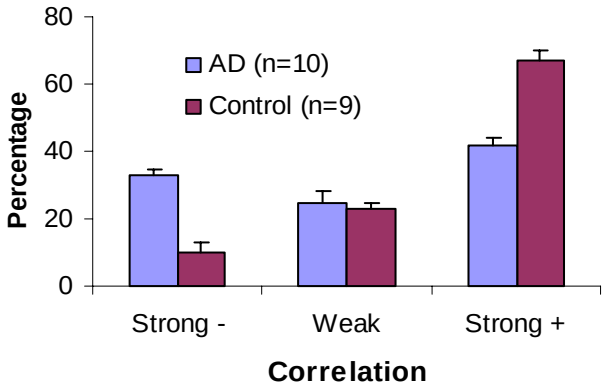

Fig 1. Histogram of correlation coefficients

Reference: 1. Li *et al*, *Radiology*, **225(1)**: 253-259, 2002.

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