Group Phase Delay Affects the Measurement of Functional Synchrony

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Introduction: COSLOF index (the mean of the cross-correlation COefficients of Spontaneous LOw Frequency) was introduced to measure the functional synchrony in the hippocampus among cognitively healthy elderly subjects, and Alzheimer's patients [1]. It was found that the subjects with Alzheimer's disease (AD) had a significantly lower COSLOF index value. To investigate the mechanism of the lower COSLOF index in the AD patients, we hypothesized that there are three possible causes: a decrease in the fluctuation intensity of the spontaneous low frequency (SLF) (0.015 – 0.1 Hz), a difference in frequency components in SLF, or phase delay between voxel time courses. In this study, we first developed a theoretical model to simulate the contribution of noise or frequency to the functional synchrony and then tested this model with our experimental data obtained from human subjects. Our results demonstrated that the lower COSLOF index in the AD patients is due to phase delay between voxel time courses instead of frequency or intensity of SLF.

Theory: Assume that SLF signal is composed of three components which are mutually independent to each other: hemodynamic signal $\boldsymbol{S}$ with neural origin, other noise $\boldsymbol{N_P}$ within the low frequency range, and the colored thermal noise $\boldsymbol{N_T}$, so that:

$$SLF(t) = S(t) + N_P(t) + N_T(t) \tag{1}$$

The cross-correlation coefficient $\boldsymbol{cc_{ij}}$ between any two voxel time courses within low frequency band can be calculated as:

$$cc_{ij} = E\left(SLF_i(t)\cdot SLF_j(t)\right)\Big/\left(\sigma_i^{SLF}\cdot\sigma_j^{SLF}\right) = E\left(S_i(t)\cdot S_j(t)\right)\Big/\left(\sqrt{\sigma_{si}^2+\sigma_{N_Pi}^2+\sigma_{N_Ti}^2}\cdot\sqrt{\sigma_{sj}^2+\sigma_{N_Pj}^2+\sigma_{N_Tj}^2}\right) \tag{2}$$

Then the COSLOF index $\boldsymbol{CI}$ is computed with selected hippocampus voxels as reported previously [1]. To explore the maximum potential of synchrony among the SLFs, voxel time course is shifted in order to reach the maximum $\boldsymbol{cc_{ij}}$ according to the following equation:

$$cc_{ij}^m = \max_{0<\tau<T} E\left(S_i(t+\tau)\cdot S_j(t)\right)\Big/\sqrt{\sigma_{si}^2+\sigma_{N_Pi}^2+\sigma_{N_Ti}^2}\cdot\sqrt{\sigma_{sj}^2+\sigma_{N_Pj}^2+\sigma_{N_Tj}^2}\ ,\quad T = 1/f_L\ ,\ f_L\text{=0.015Hz} \tag{3}$$

The mean of all cc_{ij}^m is defined as the maximum shifted COSLOF index and is denoted as $\boldsymbol{CI^m}$. Assume the signal is a cosine function, the ratio of $\boldsymbol{c_{ij}}$ to $\boldsymbol{c_{ij}^m}$ is equal to $cos(\theta)$, and the θ is the phase delay. If we average all the phase delay θ between the SLF time courses, we could have a new way to quantify the functional synchrony. Or, we could calculate a group phase delay θ_G and define $\theta_G = \arccos\left(CI/CI^m\right)$ to quantify the functional synchrony.

Materials and Methods: Fourteen AD patients (age: 72±6 yrs), 5 subjects with MCI - Mild Cognitive Impairment (age: 69±3), and 13 cognitively healthy controls (age: 68±4 yrs) were recruited from the Memory Disorders Clinic, and 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 6mm, 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 from 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. 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 – 0.1Hz. CSF voxels were also selected and grouped for each person to calculate the COSLOF index and group phase delay for comparison with the hippocampal region. Furthermore, two types of possible SLFs were also simulated for investigation. One was to assume that SLF is normal distributed noise (ND), and another was a *cosine* function with frequency randomly distributed (FD) within the low frequency band. The simulated voxel time courses also have 180 time points, the same time length as experimental data.

Results and Discussion: As shown in Fig. 1, the COSLOF indices $\boldsymbol{CI}$ (blank columns) among AD, MCI, and control groups are significantly different as previously reported [1]. However, the maximum shifted COSLOF index $\boldsymbol{CI^m}$ (black columns) among AD (0.35±0.05), MCI (0.37±0.07) and Control (0.42±0.07) groups are similar. These results suggest that although functional synchrony in the AD group is significantly lower than that in Control group because of the phase delay, and the potential functional synchrony between the groups are similar. From ND (0.23), FD (0.11), CSF (0.28±0.04) data, it is suggested that these mechanisms do not significantly contribute to the lower functional synchrony. Fig. 2 shows the group phase delay with AD (68.4°±10.6°), MCI (52.8°±6.6°), Control (39.5°±13.6°) and CSF (76.2°±12.0°). These results further demonstrated that it is the phase delay that affected the functional synchrony: the more phase delay, the less the functional synchrony (more chaotic). The above study suggested that one possible mechanism for memory loss in AD patients may be due to the phase delay of signal transmission or reception.

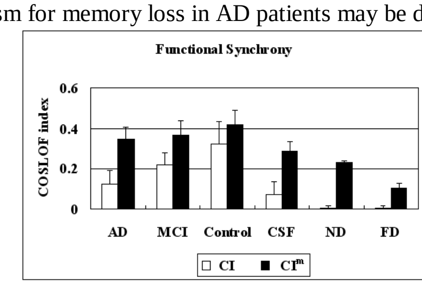

Fig.1 Functional Synchrony Based on CI - CI^m

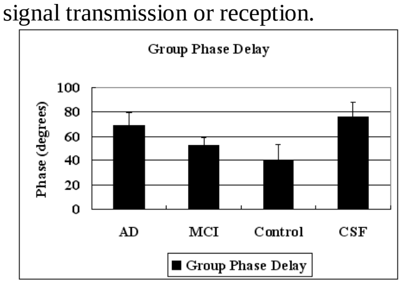

Fig.2 Group Phase Delay

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

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