

Age effects on low frequency physiological fluctuations in resting BOLD fMRI

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Introduction: Studies have shown that low frequency temporal components (<0.1Hz) in resting state BOLD fMRI reflect spontaneous fluctuations of brain physiology and metabolism, which form the basis for the widely adopted “functional connectivity” analysis to characterize the resting state using BOLD fMRI [1]. Studies also found significant linear correlations between activation induced BOLD signal changes and the magnitude of low frequency fluctuations at baseline (<0.1Hz) [2], suggesting a shared mechanism underlying the BOLD contrast and physiological noise in BOLD fMRI. In the present study, we investigated the associations between BOLD activation and low frequency fluctuations at baseline in two groups of young and elderly subjects. Our hypothesis was that the magnitude of low frequency fluctuations in resting BOLD fMRI can be used to study aging effects, in a way similar to BOLD responses to sensorimotor activation.

Methods: All experiments were performed on a Siemens 3T TIM Trio system. Fourteen healthy subjects including 7 young volunteers (age 23.4±1.7 yrs, 4 males) and 7 elderly subjects (age 65.0±3.7 yrs, 3 males) participated in this study after they provided written informed consent. All the participants had no neurological or psychiatric illness. A single-shot dual-echo gradient-echo EPI with interleaved TE was developed to acquire 4 different TE data sets for every 2 consecutive TRs (TE1=20ms and TE2=50ms for one TR, TE3=35ms and TE4=65ms for the following TR). Each subject underwent two experiments within the same scanning sessions using this dual-echo EPI sequence: 1) resting state with eyes closed; and 2) block-design 30s off/on flashing checkerboard visual stimulation. Each scan with 480 acquisitions took 8 min. Ten oblique slices with 5mm thickness and 1mm gap were scanned parallel to the anterior-posterior commissure (AC-PC). Other parameters included: FOV=220mm; matrix=64×64; bandwidth=2442Hz/pixel; TR=1s; flip angle=65°. For each subject, conventional T1 weighted 3D images were acquired using an MPRAGE sequence (TR/TE/TI=1730/ 3.96/ 1100 ms; flip angle=15°; matrix=128×128, voxel size=1.9×1.9×1.9 mm³) for anatomic MRI.

For each subject, image registration was performed to align the resting and activation scans using SPM2. The respiratory and cardiac pulsations were recorded in real time during all experiments, which were removed by retrospective correction (RETROICOR) [3]. In resting state, for each brain pixel, the magnitude of low frequency fluctuations was determined by the standard deviation (SD) of the signal time course in the low frequency band of 0–0.1Hz (normalized by mean intensity). Brain activation data were analyzed using general linear model in SPM2. The Z statistic maps were thresholded at a significance level of $p < 10^{-2}$ with at least 20 contiguous voxels for each TE dataset in each subject. For each subject, the ROI was defined by the pixels demonstrating common activation for all TE data in the visual cortex. The relationships between task-induced BOLD signal changes and low frequency fluctuations were investigated based on mean ROI values across subjects, as well as on a pixel by pixel level in the visual ROI of each individual subject.

Results: In our study, BOLD activation in response to visual stimulation was not significantly different between the two age groups for BOLD signal changes ($p=0.835$) which was consistent with earlier BOLD activation studies [4, 5], as well as the low frequency fluctuations in the resting state ($p=0.449$) for all TEs. However, we found that there were significant linear correlations between the BOLD response and the low frequency fluctuation in both age groups, and the relationship was stronger in the young subjects ($r=0.90$, $p<0.01$) than in the elderly subjects ($r=0.67$, $p<0.01$) based on mean values measured in visual ROI. Fig. 1 a & b show the scatter plots of the mean relative BOLD signal changes and the mean SDs of the low frequency fluctuations in the young and elderly group, respectively. The scatter plot in elderly subjects shows larger variances than that in young subjects. Furthermore, the above results were confirmed by performing correlation analyses between BOLD activation and low frequency fluctuation across activated pixels of visual ROI within each individual subjects for all TEs (mean $r=0.58±0.17$ and $0.43±0.14$ for young and elderly subjects, $p<0.01$). Fig. 2 a & b show the scatter plots of the mean relative BOLD signal changes and the mean SDs of the low frequency fluctuations for activated pixels within individual visual ROI at TE of 35ms from a representative young ($r=0.80$, $p<0.01$) and elderly subject ($r=0.63$, $p<0.01$), respectively. There was stronger linear correlation in the young subject than that in the elderly subject.

Discussion and conclusions: We found stronger correlations between the amplitude of BOLD response and the physiological fluctuation at baseline in young than in aged subjects, whereas the amplitudes of both BOLD hemodynamic response and baseline low frequency fluctuations between young and aged subjects remained similar. While it is arguable that the elderly group may have greater individual variations, the above finding was also replicated using correlation analyses across pixels in individual subjects. Such weaker association in elderly subjects may reflect aging effects on neurovascular coupling although BOLD activation was not different between the two age groups. Our study suggests that low frequency fluctuations at baseline may provide a valid neuroimaging marker of aging and other neuropsychological effects that may complement or even exceed the information obtained in BOLD fMRI studies.

References: [1] Biswal B, et al., *Magn Reson Med* 1995; 34(4): 537-541. [2] Hyde JS, et al., *Magn Reson Med* 2001; 46(1): 114-125. [3] Glover, GH, et al., *Magn Reson Med* 2000; 44(1):162-167. [4] Aizenstein HJ, et al., *J Cogn Neurosci* 2004; 16(5): 786-93. [5] Huettel SA, et al., *Neuroimage* 2001; 13(1): 161-75.

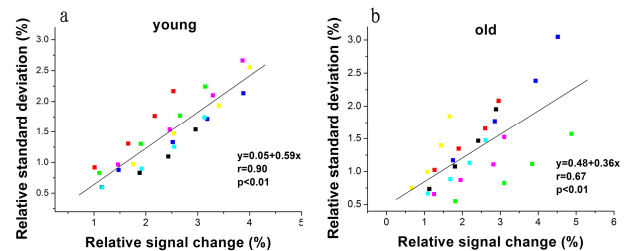


Fig. 1 Scatter plot of physiological noise (<0.1Hz) in rest state vs. relative BOLD signal change in activation in visual ROIs for young (a) and elderly (b) groups. Each color represents one subject.

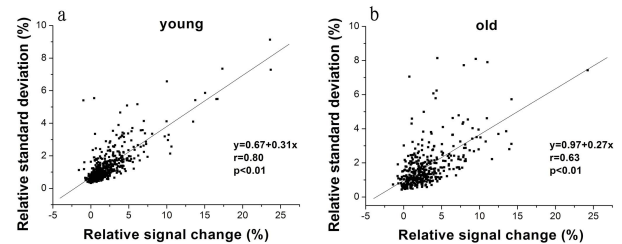


Fig. 2 Scatter plot of physiological noise (<0.1Hz) in rest state vs. relative BOLD signal change in activation across activated pixels within visual ROI of a representative young (a) and elderly subject (b)