Age Effects on the Amplitude and Frequency of Resting-State BOLD Fluctuations

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Introduction

Spontaneous low-frequency fluctuations in the BOLD (blood-oxygen level-dependent) functional MRI (fMRI) signal in the resting-state have been used extensively to investigate neural connectivity in health and disease [1,2]. For the most part, analysis of resting-state data have been predominantly limited to examining the synchronicity between the time courses in multiple brain regions through correlation calculations [3,4]. However, the correlation can be modulated by fundamental signal parameters such as the amplitude (and hence signal-to-noise ratio) of the fluctuations, which in addition to the speed of the BOLD response, have both been found to be dependent on vascular tone [5]. Furthermore, as the BOLD signal is tightly modulated by cerebral blood flow (CBF), which may provide valuable information about cerebrovascular health and tone [6]. In this work, we examine the dependence of the amplitude and frequency of spontaneous BOLD fluctuations on age and resting-state CBF in healthy adults.

Methods

Acquisition: Ninety healthy participants (48 men/42 women, ranging from 22.9 to 91.2 yrs) were imaged using a Siemens Trio 3 T system using 12-channel head coil reception and body-coil transmission. PASL datasets were obtained using FAIR QUIPSS II [7]: matrix=64x64, #slices=24, voxel size=3.4x3.4x5 mm^3, #frames=104, $TI_1/TI_2/TE/TR$ = 600 ms/1600 ms/12 ms/4 s. A 3D anatomical scan (1x1x1 mm^3) was acquired using multi-echo MPRAGE [8], based on which cortical surface models were constructed (*c.f.* FreeSurfer). Resting functional data were acquired using gradient-echo BOLD with matrix=64x64, 33 frames, voxel size=3.4x3.4x4 mm^3), 120 frames, TE/TR = 30 ms/2 s. *Data Processing:* PASL data were motion- and drift-corrected, and the difference images calculated using surround subtraction, compensating for T_1-relaxation during transit delay. These volumes were then averaged across time and datasets to maximize signal-to-noise, following which quantitative CBF maps were obtained as per the Standard Kinetic Model using local tissue-based calibration, assuming proton density and T_2* values [9]. The acquired BOLD signal was band-pass filtered to between 0.01 and 0.08 Hz [10] to reduce the contribution of nuisance parameters, such as cardiac and respiration-related noise, which were further reduced from the BOLD signal of interest by regressing out white-matter, CSF and global mean signals [4]. We applied the Wavelet transform to the resulting BOLD signal, then obtained maps of (1) spectral *energy*, by summing the Wavelet power spectrum, and (2) the average *high-frequency content*, using the Fourier-based method presented in [11]. Both maps and the CBF maps were upsampled and +boundary-registered [12] to the anatomical images, then sampled onto a cortical surface atlas. All statistical tests were performed post surface-smoothing (FWHM=10mm). The CBF analysis employed as a covariate cortical thickness, which may reflect potential signal modulations due to partial-volume effects. Regression of the BOLD spectral parameters against age and CBF was performed as independent general linear models (per-voxel).

Results

BOLD fluctuation energy was found to be highly non-uniform across the cortex (Fig 1a); this pattern was consistent across the age groups. Energy normalized by global mean BOLD amplitude, diminished regionally with advancing age (Fig 1b). The energy was further found to correlate negatively with resting CBF in the medial prefrontal and retrosplenial regions (Fig 1c). The frequency of the fluctuations were also unevenly distributed across the brain, but with a somewhat inverse spatial pattern compared to fluctuation amplitude (Fig 2a). Frequency decreased regionally with advancing age with a different spatial pattern than the effect of age on fluctuation energy (Fig 2b), and positively correlated with CBF in posterior cortex in the right hemisphere (Fig 2c). It is interesting to note the similarities and differences in the spatial distribution and age-related trends in BOLD energy, frequency and CBF (Fig 3).

Conclusion

We present a seed- and correlation-independent method to evaluate associates between resting-state BOLD fluctuations and age by targeting the spectral features of the BOLD time course, building upon regional studies of BOLD amplitude [13]. Interestingly, we found the BOLD fluctuation energy (amplitude) to negatively and very selectively correlate with CBF. This trend is consistent with prior findings regarding the resting CBF-dependence of task-related BOLD amplitude [5], but the dependence was far from being global. Regions with greater BOLD fluctuations also tended towards lower CBF and lower fluctuation frequency. These BOLD parameters are potential indicators of vascular elasticity, and can reveal interesting cerebrovascular changes in aging and disease. In addition, these data suggest common but also differential origins for the decline in BOLD-based fMRI markers in aging. Future work will target the temporal variability [14] of the BOLD frequency response and the implications on connectivity analyses [15].

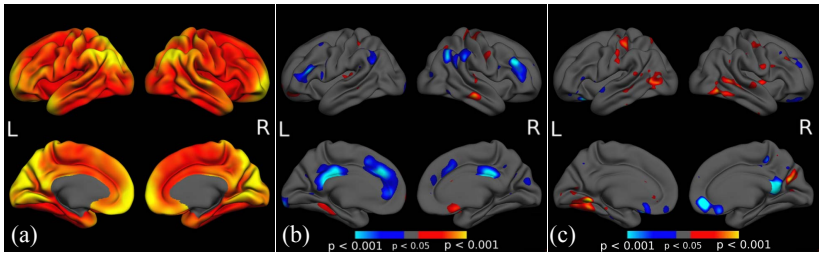

Figure 1. The normalized BOLD fluctuation energy is unevenly distributed across the cortex (a), and decreases with aging (b). It is negatively correlated with CBF in the medial prefrontal and retrosplenial regions (c).

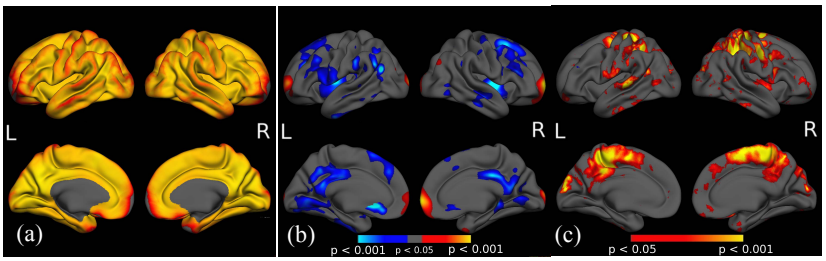

Figure 2. The normalized BOLD fluctuation frequency is also unevenly distributed (a), with gyru associated with lower frequency. High-frequency content also decreases in aging (b), and is positively correlated with CBF(c), the two effects not overlapping.

References

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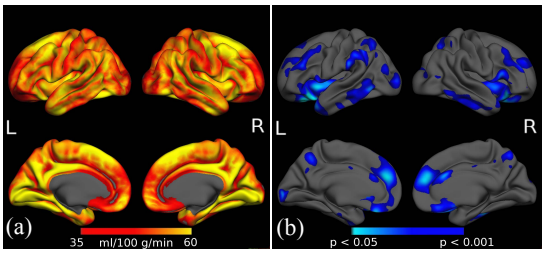

Figure 3. Average CBF (all subjects): regions of high resting CBF (a) tend to exhibit lower fluctuation amplitude (Fig 1a). Also, aging has an impact on CBF distinct from that on the BOLD parameters (Fig 1b&2b).