What you see is not what you get: BOLD signal increases with age in children may be the result of increased neuronal-vascular coupling and not increased neuronal activity

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Introduction

Using task-based fMRI (tb-fMRI), BOLD increases with age during the developmental period (ages 5-18) have been seen in a variety of tasks, including language, motor, and executive function [1-3]. Using intrinsic-connectivity ("resting-state") fMRI (ic-fMRI), increases in inter-regional BOLD correlations with age have also been seen [4]. Typically, these increases are interpreted as increases in neuronal activity or synchronous neuronal activity associated with brain maturation and development of network architecture. However, these interpretations have not been empirically validated. We investigated the etiology of increasing BOLD signal changes with age during the developmental period using an optimized whole-brain simultaneous combined functional ASL-BOLD acquisition [5] without a calibration step necessitating breathing a gas mixture or breath-holding.

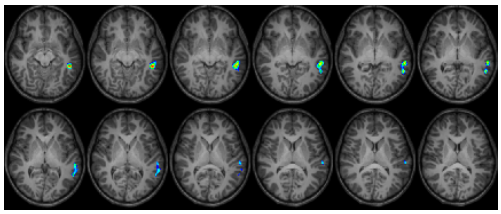

Figure 1. Left STG region with increased BOLD signal with age for 113 children ages 3-18 years performing a narrative comprehension task. Images in radiologic orientation.

Materials and Methods

Data was obtained using a Philips 3T Achieva system and a 32-channel head coil from 113 neurologically normal participants (55M, 58F, ages 3-18 years). Participants performed a narrative comprehension task comprised of 5 different stories designed by a speech-language pathologist to be appropriate for young children. Stories were presented in a 64-second alternating block design. During the control blocks, broadband noise in the frequency range of speech was presented in a gradual sweep across frequencies (500-4000 Hz) in order to control for sublexical auditory stimulation. Total scan time was 10 min. 40 sec. A double-excitation simultaneous ASL/BOLD acquisition was used, determined both theoretically and empirically to be a more optimal approach as compared to double-echo acquisitions or other methods [5]. Acquisition parameters were: TR = 4000 ms, TE1 = 11 ms, TE2 = 35 ms, matrix = 64 X 64, FOV = 25.6 X 25.6 cm, slice thickness = 5 mm, 25 slices acquired covering the whole brain. Parameters for the pseudo-continuous spin labeling (pCASL) were: labeling duration = 1500 ms, post-label delay = 700 ms, mean B1 = 1.0 μT, mean gradient = 1.0 mT/m during tag periods (0 during control), max gradient = 6 mT/m, pulse duration = 500 μs, time between pulses = 1.5 ms.

First-level fMRI data processing was carried out using FEAT, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). ASL timeseries analysis was performed on unsubtracted data [6]. Second-level analysis was performed using routines written in IDL (Exelis, Boulder, CO) using the raw % BOLD and % CBF signal changes. A one-sample T-test was used to find regions with significant activation for BOLD and ASL; subsequent analyses were restricted to the union of those regions. For BOLD, a GLM was performed with age as the variable of interest; and sex and the square root of the number of degrees of freedom in the first-level analysis as covariates of no interest. Post-hoc ROI analyses were conducted on regions found to exhibit increased BOLD signal with age. The average CBF signal change and the average BOLD signal change were computed. Developmental changes in n (neuronal-vascular coupling) and $CMRO_2$ were investigated by modeling $\Delta CMRO_2/CMRO_{20}$ and n as linear functions of age, computing modeled values of CBF and BOLD signal according to the model given in [7], and maximizing a joint likelihood goodness-of-fit function using a downhill simplex algorithm. We used literature values of the calibration constant M ranging from $M = 0.075$ to $M = 0.125$ [8-10].

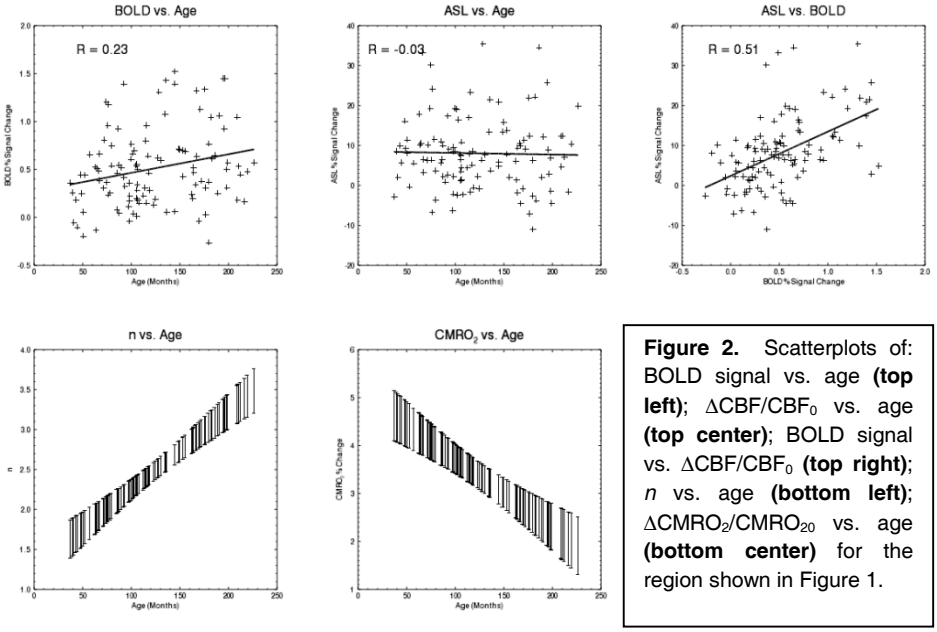

Figure 2. Scatterplots of: BOLD signal vs. age **(top left)**; $\Delta CBF/CBF_0$ vs. age **(top center)**; BOLD signal vs. $\Delta CBF/CBF_0$ **(top right)**; n vs. age **(bottom left)**; $\Delta CMRO_2/CMRO_{20}$ vs. age **(bottom center)** for the region shown in Figure 1.

Results

BOLD increases with age were seen in the left superior temporal gyrus (Figure 1). Post-hoc analyses for this region revealed (Figure 2) a significant correlation of BOLD signal with ASL signal (Spearman's R = 0.51, $p < 1e\text{-}4$); but no significant correlation of age with ASL signal (Spearman's R = -0.03, $p > 0.5$). There was a significant increase of n with age ($p < 0.001$) and a significant *decrease* of relative $\Delta CMRO_2$ with age ($p < 0.01$), irrespective of the particular choice of M used (data plotted for $M = 0.12$).

Discussion

Little is known about how much neuronal-vascular coupling may change during development. If this change is substantial, developmental pediatric fMRI studies will be highly prone to misinterpretation of an increase in BOLD signal as increased neuronal activity, whereas it is in fact the result of strengthened neuronal-vascular coupling. Our results show that in a region (left STG) of the brain exhibiting increases in BOLD signal with age during a narrative comprehension task, these increases are the result of increased neuronal-vascular coupling and not increased neuronal activity; in fact, $CMRO_2$ is actually found to *decrease* with age. The same possibility of misinterpreting changes in BOLD signal is present in ic-fMRI studies, where correlations of spontaneous BOLD signal changes are measured. Increased neuronal-vascular coupling in two brain regions will result in increased apparent functional connectivity between those regions even with similar levels of synchronous neural activity, as typically a correlation coefficient (full or partial) is used as a metric of connection strength.

Conclusion

During a narrative comprehension task increased BOLD signal with age in the left STG was found to be a likely result of increased neuronal-vascular coupling and not increased neuronal activity, with relative $CMRO_2$ actually *decreasing* with age. This finding suggests results of increased BOLD signal in tb-fMRI or increased inter-regional correlations in ic-fMRI developmental studies need to be interpreted with caution.

References

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