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BOLD-fMRI signal increases with age in selected brain regions in children

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Abstract

To determine whether the BOLD signal used in fMRI is age dependent in childhood, 332 healthy children (age 4.9–18.9 years) performed tasks in a periodic block design during 3T fMRI: 1) a verb generation task interleaved with a finger tapping task; 2) a word-picture matching task interleaved with an image discrimination task. Significant correlations between percent signal change in BOLD effect and age occurred in left Broca's, middle frontal, Wernicke's, and inferior parietal regions, and anterior cingulate during the verb generation task; in precentral, postcentral, middle frontal, supplementary motor, and precuneus regions during the finger tapping task; and in bilateral lingula gyri during the word-picture matching task. Thus, BOLD effect increases with age in children during sensorimotor and language tasks.

Keywords

functional magnetic resonance imaging (fMRI); children; brain; development; language

INTRODUCTION

It is hypothesized that there is increasing specialization and more focal localization of brain processing systems associated with the acquisition of particular skills during childhood. By adulthood, those brain processing systems utilized for particular skills are thought to be relatively fixed in specific locations in the brain [1]. This may be due to the establishment of synaptic connections in the cortical mantle during the rapid phase of synaptogenesis in early childhood [2] and, in part, to the selective synaptic stabilization associated with the decrease in synaptic number that occurs in later childhood demonstrated in postmortem studies [3]. The time course of this specialization of brain function during childhood is unclear, and how to measure it with *in vivo* brain imaging is uncertain. However, modern noninvasive MR brain imaging methods may provide a window for such observations for the first time [4].

In a previous BOLD – fMRI study, we showed that increasing activation during a verb generation task correlated with increasing age in childhood in left Broca's area (but not in other brain areas)[5]. This suggested correlations between age and statistical parameters representing

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brain activation in fMRI might be used as markers for changes in hemispheric specialization with age. However, this early study was limited to a small number of subjects, presented only one behavioral task, and used indirect statistical parameters of activation (cross-correlation coefficient and t-statistic).

In the present study we directly examined the correlations between BOLD – fMRI signal changes and age in brain regions activated during motor and language tasks. We studied healthy children from before onset of, and through the end of, puberty by which time it was expected that specialization of brain functions would be near completion. Based on functional and postmortem studies, we hypothesized that the BOLD signal would increase with age in regions known to be associated with the particular behavioral task under study. Further, because synaptogenesis and synaptic deletion in children is regionally heterochronous [6], we hypothesized that the BOLD effect would increase with age in certain (but not all) brain regions.

METHODS

Subjects

We studied 332 healthy children (range 4.9–18.9 years; mean age $\pm$ SD, 11.8 ± 3.7 ; F/M, 163/169; right-handed = 309) who were recruited for a study of language development using fMRI. All subjects were carefully screened and were free of significant brain disease. Structural MRI scans showed no abnormalities.

Written informed consent was obtained from legal guardians; verbal or written assent was obtained from subjects. The study was conducted under an approved protocol by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

MR Procedures

Up to four language tasks were administered to subjects. We report the results of: 1) a silent verb generation task interleaved with an externally cued, bilateral, sequential finger tapping task; 2) a word-picture matching task interleaved with an image discrimination task.

Performance on the verb generation task was evaluated by a *post-hoc* test of recall of the nouns presented during the examination, which measures memory encoding and engagement during the task. During the bilateral finger tapping exercise, all subjects demonstrated compliance as ascertained by frequent visual inspection during each scan. In the word-picture matching task, performance accuracy was measured with the push buttons during task presentation.

The fMRI experiments were performed using a 3 Tesla Bruker Biospec 30/60 MRI scanner. A T2*-weighted, gradient-echo, echo-planar imaging sequence was used to acquire 24 slices across 110 time points during alternating 30-s periods of control and activation tasks (imaging time 5 ½ minutes). The first ten image volumes (30 seconds) were discarded to allow for T1 equilibrium.

Cincinnati Children's Hospital Image Processing Software (CCHIPS) was used for fMRI post processing [7]. The fMRI datasets were spatially normalized into Talairach (stereotaxic) coordinate space. The percent signal change for each subject, on a voxelwise basis, was then calculated from the average signal intensity in the non-transition images acquired during the resting and active blocks [(activation – rest)/rest]. Time series transition points were discarded. Images remaining in the time series after the decimation process were coregistered to the initial image in the series to minimize the effects of head motion [8]. The percent change maps were spatially filtered using a Gaussian filter of width 4 mm. Using a within-subjects voxelwise random-effects analysis, voxels with $|T| > 6$ for significant group activation were retained for further analysis and tested for correlations with subject age. The T-scores from the voxelwise

regression analyses were converted into p-values, and regions with significant correlation of BOLD activation with subject age were determined using a threshold of $p < 0.001$ and a spatial extent threshold of 7 voxels for the verb generation/finger tapping task, and 5 voxels for the word-picture matching task. Using the fit residuals as an estimate for the intrinsic smoothness of the data, the thresholds were empirically determined via Monte Carlo simulation to result in a corrected $p < 0.05/\text{cluster}$. The coordinates of the regions of interest in the Talairach reference frame were used to define regions of interest for each individual subject.

RESULTS

Performance on the word-picture matching task versus age showed some improvement in performance with increasing age ($r^2 = 0.142$, $F = 50.960$, $p < 0.001$). On the other hand, performance on a noun recall test showed no relation with age for the 150 subjects with available data ($r^2 = 0.004$, $F = 0.551$, $p = 0.459$).

Composite activation maps (maps not shown) for the verb generation and finger tapping tasks and for the word-picture matching and image discrimination tasks were constructed for the entire group of children ($N=332$). Significant activation in the composite group was defined as any pixel for which the nominal p-value (two-tailed) for nonzero percent signal change was $p < 1e^{-9}$. For the subjects as a group (independent of age), significant activation occurred in left Broca's and Wernicke's areas and the right hemisphere homologues, anterior cingulate, superior frontal, occipital and left subcortical regions during the **verb generation task**; in the precentral, postcentral, anterior cingulate, middle frontal, medial occipital, precuneus, supplementary motor, and right subcortical regions during the **finger tapping task**; and in bilateral occipital cortex, left Broca's and Wernicke's areas and the right hemisphere homologues, and anterior cingulate for **word-picture matching task**. No significant activation occurred during the image-discrimination task.

A Pearson correlation was next performed on a voxelwise basis between percent signal intensity change for each pixel, for each subject, and the age of each subject. The voxels where the Pearson correlation is significant at $p < 0.001$ are highlighted in color in the age correlation composite map shown in Figures 1 and 2. These maps demonstrate overlap with the group composite activation maps, suggesting that some, though not all, regions that activate in the group on average have a BOLD signal intensity that correlates with the age of the subjects. Significant correlations between percent signal change in BOLD effect and age occurred in left Broca's area (extending dorsolaterally into the middle frontal gyrus), left Wernicke's area, anterior cingulate, and left inferior parietal during the **verb generation task**, and in the precentral, postcentral, middle frontal, supplementary motor, and precuneus regions during the **finger tapping task** (Figure 1). Performance was covaried for the group composite activation map for the **word-matching task**, since there was an improvement in performance with age on this task; significant correlations occurred between BOLD signal intensity and age in left and right lingula gyri (Figure 2). The significantly activated and correlated loci are shown in the Table 1.

Based on the composite activation and the correlation maps, we defined regions of interest for further analysis. As an example, Figure 3 shows a scatter plot of age versus percent signal change for left Broca's area for the verb generation task. In this task, as well as in representative regions in the bilateral finger tapping and word-picture matching tasks, increasing percent signal change was significantly associated with increasing age.

DISCUSSION

An increasing body of knowledge has largely elucidated the physiological underpinnings of the BOLD signal observed with fMRI [9]. However, little is known about impact that developmental changes in cerebral hemodynamics might have on the BOLD signal. Our results showing BOLD signal increases with age point to the importance of understanding developmental influences on the BOLD signal. Interpretation of fMRI brain activation data obtained in children will be subject to these influences and must therefore be corrected and controlled for them.

Brain processing systems for specific skills are known to be localized to specific brain regions in adults. When this **specialization** occurs and how to measure it have remained open questions, however. A few prior studies have examined how brain activation decreases in extent and becomes more localized with age in childhood [1,10,11]. However, these prior studies, in contrast to ours, did not identify changes in **BOLD effect** with age in regions of interest that, in adults, are the primary sites of the particular function under investigation. We now find that the BOLD effect increases from ages 5–19 years during performance of several tasks, with the increases in activation occur in a subset of regions known to be activated during performance of the respective tasks. As these increases in the BOLD effect with age were not global, our results suggest that brain activation as measured by fMRI can be used as a marker of regional specialization of the brain with age and may show when specialization of brain function occurs during development. In a broader context, our findings may be of particular relevance in the study of neurocognitive development during infancy. Recent work has detected lateralization of language functions in the brain during infancy using fMRI [12]. Age dependency of the BOLD effect may warrant further investigation before such studies can be fully understood.

Physiological factors must be considered as an explanation of the age-related change in BOLD signal reported in our study. For example, blood hemoglobin content increases with age in childhood [13]. As a prior study showed a relationship between increasing BOLD signal and increasing hemoglobin [14], hemoglobin increases with age in childhood could hypothetically cause an increase in the BOLD effect with age. Similarly, blood pressure increases and heart rate decreases with age through childhood [15], though the effects of such factors on the BOLD signal have not been investigated. If cerebrovascular changes with age underlie our observation, we might expect a global change in the BOLD effect. We find instead that a subset of regions of the brain known to be associated with the tasks that we used demonstrate a significant correlation of BOLD signal with age, while other regions, although activated above our thresholds, did not correlate with age.

The influence of **performance factors** should be noted. In adults, the BOLD effect increases with performance for a number of tasks, including finger tapping [16] and single word processing [17], in the specific regions of interest associated with those tasks. In our study an in-scanner performance measure was obtained for the word-picture matching task. Though performance improved with age, BOLD signal intensity still increased with age when this improvement in performance was accounted for. The finger tapping task was externally paced by a tone at five second intervals and compliance was monitored. Performance on a *post-hoc* noun recall test, a surrogate measure of performance for the verb generation task, did not show a change in performance with age. Taken together, these observations suggest that the increased BOLD signal with age is less likely to be caused by changes in performance.

The findings that the BOLD effect during behavioral task performance increased from ages 5–19 in some but not all regions during development complement previous studies measuring different aspects of developmental brain changes, including postmortem human synaptic density counts [6], and longitudinal *in vivo* structural MRI [18], diffusion-tensor MRI [19],

and resting PET-¹⁸FDG studies [20]. Limited studies suggest that MRS for NAA also would be an adequate method to elucidate *in vivo* neuronal components of brain development [21, 22]. These studies provide evidence for **heterochronous** brain development in childhood, while our current BOLD fMRI data suggest that we may now have a means of monitoring the emergence of cortical specialization in different regions at different times during brain development.

CONCLUSIONS

In summary, the percent signal change associated with the BOLD effect increases with age in children ages 5 to 19 years during both sensorimotor and language tasks. That these BOLD changes were limited to specific task related regions, rather than being a global effect, is evidence against the age effect being due to physiological factors. That the increases in the BOLD effect occur in some but not all regions suggests a differential maturation of the brain on a regional basis. These changes in the BOLD effect with age may be due to specialization of brain function, differences in task performance/effort, or some combination.

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Figure 1. Talairach composite correlation map for verb generation and finger tapping tasks showing pixels that have a percent signal change in the BOLD effect that correlates with age of the subjects. ($p < 0.001$, yellow/orange = verb generation, blue = finger tapping).

Figure 2. Talairach composite correlation map for the word – picture matching task showing pixels that have a percent signal change in the BOLD effect that correlates with age of the subjects (word – picture matching performance covaried). ($p < 0.001$).

Figure 3. Scatter plot of age versus percent signal change in left Broca's area in children performing a verb generation task. Linear regression lines are superimposed.

Table 1

Loci of peak BOLD activation in brain regions during activation tasks

Activation locus	Brodmann Area	Talairach Coordinates X, Y, Z	R-value
<u>Verb Generation Task</u>			
Left Superior Temporal Gyrus	22	-50, 11, 0	0.28
Left Inferior Frontal Gyrus	44	-46, 7, 25	0.45
Anterior Cingulate Gyrus	24/32	-6, 11, 45	0.35
Left Precuneus	19/7	-30, -61, 40	0.33
<u>Finger Tapping Task</u>			
Right Putamen		22, -5, 5	0.27
Right Postcentral Gyrus	1/2/3	30, -29, 45	0.45
Left Postcentral Gyrus	1/2/3	-46, -21, 50	0.40
Middle Frontal Gyrus	9	6, 47, 25	0.24
Posterior Cingulate Gyrus	31	2, -45, 30	0.29
Supplemental Motor	7	-2, -5, 45	0.30
<u>Word-Picture Matching Task</u>			
Right Fusiform/ Inferior Temporal Gyrus	37	38, -57, -5	0.30
Left Lingual/Fusiform Gyrus	18/19	-26, -77, -5	0.30
Right Medial Occipital Gyrus	18/19	30, -85, 10	0.22