A longitudinal MR functional connectivity study in pediatric subjects from 2wks to 2yrs old using low-frequency BOLD synchronization

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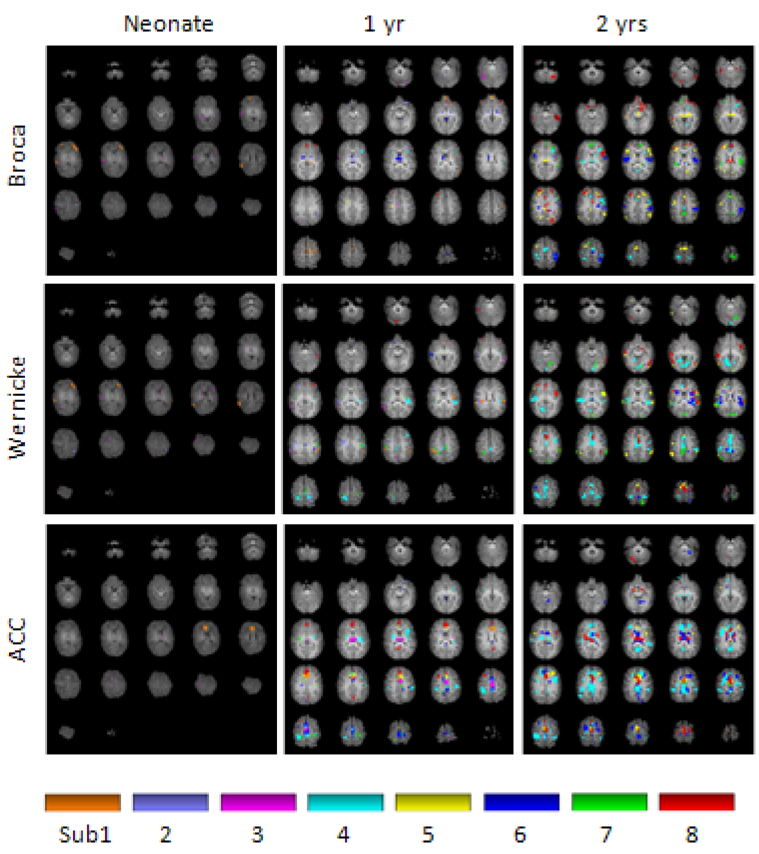
INTRODUCTION

Although fMRI has been widely employed for the study of how the brain works, it is not applicable for the study of brain functional development in the pediatric population, particularly in young children (0-2yrs). This is due to the fact that fMRI requires subjects to follow specific instructions in order to reveal regions of brain activation in response to the specific sensory/cognitive inputs. Recently, Biswal et al have observed the synchronization of low frequency blood oxygen level dependent (BOLD) signal in the brain (1). With rapid acquisition of a time series of T_2*-weighted images while subjects lie resting inside the MR scanner and the use of a low pass filter (cutoff frequency ~0.08Hz), the resulting signal in a specific cortical region exhibits a high temporal correlation with other brain regions which are functionally similar. With this approach, we have previously demonstrated that functional connectivity exists in children as early as 2wks old and results are highly age-dependent. However, the previous study was a cross-sectional study and focused on functional connectivity in the primary motor, somatosensory and visual cortices (2). In this work, we report results on a longitudinal study where BOLD synchronization was employed to explore the development of cortical connectivity in the Broca's and Wernicke's areas and Anterior Cingulate cortex (ACC) in pediatric subjects from 2wks to 2 yrs old.

MATERIALS AND METHODS

All images were acquired on a 3T head-only MR scanner (Allegra, Siemens Medical Systems Incs). A total of 8 children were recruited where 3 subjects were scanned at both 2-4 weeks and one year old, and 5 subjects were scanned at one and two years old. Informed consent was obtained from the parents prior to imaging. All of the subjects were imaged during sleep (no sedation was employed). A T_2*-weighted EPI sequence was used to acquired images every 2 seconds for 5 minutes. In addition, 3D MP-RAGE images were also acquired and used for co-registration among subjects and defining ROIs. The pre-processing of the experimentally acquired data included a 3D spatial Gaussian low-pass filter to improve SNR, correcting time shift between different slice locations, motion correction, temporal band-pass filtering of the experimental data (frequency range: 0.01- 0.08 Hz), and rigid body registration between the MR-RAGE and the T_2*-weighted images of each subject. In addition, the MP-RAGE images from one of the subjects of each age group were chosen as the template and the MP-RAGE images of the remaining subjects in the same age group were co-registered onto the template so as to allow group analysis. After the preprocessing, a board certified neuroradiologist manually drew 3 ROIs located in the Broca's and Wernicke's areas and ACC, respectively, for each subject. Cross correlation was then conducted throughout the entire brain using each voxel in each ROI as the reference signal. The cross correlation coefficients were converted to z-scores with a normal distribution using the approaches proposed by Lowe et al (3). Representative Z map for each ROI was finally obtained using a robust median operation. Pixels with a z-score > 1 were considered as the activated voxels.



RESULTS

Figure 1 shows the functional connectivity overlays in Broca's (up row) and Wernicke's (middle row) areas, and ACC (bottom row) for neonate (1st column), one year (2nd column) and two year olds (3rd column). Individual subjects are represented by different colors. It is evident that the "putative" cortical connectivity is age-dependent. The number of "activated" voxels increases as a function of age although it appears to be non-linearly dependent on the age. Specifically, a marked increase of activated voxels is observed in the Broca's and Wernicke's areas from 1yr to 2 yrs old while a major increase is observed from 2wks to 1yr old in the ACC area. In addition, the ACC area appears to have more activations when compared with those in the Broca's and Wernicke's areas at 1yr old, suggesting that the development of attention may pre-date the development of language. Moreover, it appears that there are some overlaps between the results obtained using ROIs defined in the Broca's and Wernicke's areas, respectively. In other words, when the signal in the Broca's area was used as the reference function for correlation analysis, high temporal correlation is observed in the Wernicke's area and vice versa, suggesting functional connections between the Broca's and Wernicke's areas. This finding is not surprising since the Broca's area is connected to the Wernicke's area by the arcuate fasciculus and these two areas are known to involve in the understanding and comprehension of spoken language.

DISCUSSION

It has been demonstrated that it is feasible to investigate brain functional connectivity using BOLD synchronization in pediatric subjects without sedation, even in very young ages. Our results suggest that the application of this technique could potentially improve our understanding of brain functional development.

1. Biswal BB, et al. NMR Biomed 1997;10:165-70.
2. Lin W, et al. ISMRM 2007, 392.
3. Lowe MJ, et al. Neuroimage 2000;12: 582-7