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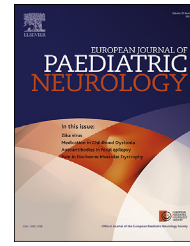

Original article

Resting state cerebral blood flow with arterial spin labeling MRI in developing human brains

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ABSTRACT

The development of brain circuits is coupled with changes in neurovascular coupling, which refers to the close relationship between neural activity and cerebral blood flow (CBF). Studying the characteristics of CBF during resting state in developing brain can be a complementary way to understand the functional connectivity of the developing brain. Arterial spin labeling (ASL), as a noninvasive MR technique, is particularly attractive for studying cerebral perfusion in children and even newborns. We have collected pulsed ASL data in resting state for 47 healthy subjects from young children to adolescence (aged from 6 to 20 years old). In addition to studying the developmental change of static CBF maps during resting state, we also analyzed the CBF time series to reveal the dynamic characteristics of CBF in differing age groups. We used the seed-based correlation analysis to examine the temporal relationship of CBF time series between the selected ROIs and other brain regions. We have shown the developmental patterns in both static CBF maps and dynamic characteristics of CBF. While higher CBF of default mode network (DMN) in all age groups supports that DMN is the prominent active network during the resting state, the CBF connectivity patterns of some typical resting state networks show distinct patterns of metabolic activity during the resting state in the developing brains.

1. Introduction

Brain maturation (both structural and functional) continues through childhood and adolescence into early adulthood. The development of brain circuits is coupled with changes in neurovascular coupling,[1] which refers to the close relationship between neural activity and cerebral blood flow (CBF).[2] Regional neural activity produces an increase of regional blood flow to meet its energy needs. Thus cerebral metabolism

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and the regional functional activity are highly correlated to CBF, i.e., cerebral perfusion. Therefore, cerebral perfusion can be used as an indirect measure of the energy demand in the brain.[3] Characterization of the regional change in cerebral metabolism during brain development is very important because it enhances our understanding of structure–function relationships in normal and diseased brains. Since cerebral perfusion reflects cerebral metabolic demand, it is important to study the trajectory of cerebral perfusion in the developing brain.

Studies have shown that regional CBF (rCBF) is closely coupled with glucose utilization, oxygen consumption, and aerobic glycolysis in resting brains.[4,5] Using positron-emission tomography (PET) imaging, changes in rCBF have been shown to be proportional to changes in regional glucose metabolism due to task activation.[6] Furthermore, the changes of regional metabolism and regional CBF throughout childhood have been measured with PET, single-photon emission computed tomography (SPECT), or perfusion computed tomography (CT).[7–9] However, CT and nuclear medicine techniques are expensive and require injection of radioactive tracers or contrast agents, which are costly, uncomfortable, and potentially harmful. As a result, these methods are not ideal for studying brain perfusion in healthy children. Though the period from birth to adolescence is the most important in brain development, pediatric CBF data are still sparse due to a lack of consensus on the technique of choice for measuring CBF and limited availability of CBF techniques.

Arterial spin labeling (ASL) is a noninvasive MR technique that has been developed to evaluate cerebral perfusion.[10] ASL has been extensively validated against the nuclear medicine methods (PET and SPECT) and other MRI perfusion technique, namely dynamic susceptibility contrast MRI (DSC-MRI).[11,12] In ASL, arterial water is used as an endogenous tracer. To distinguish static tissue water in the brain from the flowing arterial water, the water spins in the blood are inverted prior to arrival in an area proximal to the region of interest. Because ASL does not require intravenous injection of radioactive tracers or contrast agents, it can be repeated safely over time. Therefore, ASL is particularly attractive for studying cerebral perfusion in children, even newborns and infants. Since CBF maps at different ages can be used to evaluate the trajectory of brain perfusion in the developing brain, ASL MRI has been used as a biomarker for functional brain development. Several studies have investigated developmental changes of brain perfusion using ASL at 1.5 T and 3 T.[13–16] Nevertheless, these studies only focused on the developmental changes of static CBF, not the dynamic characteristics of CBF.

Historically, based on how the labeling is done, ASL techniques have been classified as continuous ASL (CASL) and pulsed ASL (PASL) before the recent developments of pseudo-continuous ASL (pCASL) and velocity selective ASL (VSASL). Until recently, PASL has been more widely used than CASL because of its easier implementation. Though CASL has higher signal-to-noise ratio (SNR) than PASL, CASL requires a long radio frequency (RF) labeling pulse (typically ~2s), which is taxing on the hardware. Therefore, CASL is not widely implemented on many commercial MR scanners. On the contrary, PASL uses short RF labeling pulse (usually 10–15 ms) and can be implemented easily on commercial MR scanners.[17] Nevertheless, a notable advantage of PASL methods in investigations of brain perfusion in infants and young kids is the reduced risk of excessive RF power deposition from the labeling pulse, since the duty cycle of this pulse over repetition time (TR) is very low.[16] In our study, we chose a multi-slice PASL method to collect CBF time courses in resting state from healthy subjects at differing ages.

The advantage of collecting baseline CBF images is that the time-series can be used to investigate the functional connectivity of brain perfusion. Resting state fMRI is becoming more popular in studying the development of functional brain connectivity. Resting state fMRI provides a method without the use of external tasks, which is more convenient than performing task activation fMRI in infants and younger children. Resting state ASL is both complementary and advantageous to blood-oxygen-level dependent (BOLD) fMRI resting state alone. Compared to the complexity of the BOLD signal, the ASL signal follows the time course of a single physiological parameter (CBF). Most relevantly, ASL is not dependent on baseline changes, and therefore is less affected by scanner drifts.[18] Consequently, ASL can detect changes in the very low frequency range, which is not achievable with BOLD fMRI. Regional CBF can be used as a reasonable surrogate of metabolism in resting states. BOLD fMRI data and ASL perfusion contrasts have been used to investigate the relationship between functional connectivity strength (FCS) and rCBF during resting and task states in adult brains.[19,20] These studies have evaluated the correlations between resting BOLD fMRI and CBF. They have suggested that resting BOLD fMRI measures are coupled with regional CBF, which reflects the underlying spontaneous brain activity.

Since analysis of CBF time series can reveal the characteristics of the development of functional connectivity, we used the seed-based correlation analysis to examine the temporal relationship of CBF between the selected ROIs and other brain regions in the subjects aged from 6 years old to 20 years old. In this study, we explore the feasibility that with the use of noninvasive ASL technique, the dynamic characteristics of CBF in developing brain can be used as a complementary way to understand the functional connectivity of the developing brain, in addition to the developmental changes of static rCBF.

2. Materials and Methods

2.1. MRI acquisition

MRI data used in this study were extracted from MRI data pool of healthy controls from several studies done on the same scanner. All MRI scans were approved by the local IRB, and informed consent was obtained from parents for subjects under the age of 18 and from subjects older than 18. During the resting state ASL scans, all subjects were instructed to stay awake and keep eyes close. We have collected ASL data for 47 healthy subjects: 6-8 year-old (N = 8, 3 males, 7.6 ± 0.6 years), 9-11 year-old (N = 9, 4 males, 10.7 ± 0.9 years), 12-14 year-old (N = 10, 4 males, 12.8 ± 0.8 years), 15-17 year-old (N = 10, 5 males, 16.1 ± 0.8 years), and 18-20 year-old (N = 10, 5 males, 19.0 ± 0.5 years). All scans were performed on a GE Signa 3T