NeuroImage 155 (2017) 322–330

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Age-related functional brain changes in young children

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ARTICLE INFO

Keywords:
Preschool
Brain development
fMRI
Local activity
Global connectivity
Age
Regional homogeneity
Amplitude of low frequency fluctuations
Default mode network
Frontoparietal network

ABSTRACT

Brain function and structure change significantly during the toddler and preschool years. However, most studies focus on older or younger children, so the specific nature of these changes is unclear. In the present study, we analyzed 77 functional magnetic resonance imaging datasets from 44 children aged 2–6 years. We extracted measures of both local (amplitude of low frequency fluctuation and regional homogeneity) and global (eigenvector centrality mapping) activity and connectivity, and examined their relationships with age using robust linear correlation analysis and strict control for head motion. Brain areas within the default mode network and the frontoparietal network, such as the middle frontal gyrus, the inferior parietal lobule and the posterior cingulate cortex, showed increases in local and global functional features with age. Several brain areas such as the superior parietal lobule and superior temporal gyrus presented opposite development trajectories of local and global functional features, suggesting a shifting connectivity framework in early childhood. This development of functional connectivity in early childhood likely underlies major advances in cognitive abilities, including language and development of theory of mind. These findings provide important insight into the development patterns of brain function during the preschool years, and lay the foundation for future studies of altered brain development in young children with brain disorders or injury.

Introduction

Early childhood is a period during which there is significant development in cognitive functions, behavior, social abilities, and emotional maturity. Many neurodevelopmental disorders are first recognized and diagnosed during this time, and investigation of human brain development can provide insight into changes in cognitive functions, behavior, and emotional development (Brown and Jernigan, 2012). Neurodevelopmental disorders are associated with functional and structural brain alterations in preschool children (Dinstein et al., 2011; Mahone et al., 2011). Developing a better understanding of typical functional brain maturation during this time is critical to fully understanding functional brain changes across the human lifespan (Zuo et al., 2017), and could inform early treatment and intervention approaches for brain disorders.

Magnetic resonance imaging (MRI) techniques have allowed us to develop a better understanding of typical functional and structural brain changes from late childhood to adulthood (Fjell et al., 2009; Lebel et al., 2008; Lebel and Beaulieu, 2011). Throughout early life, the brain undergoes structural changes; white matter volume, cortical thickness and myelination increase with age (Brain Development Cooperative Group, 2012; Brown and Jernigan, 2012; Deoni et al., 2011), and likely underlie changes in functional brain network development. Changes in the ratio of blood–oxygen-level-dependent (BOLD) signal to cerebral blood flow that represent neurovascular coupling in early childhood (Schmithorst et al., 2015) are likely related to brain changes observed in fMRI. Previous studies have shown that brain functional networks, such as the default mode network (DMN), follow a local-to-global pattern of development: younger children show a more focused, regional pattern of connections than adults who have a larger, more distributed network of connections, and this might be due to synaptic growth and myelination during the early years (Fair et al., 2009, 2008; Lebel et al., 2008; Power et al., 2010; Sowell et al., 2002; Supekar et al., 2010; Uddin, 2010; Vogel et al., 2010). Key functional networks associated with language-related brain areas are evident in infants, and show significant maturation during the first two years of life (Cao et al., 2016; Fransson et al., 2007; Gao, 2009; Gao et al., 2016, 2015; Lin et al., 2008; Manning et al., 2013; Smyser et al., 2010). However, functional brain development in the preschool period (~2–6 years) is very understudied due to the practical difficulties associated

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http://dx.doi.org/10.1016/j.neuroimage.2017.04.059
Received 2 November 2016; Accepted 25 April 2017
Available online 28 April 2017
1053-8119/

with MRI scanning in this population. A few studies have used language perception tasks during sleep or waking to investigate brain function in preschoolers (Hutton et al., 2015; Redcay et al., 2008), and one used resting state functional MRI (rs-fMRI) to look at longitudinal development of the language networks from 5–6 years (Xiao et al., 2015). However, the trajectories of healthy brain development associated with rs-fMRI measures during preschool remain poorly understood. Improving our understanding of functional brain development is critical for improving early identification of neurodevelopmental disorders during this period.

In the present study, we examine the development of brain function in young children aged 2–6 years using passive viewing fMRI, which is similar to rs-fMRI. To our knowledge, this is the youngest awake population studied with fMRI. We used data-driven approaches that measure the local activity and global connectivity of brain function, including fractional and whole amplitude of low frequency fluctuations (ALFF/fALFF) (Yu-Feng et al., 2007a; Zou et al., 2008), regional homogeneity (ReHo) (Zang et al., 2004), and eigenvector centrality mapping (ECM) (Lohmann et al., 2010; Zuo et al., 2012). The test-retest reliability of these metrics is high, and accuracy and reproducibility are improved with strict head motion control, and the use of z-scores (Yan et al., 2013; Zuo et al., 2013, 2012, 2010a; Zuo and Xing, 2014). These approaches provide valuable information to assist us in understanding brain function, and have been widely used in studies of children with developmental disorders, such as attention deficit hyperactivity disorder (ADHD) (Cao et al., 2006; Yu-Feng et al., 2007b; Zhu et al., 2008), epilepsy (Mankinena et al., 2011) and autism spectrum disorder (ASD) (Di Martino et al., 2013; Paakki et al., 2010). Previous studies have also shown that these metrics change with age in older children and adults (Biswal et al., 2009; Lopez-Larson et al., 2011; Zuo et al., 2012). Our primary aim was to characterize relationships between age and fMRI metrics in preschool children, ultimately to provide information on typical functional brain development in this young population. Considering the potential for severe head motion of preschool children during scanning, several sophisticated motion correction and exclusion criteria based on previous studies were employed in the current study.

Materials and methods

Participants

A total of 63 healthy children were recruited from Calgary to participate in this imaging study. Children were invited to return for subsequent scans approximately every six months, and provided a total of 152 fMRI datasets. Scans with either excessive head motion (see Head motion regression), or during which children fell asleep were excluded, and a total of 77 datasets from 44 healthy children were included in the present study. These 44 children were aged 2.5–5.8 (3.98 ± 0.72) years at their first scan, and included 17 females and 27 males, with 3/36/5 left-handed/right-handed/undetermined handedness. Most (n=37) were Caucasian, with the other 7 being of mixed race. 23 children successfully completed one scan, 14 children completed two scans, 3 children completed three scans, 3 children had four scans, and 1 child completed five scans. The average age across all 77 scans was 4.33 ± 0.78 years; average time between scans was 0.8 ± 0.4 years. Fig. 1a shows the age distribution of subjects included in the present study; across all scans, age was normally distributed. All participants were free of diagnosed developmental disorders. Informed consent from a parent was obtained before scanning. The study was approved by the conjoint health research ethics board at the University of Calgary.

MRI parameters

All neuroimaging data were collected at the Alberta Children's Hospital using a GE 3T MR750w (General Electric, Waukesha, WI) equipped with a 32-channel head-coil. Children were awake and watching self-selected movies during the whole MRI scan session. T1-weighted images were acquired with an FSPGR BRAVO sequence, flip angle=12°, 210 slices, TR=8.23 ms, TE=3.76 ms, voxel size=0.9×0.9×0.9 mm^3, matrix size=512×512, inversion time=540 ms. Passive viewing fMRI data were acquired with a gradient-echo echo-planar imaging (EPI) sequence, TR=2 s, TE=30 ms, flip angle=60°, 36 slices, voxel size=3.59×3.59×3.6 mm, matrix size=64×64, 250 volumes.

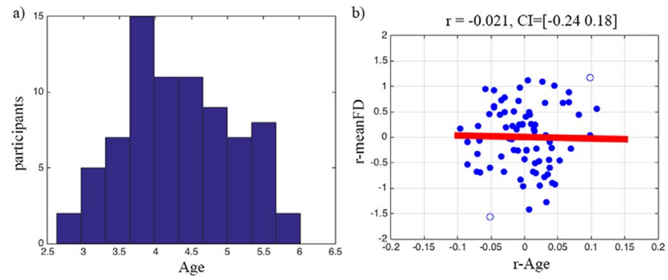

Fig. 1. Age was normally distributed in the current dataset (a), and not significantly correlated with head motion (b). This shows the result of correlation analysis between mean FD and age, controlling for sex, handedness and longitudinal information. The bold red line is the best-fit line. The blue points are the dataset and the hollow blue points were the outliers. CI is the confidence interval of the bootstrap tests.

Data preprocessing and processing

Data preprocessing

For each participant, the T1 image was skull stripped and segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) structures to create individual masks. T1 images were registered to a pediatric brain template (ages 33–47 months) in Montreal Neurological Institute (MNI) standard space (Fonov et al., 2011). The first 10 volumes of the rs-fMRI data were removed to allow for MR signal stabilization. The data were pre-processed using slice timing correction, head motion correction, co-registration to T1 image, and linear de-trending. The relative root-mean-square frame-wise displacement (FD) and its mean were calculated (Jenkinson et al., 2002). Then the pre-processed fMRI signals were put into the head motion regression analysis.

Head motion regression

Head motion regression was performed according to established methods (Ciric et al., 2016; Power et al., 2014; Satterthwaite et al., 2013). For each dataset, spike volumes were identified by high relative FD (> 0.25 mm) and a spike volumes matrix was created. A 36 parameter model was created from the averaged signals from the individual whole brain, CSF mask, WM mask, the 6 head motion parameters, their temporal derivatives and quadratic term signals. Then the 36 parameters combined with the spike matrix were regressed out of the pre-processed fMRI signals. Datasets with high mean FD (> 0.25 mm) or spike volumes long enough to make the signals shorter than 5 min were excluded. Finally, the processed fMRI signals were band-pass filtered (0.009–0.08 Hz) and transformed to MNI standard space (Satterthwaite et al., 2013) using a pediatric template (Fonov et al., 2011). Head motion (mean FD) was not significantly correlated with age (Fig. 1b). Slice timing, head motion correction, regression of the nuisance signals, linear trend removal and band-pass filtering were done using AFNI version AFNI_16.2.12 (Cox, 1996). T1 image segmentation, head motion outlier detection, co-registration, and spatial normalization were done in FSL (Jenkinson et al., 2012).

Correlation between functional metrics and age

Data analysis procedures are shown in Fig. 2. A consensus whole