Title: Age-related functional brain changes in young children

A brief running title: Functional brain development in young children

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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.

Key words: preschool, brain development, fMRI, local activity, global connectivity, age, regional homogeneity, amplitude of low frequency fluctuations, default mode network, frontoparietal network

1. 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 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 to 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.

2. Materials & Methods:

2.1 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 2.3.2 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.

2.2 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 = 12º, 210 slices, TR = 8.23 ms, TE = 3.76 ms, voxel size = 0.9 × 0.9 × 0.9 mm, 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 = 60º, 36 slices, voxel size = 3.59 × 3.59 × 3.6 mm, matrix size = 64 × 64, 250 volumes.

2.3 Data preprocessing and processing

2.3.1 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.

2.3.2 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 minutes were excluded. Finally, the processed fMRI signals were band-pass filtered (0.009 to 0.08Hz) 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).

2.3.3 Correlation between functional metrics and age

Data analysis procedures are shown in Figure 2. A consensus whole brain mask was created across all participants. Then ReHo, fALFF, ALFF were calculated for each voxel within this mask using the REST toolbox (Song et al., 2011; Yan et al., 2013; Zuo et al., 2013) and the EC of each voxel was calculated by the fastECM toolbox (Wink et al., 2012). The REST, fast ECM and BrainNet Viewer toolboxes are MATLAB-based (The MathWorks, Inc., Natick, Massachusetts, United States). All functional metric maps were converted to z-maps by subtracting the global mean and dividing by the standard deviation within the whole brain mask (Zuo et al., 2012). This standardized step is now a widely used procedure in analysis of these functional metrics. It can increase the comparability and reliability of such whole brain voxel-wise metrics across participants and does not affect the topography of centrality measures (Buckner et al., 2009; Zuo et al., 2010b). All z-maps were spatially smoothed with a 4mm full width at half maximum (FWHM) kernel in FSL. A GM mask (included 21292 voxels) was created with the combination of the consensus whole brain mask and the GM structures of the pediatric T1 image template and applied to all functional metrics z-maps for the further analysis.

Before linear correlation analysis, a constant column, sex, handedness, mean FD, and longitudinal information were combined to form a covariates matrix. The longitudinal information is a binary 77 by 21 matrix with one column for each participant with longitudinal data. In each column, multiple scans for the same individual are indicated with a 1 and all other scans have a 0. This allows the shared variance across multiple scans to be statistically accounted for. This matrix was regressed out of both age and the functional metrics across the populations before linear correlation analysis. A robust correlation paradigm was implemented to test relationships between functional metrics (i.e., ALFF, fALFF, ReHo and EC maps) and age (Cyril R. Pernet, 2013). This correlation paradigm includes bootstrapping analysis (600 ~ 1000 permutations of the dataset for each voxel), a test for variance homogeneity (Wilcox and Muska, 2001), and outlier detection, followed by selecting the most appropriate correlation method (Rousseeuw, 1984; Rousseeuw and van Driessen, 1999; Verboven and Hubert, 2005; Wilcox, 2004, 1994). For each voxel within the GM mask, the robust correlation paradigm was performed between each functional metric (separately) and age across all datasets (Fig. 2). Results were determined to be statistically significant ($p<0.05$) based on the confidence interval from the bootstrapping analysis as indicated in Fig 3.

To further verify the results of the development changes, the 21 participants who had longitudinal data were tested for between-scan differences in each functional metric using a paired t-statistic model with sex and handedness as covariates. For participants who had more than two visits, a best-fit linear regression line was generated across all their scans and the values on the best-fit line at the individual's youngest and oldest ages were extracted for the paired t-tests (Lebel and Beaulieu, 2011). Based on the effect sizes observed in the first GLM analysis (r^2=0.12-0.13), we had 85-89% power to detect effects in the longitudinal paired t-test analysis. Only voxels that met the same criteria (increase or decrease with age) for both analyses (i.e., GLM across all data at permutation-test $p < 0.05$, plus un-thresholded paired t-tests for longitudinal data) were retained and considered to have significant age-related changes. Finally, the combination map for each functional metric was corrected for multiple comparisons to $p<0.05$ (voxel-wise $p<0.05$, cluster size > 2619 mm^3) by 3dClustSim (Fig. 1) with the averaged estimated smoothing parameters by 3dFWHMx in AFNI (version: AFNI_16.2.12, Cox 1996). The aim of the cluster-level correction was removal of small regions in the statistical maps likely to be spurious findings. Therefore, the final clusters reported survived both the permutation test during correlation, and the cluster-level correction to remove small spurious findings. All results are displayed by BrainNet Viewer (M. Xia et al., 2013). For each scatter plot, the region of interest (ROI) on the conjunction map was selected and the robust correlation analysis was performed.

To assess overlap of the results, conjunction maps were created across the corrected maps. From selected ROIs, functional metrics were extracted and averaged across participants of the same age (in 1-year bins) to examine changes across the age range.

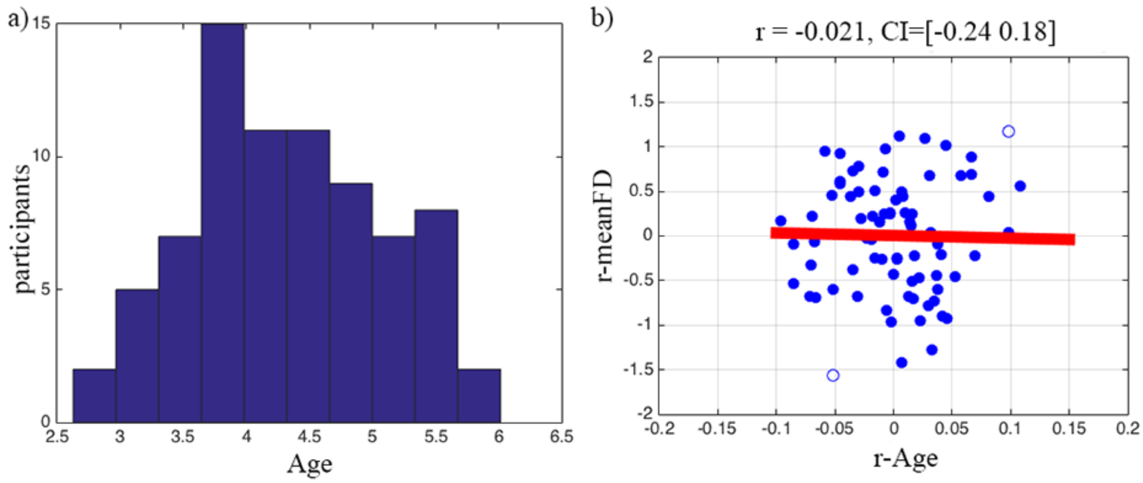

Figure 1. Age was normally distributed in the current dataset (a), and not significantly correlated with head motion (b). This shows the result of correlation analysis between mean FD and age, controlling for sex, handedness and longitudinal information. The bold red line is the best-fit line. The blue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

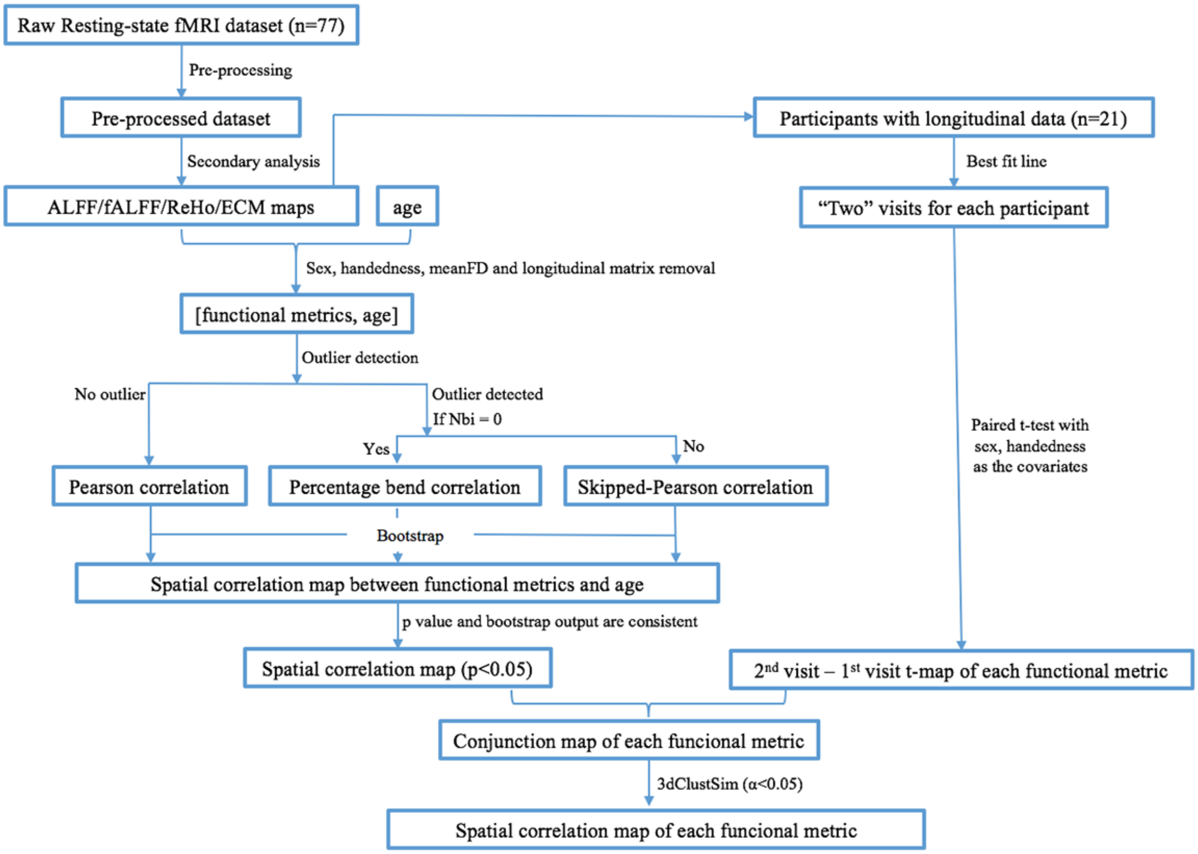

Figure 2: Data analysis procedures. Two parallel analyses were run after pre-processing the rs-fMRI data and calculating the functional metrics (ALFF/fALFF/ReHo/ECM). All subjects' data were combined and run through a robust correlation with age, using outlier detection and the most appropriate correlation technique. Additionally, data from participants with multiple scans were run through paired t-tests. Voxels that met significance thresholds ($p<0.05$) for both analyses were retained and deemed to have age-related changes. Nuni= number of univariate outliers, Nbi = number of bivariate outliers.

3. Results:

3.1 Outlier detection

In the robust correlation analysis, the dataset at each voxel was examined for outliers and homogeneity of variance. Table 2 shows the results of outlier detection and heteroscedasticity for each metric in the robust correlation analysis. Most data were heteroscedastic, and thus analyzed using Spearman correlations.

Table 2: The average percentage of voxels for each metric identified as outliers, and identified as having heterogeneous variance across participants.

Metrics	Outliers (%)	Heteroscedasticity (%)
ALFF	12.13	87.15
fALFF	12.30	62.00
ReHo	11.92	60.37
ECM	11.09	30.02

3.2 Age-related changes in functional metrics

For ALFF analysis, significant positive correlations with age were found in the left middle frontal lobe, bilateral inferior parietal lobe and bilateral precuneus; negative correlations were found in the right middle temporal lobe, right sensorimotor cortex, and bilateral medial temporal regions (Fig. 3). Only a small area of the right superior parietal lobe had significant correlations between fALFF and age (see Inline Supplementary Fig.1).

ReHo was positively correlated with age in the left middle frontal gyrus, left parietal lobe, left precuneus, bilateral middle cingulate cortex and bilateral dorsolateral frontal areas; negative correlations were found in the left middle temporal lobe and medial prefrontal cortex (Fig. 3). EC had significant positive correlations with age in bilateral temporal-parietal areas, bilateral cingulate cortex, right prefrontal cortex, and the right superior temporal gyrus; negative correlations were found in the bilateral superior partietal lobules and inferior temporal gyrus (Fig. 3).

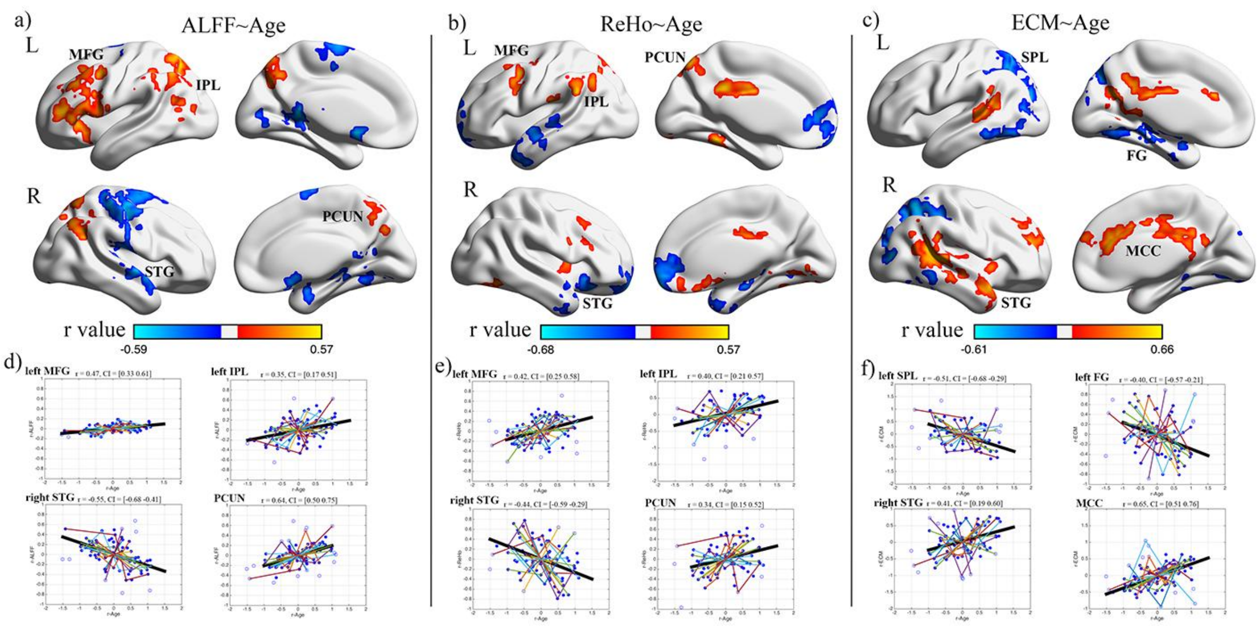

Figure 3, Age was significantly correlated with functional metrics in multiple brain regions, as shown here for a) ALFF, b) ReHo and c) ECM. Warm colors indicate positive correlations and cold colors indicate negative correlations. For key brain regions (d, e, f), scatter plots depict individual values and trend lines (black); multiple scans from the same individual are connected with lines. CI means confidence interval of the bootstrap tests. The prefix “r-” of the x and y axis means the values were residual after the covariates regression. The hollow blue circles are the identified outliers. Abbreviations: MFG: medial frontal gyrus, IPL: inferior parietal lobule, PCUN: precuneus, STG: superior temporal gyrus, MCC: middle cingulate cortex, FG: fusiform gyrus, SPL: superior parietal lobule.

3.3 Overlap of results

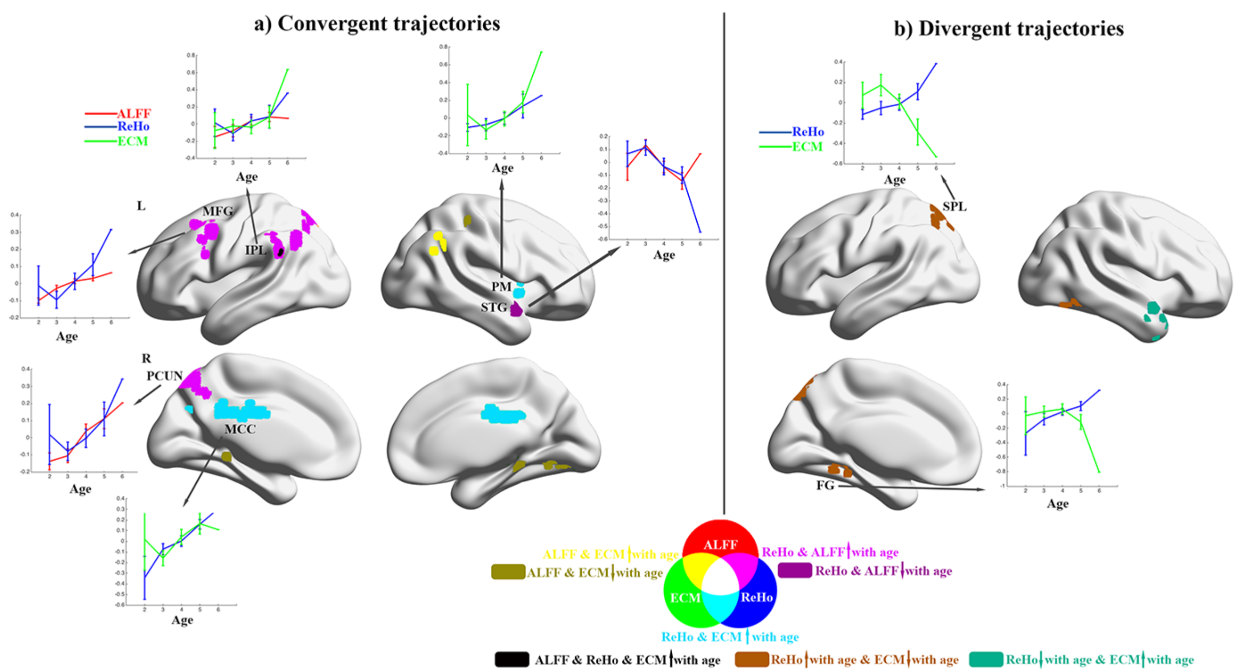

Figure 4, Conjunction maps between ALFF, ReHo and ECM. (a) shows convervent trajectories where local and global metrics both increased or decreased; b) shows divergent trajectories where local and global measures had opposite trends. Development trajectories of ALFF (red line), ReHo (blue line) and EC (green line) are shown for selected representative regions. The functional metrics were averaged across participants of the same age after correction for the covariates (i.e., sex, handedness, mean FD and longitudinal matrix); error bars indicate standard error. Only one dataset was acquired older than 6 years, so the 6-year value does not have an error bar. PM: putamen.

A conjunction analysis was performed across ALFF, ReHo and ECM results to identify regions where multiple metrics correlated with age (Fig. 4). Frontal, parietal, superior temporal, and cingulate areas showed convergent trajectories. Both local activity and connectivity (i.e., ALFF and ReHo) of the left MFG, left IPL and precuneus increased with age, while these measures in the right STG decreased with age. Both local activity and global connectivity were positively correlated with age in the bilateral IPL and PCUN, and negatively correlated with age in the left FG. Both local and global connectivity was positively correlated with age in the left IPL, MCC and right PM.

Three areas showed divergent trajectories. In the superior parietal lobe and fusiform gyrus, ReHo increased while EC decreased with age. The left STG had increasing EC and decreasing ReHo with age. All of these regions had significant correlations with age based on the bootstrap testing (Fig. 4, the scatter plots).

4. Discussion:

The present study used robust correlations and longitudinal data to examine relationships between fMRI metrics and age in preschool children. We detect highly robust age-related changes in functional metrics during early childhood that suggest increased local and global connectivity in frontal, parietal, and cingulate areas. The superior parietal and fusiform gyrus showed a shift to more local connectivity with age, while the superior temporal area had a local-to-global shift. Importantly, this study provides detailed information about functional brain development during the preschool years.

4.1 Brain development in preschool children

ALFF and ReHo measure voxel-wise local signal intensity and concordance, and have been used to characterize changes in local connectivity across different conditions within healthy populations (Biswal et al., 2009; Lopez-Larson et al., 2011; Yang et al., 2007; Yu-Feng et al., 2007b; Zang et al., 2004). Here, we find that these measures increase with age from 2-6 years in the middle frontal gyrus, inferior parietal lobe, and precuneus, which are all nodes of the frontoparietal network (FPN) (Damoiseaux et al., 2006; Scolari et al., 2015; Seeley et al., 2007). The FPN is involved in executive function, attention control, and interaction between functional networks (Cole et al., 2014; Ptak, 2012; Seeley et al., 2007; Vincent et al., 2008). Previous studies have shown that within-network connectivity of the FPN in stronger in adults than children 7-9 years old (Fair et al., 2007), and increases with age from 10 and 13 years (Sherman et al., 2014). Our findings of increased ReHo and ALFF with age in FPN areas during early childhood (2-6 years) suggest that local connectivity may develop early in this network, followed by strengthening of longer range within-network connections during late childhood. FPN connectivity is often reduced in neurodevelopmental disorders such as ADHD and ASD (Bos et al., 2014; H.-Y. Lin et al., 2015; Minshew and Keller, 2010; Silk et al., 2008), suggesting that children with these disorders may display altered or delayed development of this network.

Several nodes of the DMN, especially the left inferior parietal lobe, demonstrate increases of both local connectivity (ReHo and ALFF) and global connectivity (EC). The DMN is one of the early emerging functional networks; it develops and matures through the first year of life (Cao et al., 2016; Fransson et al., 2007; Gao, 2009; Gao et al., 2016). Changes in the DMN have also been reported later, with DMN connectivity higher in adults than children (Fair et al., 2008). In support of this, our results suggest that DMN nodes increase both local and global functional features during the preschool years. The DMN is involved in functions such as self-referential mental activity (Gusnard et al., 2001) and theory of mind (Mars et al., 2012), which develop during the preschool years (Brown and Jernigan, 2012; Frith and Frith, 2003). Thus, DMN maturation during preschool years likely underlies the development of these functions.

Most of the cingulate cortex had positive correlations between age and EC, suggesting increased global connectivity overall. The posterior cingulate cortex is part of the default mode network (Fox et al., 2005; Fransson, 2005; Fransson and Marrelec, 2008; Greicius et al., 2003; Raichle et al., 2001; Raichle and Snyder, 2007), while the middle and anterior cingulate cortex belong to the fronto-parietal network. Functional connectivity of the anterior cingulate cortex shifts from local to distant brain areas from childhood to adulthood (Kelly et al., 2009). Thus, the increasing global connectivity observed here across the cingulate supports the idea that strengthening of these networks is occurring across childhood.

The development of functional brain features might be related to the structural changes in early life. Both gray and white matter mature significantly during early childhood in the preschool years, and display changes in cortical thickness and brain volume (Brain Development Cooperative Group, 2012; Brown and Jernigan, 2012), increases of white matter myelination (Deoni et al., 2012, 2011; Leppert et al., 2009), and increases in white matter volume and structural connectivity (Hagmann et al., 2010; Krogsrud et al., 2016; Lebel and Beaulieu, 2011; Mukherjee et al., 2001). In adults, several studies have linked age-related functional connectivity changes in the DMN to structural changes in the underlying white matter tracts (e.g., the cingulum) (Andrews-Hanna et al., 2007; Khalsa et al., 2014; Wang et al., 2015). So the increased functional connectivity observed here could be supported by major development of underlying white matter connections during the same time period. The link between structural and functional brain changes will be important to investigate in future studies.

The superior temporal gyrus (STG) had decreasing local connectivity (ReHo or ALFF) and increasing global connectivity (EC), suggesting a shift from a local-to-global arrangement, which may occur as the networks become more integrated across brain regions and less focused in certain areas. These findings are consistent with a previous study showing changes in degree centrality in the same area between age 5 and 6 years (Xiao et al., 2015). Given that the STG is associated with language function, our findings suggest that increasing global connectivity may be related to the significant language development that occurs in young children.

The superior parietal area and inferior temporal region (fusiform gyrus) showed the opposite trend – a shift from a more global arrangement to being more locally connected. This shift in connectivity may be related to ongoing maturation of cognitive functions such as working memory and facial recognition, which have been related to connectivity in the superior parietal and fusiform areas, respectively, in older populations (Klingberg et al., 2002; Peelen et al., 2009). Whether those brain areas continue to show similar development patterns in the later years is a question for further studies.

Fewer results were found for fALFF than ALFF. Only one large cluster showed significant correlations between fALFF and age, located in the right parietal lobe. fALFF is considered an improved version of ALFF, and is more robust against physiological artifacts than ALFF (Zou et al., 2008). However, fALFF has lower test-retest reliability than ALFF (Zuo et al., 2010a; Zuo and Xing, 2014), and thus the robust statistics used here may miss regions that a less stringent test would find significant. Alternatively, the ALFF analysis may be influenced by physiological changes during the preschool years (Feldman, 2009; Zuo et al., 2010a). However, we implemented strict noise and motion control procedures to increase the data quality (Ciric et al., 2016), and the ALFF results overlap with the ReHo results in several regions, suggesting that there is development of regional brain activity during the preschool years. More studies are needed to confirm the nature of ALFF and fALFF changes during early childhood.

4.2 The robust linear correlation analysis against age

The functional metrics in the present study have been widely implemented to detect linear correlations with age (Biswal et al., 2009; Lopez-Larson et al., 2011; Premi et al., 2014; Zuo et al., 2012), behavioral measurements (Kwak et al., 2012; Ren et al., 2015; Schaefer et al., 2014; Tian et al., 2012; Wu et al., 2015; W. Xia et al., 2013), and clinical parameters (An et al., 2013; Cai et al., 2015; Holiga et al., 2015; W.-C. Lin et al., 2015; Qiu et al., 2011; W. Xia et al., 2013) in older pediatric and adult populations, providing much valuable information on the associations between brain function and clinical or behavioral outcomes. Pearson correlations, as used in many previous studies, may give false positives if datasets are heteroscedastic, contain outliers or are affected by head motion, as are most fMRI datasets (Cyril R. Pernet, 2013; Siegel et al., 2016). Our present study takes those issues into account by using robust correlations with bootstrapping, outlier detection and control of confound artifacts, ensuring that our results can be interpreted with confidence.

4.3 Limitations

Our study used linear correlations to model age-related changes, as our age range was relatively small (2-6 years), and linear fits are a good approximation. However, structural brain development is known to be non-linear during this period (Giedd et al., 1999; Lebel and Beaulieu, 2011), and thus functional development may also be non-linear. Test-retest reliability across short-term multiple scans was found to be relatively low for EC (Zuo and Xing, 2014). However, reliability is improved by proper head motion correction and the use of permutation tests, as was done here. The robust statistics also improve the reliability of our results by reducing the risk of false positives, but could lead to false negative results for metrics like EC and fALFF. We chose to focus on the most robust age-related changes in this age range so that our results could be interpreted with confidence with little risk of false positives. The fMRI data in the present study were obtained while participants were watching movies. Videos increase compliance and reduce head motion in children, permitting data acquisition in this generally difficult to scan population (Vanderwal et al., 2015). Networks are similar during passive viewing tasks compared to rest (Bray et al., 2015), though slight differences have been reported, for example in the visual and dorsal attention networks (Emerson et al., 2015). However, in the present study, this is only a minor concern as we conducted a within-group analysis that did not compare different brain networks, and passive viewing is unlikely to affect development trajectories. The functional metrics in the current study examined the BOLD properties and were treated as the indices of the neural activity features during resting-state (Zuo et al., 2010a, 2017). However, a recent study showed changes in the ratio of BOLD signal to cerebral blood flow during childhood (Schmithorst et al., 2015), suggesting that neurovascular coupling is not stable across our age range. Our study provides an important contribution to understanding functional brain development in young children, but future studies, including those measuring cerebral blood flow, and those with more subjects, are necessary to better understand the actual changes within the brain during the preschool years.

5. Conclusions

Using data-driven analysis and longitudinal rs-fMRI data, we show robust age-related changes in several brain regions across the preschool period. In general, we observe increased regional activity and global connectivity in the nodes within the DMN and the FPN. We also found a local-to-global shift in the superior temporal gyus, and the opposite pattern (global-to-local shift) and in the superior parietal lobule and fusiform gyrus. Our study fills an important gap in the understanding of functional brain development in preschool aged children. As early childhood is a critical development period when many neurodevelopmental disorders emerge, our results may assist future research in understanding the functional brain abnormalities underlying these disorders, and ultimately lead to earlier and more effective treatments.

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Supplementary materials:

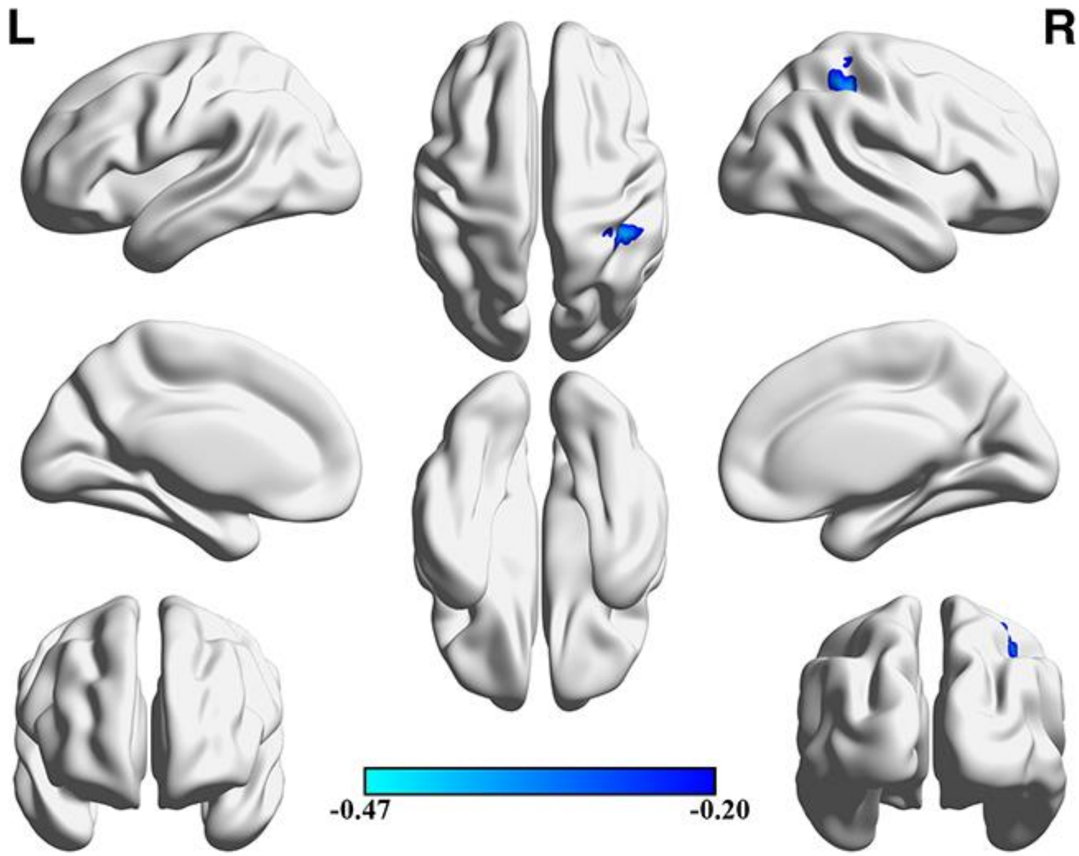

Figure S1, The correlation map between age and fALFF. A negative correlation was found in the right parietal area.

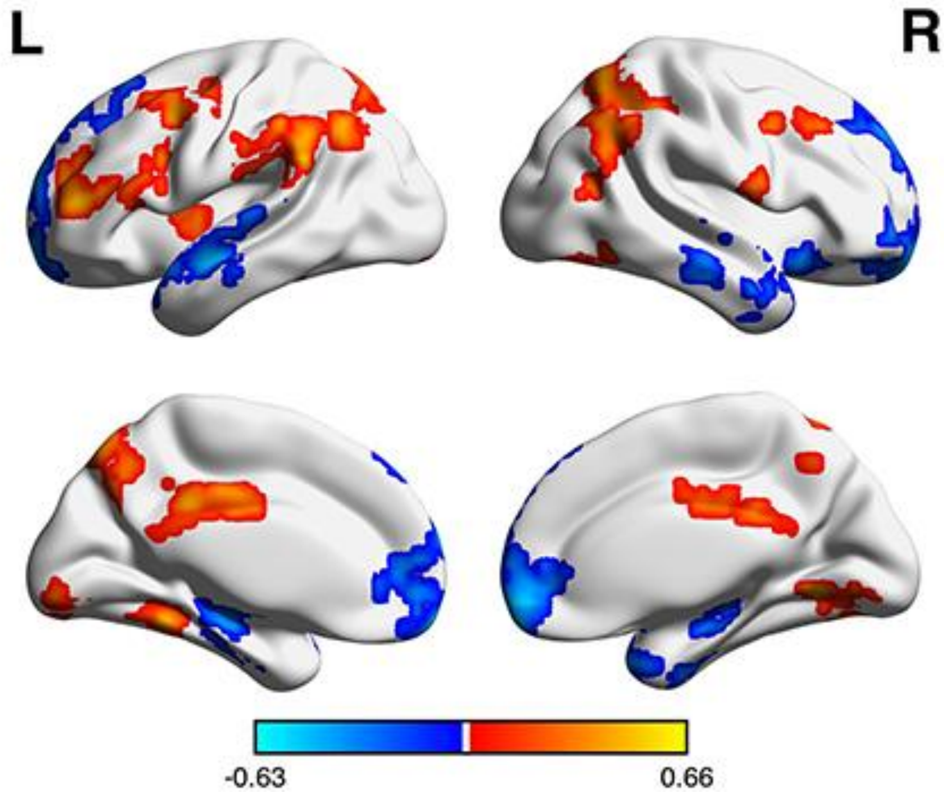

Figure S2, Brain areas with significant relationships between age and ReHo when calculated in each individual's native space. Comparing with Figure 3b, where results were calculated in MNI standard space, the main findings, such as fronal area, parietal area, cingulate cortex and precuneus, are similar. L means left and R means right. Warm colour means positive value and cold colour means negative value.

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Conflict of interest statement:

CL’s spouse is an employee of General Electric Healthcare. The other authors report no conflicts of interest.

9. Figure 1

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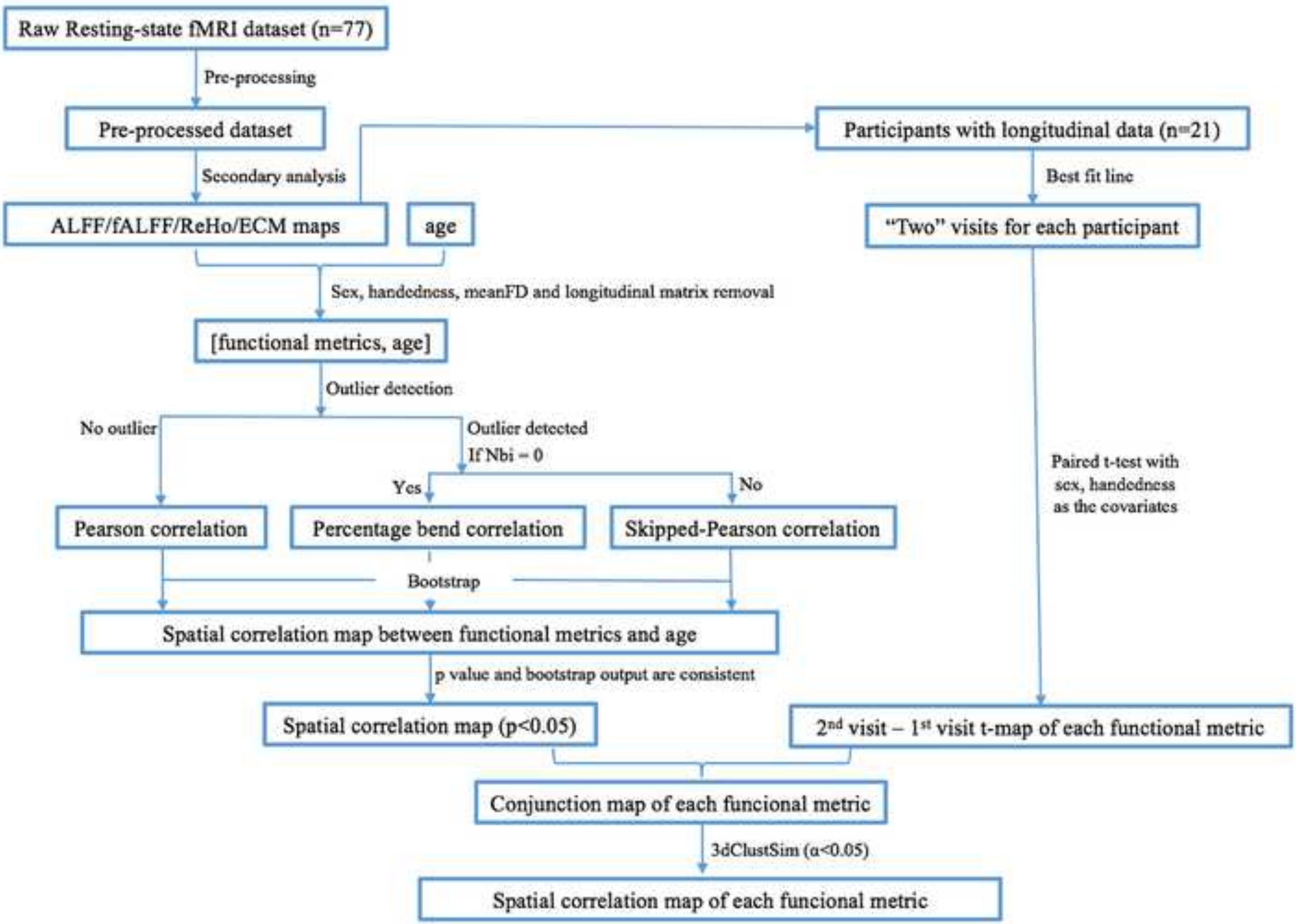

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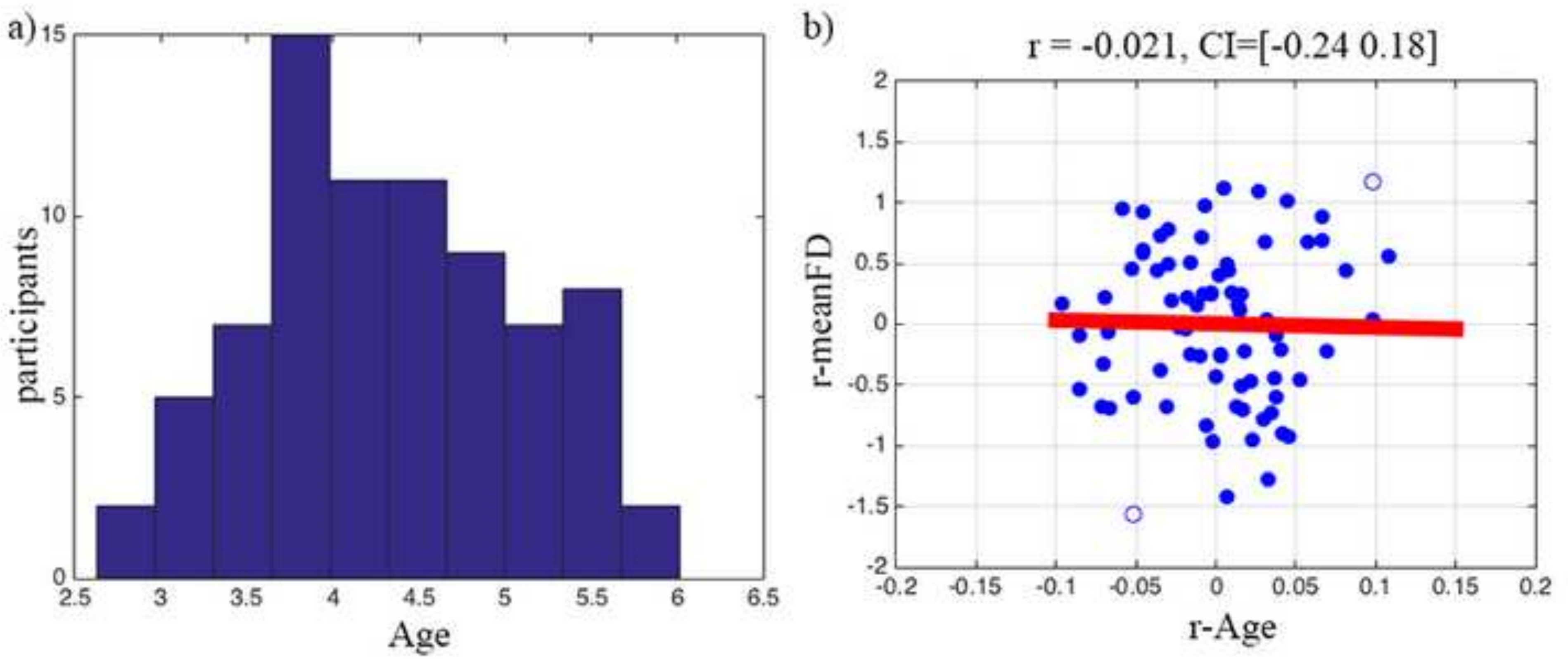

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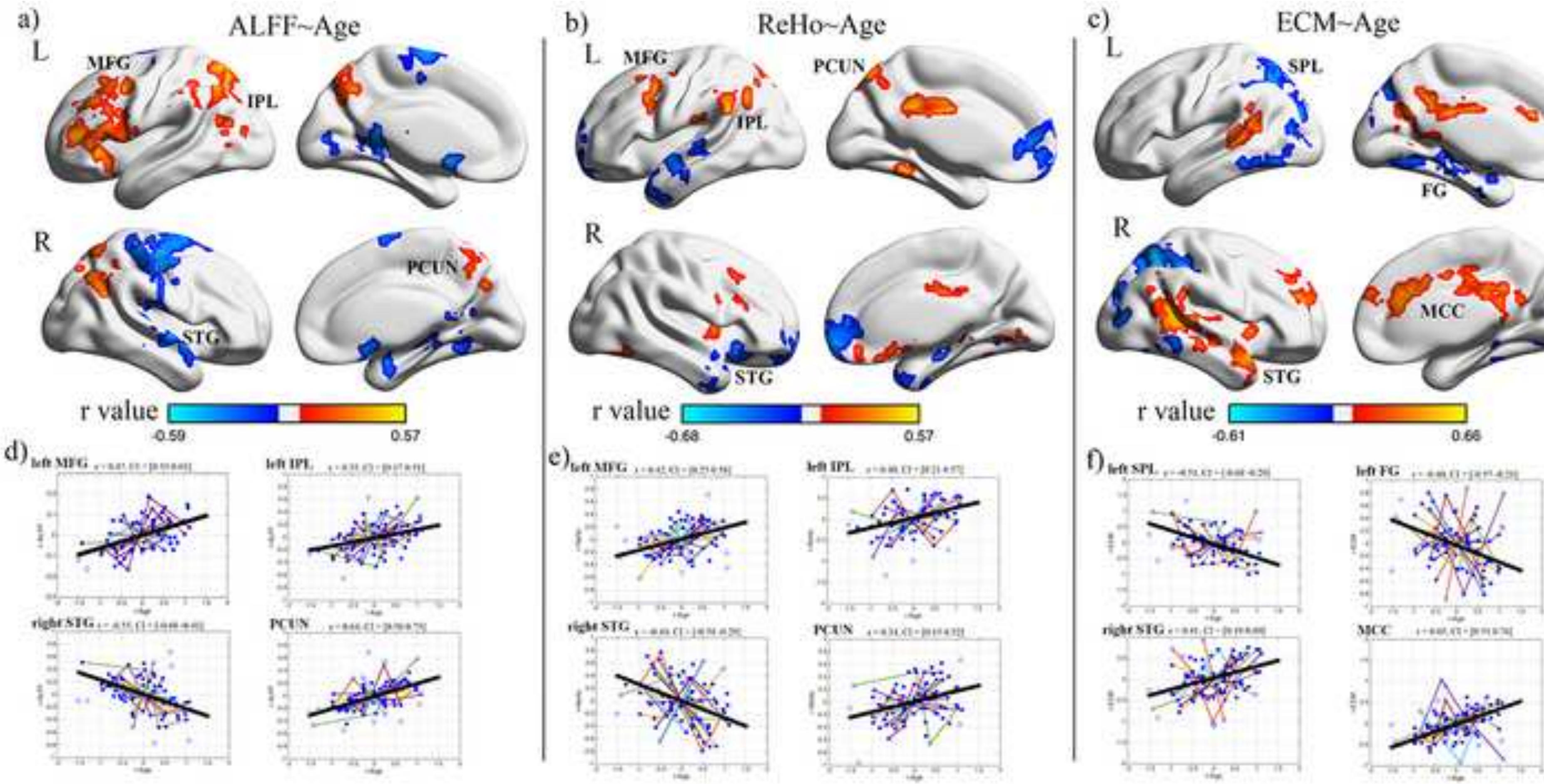

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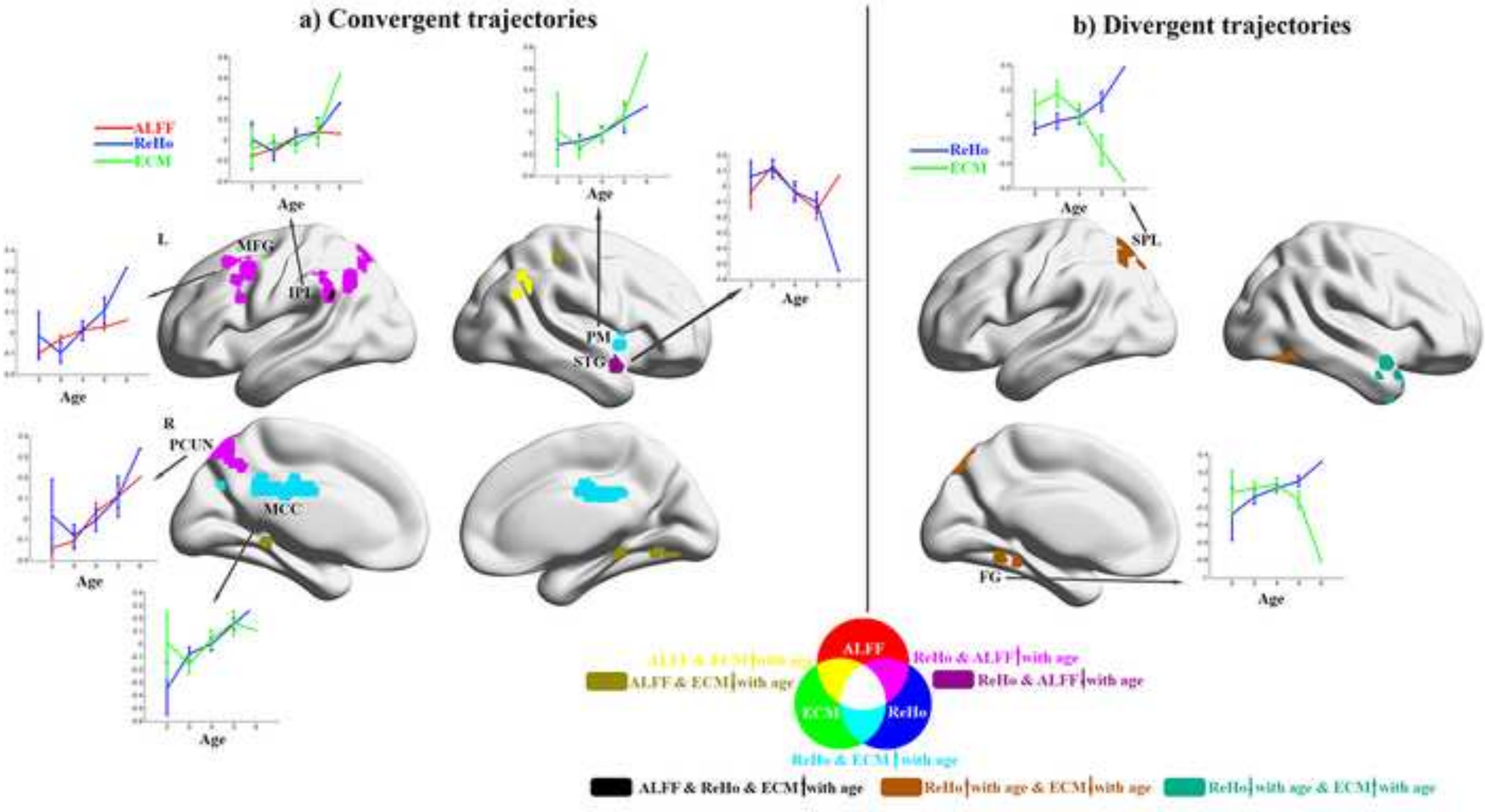

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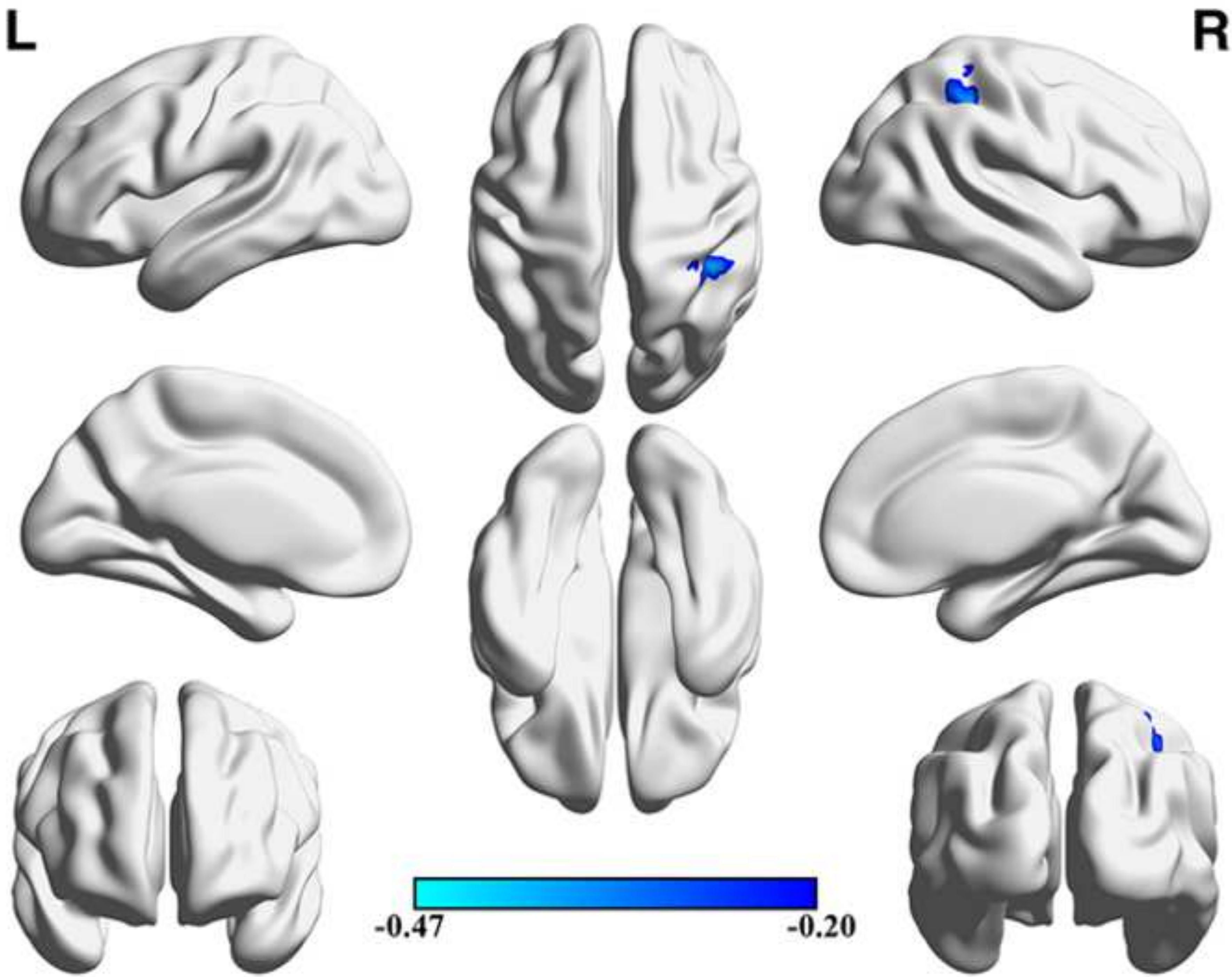

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