



Resting state neural networks for visual Chinese word processing in Chinese adults and children



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ABSTRACT

This study examined the resting state neural networks for visual Chinese word processing in Chinese children and adults. Both the functional connectivity (FC) and amplitude of low frequency fluctuation (ALFF) approaches were used to analyze the fMRI data collected when Chinese participants were not engaged in any specific explicit tasks. We correlated time series extracted from the visual word form area (VWFA) with those in other regions in the brain. We also performed ALFF analysis in the resting state FC networks. The FC results revealed that, regarding the functionally connected brain regions, there exist similar intrinsically organized resting state networks for visual Chinese word processing in adults and children, suggesting that such networks may already be functional after 3–4 years of informal exposure to reading plus 3–4 years formal schooling. The ALFF results revealed that children appear to recruit more neural resources than adults in generally reading-irrelevant brain regions. Differences between child and adult ALFF results suggest that children's intrinsic word processing network during the resting state, though similar in functional connectivity, is still undergoing development. Further exposure to visual words and experience with reading are needed for children to develop a mature intrinsic network for word processing. The developmental course of the intrinsically organized word processing network may parallel that of the explicit word processing network.

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1. Introduction

In a modern literate society, reading is one of the most important and most frequently encountered tasks we perform on a daily basis. In order to be performed successfully, the ability to visually process words is fundamental to the act of reading. Over the past several decades, neural mechanisms underlying visual word processing have been extensively studied. fMRI research has revealed a vast cortical network, distributed throughout the frontal, temporal, and occipital cortices. This network has been found to be involved in the processing of phonological, syntactic, and semantic information

associated with visual words in alphabetic languages and Chinese words (Bokde, Tagamets, Friedman, & Horwitz, 2001; Cohen, Dehaene, Chochon, Lehericy, & Naccache, 2000; Shaywitz et al., 2004; Tan, Laird, Li, & Fox, 2005; Bolger, Perfetti, & Schneider, 2005). One specific area that has attracted considerable attention is the so-called visual word form area (VWFA). The VWFA is located in the middle fusiform gyrus (FG) of the left hemisphere. It has been found to be particularly responsive to the orthographic processing of visual words during reading alphabetic scripts (Cohen et al., 2000; McCandliss, Cohen, & Dehaene, 2003; but see Price & Devlin, 2003).

Research has shown that reading non-alphabetic languages, such as Chinese, also engenders activation in the VWFA. This activation occurs despite the fact that Chinese written words are markedly different from alphabetic words (Chen, Fu, Iversen, Smith, & Matthews, 2002; Liu et al., 2008). For example, unlike words in alphabetic languages, Chinese words are logographs with distinctive configurations of components that are comprised of a number of strokes packed into a square shape according to stroke assembly rules. Generally speaking, unlike phonemes and syllables in alphabetic words, the components of Chinese words do not have obvious letter-sound correspondences. Existing functional neuroimaging studies have suggested that several brain areas are commonly activated

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in both Chinese word and alphabetic word processing. For instance, it has been reported that an area within the middle left FG is involved in the visual processing of Chinese words, the locus of which is highly consistent with the VWFA identified using alphabetic words (Liu et al., 2008; Liu, Tian, Li, Gong, & Lee, 2009; Bolger et al., 2005). The left inferior parietal lobule (IPL) and the left inferior frontal cortex are two areas that have also been found to respond to both Chinese words and alphabetic words (Bolger et al., 2005; Tan, Feng, Fox, & Gao, 2001; Tan et al., 2005; Zhao et al., 2011).

Recently, researchers have begun to explore whether there exists an intrinsically organized neural network for visual word processing even when individuals are not explicitly engaged in reading (Vogel, Miezin, Petersen, & Schlaggar, 2012; Zhao et al., 2011). Zhao et al. (2011) conducted an experiment, applying a low-frequency (0.01–0.08 Hz) functional connectivity (FC) approach used by several existing studies (Hampson et al., 2006; Koyama et al., 2010) to study intrinsic word processing networks during the resting state. It has been suggested that the synchronous low frequency (< 0.1 Hz) fluctuations (LFFs) in the blood oxygen level-dependent (BOLD) signal are temporally synchronized between functionally related brain regions during the resting state (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995; Greicius, Krasnow, Reiss, & Menon, 2003; Lowe, Mock, & Sorenson, 1998; Zhang, Tian, Liu, Li, & Lee, 2009; Zhu, Zhang, Luo, Dilks, & Liu, 2011). This LFF synchronization has been found within the primary motor, auditory, visual cortices, as well as some subcortical regions such as the hippocampus, and thalamus (Biswal et al., 1995; Chen, Zhou, Yang, & Fang, 2010; Smith et al., 2009; Yan et al., 2009; Zhao et al., 2011; Zhu et al., 2011).

In the Zhao et al. (2011) study, Chinese adults were neither made aware of the purpose of the study nor asked to perform any explicit word processing tasks. Results showed that during the resting state, there are significant low-frequency correlations between the left middle FG (i.e., VWFA) and an extensive number of cortical regions that have been implicated in visual word processing and reading, including the right FG, the left angular gyrus, the left supramarginal gyrus, the left IPL, the bilateral superior parietal lobule (SPL), the bilateral middle frontal gyrus (MFG), and the inferior frontal gyrus (IFG) (bilateral at BA 44, left at BA 45). This study demonstrates that during the resting state, there is an intrinsically organized word processing network in adults. One possible explanation for the existence of such a network is that our neural system may be in a constant state of readiness to receive visual word inputs due to the fact that reading is a highly common activity in the everyday lives of adults. Also, the resting state of the visual word processing neural network in adults may be the result of decades of extensive experience with reading and a gained expertise with the processing of visual words.

However, two outstanding issues have yet to be addressed. First, whereas FC analyses using LFF identifies the brain regions functionally involved in the resting state network for visual word processing, Zhao et al. (2011) did not consider the amplitude of the low frequency fluctuations (ALFF) for each brain region within the intrinsic network. The ALFF can be obtained by calculating the regional intensity of spontaneous fluctuations in BOLD signals. As demonstrated by several recent studies (Yang et al., 2007; Zang et al., 2007), the ALFF of the resting-state fMRI signals reflects the cerebral physiological states of brain regions, namely the magnitude of spontaneous brain activities in a resting state functional network. One possibility is that the ALFF may indicate the extent to which a brain region is engaged for a particular resting state network. However, to the best of our knowledge, no study to date has explored the ALFF within the intrinsic word processing network.

Second, Zhao et al. (2011) suggest that the intrinsic network is the product of extensive experience with reading that has been accumulated since childhood. The issue exists, however, that there is no developmental evidence to support this claim. It is entirely unclear whether children also have an intrinsic resting state neural network

for word processing. Existing developmental evidence with children performing reading tasks suggests that the VWFA is already seen at about 9–12 years of age and develops gradually throughout childhood (Booth et al., 2001, 2004). Similarities and differences between children's and adults' explicit visual word processing networks have been found. As well, the development of the VWFA has been suggested to be driven by an increase in reading expertise rather than merely by the process of maturation (McCandliss et al., 2003). Based on such existing evidence, differences may exist between children's and adults' resting state neural networks due to differences in experience and reading expertise between the two age groups.

The present study aimed to address these two outstanding issues concerning the development of the visual word processing neural network. Two experiments were conducted using a task-rest paradigm. For the first experiment, adult participants were not informed of the true purpose of the study in order to obtain resting state data. Next, participants performed a visual word discrimination task from which the participants' VWFAs were identified. Using the resting scans, for each adult, the brain regions showing dynamic activities that correlated with those of the VWFA were identified using FC analyses. Measurements were then obtained of the variations of the ALFF within the intrinsic word processing network for adults. We expected to extend the findings of Zhao et al. (2011) by showing, in adults, both the existence of an intrinsic resting state network for visual word processing with the use of the FC analyses, and the associated levels of neural activities within the network with the use of the ALFF analysis.

In the second experiment, the same method and data analysis approach were performed with 10- and 11-year-old child participants, in order to identify the resting state neural network for children, should it exist. The similarities and differences between children's and adults' resting state neural networks were then assessed. In order to do so, the FC and ALFF results for adults were compared with those of children. These comparisons were then used to identify similarities and differences between the child and adult resting state neural networks for visual word processing.

Several possible patterns of results were expected. Regarding the FC results, given the fact that 10- to 11-year-old children would have had 3–4 years of formal schooling and 3–4 years of informal reading experience before entering elementary school, children at these ages may already have a resting state network for visual word processing similar to that of adults. Alternatively, as the ability to read takes a considerable amount of practice and time to acquire, the resting state network for children may be different from that for adults. With regard to the results of the ALFF analysis, the existing fMRI findings concerning children's performance in explicit reading tasks suggest that, when reading, children engage greater neural resources than adults in brain areas that are generally considered to be reading-irrelevant (e.g., Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). Based on these findings, we hypothesized that the ALFF results may differ between children and adults with the former showing greater amplitude of spontaneous brain activities in brain regions that are generally not involved in visual word processing. Alternatively, children's existing reading experience may also be sufficient to eliminate any differences between children and adults in terms of the amplitude of the low frequency fluctuations.

2. Experiment 1

2.1. Method

2.1.1. Participants

Twenty healthy, right-handed, Chinese adults (age: 20–25; mean age: 22.60; SD: 1.35; 8 males) with normal vision participated in the present fMRI study. Participants were in good health with no history of neurological illness. Participants

were students recruited from a Chinese university. The present study was approved by the university ethics committee. Participants gave written informed consent prior to participating in the study.

2.1.2. Data acquisition

All the adults' images were scanned on a 3.0 T MRI system (SIEMENS MAGNETOM TrioTim syngo MR B17). The blood oxygenation level-dependent images of the entire brain were acquired in 32 axial slices by using an echoplanar imaging sequence [time repetition/time echo (TR/TE)=2000/30 ms, flip angle=90°, field of view=220 mm, matrix=64 × 64, slice thickness=4 mm]. For each participant, high-resolution (voxel size: 1 mm × 1 mm × 1 mm, matrix size: 256 × 256 × 176) anatomical images were acquired using a T1-weighted, three-dimensional gradient-echo imaging sequence.

2.1.3. Stimuli and experimental design

The experiment was divided into two phases. In the first phase, a 310-s resting session, participants were instructed to stay awake and close their eyes. At the same time they were also asked to relax their minds and move as little as possible. Two pieces of foam and two earplugs were used to reduce head motion and scanner noise, respectively. In the second phase, a 320-s visual discrimination task was performed. The second phase consisted of two scanning sessions, each of which included three 24-s Chinese word epochs, three high frequency Chinese face epochs, and two common objects epochs with 16-s intervals of fixation between two adjacent epochs. The presentation of stimuli alternated between Chinese word, face, and common object epochs, each of which included six trials. The face and object epochs were used as controls to ensure that any cortical activations obtained in the Chinese words epoch could be attributed specifically to visual word

processing, not the processing of any visual objects or visual objects with which participants had processing expertise.

Each task session began with a 12 s fixation prior to the task and each task session also finished with a 12 s fixation in order to account for the delay of hemodynamic response. The timing procedure in each trial was 500-ms of fixation, 500-ms of null, 500-ms of the first stimulus, 1000-ms of fixation, 500-ms of the second stimulus and 1000-ms fixation. During the last fixation, participants judged whether two sequentially presented stimuli were the same or different by pressing a button on a response device with their left or right finger (counterbalanced across participants).

2.1.4. Data processing

2.1.4.1. Preprocessing. The first 15 time points of the resting-state fMRI data were discarded leaving 140 time points to be compared to data from the second experiment. The first three time points of each task session were discarded due to the instability of the initial MRI signal and the subjects' adaptation to the situation, leaving 157 time points.

For task data and resting data, most of the preprocessing and statistical analyses steps were carried out using statistical parametric mapping (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>). After slice-timing correction, spatial realignment and normalization to the MNI template, the scans of all sessions were resampled to 3 × 3 × 3 mm³. Then, the functional images were spatially smoothed with a Gaussian kernel of 4 × 4 × 4 mm³ FWHM to decrease spatial noise. Head motions of participants were less than 2 mm. See Supplementary Table 1 for information regarding head movement in adults indexed by the mean frame-wise displacement (FD: Van Dijk, Sabuncu, & Buckner, 2012; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012; Yan et al., 2013). For the adult sample, mean FD is 0.38 mm (SD: 0.16). For the resting session, we used a linear regression process to remove the effects of head motion and other possible sources of artifacts: (1) six motion

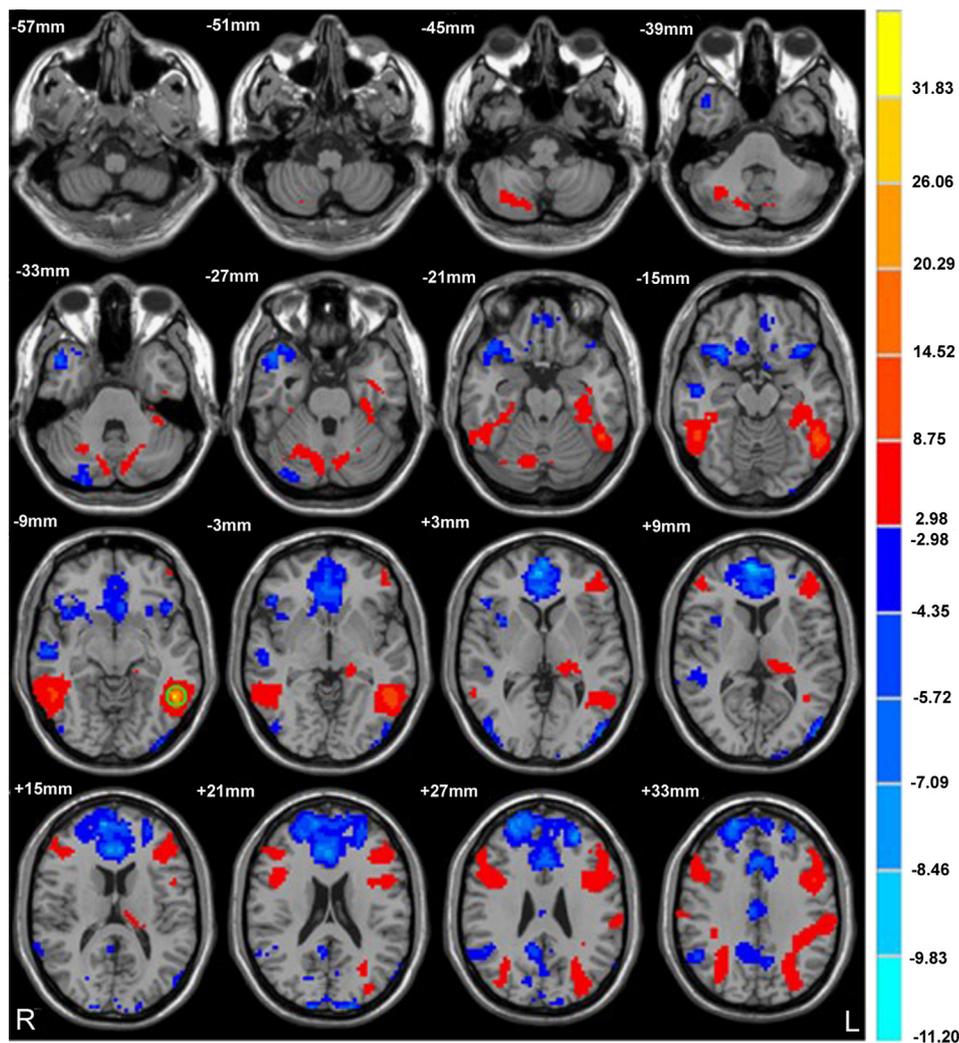


Fig. 1. The map of significant FCs for adults (one sample *t*-test). Left of the image is the right side of the brain. Maps of brain regions show significant positive (red and yellow) and negative (blue) correlations with the VWFA. Red and yellow colors denote significantly higher FCs than the mean value and blue denotes the opposite. The statistical threshold was $p < 0.05$ (FDR corrected, voxels ≥ 50). The green circle is the ROI (VWFA). *T*-score scale is shown on the right. R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

parameters, (2) whole-brain signal averaged over the entire brain, (3) white matter signal, (4) cerebrospinal fluid signal, (5) linear drift. Finally, the fMRI waveform of each voxel was temporally band-pass filtered ($0.01 \text{ Hz} < f < 0.08 \text{ Hz}$) using the Resting-State fMRI Data Analysis Toolkit (<http://www.restfmri.net>).

2.1.4.2. GLM analysis. For the task session, data were high-pass filtered to eliminate the low-frequency components (cut-off value of 128 s). A general linear model (GLM) including three condition regressors (words, faces, and objects) and six parameters for head motion was constructed for each subject. The condition regressor was created by convolving a canonical hemodynamic response function with a box function corresponding to the onset time series of each stimulus category. The VWFA was identified by the contrast of Chinese characters minus (face+common objects) at the group level with a statistical threshold $p < 0.001$ (uncorrected). The coordinate of the VWFA (MNI coordinate: $x = -51, y = -54, z = -9$) identified in the present study was consistent with that reported previously for both Chinese word processing (Liu et al., 2008) and alphabetic word processing (Talarach coordinate: $x = -43, y = -54, z = -12$, (Cohen et al., 2002)).

2.1.4.3. Functional connectivity analysis (FC analysis). To obtain the FC map, we calculated the Pearson's correlations of the spontaneous functional time course between the seed region (i.e., the VWFA) and the whole brain voxel-by-voxel. The seed region was defined as a sphere with a 6-mm radius, which centered at the peak activation of the VWFA (MNI coordinate: $x = -51, y = -54, z = -9$). The reference time course was obtained by averaging the time series of all voxels in the seed region. Finally, the correlation coefficients were transformed into z-scores using Fisher's transformation to improve normality:

$$Z = \frac{1}{2} \log_e \left(\frac{1+r}{1-r} \right) \quad (1)$$

where r is the correlation coefficient between the time course of the seed region and that of each voxel.

At the group level, the individual z-map was entered into a random effect one-sample t -test in a voxel-wise manner to identify the brain regions showing significant connectivity to the VWFA ($p < 0.05$, FDR corrected) (Tian et al., 2006; Wang et al., 2007, 2008).

2.1.4.4. Amplitude of low frequency fluctuation analysis (ALFF analysis). In the ALFF analysis, the fMRI time series was transformed to a frequency domain with a fast Fourier transform (FFT) (parameters: taper percent=0, FFT length=shortest) and the power spectrum was then obtained. Since the power of a given frequency is proportional to the square of the amplitude of this frequency component of the original time series in the time domain, the square root was calculated at each

frequency of the power spectrum and the averaged square root was obtained across a frequency band at each voxel. The frequency band of the low-frequency fluctuation is 0.01 Hz to 0.08 Hz. This averaged square root was taken as the ALFF value (Yan et al., 2007, 2009; Zang et al., 2007). In the present study, we calculated ALFF value based on the FC results. That is, we used the FC resting state network as a mask for the ALFF analysis.

2.2. Results

2.2.1. Behavioral results

The mean accuracy and average RT for Chinese word discrimination were 0.95 (SD: 0.06) and 672.20 ms (SD: 174.30), respectively.

2.3. Positive connectivity

The VWFA showed significant positive low-frequency correlations with the following brain regions: the bilateral MFG (BA 6/9), the left IFG (BA 9), the right frontal lobe sub-gyral (BA 6), the right temporal lobe sub-gyral (BA 37), the left supramarginal gyrus (BA 40), the right precuneus (BA 7), the left thalamus, the right cerebellum anterior lobe, and the left cerebellum posterior lobe, with the threshold of $p < 0.05$ (FDR corrected) and with a cluster ≥ 50 voxels (Fig. 1, Table 1).

2.3.1. Negative connectivity

Negative significant low-frequency correlations with the VWFA were found in the following brain regions: the right MFG (BA 9), the left IFG (BA 47), the right paracentral lobule (BA 3), the right superior temporal gyrus (STG, BA 21/39/41), the right postcentral gyrus (BA 3), the left middle occipital gyrus (MOG, BA 18/19), the right inferior occipital gyrus (IOG, BA 18), the right posterior cingulate (BA 23), the right sub-lobar extra-nuclear (BA 13), and the right cerebellum posterior lobe, with the threshold of $p < 0.05$ (FDR corrected) and with a cluster ≥ 50 voxels (Fig. 1, Table 1).

Table 1

Coordinates and T scores of the peak voxels of the significant adult FCs during the resting state.

Brain regions	BA	Hem	MNI			Volume (voxels)	T	
			X	Y	Z			
Positive								
Frontal lobe	Middle frontal gyrus	9	R	57	30	347	8.32	
		6	L	-30	3	277	7.04	
	Inferior frontal gyrus	9	L	-48	9	653	9.93	
Temporal lobe	Sub-gyral	6	R	30	3	89	4.92	
	Sub-gyral	37	R	54	-51	-12	494	13.53
Parietal lobe	Supramarginal gyrus	40	L	-42	-42	42	1315	13.94
	Precuneus	7	R	33	-63	45	854	9.36
Sub-lobar	Thalamus	-	L	-18	-30	6	114	8.73
Cerebellum	Anterior lobe	-	R	24	-63	-27	244	6.45
	Posterior lobe	-	L	-6	-75	-24	82	5.01
Negative								
Frontal lobe	Middle frontal gyrus	9	R	9	57	12	3410	11.2
	Inferior frontal gyrus	47	L	-39	21	-12	93	7.06
	Paracentral lobule	3	R	21	-30	63	95	5.51
Temporal lobe	Superior temporal gyrus	39	R	51	-54	30	113	5.69
		21	R	60	-15	-6	103	6.52
		41	R	51	-36	9	51	3.91
Parietal lobe	Postcentral gyrus	3	R	42	-15	45	86	4.66
Occipital lobe	Middle occipital gyrus	19	L	-48	-87	6	133	6.60
		18	L	-18	-99	21	103	6.24
	Inferior occipital gyrus	18	R	45	-87	3	58	4.87
Limbic lobe	Posterior cingulate	23	R	12	-48	27	230	5.72
Sub-lobar	Extra-nuclear	13	R	33	18	-15	429	7.35
Cerebellum	Posterior lobe	-	R	27	-87	-30	76	5.50

Note: List of brain regions show significant positive or negative correlations with the LFF of the adult VWFA (Cluster significance: $p < 0.05$, FDR corrected, voxels ≥ 50). Cluster size is in voxels. Coordinates are in standard MNI space. BA, Brodmann's area; Hem, hemisphere; R, right; L, left.

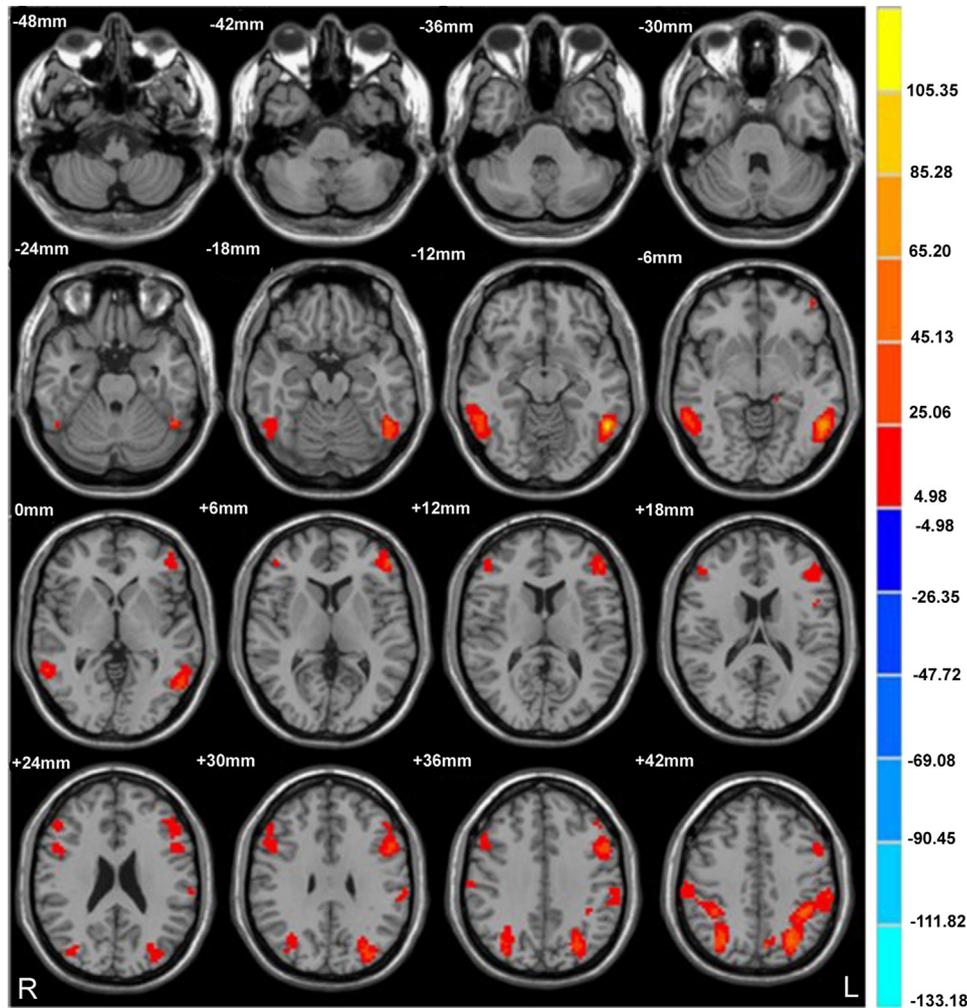


Fig. 2. The maps of ALFFs for adults (one sample *t*-test). Left of the image is the right side of the brain. Red and yellow colors denote significantly higher ALFFs than the mean value. The statistical threshold was $p < 0.0001$ (FDR corrected, voxels ≥ 100). *T*-score scale is shown on the right. R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2

Coordinates and *T* scores of the peak voxels of the significant adult ALFFs during the resting state.

Brain regions		BA	Hem	MNI			Volume (voxels)	<i>T</i>
				X	Y	Z		
Frontal lobe	Middle frontal gyrus	9	R	51	15	33	135	18.42
	Inferior frontal gyrus	6	L	-27	0	63	125	44.71
Temporal lobe	Inferior temporal gyrus	9	L	-54	12	33	396	48.63
	Inferior temporal gyrus	20	L	-54	-54	-9	274	125.43
Parietal lobe	Inferior parietal lobule	20	R	60	-48	-9	222	39.67
	Precuneus	40	L	-45	-45	57	957	73.20
	Precuneus	7	R	30	-69	42	640	48.53

Note: Cluster significance: $p < 0.0001$, FDR corrected, voxels ≥ 100 . Cluster size is in voxels. Coordinates are in standard MNI space. BA, Brodmann's area; Hem, hemisphere; R, right; L, left.

2.3.2. ALFF results

The following regions showed significantly higher ALFFs than the global mean level within the intrinsic word processing network: the bilateral MFG (BA 6/9), the left IFG (BA 9), the bilateral

inferior temporal gyrus (ITG)/FG (BA 20), the left IPL (BA 40), and the right precuneus (BA 7), with the threshold of $p < 0.0001$ (FDR corrected) and with a cluster ≥ 100 voxels (Fig. 2, Table 2).

It should be noted that we again performed FC analysis and ALFF analysis at the group-level for the adult resting-state data, but regressing out the mean FD by taking it as a covariate using SPM 8 (Fair et al., 2012). We have reported the results of such analysis in Supplementary Figs. 1–4 and Tables 2–5. Both results (with or without the mean FD regressed out) are basically the same. Thus, here we discussed the results according to the analysis without regressing out the mean FD.

3. Experiment 2

To ascertain whether there also exists an intrinsic resting state neural network for visual word processing in children, we conducted Experiment 2 with 10- to 11-year-old children who had formal schooling for about 3 to 4 years, using the same experimental and analytic procedures as Experiment 1.

3.1. Method

3.1.1. Participants

Eighteen healthy, right-handed Chinese children (age: 10–11; mean age: 10.72; SD 0.46; 9 males) participated. Participants were

in good health with no history of neurological illness. Children were primary school students with normal vision and had received formal schooling and had been learning to read and write Chinese for about 3–4 years. The present study was approved by the Human Research Protection Program of a hospital affiliated with a Chinese university. Written informed consent was obtained from all participants' parents prior to participation. Additionally, all children gave oral consent prior to participation.

3.1.2. Data acquisition

All images obtained from child participants were scanned on a 3.0 T MRI system (GE Signa HDx, Milwaukee, USA). During each session, 160 whole brain T2*-weighted axial images were obtained. The blood oxygenation level-dependent images of the entire brain were acquired in 33 axial slices by using an echo-planar imaging sequence [time repetition/time echo (TR/TE)=2000/30 ms, flip angle=90°, field of view=230 mm, matrix=64 × 64, thickness=4 mm]. For each child, high-resolution (voxel size: 0.9 mm × 0.9 mm × 1 mm, matrix size: 256 × 256 × 164) anatomical images were acquired using a T1-weighted, three-dimensional gradient-echo pulse sequence.

3.1.3. Stimuli and experimental design

These are same as those used for Experiment 1.

3.1.4. Data processing

The 15 time points of the resting-state session were discarded due to the extreme head movements of some children. Children needed more time to settle into the experimental session. Based on our visual inspection of the data, we found considerable motion artifacts in the first 15 data points and thus decided to remove them. Additionally, the first three time points of the task session were discarded like those in Experiment 1. In Experiment 2, data processing steps were the same as in Experiment 1. Head motions of children were also less than 2 mm. The child sample mean FD is 0.95 mm (SD: 0.51) as shown in Supplementary Table 1). The coordinate of the VWFA (MNI coordinate: $x=-48$, $y=-51$, $z=-12$) identified in the present experiment was consistent with the coordinate reported in previous studies (e.g., Talarach coordinate: $x=-43$, $y=-54$, $z=-12$ (Cohen et al., 2002)).

For the purpose of FC analysis from the fMRI data during the resting session, the ROI was defined as a sphere with a 6-mm radius, which was centered at the peak activation of the VWFA (MNI coordinate: $x=-48$, $y=-51$, $z=-12$).

The FC and the ALFF methods were the same as those in Experiment 1.

3.2. Results

3.2.1. Behavioral results

Child participants' mean accuracy for Chinese word discrimination was 0.80 (SD: 0.23). Child participants' average RT for Chinese word discrimination was 819.00 ms (SD: 166.90).

3.2.2. Positive connectivity

In the child FC analysis, positive significant low frequency correlations with VWFA were found in the following regions: the bilateral MFG (BA 46), the right IFG (BA 9), the right FG (BA 37), the right SPL (BA 7), and the left precuneus (BA 7), and with the threshold of $p < 0.05$, (FDR corrected) and a cluster ≥ 50 voxels (>/>Fig. 3, Table 3).

3.2.3. Negative connectivity

Negative significant low frequency correlations with VWFA were found in the following regions: the right MFG (BA 10), the

left cuneus (BA 18), the right MOG (BA 18), the right middle cingulate gyrus (BA 24), and the right insula (BA 13), with the threshold of $p < 0.05$, (FDR corrected) and a cluster ≥ 50 voxels (Fig. 3, Table 3).

3.2.4. ALFF results

ALFF analysis of the child data showed a higher ALFF than the global mean level was found in the following brain regions: the left superior frontal gyrus (SFG, BA 6), the right MFG (BA 46), the left IFG (BA 9), the left ITG/FG (BA 20), the right FG (BA 37), the left precuneus (BA 19), and the right MOG (BA 19), with the threshold of $p < 0.0001$ (FDR corrected) and a cluster ≥ 100 voxels (Fig. 4, Table 4).

It should be noted that we again performed FC analysis and ALFF analysis at group-level for the child resting-state data, but regressing out the mean FD by taking it as a covariate using SPM 8 (Fair et al., 2012). We have reported the results of such analysis in Supplementary Figs. 5–8 and Tables 6–9. Both results (with or without regressing the mean FD) are basically the same. Thus, here we discussed the results according to the analysis without regressing out the mean FD.

3.2.5. Results of conjunction analyses of the adult and child data

To ascertain similarities and differences in the resting state neural networks for visual word processing between children and adults, we performed the following analyses.

First, we performed the FC group conjunction analysis to identify the brain regions for both adults and children that showed significant common low frequency correlations with the VWFA. The only significant region was the right FG (BA 37), with the threshold of $p < 0.05$ (FWE Corrected) and a cluster ≥ 50 voxels (Fig. 5, Table 5).

We also performed the ALFF group conjunction analysis with the same statistical criterion to identify the brain areas for both adults and children that showed overall higher ALFF activities than the global mean level. No significant results were obtained.

3.2.6. Results of contrast analyses between the adult and child data

We applied two-sample *t*-tests to analyze FC differences between adults and children, with the threshold of $p < 0.05$, (FDR corrected) and a cluster ≥ 50 voxels. No regions showed significant differences in FC between children and adults, suggesting that children and adults had a similar resting state network for visual word processing.

Then, we applied two-sample *t*-tests to analyze ALFF differences between adults and children. We found that several regions showed significantly higher ALFF activities for children than for adults, with the threshold of $p < 0.005$ (FDR corrected) and a cluster ≥ 50 voxels. They included the left medial frontal gyrus (BA 10), the left precentral gyrus (BA 6), the left ITG (BA 20), the right temporal lobe sub-gyral (BA 21), the right cerebellum posterior lobe and the left cerebellum anterior lobe. On the contrary, with the same statistical criteria, only three cortical regions had significantly greater ALFF activities for adults than children: the right precuneus (BA 19), and the bilateral middle cingulate gyrus (BA 31) (Fig. 6, Table 6).

4. Discussion

4.1. Findings from Experiment 1

In Experiment 1, the FC analysis revealed significant positive low-frequency correlations between the VWFA and a number of brain regions, including the bilateral MFG (BA 6/9), the left IFG (BA 9), the right temporal lobe sub-gyral (BA 37), the left

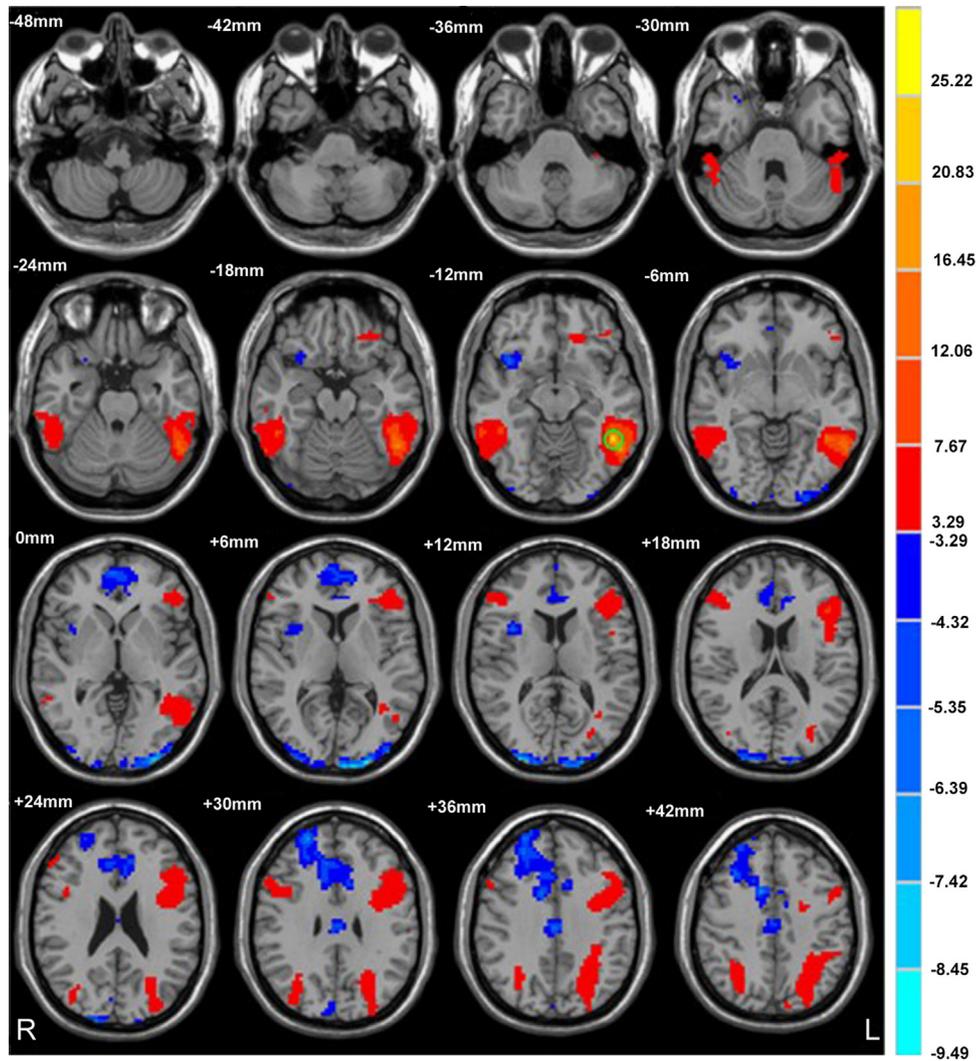


Fig. 3. The map of significant FCs for children (one sample *t*-test). Left of the image is the right side of the brain. Maps of brain regions show significant positive (red and yellow) and negative (blue) correlations with the VWFA. Red and yellow colors denote significantly higher FCs than the mean value and blue denotes the opposite. The statistical threshold was $p < 0.05$ (FDR corrected, voxels ≥ 50). The green circle is the ROI (VWFA). *T*-score scale is shown on the right. R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3

Coordinates and *T* scores of the peak voxels of the significant child FCs during the resting state.

Brain regions	BA	Hem	MNI			Volume (voxels)	<i>T</i>	
			X	Y	Z			
<i>Positive</i>								
Frontal lobe	Middle frontal gyrus	46	L	-45	24	18	965	7.99
		46	R	57	36	12	105	5.75
	Inferior frontal gyrus	9	R	51	9	30	73	4.24
Temporal lobe	Fusiform gyrus	37	R	60	-60	-18	534	9.22
Parietal lobe	Superior parietal lobule	7	R	33	-54	48	270	6.93
	Precuneus	7	L	-27	-66	39	879	7.71
<i>Negative</i>								
Frontal lobe	Middle frontal gyrus	10	R	6	60	3	197	5.77
Occipital lobe	Cuneus	18	L	-24	-102	6	242	9.49
	Middle occipital gyrus	18	R	27	-99	15	186	8.25
Limbic lobe	Middle cingulate gyrus	24	R	12	9	39	942	7.12
Sub-lobar		24	R	3	-18	39	130	6.53
	Insula	13	R	39	15	-12	162	6.25

Note: List of brain regions show significant positive or negative correlations with the LFF of the child VWFA (Cluster significance: $p < 0.05$, FDR corrected, voxels ≥ 50). Cluster size is in voxels. Coordinates are in standard MNI space. BA, Brodmann's area; Hem, hemisphere; R, right; L, left.

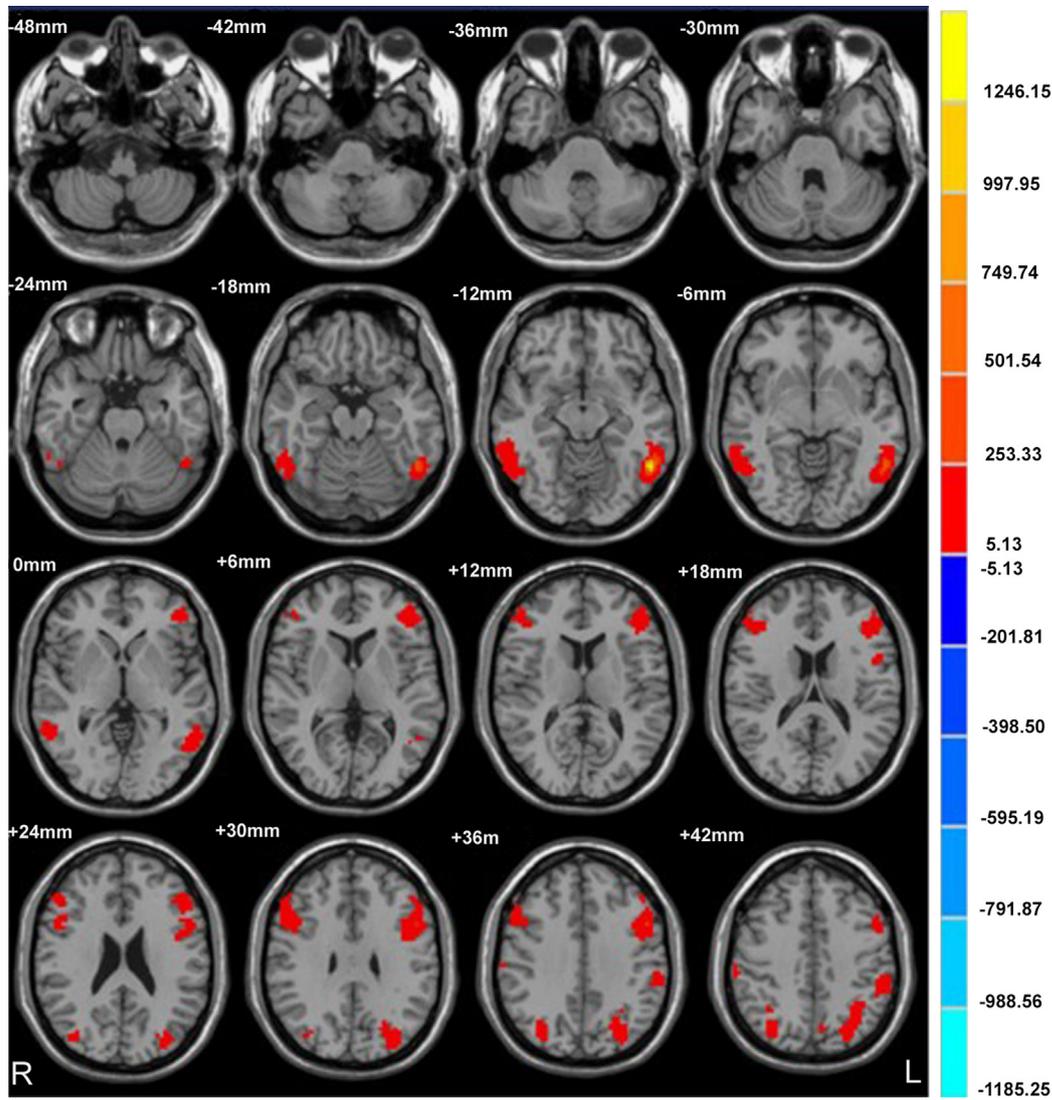


Fig. 4. The maps of ALFFs for children (one sample *t*-test). Left of the image is the right side of the brain. Red and yellow colors denote significantly higher ALFFs than the mean value. Red and yellow color means significantly higher ALFF than the average value. The statistical threshold was $p < 0.0001$ (FDR corrected, voxels ≥ 100). *T*-score scale is shown on the right. R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 4
Coordinates and *T* scores of the peak voxels of the significant child ALFFs during the resting state.

Brain regions	BA	Hem	MNI			Volume (voxels)	<i>T</i>	
			X	Y	Z			
Frontal lobe	Superior frontal gyrus	6	L	-24	15	63	113	62.30
	Middle frontal gyrus	46	R	51	36	15	244	119.82
Temporal lobe	Inferior frontal gyrus	9	L	-51	12	33	510	389.71
	Inferior temporal gyrus	20	L	-54	-57	-12	301	1494.36
Parietal lobe	Fusiform gyrus	37	R	54	-51	-15	257	245.68
	Precuneus	19	L	-27	-78	42	714	171.05
Occipital lobe	Middle occipital gyrus	19	R	39	-81	24	310	119.89

Note. Cluster significance: $p < 0.0001$, FDR corrected, voxels ≥ 100 . Cluster size is in voxels. Coordinates are in standard MNI space. BA, Brodmann's area; Hem, hemisphere; R, right; L, left.

supramarginal gyrus (BA 40), and the right precuneus (BA 7). The results from the present study are highly similar to those of Zhao et al. (2011) who also used the FC method. Additionally, the results

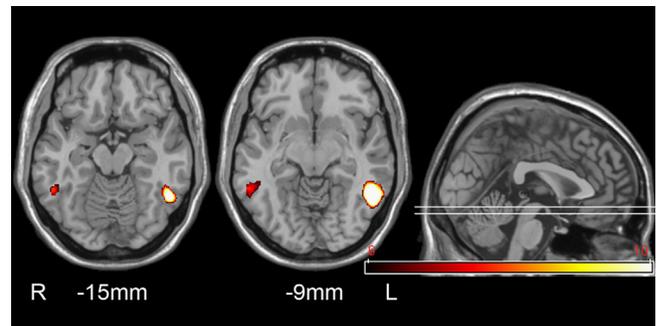


Fig. 5. The maps of conjunction analyses for FC of adults and children. Left of the image is the right side of the brain. The statistical threshold was $p < 0.05$ (FWE corrected, voxels ≥ 50). *T*-score scale is shown. R, right; L, left.

from the present study are consistent with those of Tan et al. (2001a, 2001b, 2005) who asked their participants to perform explicit Chinese word processing tasks. These findings taken together suggested the existence of an intrinsically organized word processing network during the resting state in adult readers.

As ALFF can reflect the cerebral physiological states during the resting state (Yang et al., 2007), one of the primary aims of the

present study was to examine whether certain brain regions within the intrinsically organized word processing network would show increased ALFF. Several brain regions indeed showed significantly higher ALFF than the global mean level. They included the bilateral MFG (BA 6/9), the left IFG (BA 9), the bilateral ITG/FG (BA 20),

the left IPL (BA 40), and the right precuneus (BA 7). This finding further supports the hypothesis that there exists an intrinsic neural network for word processing during the resting state in adult readers.

Now, the key components of the ALFF results within this network will be discussed in more detail.

Based on previous studies, it has been suggested that the left dorsal lateral prefrontal cortex (DLPFC, BA 9) is responsible for the coordination and integration of the intensive visuospatial analysis which is necessary for the processing of the unique square configuration of the Chinese words (Tan et al., 2001a,b, 2005). Different from alphabetic words with a linear structure, Chinese logographs are comprised of a number of strokes that are packed into a square shape according to stroke assembly rules (Chen et al., 2002). When reading Chinese words, it is necessary to analyze the relative visual-spatial locations of the strokes and subcharacter components (Tan et al., 2001a,b). The DLPFC region is crucial to normal Chinese reading, as its dysfunction is associated with Chinese reading difficulty (Siok, Perfetti, Jin, & Tan, 2004). Here, the increased ALFF for the left DLPFC (BA 9) may further underscore the crucial role that this region may play in Chinese word processing as it is also highlighted during the resting state.

Table 5

Coordinates and *T* scores of the peak voxels of the significant conjunction analysis results of FC and ALFF of the child and adult data.

Brain regions	BA	Hem	MNI			Volume (voxels)	<i>T</i>	
			X	Y	Z			
FC								
Temporal lobe	Fusiform gyrus	37	R	54	-51	-15	88	9.11
ALFF								
No significant region								

Note: FC: Cluster significance: $p < 0.05$, FWE corrected, voxels ≥ 50 . ALFF: Cluster significance: $p < 0.05$, FWE corrected, voxels ≥ 50 . Cluster size is in voxels. Coordinates are in standard MNI space. BA, Brodmann's area; Hem, hemisphere; R, right; L, left.

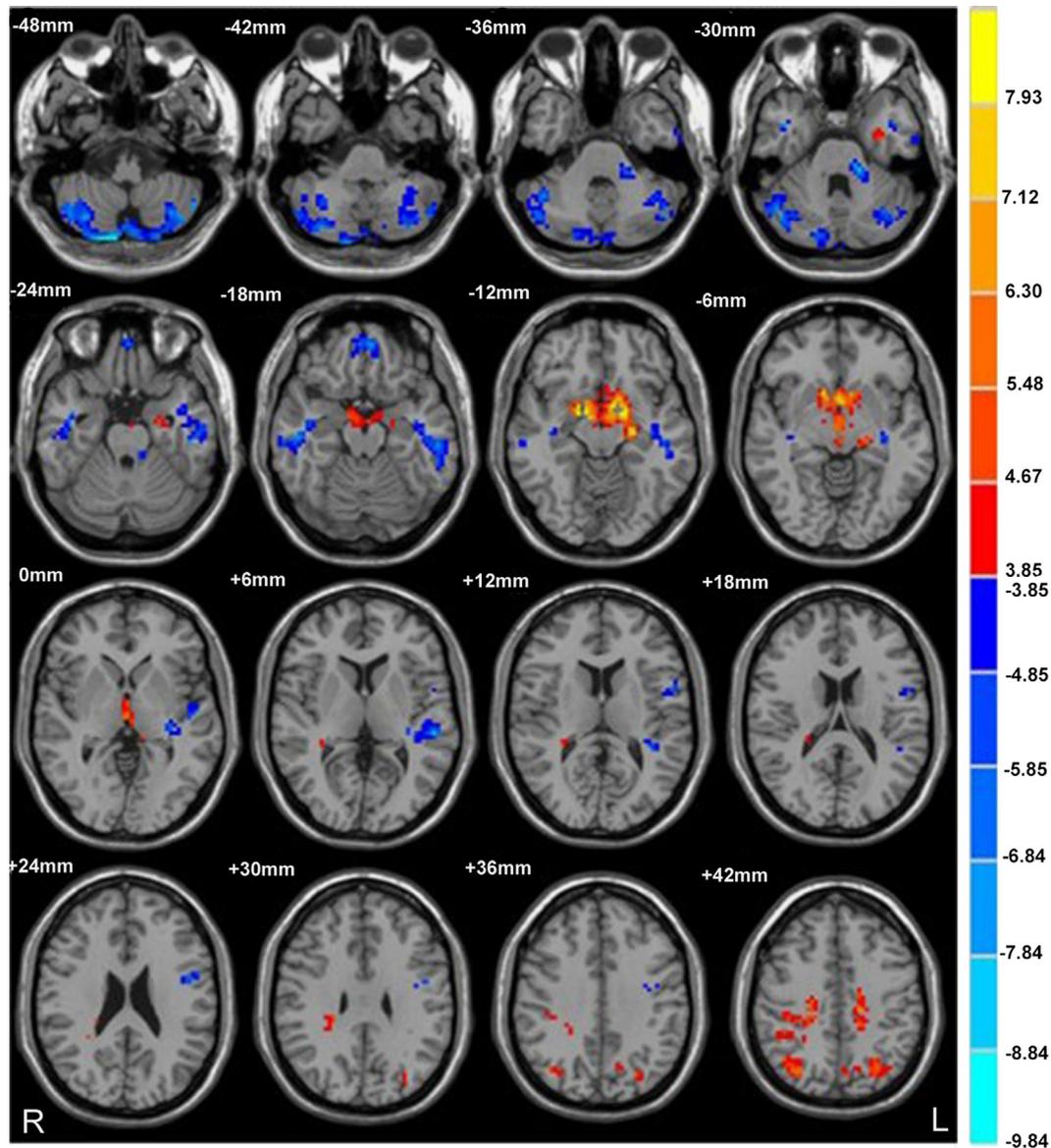


Fig. 6. Maps of two sample *t*-tests between the ALFFs of adults and children. Left of the image is the right side of the brain. Red and yellow colors denote that ALFF is larger in adults than in children and the blue color denotes the opposite. The statistical threshold was $p < 0.005$ (FDR corrected, voxels ≥ 50). *T*-score scale is shown on the right. R, right; L, left. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 6
Coordinates and *T* scores of peak voxels of the significant contrasts of FC and ALFF between the child and adult data.

Brain regions	BA	Hem	MNI			Volume (voxels)	<i>T</i>	
			X	Y	Z			
<i>FC</i>								
Adults > children								
No significant region								
Children > adults								
No significant region								
<i>ALFF</i>								
Adults > children								
Parietal lobe	Precuneus	19	R	36	-72	39	338	7.14
Limbic lobe	Middle cingulate gyrus	31	L	-15	-39	45	501	8.37
	Middle cingulate gyrus	31	R	27	-36	27	103	6.17
Sub-lobar	Lentiform nucleus	-	L	-18	0	-12	456	8.51
Children > adults								
Frontal lobe	Medial frontal gyrus	10	L	-3	51	-18	73	7.13
	Precentral gyrus	6	L	-48	0	24	64	5.92
Temporal lobe	Inferior temporal gyrus	20	L	-57	-24	-21	327	7.47
	Sub-gyral	21	R	45	-9	-21	123	7.74
Cerebellum	Anterior lobe	-	L	-15	-33	-33	68	7.62
	Posterior lobe	-	R	15	-87	-48	781	8.80

Note: FC: Cluster significance: $p < 0.05$, FDR corrected, voxels ≥ 50 . ALFF: Cluster significance: $p < 0.005$, FDR corrected, voxels ≥ 50 . Cluster size is in voxels. Coordinates are in standard MNI space. BA, Brodmann's area; Hem, hemisphere; R, right; L, left.

It has been suggested that the left ventral occipitotemporal system (i.e., the left FG) is involved in visual word form identification for processing alphabetic words (Cohen & Dehaene, 2004; Cohen et al., 2000, 2002). However, the activity of the ventral occipitotemporal system is bilateral in Chinese words processing (Liu et al., 2008, 2009; Tan et al., 2005; Zhao et al., 2011). Compared to alphabetic words, Chinese words include more spatial configural information (Liu et al., 2008). As a result, reading Chinese words requires much more orthographic processing than alphabetic words. It is, therefore, reasonable to suggest that the bilateral ventral occipitotemporal system is related to the processing of the spatial locations of the strokes and the stroke combinations for Chinese words (Tan et al., 2001a,b). In the present study, the enhanced ALFF for the bilateral ITG/FG also suggests that these areas are related to Chinese word processing due to the unique visual characteristics of Chinese words.

The left IPL has been frequently reported to be involved in the phonological processing of alphabetic (e.g., Booth et al., 2006; Ravizza, Delgado, Chein, Becker, & Fiez, 2004) as well as Chinese words (Tan et al., 2003, 2005). Unlike alphabetic words, which can be read by relying on the letter-sound correspondence rules, Chinese words alone cannot provide direct phonological information. They have to be read based on memory mapping from the shape of Chinese words to their sound. The shape-sound relationship of Chinese words is similar to that of English letters. Each letter has a distinct shape and a distinct sound, and the reading of a letter is also dependent on the retrieval of sound from memory. Booth et al. (2006) have reported that the left IPL is involved in mapping between orthographic and phonological representations, the locus of which is highly consistent with that of the present study. The function of the IPL is to temporarily store phonological information in working memory (Ravizza et al., 2004). Thus, the increased ALFF of the left IPL suggests that this region may play a significant role in the retrieval of Chinese word sounds, both when the adult readers are performing an explicit word processing task and when the adults are at rest.

In sum, our adult FC and ALFF results, above and beyond the results of Zhao et al. (2011), further demonstrate the existence of an intrinsically organized word processing network during the resting state in adult readers. The word processing resting network is likely the result of the high frequency of encounters that people have with words as well as the high level of visual processing expertise that adult readers have acquired over a long period of time. The function of the intrinsic network, as suggested by Zhao et al. (2011), may be to

prepare the adult reader to anticipate highly probable visual word input, even when individuals are not currently seeing any words (Zhao et al., 2011).

The FC analysis also revealed negative low-frequency correlations between the VWFA and particular brain regions. It is unclear what factors could have led to these negative correlations. Recent resting state fMRI studies have provided some speculative insights. Kelly, Uddin, Biswal, Castellanos, and Milham (2008) found that the strength of negative connectivity has been related to behavior variability (e.g., RT in an attentional task). They suggested that the strength of negative connectivity between some systems could potentially be an index of optimally balanced competition between neural systems, which might be one of the keys to successful behavior (Kelly et al., 2008; Koyama et al., 2010). Additionally, some other researchers have demonstrated that the negative resting-state FC was, at least in part, a consequence of preprocessing strategies such as global correction (Murphy, Birn, Handwerker, Jones, & Bandettini, 2009). This problem needs to be further explored in the future.

4.2. Findings from Experiment 2

In Experiment 2, children's VWFA ($x = -48$, $y = -51$, $z = -12$, MNI coordinates) was identified in the left middle fusiform gyrus, the locus of which was similar to that of the adult VWFA ($x = -51$, $y = -54$, $z = -9$, MNI coordinates) identified in Experiment 1. Similar coordinates have been reported in children learning to read alphabetic words (Booth et al., 2004; Van Der Mark et al., 2011). In Booth et al.'s (2004) study, the coordinates identified by a visual spelling task and a visual rhyming task, respectively, were $(-36 -72 -12)$ and $(-39 -48 -21)$ when children (9- to 12-year-olds) were reading English. In Van Der Mark et al.'s (2011) study, the coordinate identified by a phonological lexical decision task was $(-42 -54 -17)$ in children (9.7–12.5 years) reading German.

Reading is not an innate ability and needs to be learned through extensive practice and experience. Previous studies have demonstrated that the development of the VWFA may be driven by the progression of expertise rather than merely a matter of maturation (McCandliss et al., 2003). The children (ages: 10–11) in the present study had been learning to read informally since approximately 2 years of age and formally since about 7 years of age. With such significant exposure to reading, some brain areas may begin to adapt to the functions necessary for visual word

processing. Consequently, though still far from the adult state, an adult-like VWFA and associated specialized reading network begins to emerge and develop (Brem et al., 2006; Maurer, Brem, Bucher, & Brandeis, 2005).

The child FC analysis revealed positive low-frequency correlations between the VWFA and a number of brain areas, including the bilateral MFG (BA 46), the right IFG (BA 9), the right FG (BA 37), the right SPL (BA 7), and the left precuneus (BA 7). These results suggest an intrinsically organized network may also exist in children during the resting state. Similar to the emergence and development of the VWFA and reading network, children's extensive informal and formal experience with reading may also lead children to develop an intrinsically organized reading network, ostensibly to prepare children to anticipate highly probable visual word input.

The FC analyses of the child data also revealed negative low-frequency correlations between the VWFA and many brain regions, including the right MFG (BA 10), the left cuneus (BA 18), the right MOG (BA 18), the right middle cingulate gyrus (BA 24), and the right insula (BA 13). As discussed above, the implications of these findings are ambiguous and need to be explored in future studies.

4.3. Findings from the conjunction analyses between Experiments 1 and 2

The conjunction analyses of the FC data allowed us to ascertain whether certain brain regions in children's and adults' resting state network for visual word processing had significant common low frequency correlations with the VWFA. The only significant region was the right FG (BA 37). Interestingly, based on previous studies (Tan et al., 2001a,b; Zhao et al., 2011), the right FG has been consistently identified to be uniquely involved in Chinese visual word processing due to the unique characteristics of Chinese visual words, for example, the spatial locations of the strokes and the stroke combinations. Thus, this finding may apply to the resting state networks of young and experienced readers who have learned to read Chinese characters or similar scripts (e.g., Kanji in Japanese). This is an intriguing possibility that should be tested in future studies. The FC conjunction results further suggest that the right FG may be the essential component of the resting state network for Chinese visual word processing. Thus, it is likely that a few years of informal and formal reading exposure may be sufficient for this part of the word processing resting state network to reach the adult level.

The conjunction analyses of the ALFF data allowed us to ascertain whether certain brain regions in children's and adults' resting state network for visual word processing had significant common magnitudes of neural activities during the resting state. The ALFF group conjunction analysis failed to show any significant results, the implication of which needs to be considered in light of the results from the contrast analyses of the ALFF data between children and adults (see below).

4.4. Findings from the contrast analyses between Experiments 1 and 2

To determine whether FCs differed between adult and child resting state word processing networks, direct contrast analyses were performed between the child and adult data. Interestingly, no significant differences were found in terms of the time course of the low frequency activities between the VWFA and other brain regions in the child and adult resting state networks for visual word processing. This finding suggests that insofar as the specific brain regions involved the resting state word processing networks are concerned, the network of 10- and 11-year-old child readers is highly similar to that of adult readers. In other words, 3–4 years of

formal schooling plus 3–4 years of informal reading experience are sufficient for children to develop a resting state network similar that of adults in terms of the functional network structure. Future studies need to recruit younger elementary school children and even preschoolers to ascertain how children's resting state network for visual word processing emerges and develops into an adult-like one, and the extent of reading experience that is needed for such development.

In contrast to the FC findings, the contrast between children and adults in terms of the ALFF revealed that several brain areas had significantly higher ALFF amplitudes for children than for adults. These regions included the left medial frontal gyrus (BA 10), the left precentral gyrus (BA 6), the left ITG (BA 20), the right temporal lobe sub-gyral (BA 21), the right cerebellum anterior lobe, and the left cerebellum posterior lobe. Note that these regions are generally not part of the network for the explicit processing of visual words, nor are they a part of the adult resting state network for visual word processing. Thus, it appears that during the resting state, some brain regions irrelevant to visual word processing might have become unnecessarily more active in low frequency fluctuation amplitude in children relative to adults. Among most adults with extensive reading experience, word reading is a relatively automatized process. By comparison, children have less word processing experience and have a smaller sight vocabulary of Chinese words. This difference in proficiency between children and adults in reading may explain the current finding. Consistent with this speculation, the current behavioral results showed that, on average, adults had higher accuracy and less reaction time than children in the explicit Chinese word discrimination task. Thus, the increased amplitude in these brain regions among children might suggest the relatively excessive engagement of superfluous neural resources and thus reflect children's relative inexperience in reading, an intriguing possibility to be tested in future studies.

Contrary to the contrast between the child ALFF data and the adult ALFF data, the reverse contrast (i.e., the contrast between the adult ALFF data and the child ALFF data) revealed that only three cortical regions had greater magnitude in low frequency fluctuation in adults than in children. They were the right precuneus (BA 19) and the bilateral middle cingulate gyrus (BA 31). The right precuneus has been found to be involved in Chinese word processing (Chen et al., 2002; Fu, Chen, Smith, Iversen, & Matthews, 2002). Further, converging evidence has suggested that the precuneus is involved in the successful retrieval of source memory (Lundstorm, Ingvar, & Petersson, 2005). Additionally, converging evidence has suggested that the cingulated gyrus might be involved in the phonological processing of visual word recognition of Chinese words (Chen et al., 2002; Tan et al., 2005). It is therefore reasonable to predict that these brain regions may be recruited for the perceptual decoding of the visual forms of Chinese characters.

5. Limitations

It should be noted that, in our experiments, resting state data were collected when subjects closed eyes to avoid some unexpected brain activities caused by opening their eyes. Eye-open is another preparatory state for the study of resting state. Some studies (Yan et al., 2009; Zou et al., 2009) have demonstrated differences in resting state FC patterns between eye-close and eye-open conditions in the default mode network and visual networks. The influence of the eye-open and eye-closed conditions within the resting state word processing network can be investigated in the future. In addition, in the current study, there were no significant correlations between behavioral data (i.e., reaction time & accuracy) and functional data. This lack of significant correlations was likely due the simplicity of the task used (judging whether the pictures were the same or

different). We used a simple task due to the fact that our study involved both adults and children and we needed to make the task relatively easy for all in order to prevent task difficulty from confounding our age-related findings. Future studies could vary the difficulty of the reading tasks to ascertain whether behavioral data could be predicted by neural activities during both the resting and explicit reading task states.

6. Summary

In this study, we used both the functional connectivity (FC) and amplitude of low frequency fluctuation (ALFF) approaches to analyze Chinese children's and adults' fMRI data collected during the resting state. The FC approach was performed to correlate the time courses of the low frequency fluctuation activities in the VWFA and those of other brain regions. The ALFF approach was applied to obtain the amplitude of the low frequency fluctuation in both the VWFA and in other brain regions.

The FC results revealed that there exists a largely similar intrinsically organized word processing network in both adults and children during the resting state. The similarities of the FC results between children and adults suggest that such a network may begin to function after only 3–4 years of informal exposure to reading combined with 3–4 years of formal schooling. The child and adult intrinsic neural networks for word processing recruit largely similar brain regions, which are also involved in the task-dependent word processing networks. In contrast to the FC results, the ALFF analyses have revealed that children appear to recruit more neural resources than adults in largely reading-irrelevant brain regions. The differences of the ALFF results between children and adults suggest that children's intrinsic word processing network during the resting state, though similar in functional connectivity to that of adults, is still undergoing development. Further exposure to visual words and experience with reading appear to be needed for children to develop a mature intrinsic network for visual word processing. The developmental course of the intrinsically organized word processing network may parallel that of the explicit word processing network. The findings from the present study thus provide new insights into neural mechanisms underlying reading, visual word processing in particular, in both children and adults.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.neuropsychologia.2013.05.011>.

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