



## Intrinsically organized network for word processing during the resting state

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### ABSTRACT

Neural mechanisms underlying word processing have been extensively studied. It has been revealed that when individuals are engaged in active word processing, a complex network of cortical regions is activated. However, it is entirely unknown whether the word-processing regions are intrinsically organized without any explicit processing tasks during the resting state. The present study investigated the intrinsic functional connectivity between word-processing regions during the resting state with the use of fMRI methodology. The low-frequency fluctuations were observed between the left middle fusiform gyrus and a number of cortical regions. They included the left angular gyrus, left supramarginal gyrus, bilateral pars opercularis, and left pars triangularis of the inferior frontal gyrus, which have been implicated in phonological and semantic processing. Additionally, the activations were also observed in the bilateral superior parietal lobule and dorsal lateral prefrontal cortex, which have been suggested to provide top-down monitoring on the visual-spatial processing of words. The findings of our study indicate an intrinsically organized network during the resting state that likely prepares the visual system to anticipate the highly probable word input for ready and effective processing.

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Reading is an essential part of our everyday life in a modern literary society, of which word processing plays an important role. In the last several decades, there has been extensive research on the neural mechanisms underlying word processing. Based on these findings, a dual route model has been proposed, which includes first a common visual neural pathway for processing the word form, and then two parallel phonological and lexico-semantic routes. For the visual processing of words, Cohen et al. [3] propose the left middle fusiform gyrus to be specifically responsible for the visual form processing of words (i.e., the visual word form area, VWFA, but see [18]). Beyond the visual processing route, the left superior temporal gyrus, left supramarginal gyrus, and left inferior frontal gyrus (pars opercularis) are suggested to belong to the phonological

route to subserve the phonological decoding of words [2]. Meanwhile, the left inferior temporal gyrus, left angular gyrus, and left inferior frontal gyrus (pars triangularis) are thought to be part of the lexico-semantic route for the semantic retrieval of words [1]. Additionally, the superior parietal lobule and intraparietal sulcus have been suggested to be involved in visual attention modulation during word processing [9].

A similar set of neural pathways has been identified by studies examining Chinese character-processing. Consistent with the VWFA identified with alphabetic scripts, Liu et al. [14] identified Chinese character-preferential regions in the ventral occipitotemporal cortex. The anterior (BA 45) and posterior (BA 44) inferior frontal gyri are found to respond to both Chinese characters and alphabetic words [2,13]. Additionally, some regions are uniquely recruited in Chinese character processing for their special square configurations (e.g., the left middle frontal gyrus [21]).

In addition to the investigation of neural regions involved in active word processing, researchers employ various functional connectivity methods to explore the functional and effective connectivity among these regions (structural equation modelling [11] and dynamic causal model [2]). These analyses have revealed active interactions between the specific word-processing regions (e.g., [7]) and provided new insights into the neural organization of the word-processing network.

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However, these studies have examined only the functional or effective connectivity between the word-processing regions when individuals are actively engaged in a particular word-processing task. It is unclear whether the word-processing regions are intrinsically organized during the resting state without any explicit task demand. In recent years, resting state functional connectivity MRI analysis (rs-fcMRI) has been extensively employed to examine the intrinsically organized functional connectivity patterns within or between distinct subsystems of the brain [22]. Recently, Zhang et al. [23] identified strong functional connectivity between face preferentially responsive regions during the resting state, namely the bilateral posterior fusiform gyrus, inferior occipital gyrus, and superior temporal sulcus. They suggested that “the existence of such network may reflect the fact that faces are not only the visual stimuli that we tend to have the highest processing expertise [24] but also the most common visual stimuli we tend to encounter in our everyday social life. Thus, this intrinsically organized face resting state network may prepare the visual system to anticipate to process faces, the most socially significant category of visual stimuli” (page 5).

Words are in many ways similar to faces. In a modern society, we encounter words frequently and extensively on a daily basis. We see words in books, magazines, newspapers as well as traffic signs and billboards. Further, most literate adults are expert at processing words. Thus, similar to face processing, even when individuals are not encountering any words, the visual system may also be prepared to anticipate a highly probable word input. If it is the case, one should expect an intrinsically organized word-processing network to be present even without explicit word-processing tasks. To the best of our knowledge, no study has directly tested this intriguing hypothesis. It should be noted, however, that Hampson et al. [6] examined the resting state functional connectivities of language-processing cortexes. Their analysis was only limited to Broca's areas, Wernicke's areas and premotor regions known to be involved in speech processing; they did not explore the functional connectivities of these areas to the early perceptual areas involved in the decoding of linguistic input generally and word input in particular. The aim of our study was thus to bridge this gap in the literature by investigating the intrinsic functional connectivity between the word-processing regions using the rs-fcMRI analysis.

Twenty-four right-handed Chinese undergraduates (mean age: 23 years, SD: 2.5 years, 8 females) with normal vision participated in this study. All subjects gave their written informed consent. The study was approved by the Human Research Protection Program of Tiantan Hospital, Beijing, PR China.

The experiment was divided into three phases. In the first phase, a 310-s resting session was scanned. Participants, unaware of the exact experimental design, were instructed to lie with their eyes closed, thinking of nothing in particular. In the second phase, a 240-s visual discrimination task was performed. At the beginning, a 6-s scanning of fixation was shown to allow for stabilization of magnetization, and another 10-s scanning of fixation was included at the end for the delay of hemodynamic response. The session included six 24-s blocks interleaved with five 16-s fixation epochs in which cross hair was presented (Fig. 1). Each block included six trials. 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 of fixation. During the last fixation, participants judged whether the two stimuli were identical. Equal number of the same and different trials was included. The third phase was a localizing session in which the localizer consists of a Chinese character localizer task and a face localizer task (Fig. 1).

MRI scans were performed in a 3 T (Siemens Trio a Tim, German) scanner. A T2-weighted gradient-echo planar imaging sequence was used for fMRI scans, with the slice thickness = 4 mm, in-

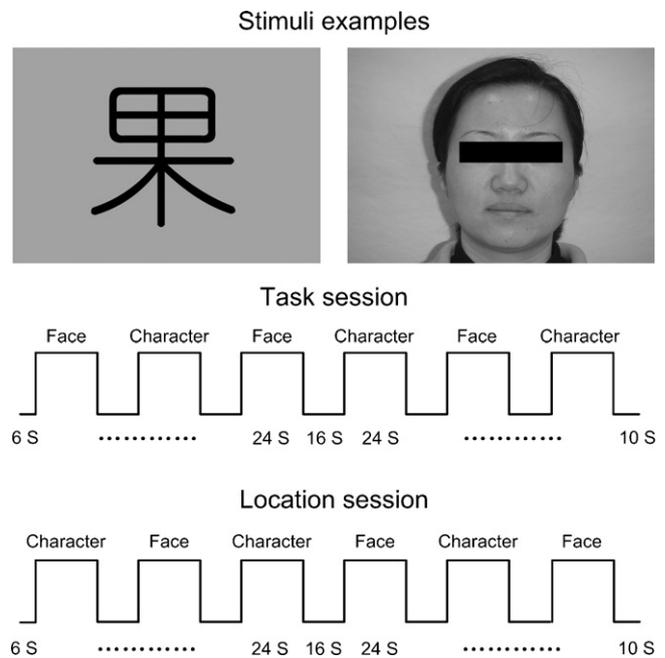


Fig. 1. Sample stimuli and the experiment design (eye region was shown during the experimental sessions but masked here for protection of privacy).

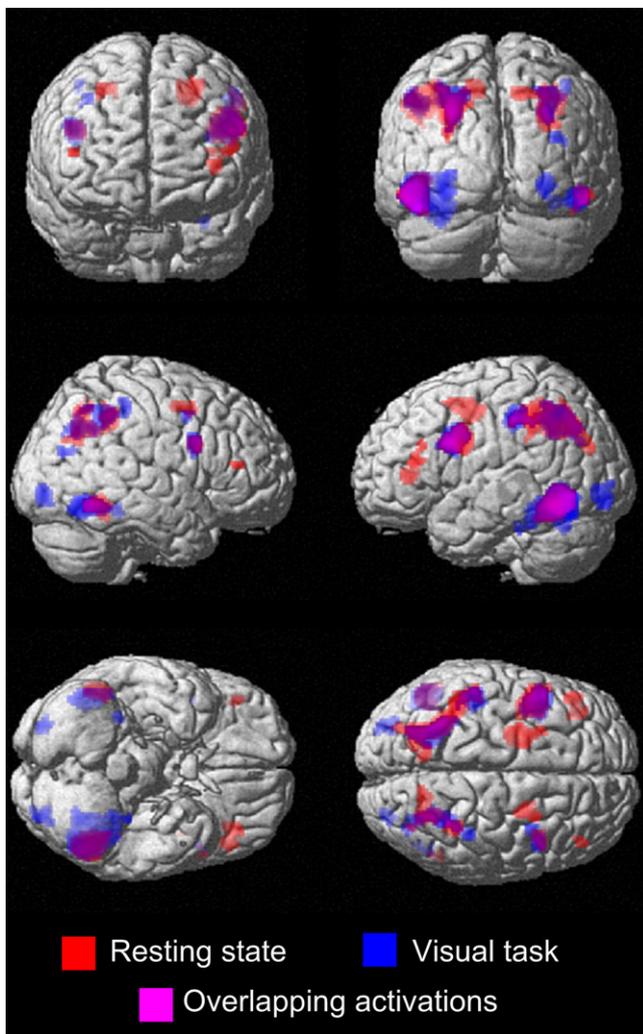
plane resolution = 3.75 mm × 3.75 mm, and repetition time/echo time = 2000 ms/30 ms. For each participant, high-resolution (voxel size: 1 mm × 1 mm × 1 mm, matrix size: 256 × 256 × 256) anatomical images were acquired using a T1-weighted, three-dimensional gradient-echo imaging sequence.

Before processing, the first three scans of each session were discarded. Data were analyzed using SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>). Preprocess included slice timing, realignment, normalization to the standard EPI (MNI) template, and smoothness with a Gaussian kernel of 6-mm FWHM. For the resting and task sessions, global proportional scaling was performed respectively to yield a whole brain intensity value of 1000. Then, the data were temporally band-pass filtered (0.01 Hz <  $f$  < 0.08 Hz) using Resting-State fMRI Data Analysis Toolkit (<http://www.restfmri.net>).

For the localizer session, data were high-pass filtered to eliminate the low-frequency components (cut-off value of 128 s). A general linear model including two condition regressors (characters and faces) and six parameters for head motion was constructed for each participant. The condition regressor was created by convolving a canonical hemodynamic response function with a delta function corresponding to the onset time series of each stimulus category.

The seeding region of Chinese characters and faces were defined by the contrast of characters vs. faces and the reverse, with a statistical threshold  $p < 0.0001$ . The reason to contrast Chinese characters with faces was that Chinese characters and faces often activated similar regions in the ventral occipitotemporal cortex of Chinese participants. These contrasts thus allowed for identifying word-processing specific brain regions.

For the resting and task sessions, the time series averaged over the character-preferential region and face-preferential region, three null regressors of signals averaged over the whole brain (global signal), ventricles, and a region in deep cerebral white matter (picked by a sphere of 6-mm radius, centered at (26, -20, 30)), as well as six parameters for head motion were used as regressors to construct general linear model for each participant [22]. The functional connectivity mappings between the character-preferential region and all the other whole brain voxels were obtained using random-effect analysis across all subjects. The regions exceeding



**Fig. 2.** Functional connectivity maps of the left middle fusiform gyrus during the resting state (red) and the visual discrimination tasks (blue) (purple regions are the overlapping regions of those two types of activations,  $p=0.0001$ , uncorrected, cluster size  $>20$ ). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

the threshold of  $p=0.0001$  (uncorrected) and with a cluster  $>20$  voxels were analyzed. Additionally, paired  $t$ -tests and conjunction analyses were performed on the correlation maps under the resting state and visual tasks with the threshold of  $p=0.001$  (uncorrected) and cluster  $>20$  voxels.

During the localizer task, character-preferential regions were identified within the left middle fusiform gyrus ( $-47 \pm 4$ ,  $-58 \pm 6$ ,  $-12 \pm 4$ , mean size: 67 voxels) in 14 subjects [3]. Face-preferential regions were identified within the right posterior fusiform gyrus ( $42 \pm 5$ ,  $-50 \pm 6$ ,  $-22 \pm 4$ , mean size: 182 voxels) in 20 subjects [10]. Thus, the 14 subjects with both of their character-preferential region and face-preferential region identified were included for further analysis.

During the resting state, the functional connectivity analysis revealed a significant low-frequency correlation between the left middle fusiform gyrus and an extensive number of cortical regions, including the bilateral middle occipital gyrus, right fusiform gyrus, left middle temporal gyrus, left angular gyrus, left supramarginal gyrus, left inferior parietal lobule, right intraparietal sulcus, bilateral superior parietal lobule, bilateral precuneus, inferior frontal gyrus (bilateral at BA 44, left at BA 45), bilateral middle frontal gyrus, left precentral gyrus, and left cingulate gyrus (Fig. 2, Table 1). During the visual task, the left middle fusiform gyrus was coupled

strongly with several regions, including the bilateral culmen, left declive, bilateral lingual gyrus, bilateral inferior and middle occipital gyrus, right fusiform gyrus, left supplementary motor area, and right superior temporal gyrus (Fig. 2, Table 2). The paired  $t$ -tests revealed greater functional connectivity between the left middle fusiform gyrus with the left middle frontal gyrus (BA 9) and right parahippocampal gyrus during the resting state than during the visual task.

The conjunction analysis revealed several common regions activated in the functional connectivity mappings of the resting state and the visual task. They included the left middle occipital gyrus, right fusiform gyrus, left angular gyrus, left supramarginal gyrus, left inferior parietal lobule, right intraparietal sulcus, bilateral superior parietal lobule, bilateral precuneus, inferior frontal gyrus (bilateral at BA 44, left at BA 9 and BA 45), and left middle frontal gyrus (Tables S1 and S2 in supplementary materials).

The present study investigated the intrinsic functional connectivity between the word-processing regions using the rs-fcMRI analysis. During the resting state condition, we found low-frequency functional fluctuations between the left middle fusiform gyrus and extensive number of brain regions that have been identified to play an important part in word processing. These findings provide direct evidence to suggest the presence of spontaneous activities within the word-processing network during the resting state. The paired  $t$ -tests comparing the resting state and visual task further suggested modulation in the functional connectivity of this network due to task demands. In the following, we will discuss the key components of this intrinsic network in detail.

During the *resting state*, we found the right middle fusiform gyrus to be significantly co-activated with the left middle fusiform gyrus (also during the active word-processing task). In the visual form processing of *alphabetic words*, the right middle fusiform gyrus is typically considered to play only a secondary role when compared to the left middle fusiform gyrus [4]. In contrast to alphabetic word processing, several studies with Chinese adults have found a parallel involvement of the bilateral middle fusiform gyrus in Chinese character processing [21]. The low frequency functional fluctuations between the left and the right middle fusiform gyri may reflect the spontaneous participation of the right middle fusiform gyrus in word processing unique to Chinese literate adults.

Consistent with Hampson et al.'s findings [6], extensive activation was observed within the posterior parietal cortex and ventral frontal regions during the resting state, including the left angular gyrus, left supramarginal gyrus, pars opercularis and pars triangularis of the left inferior frontal gyrus. In their study, the functional connectivity of the Broca's and Wernicke's areas was calculated directly by selected regions of interest. In the current study, those regions were observed to be functionally coupled with the left middle fusiform gyrus synchronously. This result once again confirms the critical roles of the Broca's and Wernicke's areas in general language processing.

The supramarginal gyrus has been shown to be involved in the orthography-to-phonology mapping [20]. Recent studies have found that the co-activations of the left supramarginal gyrus and left middle fusiform gyrus are closely related to an individual's reading ability [2]. The angular gyrus has been hypothesized to be essential for the access of stored orthographic knowledge during semantic processing [11]. Cerebral lesion studies have indeed shown a reduced functional connectivity between the left middle fusiform gyrus and the left angular gyrus among reading-impaired subjects when compared to normal readers [8]. The posterior left inferior frontal gyrus (pars opercularis) has also been found to be involved in the grapheme-to-phoneme conversion [16,1]. The anterior left inferior frontal gyrus (pars triangularis) has been demonstrated to be engaged in the word-level semantic processing [12,21]. Previous studies have revealed a strengthened connectivity

**Table 1**The foci of brain areas functionally coupled with the left middle fusiform gyrus during the resting state ( $p = 0.0001$ , uncorrected, cluster size > 20).

Region	BA	Voxel	Z	Talairach		
				x	y	z
L. fusiform gyrus	37	538	5.95	-47	-52	-16
L. middle temporal gyrus	37		4.61	-40	-53	-5
L. precuneus	7	960	5.64	-26	-64	30
L. angular gyrus	39		5.36	-28	-59	31
L. superior parietal lobule	7		4.58	-17	-62	47
L. inferior parietal lobule	40		4.46	-37	-49	46
L. supramarginal gyrus	40		4.34	-40	-44	34
L. middle occipital gyrus	19		4.31	-27	-78	18
R. intraparietal sulcus	40	396	4.98	30	-47	40
R. precuneus	7		4.71	24	-61	33
R. superior parietal lobule	7		4.64	26	-60	44
R. middle occipital gyrus	19		3.97	32	-71	23
L. middle frontal gyrus	6	245	4.79	-24	-9	43
L. cingulate gyrus	24		4.53	-24	-15	46
L. middle frontal gyrus	6		4.36	-26	3	53
L. precentral gyrus	6	496	4.75	-38	-4	25
L. inferior frontal gyrus	44		4.61	-38	4	27
L. inferior frontal gyrus	44		4.58	-49	2	27
R. fusiform gyrus	37	133	4.74	47	-53	-11
R. fusiform gyrus	37		4	43	-47	-16
R. inferior frontal gyrus	44	74	4.53	36	5	27
R. middle frontal gyrus	6	80	4.39	21	-8	49
R. middle frontal gyrus	6		4.29	26	-1	48
R. cingulate gyrus	24		4	17	0	48
L. middle frontal gyrus	46	65	4.34	-46	27	20
L. middle frontal gyrus	46		4.11	-46	22	27
L. inferior frontal gyrus	45		3.8	-34	25	19
L. inferior frontal gyrus	45	45	4.29	-36	33	12
R. middle frontal gyrus	46	20	4.17	40	30	20

of the anterior and posterior parts of the left inferior frontal gyrus with the left fusiform gyrus respectively due to increased semantic retrieval demands [1] and phonological processing requirements [2]. The intrinsic connectivity of those four regions with the left middle fusiform gyrus found here probably forms a resting state network that readies the word-processing system to anticipate the processing of phonological and semantic word information.

Furthermore, we found the superior parietal cortex and dorsal lateral prefrontal cortex (DLPFC) to be functionally coupled with the left middle fusiform gyrus during the resting state. The left superior parietal lobule (SPL) has been shown to be activated in visual-spatial processing tasks and to execute the top-down visual attention control [19]. The DLPFC (BA 46) has been implicated in attention maintenance and to play an executive control

role in working memory tasks [17]. Within the Chinese character processing literature, those two regions are proposed to serve the monitoring of visual-spatial mapping from the stroke components in a Chinese character to its phonology and the short term maintenance of phonological codes [2,14]. The function of the low-frequency fluctuations between those two regions and the left middle fusiform gyrus during the resting state is possibly similar to that of the top-down control in real words processing [15], which reflects the synchronous neural activation of the anterior brain regions with the posterior visual cortex for the perceptual analysis of Chinese characters.

During the visual task, extensive visual cortical regions were functionally correlated with the left middle fusiform gyrus, reflecting the effect of visual stimuli and task demands. Similar phe-

**Table 2**The results of paired *t*-test on the functional connectivity mappings of the resting state and the visual task ( $p = 0.001$ , uncorrected, cluster size > 20).

Region	BA	Voxel	Z	Talairach		
				x	y	z
Resting state vs. visual task						
L. middle frontal gyrus	9/46	57	4.59	-33	20	31
R. parahippocampal gyrus	Hippocampus	22	4.17	33	-11	-14
Visual task vs. resting state						
R. inferior occipital gyrus	19	281	4.33	34	-76	-8
R. middle occipital gyrus	18		4.04	27	-82	-8
R. lingual gyrus	17		3.29	15	-89	-6
L. inferior occipital gyrus	19	381	4.31	-31	-76	-7
L. middle occipital gyrus	18		4.04	-29	-83	-8
L. lingual gyrus	18		3.81	-18	-89	-12
L. culmen	*	161	4.13	-27	-52	-19
L. declive	*		4.06	-29	-59	-22
L. supplementary motor area	6	90	4.04	-9	-11	57
R. culmen	*	104	3.89	27	-38	-28
R. superior temporal gyrus	22	24	3.56	41	-32	6
R. fusiform gyrus	37	59	3.54	40	-59	-10

\* Represents that the activated area is not located in the Brodmann areas.

nomena were also observed in the left supplementary motor area and right superior temporal gyrus. Those two regions have been demonstrated to be related to speech production [7] and semantic processing [21] of words, respectively. Interestingly, the functional connectivity between the left middle frontal gyrus and the left middle fusiform gyrus during the resting state was stronger than that during the visual task. One possibility is that these regions are co-activated during the abstraction from stroke-level visual forms to character-level visual forms but our regression analysis with the low-frequency signal failed to capture this relationship. With respect to the right parahippocampal gyrus, the low-frequency fluctuation between this region and the left middle fusiform gyrus may reflect the role of visual memory in word processing [5].

It should be noted that our resting state data were collected when participants closed their eyes to avoid the potential spurious confounds caused by eye opening and blinks. Recent findings suggest stronger regional amplitudes of low frequency fluctuation within the visual cortex in the eye-open than in the eye-closed condition [22]. Because the resting state with eye-open is another important preparatory state for the word processing system, the influence of the eye-open and eye-closed conditions on this system should be empirically investigated with specifically designed future studies.

In summary, the present study examined the intrinsic functional connectivity between word-processing regions using the rs-fcMRI analysis. Our findings suggest the existence of an intrinsic-organized neural network preparing for word processing. This network includes both the cortical regions for phonological and semantic decoding of the words and the regions for modulating the visual processing of the words. Similar to the face-processing resting network, this word-processing resting network is likely the result of high frequency encounters that we have with words as well as high level visual process expertise acquired over two decades [23,11]. This network perhaps serves to prepare the word-processing system to anticipate highly probable word input for ready and effective processing.

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### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neulet.2010.09.067.

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