

Investigating the neural substrates of Chinese character processing

Wu, Chiao-Yi

2014

Wu, C. (2014). Investigating the neural substrates of Chinese character processing. Doctoral thesis, Nanyang Technological University, Singapore.

<https://hdl.handle.net/10356/55297>

<https://doi.org/10.32657/10356/55297>

INVESTIGATING THE NEURAL SUBSTRATES OF CHINESE CHARACTER PROCESSING

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A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

2014

ACKNOWLEDGEMENT

It has been a memorable journey and a valuable experience for me to work on my Ph.D. research. This thesis would never have been possible without the support of many people and institutions, as well as the dedication of all the participants.

First of all, I would like to express my most sincere gratitude to my supervisor, Prof. Shen-Hsing Annabel Chen, for her guidance throughout my graduate studies in the Division of Psychology at Nanyang Technological University. Prof. Annabel has started to teach me, inspire me, and guide me in research since I first joined her lab in the Department of Psychology at the National Taiwan University back in 2006. She brought me into the world of cognitive neuroscience and enlightened me with her excellent research skills. She has been patiently leading me along the road of scientific research, and meanwhile she allowed freedom for me to develop as an independent researcher. In the past few years, what I have learnt from her is tremendous. I am very lucky and thankful to be one of her students, and it has been a very enjoyable time to be working with her. I am truly grateful for her guidance, encouragement, and patience that have helped me overcome several challenges in my research and studies.

I would also like to thank the anonymous thesis examiners and the oral defense committee: Prof. Moon-Ho Ringo Ho, Prof. Hong Xu, and Prof. Alice Hiu Dan Chan for their constructive comments that have helped me improve my thesis substantially.

Many thanks go to the former members in Prof. Annabel's lab who have assisted me with participant recruitment and fMRI data collection for my studies. In particular, I am very grateful for the support and help from Dr. Kayako Matsuo, Dr. Ching-I Lu, Yu-Ju Peng, and Shih-Shiu Hou. In addition, I would like to thank Dr. Wen-Yih Isaac Tseng and his lab members at the Center for Optoelectronic Biomedicine at the National Taiwan University College of Medicine and Hospital for their assistance in setting up imaging protocols and their support with imaging facilities.

I would like to take this opportunity to thank the National Science Council in Taiwan for funding the research in my thesis and Nanyang Technological University for awarding the Research Scholarship to support my graduate studies.

Last but not the least, my heartfelt thanks go to my friends and families who have given me support and company at the good times and bad. Without my fellow friends' companion and encouragement, especially from Han Lin, this Ph.D. journey

would have been even more difficult and challenging. Most importantly, I am indebted to my parents for their unwavering faith in me, for providing me the liberty to pursue my dreams, and for buttressing me regardless of success or failure. Their unfailing love and caring are the most essential elements that have given me the strength to keep going through these years.

Publication: Study 1 in the thesis has been published in full as a journal article as it appears in “Wu, C.-Y., Ho, M.-H. R., & Chen, S.-H. A. (2012). A meta-analysis of fMRI studies on Chinese orthographic, phonological, and semantic processing. *NeuroImage*, 63(1), 381-391.”

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ABSTRACT

Most of the existing models of language have been based on alphabetic languages; however, growing evidence has shown that character language processing, such as Chinese, might recruit differentiated brain networks due to its unique linguistic features. This thesis proposed a research framework by using functional magnetic resonance imaging (fMRI) to investigate the neural mechanisms underlying Chinese character processing. We hoped to further explore whether Chinese character processing involved differential neuroanatomical representations as compared with the universal language network that has been based on alphabetic languages. The research framework consisted of two levels: direct and converging evidence, through three lines of investigations.

Study 1 and Study 2 provided direct evidence of the neural mechanisms for Chinese character processing. Study 1 set the stage for this research by summarizing the neural networks underlying Chinese orthographic, phonological, and semantic processing independently. A meta-analysis was conducted on existing fMRI studies that investigated the neural substrates underlying Chinese character processing. The results demonstrated the divergent activation for three language-processing components and consolidated the findings of additional recruitment of the left middle frontal gyrus and the right ventral occipito-temporal cortex for Chinese character processing as compared with the universal language network. The additional regions are thought to form a sub-network that might be specific to Chinese character processing. Regions-of-interest (ROIs) were defined based on the meta-analysis findings and a priori ROI approaches were implemented in the subsequent studies to examine the involvement and integrity of the sub-network. Study 2 directly examined the involvement of the sub-network in Chinese character identification and

homophone judgment with the aims to elucidate the functional roles of the ventral occipito-temporal cortex and the middle frontal gyrus in orthographic (Study 2a) and phonological processing (Study 2b), respectively. The bilateral ventral occipito-temporal cortices are involved in character form recognition, with the amount of activation modulated by lexicality effect and demands of orthographic analysis. The middle frontal gyrus is suggested to be a domain-general region that coordinates information from different domains, and thus it might be associated with orthography-to-phonology transformation in reading Chinese.

Study 3 provided indirect evidence for the involvement of the sub-network in Chinese character processing by investigating the integrity of the sub-network in terms of how it might be affected by individual characteristics such as age and handedness. Study 3a examined age effects on the sub-network during word retrieval. Consistent with previous studies on alphabetic language speakers, the results showed increased bilateral inferior frontal activation and reduced default mode network deactivation in the older adults during the language tasks, indicating age-related changes in the neural correlates underlying word retrieval to be universal. However, age-related changes in the sub-network were also revealed by the ROI analysis, which suggest language-specific vulnerability to aging. Study 3b explored language dominance within the inferior frontal gyrus and the sub-network with respect to handedness. Handedness was indicative of the lateralization of all selected regions, and the lateralization was correlated between regions. While the lateralization of the inferior frontal gyrus seemed to be universal across speakers of different languages, spatial heterogeneity in language dominance was observed in the sub-network especially in the left-handers.

These investigations shed light on the understanding of the functional roles and the integrity of the specialized sub-network for Chinese character processing.

Identifying the differential activation of Chinese character processing provided important implications for clinical applications, such as pre-surgical planning and establishing models for intervention in language disorders.

CHAPTER I: INTRODUCTION

Language, being a unique ability evolved in humans, serves a universal function in communication. Yet, there are more than 6,000 spoken languages in the world, and these languages vary in many aspects, such as orthography, phonology, morphology, semantics, and syntax (Lewis, 2009). The linguistic variations across language systems reflect differences in the cultural environments in which language systems are developed, and they also contribute to differences in the ways languages are represented in the human mind. Furthermore, language experiences are believed to lead to diversity in the representations at the neural level, both anatomically and functionally (C. Chen, Xue, Mei, & Dong, 2009).

Among the languages in the world, Mandarin Chinese is the most widely used as a native language, with more than a billion native speakers. On the other hand, although English is the global language which many people speak as a second language, it has the third largest population of native speakers (Lewis, 2009). Nevertheless, most of our knowledge about language representations in the brain has come from studies on speakers of alphabetic languages, such as English. In the past, research findings from neuroimaging studies of alphabetic language processing have been regarded to be representative of all languages. However, recent research evidence has supported the idea that language experience might shape the neural organization of language representations. Before this line of research becomes more recognized, there is a need to further understand similarities and differences between the major languages to fill in the gap. Mandarin Chinese is a character language that stands in contrast to alphabetic languages in many linguistic features. This thesis will focus on Mandarin Chinese and investigate the neural mechanisms underlying Chinese character processing. By comparing our findings with the existing evidence for alphabetic language processing, we hope to provide further insight to understand

whether the processing of character languages has differential neuroanatomical representations from the processing of alphabetic languages.

In this chapter, I will first compare the linguistic differences between character languages and alphabetic languages to show that the vast differences between the two language systems could possibly be represented in different ways in cognitive processing and thus at the neural level. Next, I will review previous studies that have made attempts to answer this question from different angles, such as studying language processing in Chinese-English bilinguals and individuals with reading disorders (e.g., dyslexia). Finally, I will present the research framework of the thesis to investigate the neural mechanisms underlying Chinese character processing.

Character Languages *versus* Alphabetic Languages

Several linguistic features of character languages differ from those of alphabetic languages. Examples of the respective types of languages are Mandarin Chinese and English. English words are composed of letters (e.g., river), whereas Chinese characters consist of strokes or radicals that fit into a square-shaped space (e.g., 河 /he2/, meaning “river”) (Tan, Laird, Li, & Fox, 2005). There are at least one or more syllables in English words, whereas Chinese characters are mapped onto phonology at the mono-morpheme level. Reading English words follows the rule of grapheme to phoneme conversion, in which printed letters are converted to minimal sound units (Tan, Laird, et al., 2005), whereas reading Chinese characters requires orthography-to-phonology transformation, in which one character is mapped with one syllable. Pronunciations of English words are determined by compositions of phonemes in a word, which is called assembled phonology, whereas pronunciations of Chinese characters are only accessible by direct retrieval of phonological information from the cognitive network, which is called addressed phonology (Tan, Laird, et al.,

2005). English is a stressed accent language, whereas Chinese is considered as a tonal language that has four tones (i.e., level, rising, departing, and entering tones). Moreover, there are an immense number of heterographic homophones in Chinese, i.e., characters that have different physical representations but share the same pronunciation. For instance, 河 and 盒 are both pronounced as /he2/, but they mean river and box, respectively.

In addition, the design principles of Chinese characters also mark prominent differences between Chinese and alphabetic languages. While Chinese characters are created in several different ways, the majority (over 90%) are radical-phonetic characters, which are composed by a phonetic component and a semantic component. The phonetic component might provide a hint of the exact or approximate pronunciation of the whole character, while the semantic component might suggest its associated meaning. For example, the character “按” (/an4/, meaning press) is composed of the phonetic component “安” and the semantic radical “扌”. The phonetic component is pronounced as /an1/, which hints at the pronunciation of the whole character. The semantic component is the radical form of “手 (hand)”, suggesting this character is related to hands. Although the correspondence between characters with their pronunciations and meanings are acquired via learning, in some cases we can guess the pronunciation and meaning of a character that has not been learned using this phono-semantic compound principle. Nevertheless, it should be noted that less than 30 % of characters are pronounced identically as their phonetic components (Tan & Perfetti, 1998). Overall, these discrepancies in linguistic features may lead to differential neural representations for Chinese and English processing.

Review of Functional Neuroimaging Literature on Chinese Character Processing

The development of functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), has provided a non-invasive approach to studying how cognitive processes are represented in the brain. Given that neural activity is coupled with cerebral blood flow, fMRI measures neural activity by detecting changes of the oxygen level in blood. That is, when a brain region is active, neural activity increases and blood flow to that brain region also increases. Functional MRI provides good spatial resolution down to millimeters and fair temporal resolution within a few seconds. It is a non-invasive and repeatable procedure, and thus it is now widely used in research. With the development of fMRI, one fundamental problem investigated by many language studies, of whether the surface of written languages influences the cognitive process of reading, can also be revisited in terms of the cortical representation of reading. In the current investigations, we are particularly interested in applying fMRI to study the neural network underlying Chinese character processing.

Reading engages a distributed network of brain regions. In the past two decades, functional neuroimaging studies have made significant contribution to unveiling the neurobiology of reading, although most work has been done in alphabetic languages. For alphabetic language reading (e.g., English), a left-lateralized set of activation has been consistently reported in the ventral occipito-temporal cortex, the inferior frontal gyrus, the middle and superior temporal cortex, and the lateral parietal cortex (for reviews, see C. Chen et al., 2009; Fiez & Petersen, 1998; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Poldrack et al., 1999; Price, 2000, 2010, 2012; Vigneau et al., 2006). Different processing demands recruit differential regions to different extents. For example, the left ventral occipito-temporal cortex is known as an

important region for visual word recognition, and the consistent involvement has attracted a large body of research to investigate its functional role in the reading network. In a review of the first 20 years of Positron Emission Tomography (PET) and fMRI studies of early visual word form processing, Price (2012) summarized that the posterior regions in the left ventral occipito-temporal cortex are involved in visual feature extraction and sublexical processing while the more anterior areas are involved in lexico-semantic processing of the whole word. The anterior-posterior segregation in the left ventral occipito-temporal cortex has been supported in many empirical studies comparing pseudoword and real word reading (e.g., Seghier, Lee, Schofield, Ellis, & Price, 2008; Vinckier et al., 2007; Woollams, Silani, Okada, Patterson, & Price, 2011). Differential engagement due to task demands has also been reported in the left inferior frontal gyrus. It has been shown that semantic processing recruited greater activation in the ventral anterior part of the left inferior frontal gyrus, whereas phonological processing showed greater activation in the dorsal posterior region (Poldrack et al., 1999; Price & Mechelli, 2005). With the explosion of neuroimaging research into the neurobiology of language processing, the attention to Chinese character reading emerged approximately a decade ago.

Some early fMRI studies on Chinese character processing were performed in Chinese-English bilinguals. Chee and colleagues found that proficient bilinguals exposed to both languages early in life utilized common cortical regions during single word processing (Chee, Tan, & Thiel, 1999) and sentence processing (Chee, Caplan, et al., 1999), irrespective of the differences in their surface features. However, direct comparisons between Chinese-English bilinguals and English monolinguals revealed cultural differences. For instance, Tan et al. (2003) found that Chinese-English bilinguals recruited similar activation when performing Chinese and English rhyming

judgment tasks, and greater activation was found in the left middle frontal gyrus (Brodmann Areas [BAs] 9 and 46); in contrast, native English speakers showed greater activation in the left superior temporal gyrus (BA 22) and inferior frontal cortex when performing an English rhyming judgment task. Their findings demonstrated that Chinese-English bilinguals were applying strategies of processing Chinese characters to process English words, and their cortical recruitment was different from that of native English speakers. In addition, several studies also found similar evidence to support the theory that reading involves language-specific neurocognitive systems that are modulated by language environments (e.g., Siok, Niu, Jin, Perfetti, & Tan, 2008; Siok, Perfetti, Jin, & Tan, 2004; Tan, Spinks, Eden, Perfetti, & Siok, 2005; Tan et al., 2003).

Other early studies tested the hypothesis that the cortical representation of reading single Chinese characters might be different from reading two-character Chinese words. This hypothesis was initially proposed by non-neuroimaging studies using the visual hemifield paradigm (Cheng & Yang, 1989; Tzeng, Hung, Cotton, & Wang, 1979). These studies showed that the right cerebral hemisphere was more efficient in processing single Chinese characters, whereas the left cerebral hemisphere showed a tendency in processing two-character Chinese words. The Chinese character-word dissociation hypothesis in lateralization was thought to suggest that the neuroanatomical mechanism underlying Chinese reading is different from that of English word reading. However, the findings from Tan et al.'s (2000) fMRI study did not support this hypothesis. Instead, they found that reading of both single characters and two-character words were left lateralized in the frontal and temporal cortices and right lateralized in the occipital cortex, parietal cortex and cerebellum.

Studies in dyslexia have also provided divergent findings. Rozin, Poritsky, & Sotsky (1971) showed that when American children with reading disability were taught to read English words presented by Chinese characters, they were able to learn the reading quickly. In their study, eight African American children with difficulty in mapping written letters into phonemic representations were taught a list of Chinese characters which were read directly in their actual English translation. During the tutoring sessions, they learned the mapping between the Chinese characters and their English translation, and afterwards they were tested on reading aloud some sentences and short stories composed of those Chinese characters. The results showed that these children could learn the mapping quickly and were also able to form and rearrange sentences using the characters they learned. The authors suggested that reading English words rely on letter-to-sound mapping, whereas Chinese characters map onto language at the morphemic level instead of the phonemic level. They reasoned that this difference in reading processes allowed children with reading disability in English, which was attributed to deficiency in phonemic representations, to learn to read Chinese characters. On the other hand, Ho and Fong (2005) found that Chinese children with dyslexia had difficulties in learning English as a second language, and they performed poorly in phonological processing in both English and Chinese. However, they also found a case of dissociation that had dyslexia in Chinese but performed above average in English word reading. In general, these inconsistent findings suggest that there may be both common and specific causes to reading disabilities in Chinese and English.

Apart from the evidence at the cognitive level, neuroimaging studies in Chinese children with dyslexia have also provided neural evidence that showed Chinese character processing might differ from English word processing. Reading

disability in alphabetic languages has been found to be associated with structural and functional abnormalities in the left temporo-parietal region, which is thought to be involved in grapheme-to-phoneme conversion (Hoeft et al., 2007; B. A. Shaywitz et al., 2002; S. E. Shaywitz et al., 1998), whereas reading impairment in Chinese is associated with reduced gray matter volume and reduced activation in the left middle frontal gyrus, which is thought to mediate orthography-to-phonology mapping (Siok et al., 2008; Siok et al., 2004). However, inconsistent findings were demonstrated in Hu et al.'s (2010) study, which directly compared the effects of dyslexia (normal readers vs. dyslexics) on brain activation in both monolingual Chinese and English adolescents. While differentiated activation was identified between Chinese and English normal readers (greater activation in the left inferior frontal sulcus for Chinese relative to English and greater activation in the left posterior superior temporal sulcus for English relative to Chinese), Chinese and English dyslexics were found to show similar brain activation during semantic word matching. In particular, reduced activation for both Chinese and English dyslexics compared to normal readers was found in the middle frontal cortex, occipito-temporal cortex, middle temporal cortex and angular gyrus in the left hemisphere. Their results suggest a common neural basis for dyslexia regardless of differences in the written languages.

Interestingly, developmental differences in the neural correlates of language processing between English and Chinese normal readers have been shown. For example during auditory rhyming judgment to spoken words that does not require access to orthographic information, English-speaking children showed a developmental increase in the recruitment of orthographic processing in the left fusiform gyrus (Cone, Burman, Bitan, Bolger, & Booth, 2008), whereas Chinese speakers showed a developmental decrease in the involvement of orthography (Cao et

al., 2011). While the increased recruitment of orthography for spoken word processing in English suggests an enhanced connection between orthographic and phonological representations over development, the reduced involvement of orthography for Chinese may arise from the acquisition of the extensive Chinese heterographic homophones in adults. Since many Chinese characters have the many-to-one mapping from orthography to phonology, Chinese children will encounter increased interference from orthographic information during phonological processing as they learn more characters. Thus, the reduced involvement of orthographic processing may be necessary to eliminate the interference of orthography.

Moreover, from a direct comparison on the effects of orthographic systems on spoken word processing between English and Chinese (Brennan, Cao, Pedroarena-Leal, McNorgan, & Booth, 2012), developmental increases were found only for English speakers in recruiting the brain regions associated with the phonological awareness network, including the left superior temporal gyrus, left inferior parietal lobule, and the left inferior frontal gyrus. Greater recruitment of the left superior temporal gyrus was found for English words with conflicting orthographic and phonological representations, and it was correlated with higher reading skills only for English-speaking children. These results suggest that the acquisition of orthographic systems restructures the phonological awareness network more for alphabetic (e.g., English) than for non-alphabetic languages (e.g., Chinese). As there is a systematic correspondence between letters and phonemes in English words but Chinese has relatively arbitrary mapping between characters and syllables, the developmental differences in the effects of orthographic systems on phonological processing have been attributed to the different nature of mapping between orthographic and phonological representations in the two languages.

Finally, even though it remains debatable whether reading Chinese characters utilizes a similar neural mechanism as reading alphabetic words, it is worthwhile to recognize some additional regions that have been reported to be involved in Chinese character processing. For example, the left middle frontal gyrus (BA 9) has been identified in many studies with Chinese characters but not in most of the studies with alphabets (e.g., Booth et al., 2006; Dong et al., 2005; Kuo et al., 2001; Kuo et al., 2004; C. L. Liu et al., 2006; Tan, Feng, Fox, & Gao, 2001; Tan, Liu, et al., 2001). Chinese character processing has also been shown to recruit more bilateral activation in regions such as the inferior frontal gyrus, the middle frontal gyrus, and the ventral occipito-temporal cortex as compared with alphabetic word processing (e.g., Dong et al., 2005; Kuo et al., 2004; Tan, Feng, et al., 2001; Tan, Liu, et al., 2001).

The Research Framework

The orthographic features and the mapping between orthography and phonology mark two prominent differences between Chinese and alphabetic language reading at the character/word level. Unlike alphabetic languages of which the pronunciation of a word is assembled by the phonetic components within a word, the pronunciation of a Chinese character is assigned to the square-shaped form and the orthography-to-phonology mapping is only acquired through learning. As reading Chinese characters is substantially different from reading alphabetic languages in terms of orthography and the relationship between orthography and phonology, it is important to investigate the neural mechanisms underlying orthographic processing, phonological processing, as well as the mapping from orthography to phonology. Research on the neural mechanisms for Chinese character processing has a relatively shorter history as compared with alphabetic languages. The early studies have provided a good basis to address this question, and more studies have been conducted

recently to investigate a variety of aspects in Chinese character processing. However, most of the earlier studies had a small number of participants (less than 20) and more investigations are still needed to determine the functional roles of the underlying mechanisms.

Hence, the objectives of the current investigations are to understand the cortical mechanisms for character language processing in Chinese, with particular interests in orthographic and phonological processing, and to elucidate the functional roles of the underlying neural substrates. Moreover, we hope to provide further insight as to whether the processing of character languages has differential neuroanatomical representations from the processing of alphabetic languages. This thesis approached the research question from two levels of direct and converging evidence by three lines of research. The research framework is illustrated in Figure 1-1. Study 1 and Study 2 searched for direct evidence, and Study 3 provided converging evidence with regard to the neuroanatomical representations underlying Chinese character processing. In Study 1, a meta-analysis on the existing fMRI studies that investigated Chinese character processing was conducted, in which the fMRI tasks were classified into orthographic, phonological, and semantic processing so as to examine each language-processing component independently. From the meta-analysis, a sub-network that might be specific to Chinese character processing was proposed. The regions in the sub-network were extracted from the meta-analysis findings and then used as a priori regions-of-interest (ROIs) in the subsequent studies. In Study 2, we further investigated how this sub-network was involved in orthographic (Study 2a) and phonological processing (Study 2b) with the aim to elucidate the functional roles of the sub-network. In particular, we studied how differential task manipulation (orthographic and phonological) had effects on the activation in the sub-network. To seek for converging

evidence in Study 3, we examined the integrity of this sub-network in language processing and how it might be affected by individual characteristics such as age and handedness in terms of age effects (Study 3a) and hemispheric lateralization (Study 3b), respectively. The universal and differential neural representations between Chinese character processing and alphabetic word processing were discussed based on qualitative comparisons between our results and the findings of other studies on alphabetic languages.

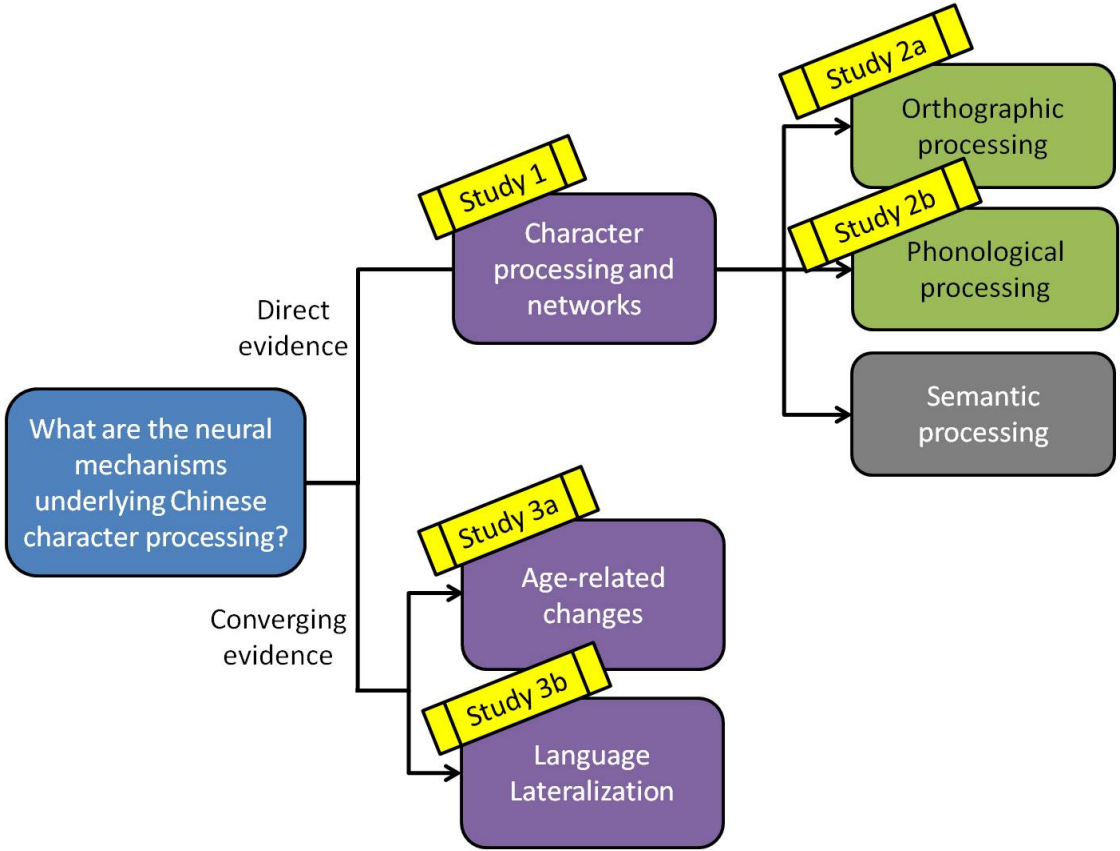


Figure 1-1. Research framework.

CHAPTER II: STUDY 1

A Meta-Analysis of fMRI Studies on Chinese Orthographic, Phonological, and
Semantic Processing

Introduction

Most of the existing models of language have been based on alphabetic languages. However, there is growing evidence showing that processing of Chinese characters, a character language, may have differential activation due to their unique linguistic features from alphabetic languages. Although more studies investigating Chinese character processing have recently become available, the findings are still inconclusive. Hence, there is a need for a meta-analytic approach to provide a quantitative measure in identifying consistently reported regions of activation across a number of studies. We began our investigations from a meta-analysis to summarize the existing findings regarding the neural underpinnings of Chinese character processing.

A literature review found two meta-analytic studies comparing the neural representation underlying Chinese character processing with that of other languages. Tan, Laird, et al. (2005) utilized the activation likelihood estimation (ALE) method (Laird et al., 2005; Turkeltaub, Eden, Jones, & Zeffiro, 2002) to investigate phonological processing of Chinese characters and alphabetic words. Six functional imaging studies with Chinese and thirteen studies with English or German using explicit phonological judgment tasks were included in their analyses. Convergent neural systems for both language systems were identified: (a) the left superior part of the inferior frontal regions responsible for sub-vocal rehearsal; and (b) the ventral occipito-temporal system, left for alphabetic languages and bilateral for Chinese, involved in word form recognition and providing feedback of phonology to orthography. Divergent neural systems were also recognized. For phonological processing of Chinese characters, the left dorsal lateral frontal region (Brodmann Area [BA] 9) was found to be involved and thought to be responsible for visuospatial

analysis and orthography-to-phonology mapping of Chinese characters, and the left dorsal aspect of the inferior parietal regions might serve as a temporary storage for phonological information in working memory. On the other hand, for alphabetic languages the left posterior temporo-parietal regions are known to mediate grapheme-to-phoneme conversion and fine-grained phonemic analysis. In particular, their results suggest that the left dorsal lateral frontal region is responsible for addressed phonology in Chinese character processing, and the left posterior temporo-parietal region for assembled phonology in alphabetic word processing.

In the other meta-analysis, Bolger et al. (2005) used a different quantitative approach that aggregated Gaussian estimated sources (AGES; Chein, Fissell, Jacobs, & Fiez, 2002) to examine the reading processes of alphabetic words, Japanese kanji and kana, and Chinese characters. The data were gathered from twenty-five functional neuroimaging studies with Western languages, five with Japanese Kana, four with Japanese Kanji, and nine with Chinese investigating single word recognition. They proposed a universal reading network across the writing systems as well as identified some differential activation for Chinese character processing, which were highly consistent with those found in Tan, Laird, et al.'s (2005) meta-analysis. For example, three language systems recruited strong activation in the superior posterior region of the left inferior frontal gyrus (BA 6/9), but Chinese character processing involved a broader foci extending anteriorly along the lateral surface of the frontal cortex, which was identified by Tan, Laird, et al. as being associated with processing of addressed phonology in Chinese characters. In addition, Chinese character processing recruited the bilateral fusiform gyri, whereas the other language systems only activated the left counterpart.

In summary, both meta-analytic studies indicated additional engagement of the left dorsal lateral frontal region (BA 9) and the right ventral occipito-temporal region for Chinese character processing as compared with other languages. These additional activations might point out that differential linguistic features are represented by differences in the underlying processes at the neural level.

Objectives

Both previous meta-analyses contributed greatly to our understanding of the brain networks underlying Chinese character processing. However, Tan, Laird, et al.'s (2005) meta-analysis only investigated phonological processing of Chinese character reading and Bolger et al.'s (2005) did not break down the reading process, which could involve orthographic, phonological, and semantic processing. Task variations across different language-processing components (e.g., orthography, phonology, or semantics) could have evoked differential activations reported (Vigneau et al., 2006). In addition, functional neuroimaging research on Chinese character processing has been developing vigorously over the past few years, which allows us to include more studies into a meta-analysis to synthesize more comprehensive results. Therefore, the first purpose of the current meta-analysis was to summarize the cortical networks for Chinese character processing on the basis of a larger set of functional magnetic resonance imaging (fMRI) studies. Second, we aimed to provide additional information to the previous meta-analyses by classifying the fMRI tasks into orthographic, phonological, and semantic processing so as to examine each component independently.

Methods

Literature Selection

Imaging studies published before December 2011 were searched through the following databases: PubMed, PsycINFO, Scopus, ScienceDirect, and Web of Science, with keywords including “Chinese”, “language”, “fMRI”, and “character”. Out of 785 articles identified, 23 studies fulfilling the following criteria were included in the meta-analysis: (a) used fMRI as the imaging modality; (b) applied visual fMRI tasks to study Chinese orthographic, phonological, or semantic processing at the character-level or word-level; (c) used whole-brain scanning and reported complete coordinates of the activation in standardized stereotaxic space, i.e., the Talairach atlas (Talairach & Tournoux, 1988) or the MNI (Montreal Neurological Institute) atlas (Collins et al., 1998); (d) in which participants were normal young adults whose native language was Chinese (i.e., not early bilinguals nor early multilinguals); and (e) were published in English journals. All the selected studies, published between 2000 and 2011, were then categorized into orthographic, phonological or semantic categories according to the fMRI tasks applied. The participants in the selected studies were all right-handed.

Notably, three of the selected studies (Chee, Hon, Lee, & Soon, 2001; Ding et al., 2003; Tan et al., 2003) reported findings with late Chinese-English bilinguals performing Chinese language tasks. In Chee et al.’s (2001) and Tan et al.’s (2003) articles, the late bilinguals were young adults from China who moved to Singapore and the United States, respectively, for postgraduate studies or work, but they received formal schooling from elementary school to college in China; in another study by Ding et al. (2003), the participants were undergraduates majoring in English in China. These late bilinguals were native Chinese speakers who were exposed to English only

after the age of 12 on average and used Chinese as the predominant language in social interaction. Their language exposure history was distinct from that of early Chinese-English bilinguals who were exposed to both Chinese and English before the age of 5-6 and used English as the predominant language in daily interaction and instruction. Therefore, the late Chinese-English bilinguals might share an equivalent language exposure experience with the native Chinese speakers in the other selected studies. Although the studies with the native speakers did not report language experience history of the participants, most of them were young adults/college students who had normal education in which they received formal training of English as a second language since junior high school (i.e., about the age of 12). Thus, the “late bilinguals” in the three bilingual studies and the native Chinese speakers in the other studies actually have similar language experience in spite of different classifications used by the researchers.

Task Categorization

Table 2-1 summarizes the studies and contrasts selected for the current meta-analysis. Among 23 selected studies, some included more than one type of language tasks, and some language tasks included more than two conditions, which allowed implementation of more than one contrast in a study. Thus, we categorized the studies according to the targeted language components of the contrasts from which the reported activation peaks were obtained. However, various types of control conditions were used in the contrasts in different studies. Some studies reported activation results from contrasting the task condition with a low-demanding control condition such as fixation, and others provided results from contrasting the task condition with a higher-demanding control condition than fixation or perceptual control, e.g., font size judgment in contrast to a phonological or semantic task. The contrasts we selected

were all direct comparisons between the original conditions designed in the tasks. Although the processing levels of the control conditions varied, we think these contrasts could be considered as basic contrasts as they were either subtractions of a lower-level processing from a higher-level processing (e.g., rhyming judgment > font size judgment) or subtractions between two processing of an equivalent level (e.g., discrimination task of upright characters > inverted characters), rather than subtractions of a higher-level processing from a lower-level processing (e.g., font size judgment > semantic association judgment). The reason for which these basic contrasts were selected was that we intended to first use the basic contrasts for meta-analyses on each task category and then perform the second-level comparisons between categories using the meta-analytic approach to reveal component-specific regions. Hence, for the first-level meta-analyses we only included basic contrasts but did not select comparisons between two contrasts (e.g., rhyming judgment > fixation vs. semantic judgment > fixation, provided in Booth et al.'s (2006) study).

Nine contrasts from eight studies with a total of 93 foci were included in the orthographic task category. Orthographic processing in Chinese is considered to involve visuospatial analysis of characters and application of a set of orthographic rules (e.g., radical position, orthographic legality) to help with character identification. Tasks in this category included (a) orthographic judgment: whether a visually presented item was orthographically legal or illegal (Dong et al., 2005), (b) stroke analysis: counting the number of a designated stroke within each presented character (C. C. H. Chan, Leung, Luo, & Lee, 2007), (c) orthographic search: whether the character contained a designated radical component (Ding et al., 2003), (d) physical identical judgment: whether two characters or pseudo-characters presented in one trial were identical (S.-T. Chan et al., 2009; J. Liu, Tian, Li, Gong, & Lee, 2009; Wang,

Yang, Shu, & Zevin, 2011; Zhao et al., 2010), and (e) font size judgment: whether the size of stimuli was small or large (C. Liu et al., 2008).

The phonological task category comprised of fourteen contrasts extracted from eleven studies with a total of 233 foci. Phonological processing concerns retrieval and analysis of phonological representations of characters. Tasks selected for this category included (a) homophone judgment: whether two characters had the same pronunciation (Kuo et al., 2004; Siok, Jin, Fletcher, & Tan, 2003; Tan, Liu, et al., 2001), (b) rhyming judgment: whether two characters rhymed with each other (L. Liu et al., 2009; Tan et al., 2003) or whether a probe word rhymed with either of the two target words (Booth et al., 2006; Cao et al., 2009), (c) consonant matching: whether a pair of two characters shared the same initial consonant (Dong et al., 2005; Siok et al., 2003), (d) reading aloud characters (L. Liu et al., 2006; Tan, Feng, et al., 2001), and (e) homophonic word judgment: whether a two-character word replaced by their homophonic characters sounded like a real word (Y. Chen, Fu, Iversen, Smith, & Matthews, 2002).

The semantic task category consisted of seventeen contrasts from twelve studies with a total of 208 foci. Semantic processing evokes retrieval and analysis of meaning components of stimuli at the character-, or word-level given the input orthography. Tasks included in this category covered (a) character-level semantic decision judgment: whether two characters are semantically related (S.-T. Chan et al., 2009; Chou, Chen, Wu, & Booth, 2009; Tan, Liu, et al., 2001) or selecting one character from two that was closest in meaning to the target character (Chee et al., 2001), (b) word-level semantic association judgment: whether two words were semantically related to each other (Dong et al., 2005; L. Liu et al., 2009) or whether a probe word was semantically related to either of the two target words (Booth et al.,

2006; Cao et al., 2009; Xiang et al., 2003), (c) word semantic judgment: whether the presented item was semantically dangerous (Wu et al., 2009) or whether the item was a type of animal (Ding et al., 2003), and (d) semantic generation task: generating a word that was semantically related to the stimulus (Tan et al., 2000).

There is another consideration in studying Chinese character processing: there are two forms of Chinese characters used in the world, traditional and simplified Chinese characters. As they differ in character forms and visual complexity, one may argue whether reading of traditional Chinese characters would have different cortical representations from reading of simplified Chinese characters. Hence, an attempt to identify which type of Chinese characters was investigated in the studies included in the meta-analysis was conducted. However, it was not specified in most of the studies. We operationalized the categorization based on the fact that traditional Chinese characters are used as the official written scripts only in Taiwan and Hong Kong. Therefore, the studies were categorized according to where the studies were conducted, the origin of the participants, and the form of the Chinese characters provided in the examples (see Table 2-1). It was found that the majority of previous studies were done using simplified Chinese characters and the number of studies using traditional Chinese characters (2 orthographic, 1 phonological and 2 semantic) may be too small for a comparison in the current meta-analysis. All studies regardless of using traditional or simplified Chinese characters were included in the meta-analysis.

Table 2-1. *Summary of studies selected for the meta-analysis.*

Category/Paper	Place	Simplified/ Traditional	Scanner	N	Task and Contrast	No. of Foci
<i>Orthographic</i>						93
C. C. H. Chan et al. (2007)	Hong Kong	Traditional	3 T	20	Stroke analysis of nonpictographic > pictographic orthographs	23
S.-T. Chan et al. (2009)	Hong Kong	Traditional	1.5 T	22	Identical judgment of pseudo-characters > Fixation	4
Ding et al. (2003)	China	Simplified	1.5 T	6	Orthographic search > Fixation	9
Dong et al. (2005)	Japan	Not clear ^a	1.5 T	12	Orthographic judgment > Fixation	12
C. Liu et al. (2008)	China	Simplified	3 T	14	Font size judgment of real characters > artificial characters	7
					Font size judgment of pseudo characters > artificial characters	7
J. Liu et al. (2009)	China	Simplified	3 T	11	Discrimination task of characters > Fixation on noise pictures	12
Wang et al. (2011)	China	Simplified	3 T	18	One-back task of real, pseudo, and artificial characters > rest	12
Zhao et al. (2010)	China	Simplified	3 T	14	Discrimination task of upright characters > inverted characters	7
<i>Phonological</i>						233
Booth et al. (2006)	China	Simplified	2 T	13	Rhyming judgment > Line judgment	6
Cao et al. (2009)	China	Simplified	2 T	13	Rhyming judgment > Line judgment	5
Y. Chen et al. (2002)	UK	Simplified	3 T	9	Homophonic word judgment > Fixation	24
Dong et al. (2005)	Japan	Not clear ^a	1.5 T	12	Phonological matching task > Fixation	13
Kuo et al. (2004)	Taiwan	Traditional	3 T	10	Homophone judgment > Character form judgment	16
L. Liu et al. (2009)	China	Simplified	2 T	16	Rhyming judgment > Line judgment	12
L. Liu et al. (2006)	China	Simplified	2 T	10	Naming of tone-changing characters > Fixation	8
					Naming of vowel-changing characters > Fixation	9

(table continues)

Table 2-1 (*continued*)

Category/Paper	Place	Simplified/ Traditional	Scanner	N	Task and Contrast	No. of Foci
Siok et al. (2003)	China	Simplified	2 T	11	Homophone judgment > Font size judgment	4
					Initial consonant judgment > Font size judgment	6
Tan, Feng, et al.(2001)	USA	Simplified	1.9 T	10	Read aloud regular characters > Fixation	37
					Read aloud irregular characters > Fixation	51
Tan, Liu, et al. (2001)	USA	Simplified	1.9 T	6	Homophone judgment > Fixation	38
Tan et al. (2003)	USA	Simplified	1.9 T	12	Rhyming judgment > Font size judgment	4
<i>Semantic</i>						208
Booth et al. (2006)	China	Simplified	2 T	13	Meaning judgment > Line judgment	8
Cao et al. (2009)	China	Simplified	2 T	13	Meaning judgment > Line judgment	11
S.-T. Chan et al. (2009)	Hong Kong	Traditional	1.5 T	22	Synonym judgment > fixation	8
Chee et al. (2001)	Singapore	Simplified	2 T	9	Semantic matching > Font size matching	4
Chou et al. (2009)	Taiwan	Traditional	1.5 T	31	Meaning judgment task: Related > Perceptual control	4
					Meaning judgment task: Unrelated > Perceptual control	3
			3 T	32	Meaning judgment task: Related > Perceptual control	7
					Meaning judgment task: Unrelated > Perceptual control	6
Ding et al. (2003)	China	Simplified	1.5 T	6	Semantic classification > Fixation	4
Dong et al. (2005)	Japan	Not clear ^a	1.5 T	12	Semantic association > Fixation	21
L. Liu et al. (2009)	China	Simplified	2 T	16	Meaning judgment > Line judgment	12
Tan, Liu, et al. (2001)	USA	Simplified	1.9 T	6	Semantic decision > Fixation	36

(table continues)

Table 2-1 (*continued*)

Category/Paper	Place	Simplified/ Traditional	Scanner	<i>N</i>	Task and Contrast	No. of Foci
Tan et al. (2000)	USA	Simplified	1.9 T	6	Semantic generation (Vague-meaning) > Fixation	18
					Semantic generation (Precise-meaning) > Fixation	18
					Semantic generation (Two-character word) > Fixation	20
Wu et al. (2009)	China	Simplified	1.5 T	14	Word semantic judgment > Fixation	16
Xiang et al. (2003)	China	Simplified	1.5 T	6	Semantic discrimination > Fixation	12

Note. *N*: number of subjects. The places where these studies were conducted and whether simplified or traditional Chinese characters were used as stimuli are specified in the Place and Simplified/Traditional columns, respectively.

^aThis study was conducted in Japan and it could not be identified which form of characters was used.

Analyses

The meta-analyses were performed using the revised algorithm of the activation likelihood estimation (ALE) approach (Eickhoff, Bzdok, Laird, Kurth, & Fox, 2012; Eickhoff et al., 2009; Laird et al., 2005; Turkeltaub et al., 2002) implemented in a JAVA-based software, GingerALE (version 2.3.1, available at www.brainmap.org/ale). This approach generates an estimate of how likely the convergence of activation among experiments is located at specific coordinates. The foci extracted from the selected studies are not treated as single points, but rather are modeled as the centers of three-dimensional Gaussian spatial probability distributions taking into account spatial uncertainty. In the revised algorithm (details described in Eickhoff et al., 2009), the spatial uncertainty is estimated based on empirical data on between-subject and between-template variances, which are reflected in the width of the modeled probability distributions. Notably, to account for the between-subject variances, the width of probability distributions (i.e., full-width at half-maximum, FWHM) is determined by the number of subjects in each experiment, resulting in smaller FWHMs for experiments investigating larger samples. The probability distributions of all foci reported in an experiment are then combined in a modeled activation (MA) map, which can be conceptualized as a summary of all foci in an experiment. With the union of all MA maps for a single meta-analysis, the ALE scores are computed on a voxel-by-voxel basis, which represent the likelihood of activation convergent at particular positions among the experiments. To distinguish “true” convergence from random convergence, the ALE scores are compared with an analytically-computed null-distribution that reflects random spatial associations between experiments (Eickhoff et al., 2012). This comparison, thus, yields a random-effects inference, which marks another key modification to the previous ALE

approach and focuses on “above-chance” convergence between experiments (random-effects) rather than convergence between foci within a single experiment (fixed-effects).

In the current study, all foci reported in the selected contrasts were extracted for ALE analyses. Coordinates reported in the Talairach space were first transformed into the MNI brain template using the appropriate transformation algorithms implemented in GingerALE. Individual meta-analyses were performed in each task category. The resulting p -values from the comparisons of ALE scores with the null-distribution were thresholded with a false discovery rate (FDR) at $p < 0.05$ and with a minimum cluster volume of 150 mm^3 . The thresholded ALE maps were overlaid onto the colin27_T1_seg_MNI.nii brain template in the software MRICron (available at www.mccauslandcenter.sc.edu/mricro/mricron/) for display.

To evaluate the differences between language-processing components, we conducted subtraction analyses on any two of the task categories in GingerALE. The approach for subtraction analyses adopted in the current version is described in Eickhoff et al. (2011), which first examines the differences in ALE scores between two categories and compares those contrasted differences with a null-distribution. In this revised algorithm, all experiments for either of the two categories for comparison are pooled and then randomly divided into two groups of the same size as the original sets of experiments for each category. The differences in ALE scores for the two randomly assembled groups are calculated and recorded for each voxel. Repeating this process for 10,000 times yields a null-distribution of ALE-score differences for the two categories. The observed ALE-score differences are tested against this null-distribution. To perform subtraction analyses in GingerALE, individual ALE analyses were first performed separately in each task category. Then all experiments selected

for either of the two categories for comparison were pooled and another ALE analysis was conducted on this pooled dataset. The resulting ALE maps from both individual categories and the pooled dataset were thresholded at voxel-level $p < 0.05$ (FDR) and then loaded into the software for subtraction analyses. The results from direct subtraction analyses were reported with a threshold at voxel-level $p < 0.01$ (uncorrected) with a minimum cluster volume of 50 mm^3 .

In addition, we considered two potential problems with the direct subtractions between two categories. First, as the numbers of contrasts in each category were not equivalent, there was a possibility of direct subtractions simply revealing differences due to the statistical power for each component. Second, it was likely that a phonological or semantic task might have involved some shallow or automatic semantic or phonological processing, respectively, in addition to the task-required processing. Thus, when the phonological category was compared with the orthographic category, the difference might represent processes not only specific to phonology but also to shallow semantics. Similar situations might happen for comparing semantic with orthographic categories. Therefore, two additional comparisons were performed to account for these potential issues: (a) phonological vs. (orthographic & semantic): Orthographic and semantic categories were grouped together and compared with phonological category; and (b) semantic vs. (orthographic & phonological): Orthographic and phonological categories were grouped together and compared with semantic category. These additional comparisons could help verify the findings from direct comparisons. Each group for comparison (e.g., *phonological* and *orthographic & semantic*) and the pooled dataset (e.g., *phonological + orthographic & semantic*) were loaded into GingerALE separately for individual ALE analysis. Similar to direct subtraction analyses, the resulting ALE maps of each group and the

pooled dataset were thresholded at voxel-level $p < 0.05$ (FDR) and loaded for subtraction analyses, with results reported at a threshold of voxel-level $p < 0.01$ (uncorrected) with a minimum cluster volume of 50 mm^3 .

Results

Three ALE analyses on orthographic, phonological and semantic processing of written Chinese characters (Table 2-2; Figure 2-1) showed high convergence in the left middle frontal gyrus (BAs 9/46), the left superior parietal lobule (BA 7), and the left mid-fusiform gyrus (BAs 19/37). Comparisons between task categories revealed some component-specific regions as summarized in Table 2-3 and illustrated in Figure 2-2.

Table 2-2. *ALE results of the orthographic, phonological, and semantic categories.*

Volume (mm^3)	Regions	L/R	BA	x	y	z	ALE ($\times 10^{-2}$)
<i>Orthographic</i>							
2224	Fusiform gyrus	L	19	-42	-70	-10	1.46
	Cerebellum – Lobule VI	L	-	-40	-56	-20	1.15
1488	Middle frontal gyrus	L	9	-48	14	32	1.32
1240	Superior parietal lobule	L	7	-26	-66	54	1.43
	Precuneus	L	19	-22	-78	48	0.87
416	Precuneus	R	7	26	-54	46	1.34
296	Cingulate gyrus	L	32	-8	24	38	1.09
264	Middle occipital gyrus	L	19	-28	-84	24	0.99
	Cuneus	L	18	-26	-80	24	0.98
<i>Phonological</i>							
9248	Inferior frontal gyrus	L	9	-48	16	28	2.19
		L	9	-48	22	24	2.07
		L	44	-50	20	10	2.01
	Insula	L	13	-46	6	16	1.57
	Precentral gyrus	L	6	-52	6	48	1.01
4776	Medial frontal gyrus	L	6	-2	22	46	3.09
	Cingulate gyrus	L	32	-4	30	34	1.51
		L	24	-2	18	32	1.05
2640	Middle occipital gyrus	R	18	28	-86	0	2.06
1376	Cerebellum – Lobule VI	L	-	-42	-58	-20	1.47
		L	-	-40	-66	-14	1.31
912	Inferior frontal gyrus	L	47	-40	26	-12	1.62

(table continues)

Table 2-2 (*continued*)

Volume (mm ³)	Regions	L/R	BA	x	y	z	ALE ($\times 10^{-2}$)
840	Insula	R	13	36	22	-6	1.38
		R	13	40	20	6	1.10
712	Inferior parietal lobule	L	40	-32	-46	50	1.31
496	Middle frontal gyrus	R	6	56	10	38	1.21
	Inferior frontal gyrus	R	9	58	14	28	1.04
456	Postcentral gyrus	R	43	66	-4	16	1.42
448	Precuneus	L	7	-24	-62	44	1.41
312	Inferior frontal gyrus	R	44	62	14	10	1.25
248	Superior temporal gyrus	R	22	56	12	-12	1.11
232	Precentral gyrus	L	6	-66	6	4	1.26
192	Lingual gyrus	L	18	-12	-94	-10	1.00
168	Middle frontal gyrus	L	46	-50	50	4	1.03
		L	46	-48	52	8	1.03
<i>Semantic</i>							
8960	Middle frontal gyrus	L	9	-44	16	28	3.91
		L	46	-48	26	16	3.29
	Inferior frontal gyrus	L	47	-46	28	4	2.80
5448	Medial frontal gyrus	L	6	-2	10	52	2.47
		L	6	-2	22	44	2.41
		L	8	-4	34	40	2.20
4232	Fusiform gyrus	L	37	-44	-60	-14	2.06
	Cerebellum – Lobule VI	L	-	-38	-56	-22	1.45
2664	Lingual gyrus	R	17	26	-92	4	2.31
	Fusiform gyrus	R	18	28	-96	-10	1.18
2152	Inferior frontal gyrus	R	9	54	14	26	1.60
	Middle frontal gyrus	R	46	54	26	18	1.39
1680	Insula	R	13	38	24	-2	2.09
1544	Middle temporal gyrus	L	21	-58	-44	0	3.04
936	Middle occipital gyrus	L	18	-30	-92	4	1.52
768	Cerebellum – Lobule VI	R	-	30	-68	-30	1.30
352	Parahippocampal gyrus	R	35	32	-24	-24	1.42
344	Fusiform gyrus	L	18	-24	-96	-10	1.06
256	Fusiform gyrus	R	37	44	-58	-12	1.13
248	Cerebellum – Lobule VIIIA	R	-	6	-64	-32	1.26
192	Superior parietal lobule	L	7	-38	-64	58	1.30

Note. Volume: the cluster volume; L/R: left or right hemisphere; BA: Brodmann area;

x, y, z: MNI coordinates; ALE: activation likelihood estimation values. $p < 0.05$ (FDR corrected), minimum cluster volume of 150 mm³.

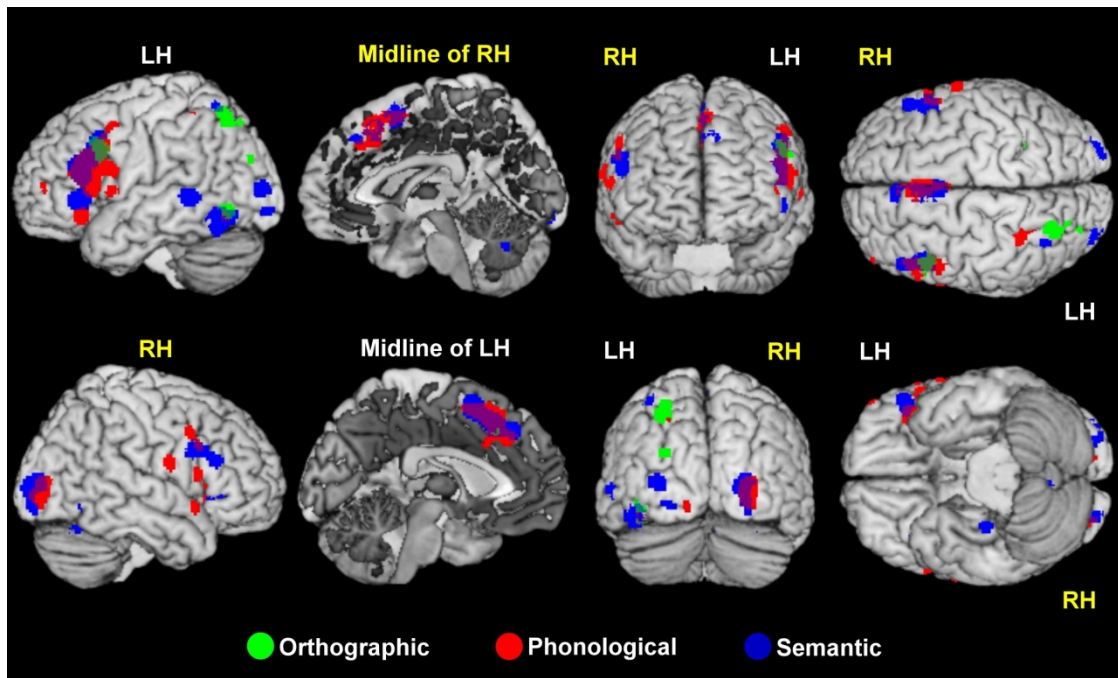


Figure 2-1. ALE activation maps for orthographic (green; 93 foci), phonological (red; 233 foci), and semantic (blue; 208 foci) processing overlaid onto the Colin27 brain template. LH: left hemisphere; RH: right hemisphere. $p < 0.05$ (FDR corrected), minimum cluster volume of 150 mm^3 .

Orthographic vs. Phonological

Orthographic processing did not show more activation as compared with phonological processing. Compared to orthographic processing, phonological processing recruited more activation in the left precentral gyrus (BA 44), the left inferior frontal gyrus (BA 44), and the right inferior occipital gyrus (BA 18) (Figure 2-2a).

Orthographic vs. Semantic

Orthographic processing did not show more activation as compared with semantic processing. Compared to orthographic processing, semantic processing involved more activation in the left inferior frontal gyrus (BAs 45/47) and the left middle frontal gyrus (BA 46) (Figure 2-2a).

Phonological vs. Semantic

The direct comparison between phonological and semantic processing revealed that phonological processing had more activation peaks in the left insula (BA 13), the left inferior frontal gyrus (BA 44), the left precentral gyrus (BA 6), and the right lingual gyrus (BA 18) (Figure 2-2b). However, semantic processing did not show more activation as compared with phonological processing.

Phonological vs. (Orthographic & Semantic)

As compared with orthographic and semantic processing together, phonological processing showed greater involvement in the left inferior frontal gyrus (BAs 44/47), the right middle occipital gyrus (BA 18), the right lingual gyrus (BA 18), the left superior frontal gyrus (BA 6), and the left inferior parietal lobule (BA 40) (Figure 2-2c). No regions were found in the reversed subtraction.

Semantic vs. (Orthographic & Phonological)

When compared with orthographic and phonological processing together, semantic processing recruited more activation in the left inferior frontal gyrus (BA 47), the right inferior frontal gyrus (BA 9), the right cuneus (BA 17), the left middle temporal gyrus (BAs 21/22), and the right cerebellum (Figure 2-2c). The group of orthographic and phonological processing showed greater recruitment in the left inferior frontal gyrus (BA 44) and the left insula (BA 13) as compared with semantic processing.

Table 2-3. *ALE results from comparisons among three task categories.*

Phonological vs. Others								Semantic vs. Others							
Volume	Region	L/R	BA	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	Volume	Region	L/R	BA	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>
<i>Phonological > Orthographic</i>								<i>Semantic > Orthographic</i>							
3944	Precentral gyrus	L	44	-47	25	12	3.72	5136	Inferior frontal gyrus	L	45	-47	28	11	3.72
	Inferior frontal gyrus	L	44	-58	20	10	3.35		Middle frontal gyrus	L	46	-42	30	18	3.54
		L	44	-55	15	11	3.16		Inferior frontal gyrus	L	47	-44	30	3	3.35
		L	44	-50	16	14	3.04			L	47	-48	27	-2	2.99
336	Inferior occipital gyrus	R	18	33	-89	-3	2.88			L	47	-48	34	-6	2.95
										L	47	-48	24	-6	2.85
										L	47	-41	25	-7	2.79
										L	47	-38	30	-1	2.69
<i>Phonological > Semantic</i>								<i>Semantic > Phonological</i>							
784	Insula	L	13	-48	6	13	3.72	<i>No significant clusters</i>							
	Inferior frontal gyrus	L	44	-52	12	16	3.16								
	Insula	L	13	-48	12	14	3.04								
	Inferior frontal gyrus	L	44	-52	14	10	2.95								
128	Lingual gyrus	R	18	30	-84	-8	2.62								
64	Precentral gyrus	L	6	-65	5	6	2.65								

(table continues)

Table 2-3 (continued)

Phonological vs. Others								Semantic vs. Others							
Volume	Region	L/R	BA	x	y	z	Z	Volume	Region	L/R	BA	x	y	z	Z
<i>Phonological > (Orthographic & Semantic)</i>								<i>Semantic > (Orthographic & Phonological)</i>							
1528	Inferior frontal gyrus	L	44	-49	9	12	3.72	720	Inferior frontal gyrus	L	47	-40	32	-2	3.35
480	Middle occipital gyrus	R	18	31	-88	-5	3.54			L	47	-46	27	-4	2.77
	Lingual gyrus	R	18	24	-82	-8	2.69	576	Cerebellum – Crus I	R	-	27	-69	-33	2.75
360	Inferior frontal gyrus	L	47	-42	26	-18	3.16			R	-	28	-72	-30	2.73
		L	47	-46	26	-18	3.09		Cerebellum – Lobule VI	R	-	29	-70	-26	2.71
120	Superior frontal gyrus	L	6	2	20	54	2.91			R	-	31	-64	-30	2.39
56	Inferior parietal lobule	L	40	-32	-42	51	2.48		Cerebellum – Crus I	R	-	32	-66	-34	2.38
								136	Inferior frontal gyrus	R	9	53	21	21	2.50
								120	Cuneus	R	17	20	-96	6	2.48
										R	17	24	-98	6	2.45
								88	Middle temporal gyrus	L	21	-58	-46	-2	2.48
										L	22	-58	-46	2	2.47
<i>(Orthographic & Semantic) > Phonological</i>								<i>(Orthographic & Phonological) > Semantic</i>							
<i>No significant clusters</i>								168	Inferior frontal gyrus	L	44	-48	6	14	2.91
									Insula	L	13	-48	2	14	2.85

Note. Uncorrected $p < 0.01$, minimum cluster volume of 50 mm³.

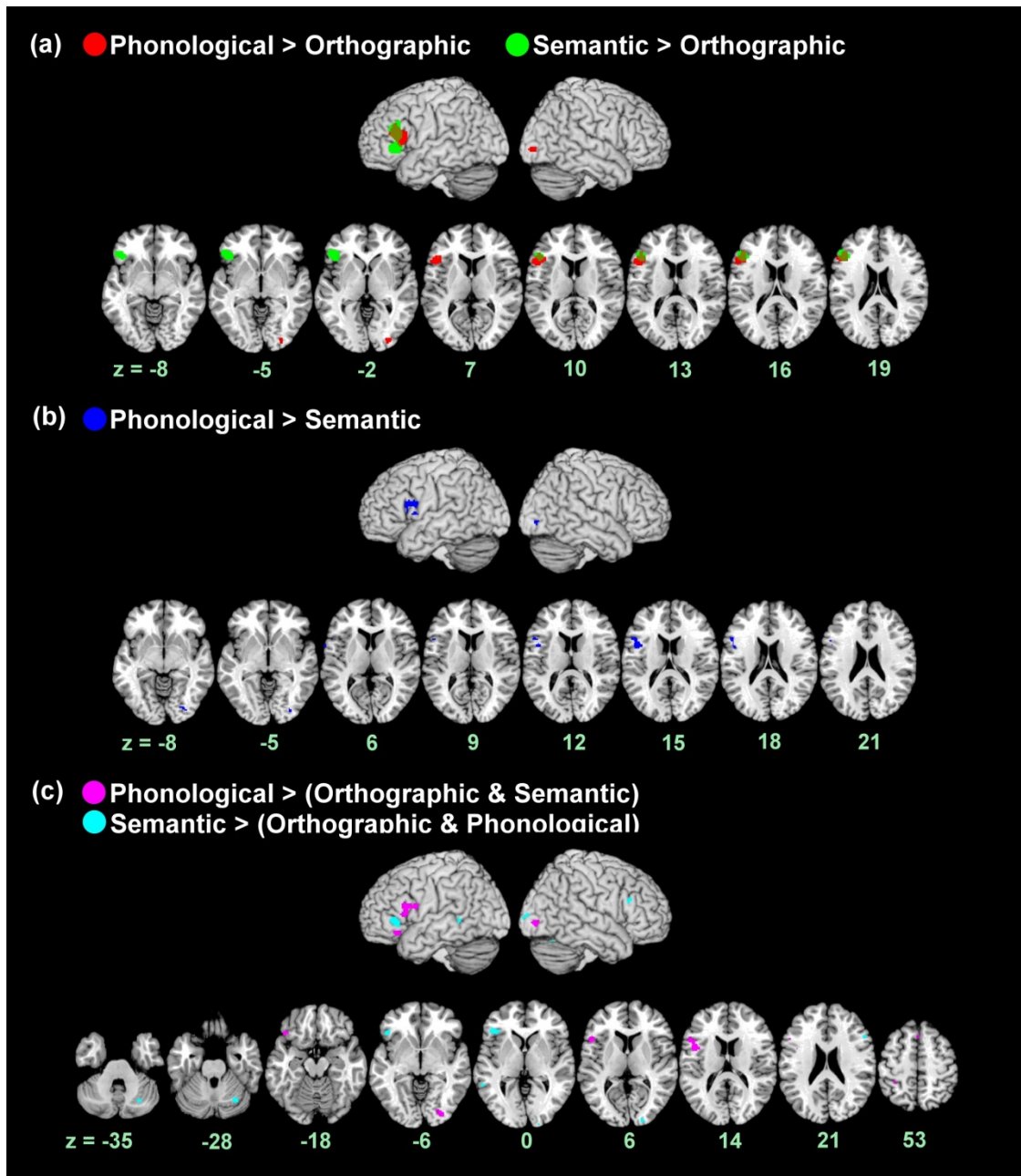


Figure 2-2. The overlaid results from subtraction analyses of (a) phonological > orthographic (red) and semantic > orthographic (green), (b) phonological > semantic (blue), and (c) phonological > (orthographic & semantic) (violet) and semantic > (orthographic & phonological) (cyan). The images are displayed in the neurological convention and the activation shown here was thresholded at $p < 0.01$ (uncorrected) with minimum cluster volume of 50 mm^3 .

Localization of Dissociation

Localization of the activation revealed some dissociation within specific areas. First, in the left inferior frontal region (Figure 2-3a), the activation for phonological processing was more posterior and dorsal (BA 44), whereas for semantic processing it was more anterior and ventral (BAs 45/47). Second, while the engagement of the left mid-fusiform gyrus (BAs 19/37) was largely overlapped across the three task categories (Figure 2-3b), semantic processing showed another activation clusters in the right mid-fusiform gyrus (BA 37) and the bilateral posterior fusiform gyri (BA 18). Phonological processing also recruited the posterior fusiform gyrus (BA 18) in the right hemisphere. The activation in the right posterior fusiform gyrus for both semantic and phonological categories was within a large cluster that was centered at and extended from the right middle and inferior occipital gyri. When compared with the orthographic category, however, only the cluster in the right inferior occipital gyrus (BA 18) was significantly greater for the phonological category, whereas the other clusters in the bilateral fusiform gyri did not reach statistical significance. In addition, phonological processing showed greater involvement of the right lingual gyrus (BA 18) as compared with semantic processing as well as the orthographic and semantic processing together.

Notably, phonological processing showed greater involvement of the left inferior parietal lobule (BA 40) as compared with orthographic and semantic processing together; semantic processing showed greater activation in the left middle temporal gyrus (BAs 21/22) as compared with the other two processing together. In addition, the right superior temporal gyrus (BA 22) showed significant involvement in the phonological category but the cluster did not survive from the subtraction analyses

as compared with other categories. Possible reasons for the lack of statistical significance are discussed below.

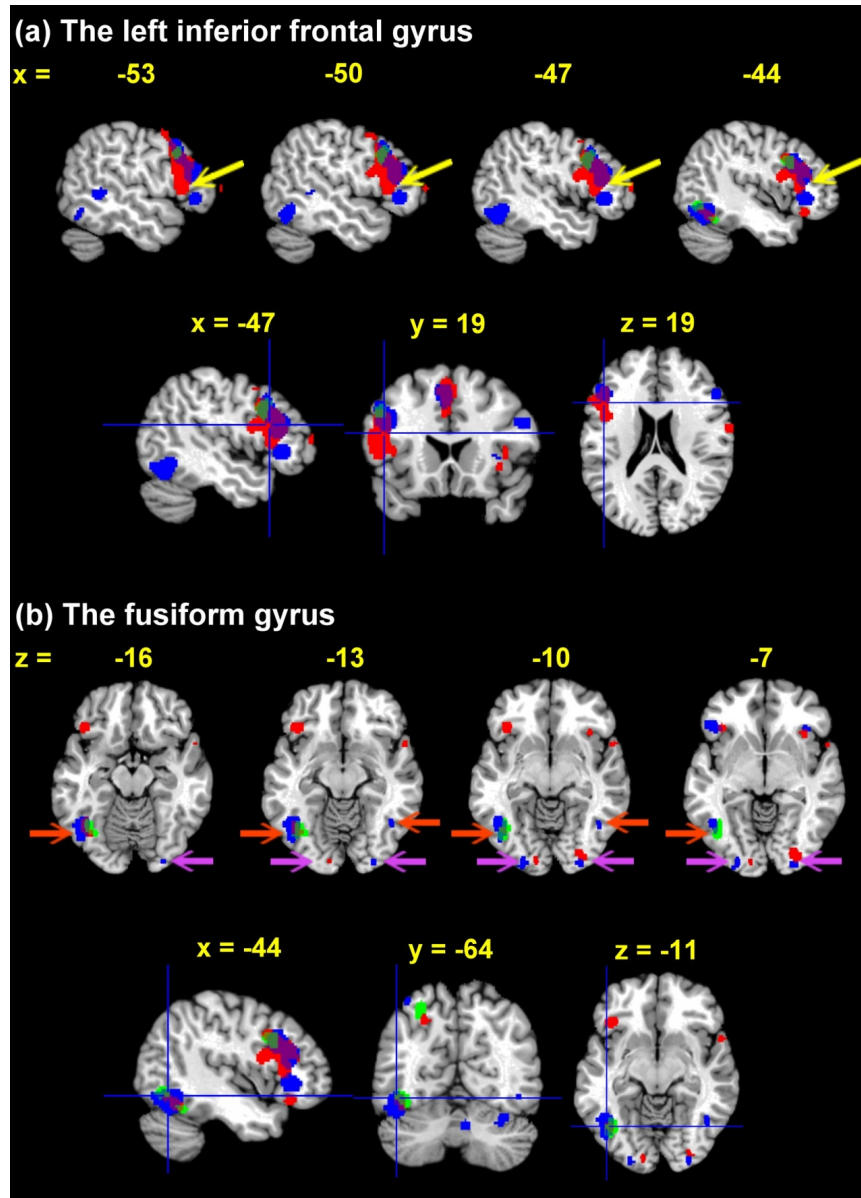


Figure 2-3. The overlapped activation in (a) the left inferior frontal gyrus and (b) the bilateral ventral occipito-temporal regions for orthographic (green), phonological (red), and semantic (blue) processing. Yellow arrows: the left inferior frontal gyrus; orange arrows: the bilateral mid-fusiform gyri; purple arrows: the bilateral posterior fusiform gyri and inferior occipital gyri. The activation was thresholded at $p < 0.05$ (FDR corrected) with a minimum cluster volume of 150 mm³.

Discussion

The current meta-analysis summarized the existing fMRI studies on Chinese character processing and demonstrated the neural networks for orthographic, phonological, and semantic processing of Chinese characters. Our results showed that the overall activation patterns across three language-processing components resembled the results of the previous meta-analyses (Bolger et al., 2005; Tan, Laird, et al., 2005), which revealed strong activation for Chinese character processing in the left middle frontal gyrus (BA 9) and the bilateral ventral occipito-temporal cortices including portions of the fusiform gyrus (BA 37) and the inferior/middle occipital gyrus (BAs 18/19). Additionally, component-specific dissociation within particular regions was also identified in the current study.

Convergent Regions

Highly convergent activation for three task categories in the left middle frontal gyrus (BAs 9/46), the left superior parietal lobule (BA 7) and the left mid-fusiform gyrus (BAs 19/37) suggests that these regions serve the underlying character processing regardless of the nature of the task. This underlying processing could be the initial orthographic recognition of visual character forms that is required for all three types of language tasks.

The activation of the left middle frontal gyrus (BAs 9/46) has been reported in several functional neuroimaging studies on Chinese character processing (e.g., Booth et al., 2006; Dong et al., 2005; Kuo et al., 2001; Kuo et al., 2004; C. L. Liu et al., 2006; Tan, Feng, et al., 2001; Tan, Liu, et al., 2001; Tan et al., 2000). Some suggest that the left middle frontal gyrus is recruited for the intensive visuospatial analysis of Chinese logographs demanded by the visual forms of characters (L. Liu et al., 2009; Tan, Feng, et al., 2001; Tan, Liu, et al., 2001) and the coordination of phonological or semantic

processing required by experimental tasks (L. Liu et al., 2009; Tan, Liu, et al., 2001; Tan et al., 2000). Others found that the activation of the left middle/inferior frontal gyri occurred with that of the left premotor cortex and supplementary motor area, indicating a motoric representation or articulatory rehearsal of vocally/sub-vocally phonological information generated for the characters (Kuo et al., 2004). In our results, the consistent activation of the left middle frontal gyrus across three task categories might underlie visuospatial analysis of Chinese characters, while increased activation of this region for phonological and semantic categories might be associated with orthography-to-phonology and orthography-to-semantics processing required for each type of tasks, respectively.

The left superior parietal lobule (BA 7) has been attributed to visual search and spatial selective attention (Booth et al., 2003), visuomotor intention (Rushworth, Paus, & Sipila, 2001) and analysis of visuospatial information of objects that is thought to be part of the “where” pathway (Haxby et al., 1991). Furthermore, in terms of functional connectivity, Xiong et al. (2000) found strong correlation between the left middle frontal gyrus (BA 9) and the left superior parietal lobule (BA 7), suggesting that the two regions engage in extensive processing of spatial information during Chinese language tasks.

The left fusiform gyrus (BAs 19/37) is within the ventral occipito-temporal cortex (vOT) and is known as the visual word form area (VWFA) for word recognition (Cohen et al., 2002). It is suggested to be responsible for recognizing word forms and relaying the information onto those regions central to phonological and lexical/semantic processing (Jobard et al., 2003). Although the left vOT has been found to be involved in processing of several language systems, there is language-specific differentiation. In particular, while alphabetic language processing seemed to

activate only the left vOT, previous studies have found that Chinese character processing showed bilateral recruitment of the vOT, which might imply that reading Chinese characters requires additional word form analysis (Bolger et al., 2005; Tan, Laird, et al., 2005). In the current study, bilateral involvement of the vOT was observed in the phonological and semantic categories. One possible explanation for the bilateral recruitment is that while the left vOT is responsible for identifying the radicals of a Chinese character, the right counterpart is also required for arrangement of the radicals within the character (Y. Liu & Perfetti, 2003). Moreover, another study (Nelson, Liu, Fiez, & Perfetti, 2009) found that English learners of Chinese showed activity in the bilateral vOT for reading Chinese characters but only the left vOT for viewing English words. This suggested that they needed to adopt the right counterpart to process global character forms that was required for Chinese characters but not so for English alphabets. Nevertheless, in terms of lateralization, the involvement of the left vOT was found to be greater than that of the right counterpart, so the bilateral involvement of the vOT was left-lateralized.

Divergent Regions

In addition to the convergent regions that were thought to underlie the basic orthographic recognition of Character processing, other regions were found to be involved with increasing processing demands. First, phonological processing was found to recruit the left inferior parietal lobule (BA 40) and the more posterior dorsal part of the left inferior frontal gyrus (BA 44). Previous studies suggest that the function of the left inferior parietal lobule might be to temporarily store phonological information in working memory (Fiez et al., 1996) and that the posterior dorsal part of the left inferior frontal gyrus might be specialized for processing phonological representations (Poldrack et al., 1999). As compared with orthographic and semantic

processing, phonological processing was found to recruit more involvement of the left insula, the role of which has often been related to motor planning of articulation (Dronkers, 1996; Price, 2010; Wise, Greene, Büchel, & Scott, 1999) while other studies have also found its relationship with phonological retrieval deficits (Harasty et al., 2001; Shafto, Burke, Stamatakis, Tam, & Tyler, 2007; Shafto, Stamatakis, Tam, & Tyler, 2009). Although the functions of the left insula remain controversial, our results support its greater involvement in phonological processing as compared with other language-processing components. In addition, phonological processing was also found to activate the superior temporal gyrus (BA 22), mainly in the right hemisphere, which has been suggested to be associated with tonal representations of Chinese logographs (Tan, Feng, et al., 2001) and sensitive to perception of intonation in speech prosody (Zhang, Shu, Zhou, Wang, & Li, 2010). However, this region did not show significantly greater involvement in phonological processing as compared with other components in the subtraction analyses, which could indicate that the involvement of the superior temporal gyrus was not significantly differentiated across the three language-processing components. However, it should be noted that the current approach used for subtraction analysis in GingerALE is highly conservative, especially for studies dealing with a relatively limited number of experiments (e.g., 10 – 20) per group. Therefore, the current meta-analysis found consistent recruitment of the right superior temporal gyrus for phonological processing, but the limited number of experiments in each category restricted us from concluding whether the involvement of this region was differentiated from other language-processing components.

Second, for semantic processing, additional activation was found in the left middle temporal gyrus (BAs 21/22) and the anterior ventral part of the left inferior frontal gyrus (BAs 45/47). Researchers propose that the left middle temporal gyrus

includes verbal semantic representations (Booth et al., 2002; Booth et al., 2006) and the anterior ventral part of the left inferior frontal gyrus is specialized for access and manipulation of these representations (Poldrack et al., 1999). The posterior-dorsal (BA 44) and anterior-ventral (BAs 45/47) dissociation within the left inferior frontal gyrus for phonological processing and semantic processing, respectively, was verified by direct subtraction analyses, i.e., *phonological* > *orthographic* and *semantic* > *orthographic*, as well as by the additional comparisons, i.e., *phonological* > (*orthographic* & *semantic*) and *semantic* > (*orthographic* & *phonological*). Furthermore, this dissociation within the left inferior frontal gyrus is consistent with previous findings on other languages (Poldrack et al., 1999; Vigneau et al., 2006).

Third, although all three components activated the left ventral occipito-temporal cortex, semantic processing showed the largest extent of activation while orthographic processing showed the smallest. Only semantic processing recruited activity in the right mid-fusiform gyrus. In addition, semantic processing involved bilateral posterior fusiform gyri and phonological processing activated the right posterior fusiform gyrus, the activation of which was extended from a large cluster within the middle and inferior occipital gyri. When compared with orthographic processing, however, neither phonological nor semantic processing showed significantly greater recruitment of the mid-fusiform gyrus. Instead, greater activation was found in the right inferior/middle occipital gyrus and the right lingual gyrus only for phonological processing. Since all experiments selected in the current meta-analysis employed visual stimuli, the bilateral extrastriate visual cortices, mainly the middle and inferior occipital gyri (BAs 18/19), could be related to extensive visual processing of the character stimuli as opposed to the control conditions that had less

demands in visual processing, such as fixation or perceptual control (Dong et al., 2005).

The Universal Language Brain

There has been accumulated evidence for neural representations underlying processing of a written language; however, the languages commonly studied have been alphabetic languages such as English. Thus, what has been known as the universal language network seems to be biased toward alphabetic language systems. It has been shown in these studies that comprehension of a written script would involve the occipital cortex for primary visual processing, the inferior occipito-temporal regions for visual word form processing, the posterior temporo-parietal regions for grapheme-to-phoneme conversion, the inferior/middle temporal gyrus for semantic analysis, the inferior frontal gyrus for phonological and semantic processing, and the precentral gyrus and the insula for speech production (C. Chen et al., 2009; Fiez & Petersen, 1998; Jobard et al., 2003). On the other hand, more and more studies on Chinese character processing have recently become available and have shown that, although recruiting similar cortical regions as alphabetic languages, Chinese character processing involved some differential activation. In particular, as consolidated in our meta-analysis, Chinese character processing did not involve the posterior temporo-parietal regions for grapheme-to-phoneme conversion, but instead, recruited the left middle frontal gyrus and the right ventral occipito-temporal regions for more complex orthographic processing of Chinese characters as well as orthography-to-phonology/orthography-to-semantics transformation.

In addition, unlike the left-dominant language network for alphabetic languages, the current meta-analysis showed significant activation in many regions in the right hemisphere for Chinese phonological and semantic processing, including the

inferior and middle frontal gyri, the superior temporal gyrus, and the ventral occipito-temporal regions. The involvement of the right hemisphere in Chinese language processing has not been widely discussed in the literature. However, activation in the right hemisphere has been reported in a few studies, and thus significant convergence was shown in the current meta-analysis. Some researchers attributed the involvement of the right frontal and ventral occipito-temporal regions to intensive visuo-spatial analysis for the complex Chinese character forms, for which the right hemisphere might be involved in perceiving the spatial location of strokes and processing strokes combination (Y. Liu & Perfetti, 2003; Tan, Feng, et al., 2001; Tan, Liu, et al., 2001). Others have suggested that while the left hemisphere is engaged in syllable and rhyme processing, the right hemisphere might subserve Chinese lexical tones (Li et al., 2010; L. Liu et al., 2006). This view is consistent with the role of the right hemisphere in processing speech prosody in other languages (Friederici & Alter, 2004; Gandour et al., 2004; Tong et al., 2005). Nevertheless, the functional roles of the right hemisphere recruitment for Chinese character processing need to be further investigated in future studies.

Limitations

Although efforts have been made to optimize the methodologies, there are still some limitations to be considered. First, there were unequal numbers of contrasts included in each task category (orthographic: nine contrasts; phonological: fourteen contrasts; semantic: seventeen contrasts). Increasing and balancing the numbers of contrasts in all task categories for future meta-analyses would increase the statistical power and validity of between-category comparisons.

Second, we included three studies that reported findings with late Chinese-English bilinguals (details described in the Literature Selection section in Methods). It

could be argued that the late bilinguals in these three studies might have higher proficiency in their second language (L2: English), which might influence the neuroanatomical mechanisms underlying processing of the first language (L1: Chinese), so their language networks might differ from bilinguals with low proficiency in L2. However, we think that the difference, if any, should not have significant influence on the current meta-analysis for the following reasons. First, there is possibly a variation in the proficiency level of L2 of the native Chinese speakers in the other selected studies; that is, some of them might be fluent bilinguals as the participants in these three studies, while others might not. The lack of information about their language exposure history hindered us from confirming whether they were late bilinguals with high or low proficiency in L2. Second, researchers have examined late proficient Chinese-English bilinguals performing language tasks in Chinese and English, and similar cortical regions involved for both languages were observed (Chee, Tan, et al., 1999; Tan et al., 2003). It has been suggested that late bilinguals seemed to apply their L1 (Chinese) system to L2 (English) reading. Other studies have examined the effect of L2 proficiency on the language network underlying L2 processing (e.g., Wartenburger et al., 2003), but to our knowledge, no studies have reported any effect of L2 proficiency on the neural network underlying processing of L1 in Chinese-English bilinguals and thus the effect is not clear. We agree that variations in the participants' L2 proficiency could be a potential limitation; however, the effect has not been evidenced in the research to date. Moreover, the effect, if any, would have been minimized through a meta-analytic procedure given the number of these bilingual studies were relatively small.

Third, a particular difficulty we encountered when retrieving activation foci from the studies was the inconsistency of the coordinate templates. Some studies

reported coordinates in the MNI space, while others used the Talairach template. Even more challenging was the varied coordinate transformation methods used in different studies. Although we identified the transformation methods and used the corresponding transformations implemented in GingerALE to transform all Talairach coordinates into MNI space, the process of transformation and back-transformation might have brought some inevitable discrepancies in the final set of coordinates for analyses. Nevertheless, we believe that the potential errors caused by these discrepancies could be reduced to a certain extent with the key idea of the ALE method to treat reported foci as three-dimensional Gaussian probability distributions rather than single points. Moreover, with the revised algorithm, the spatial uncertainty contributed by between-template variances was also taken into account.

Fourth, it should be noted that we did not include studies on alphabetic language processing in the current meta-analysis; thus, the observation that Chinese character processing recruited differential activation in the left middle frontal gyrus and the right ventral occipito-temporal regions was based on qualitative comparisons between our findings and those reported in the existing empirical studies, meta-analytic studies and review papers on alphabetic language processing. In order to provide quantitative evidence, future studies need to include studies on both Chinese character processing and alphabetic language processing in the meta-analysis and make direct comparisons between the two language systems.

Finally, it remains unclear whether the differential cortical recruitment for Chinese and alphabetic language processing is only represented as activation in different regions. Rather, would there be any regions that are involved in both types of language processing but their functional roles in Chinese and alphabetic language processing might be different? It is an intriguing question but it would require

investigations beyond the current meta-analysis. Nevertheless, this question could be addressed in future studies by examination of whether deficits in the same brain region would cause similar or dissimilar language impairment for Chinese and alphabetic language speakers. For instance, quantitative meta-analysis of neuroimaging studies on the neural basis of dyslexia in Chinese and alphabetic languages can summarize the consistent findings regarding structural and functional deficits in dyslexics as well as how the deficits relate to language or non-language impairment. If the same cortical regions are found to show abnormal activation in both Chinese and English dyslexics, researchers can then examine whether the deficits are associated with similar impairment in language performance for both groups. A literature review identified three meta-analytic studies on the neural basis of dyslexia, but the studies included were all on alphabetic languages (Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, Kronbichler, & Wimmer, 2009, 2011). On the other hand, although more neuroimaging studies have examined the neural basis of dyslexia in Chinese in the recent years, the findings are still inconclusive. Therefore, more empirical studies and systematic reviews or meta-analyses are required to provide further understanding of Chinese dyslexia. In addition, researchers can examine whether damage to the same language-related brain regions would cause similar or dissimilar impairment in Chinese and alphabetic language speakers with aphasia.

Summary

Results from the current study, though generally consistent with prior meta-analyses by Tan, Laird, et al. (2005) and Bolger et al. (2005), extended our understanding of Chinese character processing by including a larger set of studies and providing further insights into specific networks for orthographic, phonological, and semantic processing. The findings showed an underlying sub-network that was

consistently involved in the three language-processing components and might serve the orthographic recognition of visual character forms across all tasks, which included the left middle frontal gyrus, the left superior parietal lobule and the left ventral occipito-temporal cortex. With increasing task demands, particularly phonological and semantic processing, additional activity for specific components was also identified. Although the overall networks for Chinese character processing were congruent with the alphabetic language networks, the current results consolidated the findings of differential recruitment for Chinese character processing in the left middle frontal gyrus and the right ventral occipito-temporal regions. The distinct activation suggests that writing systems and language experience shape the functional neuroanatomy of language representations.

A Priori Regions-of-interest for Subsequent Studies

The left middle frontal gyrus and the right ventral occipito-temporal cortex seem to form a sub-network that is specific to Chinese character processing. In the subsequent studies, we examined the involvement of this sub-network in Chinese character processing. Thus, the middle frontal gyrus and the ventral occipito-temporal cortex were selected as a priori regions-of-interest (ROIs) to allow for an ROI approach to investigate the functional roles of these regions. In particular, we examined the effects of task manipulation on the ROIs, as well as how their involvement might be influenced by age and handedness. As the subsequent studies focused on orthographic and phonological processing, we identified the center coordinates of the left middle frontal gyrus (BA 9) and the left fusiform gyrus (BA 37) from the conjunction result of the orthographic and phonological categories. The coordinates in the left hemisphere were flipped to obtain the center coordinates of the ROIs in the right hemisphere. Using the MarsBaR toolbox (Brett, Anton, Valabregue,

& Poline, 2002), the ROIs of the left and right middle frontal gyri were defined as 10-mm spheres centered at (-48, 14, 32) and (48, 14, 32), respectively. The ROIs of the bilateral vOT were defined as 10-mm spheres centered at (-40, -66, -12) and (40, -66, -12). In addition to the sub-network, we also identified an ROI within the left inferior frontal gyrus from the contrast analysis of phonological > orthographic categories. The left inferior frontal gyrus (BA 44) is part of the Broca's area, and it is commonly activated in both Chinese and alphabetic phonological processing. The bilateral ROIs of the inferior frontal gyrus were defined as 10-mm spheres centered at (-47, 27, 11) and (47, 27, 11).

The following set of research (Study 2a and Study 2b) aimed to directly examine the involvement of the sub-network in orthographic processing and phonological processing of Chinese characters, respectively. In particular, different types of task manipulation were applied to help elucidate the functional roles of the vOT in orthographic processing and the middle frontal gyrus in phonological processing. Furthermore, one of the aims of this thesis was to investigate the integrity of this sub-network for language processing in Chinese speakers. Thus, how the activity in this sub-network would be influenced by age (Study 3a) and handedness (Study 3b) was examined in Study 3.

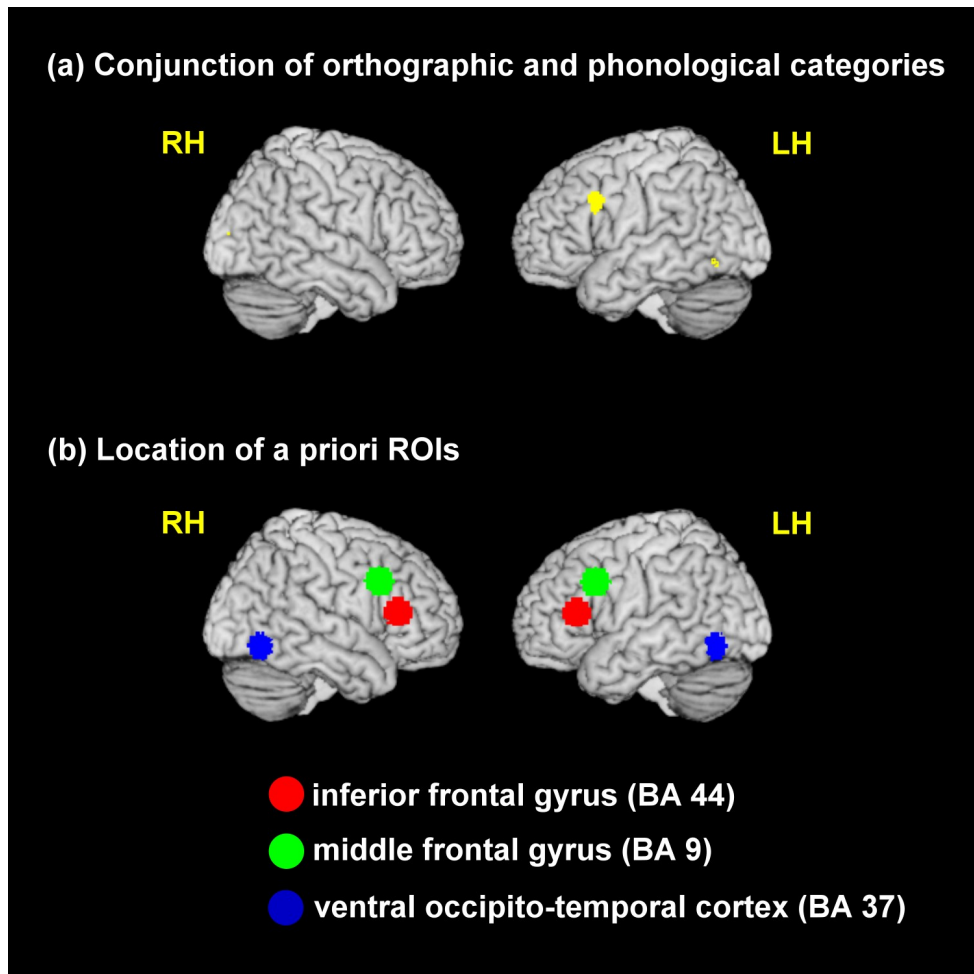


Figure 2-4. (a) The conjunction result of orthographic and phonological categories and (b) the location of a priori ROIs. Yellow region: the convergent regions of the orthographic and phonological categories; red regions: the left and right inferior frontal gyri ROIs centered at $(-47, 27, 11)$ and $(47, 27, 11)$; green regions: the left and right middle frontal gyri ROIs centered at $(-48, 14, 32)$ and $(48, 14, 32)$; blue regions: the left and right ventral occipito-temporal regions (vOT) ROIs centered at $(-40, -66, -12)$ and $(40, -66, -12)$. LH: left hemisphere; RH: right hemisphere.

CHAPTER III: STUDY 2

The Involvement of the Specialized Sub-Network in Orthographic and Phonological
Processing for Reading Chinese Characters

Overview

The meta-analysis in Study 1 identified a sub-network that might be specific to Chinese character processing, which included the left middle frontal gyrus (BA 9) and the right ventral occipito-temporal cortex (BA 37). Based on this finding, Study 2 further investigated the involvement of this sub-network specifically in orthographic and phonological processing in Chinese reading. Two tasks, a lexical decision/recognition task and a homophone judgment task, were designed using the unique characteristics of Chinese characters to examine the functional roles of the sub-network in character identification process and phonological processing, respectively. A group of participants were recruited and asked to perform both tasks in one session. This chapter will introduce the two studies: Study 2a focusing on the process of Chinese character identification and Study 2b on phonological processing.

STUDY 2a

Chinese Character Identification

Introduction

The current study investigated how the sub-network specific to Chinese character processing is involved in character identification, with particular interests in the involvement of the ventral occipito-temporal cortex (vOT) in Chinese orthographic processing. Word identification has been defined as an initial stage of visual word processing including orthographic decoding of the visual word forms and the selection of a correct lexical entry (Fiebach, Friederici, Müller, & Cramon, 2002). In other words, it is a two-step process in which readers (a) examine orthographic legality while performing visuospatial analysis on visual scripts and then (b) search for matched lexical representations in the mental lexicon.

Many of the previous studies that tapped on orthographic processing examined lexicality effect (i.e., pseudowords vs. words) and frequency effect (i.e., high-frequency vs. low-frequency words) of word reading. Approaches that have often been used are naming and lexical decision, in which participants judge whether a visually displayed stimulus is a real word (in alphabets) or character (in Chinese). Brain activation in response to pseudoword reading was compared with that to word reading, and differential activation was identified. Of our particular interest, the left vOT is one of the regions that have been reported to show differential sensitivity to pseudoword and word reading. The vOT is also referred to as the fusiform gyrus (Price, 2012), so here we use these two names interchangeably. Several studies have found higher activity for pseudowords than for words in the posterior part of the left vOT ($y = -60$ to $y = -70$ in MNI space) and higher activity for words than for pseudowords in the

anterior part ($y = -40$ to $y = -50$ in MNI space) (Mechelli, Gorno-Tempini, & Price, 2003; Price & Devlin, 2011; Price & Mechelli, 2005; Woollams et al., 2011; Xu et al., 2001). Reading pseudowords also increases activity in the left inferior frontal operculum as compared with reading words (Fiez, Balota, Raichle, & Petersen, 1999; Mechelli et al., 2003; Paulesu et al., 2000; Xu et al., 2001).

For Chinese characters, the neural differences underlying reading between orthographically legal characters and pseudo-characters, and orthographically illegal artificial characters have been studied using different tasks and the findings have been inconsistent. C. Liu et al. (2008) examined implicit Chinese character processing by asking their participants to make font size judgment of the stimuli. Notably they found that real characters and pseudo-characters showed stronger activation in the left middle frontal gyrus (BA 9) and the left middle fusiform gyrus (BA 37) as compared with artificial characters. On the contrary, Wang et al. (2011) showed that, in a one-back discrimination task, the activity in the left mid-fusiform gyrus was inversely related to word-likeness, with the greatest activity observed in response to artificial characters and the least activity to real characters.

At the behavioral level, Hue and Tzeng (2000) used a lexical decision task to study the character identification process of high-frequency characters (HF), low-frequency characters (LF), pseudo-characters (PC) and non-characters (NC) in Chinese. Their findings showed that LF characters required longer reaction time than HF characters. Among the four types of stimuli, PC took the longest reaction time and elicited the highest error rate. PC in Chinese are orthographically legal as they are composed of a semantic radical and a phonetic radical, and the organization of the radicals conforms to the word form rules; however, they are not pronounceable and do not have meanings. The Chinese pseudo-characters have different properties from

alphabetic pseudowords in that one could not make up a pronunciation of the whole pseudo-character from sublexical pronunciations of its parts. As pseudo-characters look very much like real characters, the lexical decision to process a pseudo-character is assumed to resemble that to process a character of very low frequency in occurrence and thus they are much more difficult to reject.

In addition, Hue and Tzeng (2000) proposed a new task, called the lexical recognition task, to investigate character recognition process. In this task, instead of judging if a stimulus is a real character, participants are asked to indicate whether or not they “know” the stimulus. While the lexical decision task requires both orthographic analysis and lexical access, they believe that the lexical recognition task relies more on lexical access but less likely on orthographic analysis. When comparing the behavioral differences between these two tasks, they found that participants who were given the instruction of lexical recognition made fewer errors in the PC condition than those given the lexical decision instruction did.

The lexical decision/recognition task implemented in Hue and Tzeng’s (2000) study appeared to be a suitable task for us to investigate the different aspects of orthographic processing in Chinese character reading. First, comparing identification of non-real characters with real characters allowed us to examine differential activation induced by lexicality effect in Chinese character identification process. Second, the differential processes involved in lexical decision and lexical recognition might provide a venue to investigate the neural representations underlying orthographic analysis. Therefore, we designed an event-related fMRI task adapted from the experimental design in Hue & Tzeng’s (2000) paper, and asked two groups of participants to perform lexical decision and lexical recognition on the same task.

The current study aimed to examine the involvement of the sub-network in Chinese character identification processes by the manipulation of lexicality effect and orthographic analysis. For lexicality effect, we hypothesized that the pseudo-characters and non-characters would show greater activity in the posterior vOT and the inferior frontal operculum as compared with real characters as shown in previous studies. In addition, others suggest that the left middle frontal gyrus might be associated with orthography-to-phonology and orthography-to-semantics transformation (L. Liu et al., 2009; Tan, Liu, et al., 2001; Tan et al., 2000). As lexical decision/recognition to pseudo-characters and non-characters might increase the demands in searching for phonological and semantic representations to match with the orthographic inputs, we would expect to see increased activity in the middle frontal gyrus for pseudo-characters and non-characters as compared with real characters. For orthographic analysis, we hypothesized that the lexical decision group would show greater activity in the vOT than the lexical recognition group. As discussed in Study 1, the left middle frontal gyrus has also been suggested to be responsible for visuospatial analysis of Chinese characters (L. Liu et al., 2009; Tan, Feng, et al., 2001; Tan, Liu, et al., 2001). If the function of visuospatial analysis is true, we would expect to see greater activity in the middle frontal gyrus for the lexical decision group than the lexical recognition group.

Methods

Participants

A group of forty-one right-handed young adults were recruited to participate in the tasks for Study 2a and Study 2b. Participants were screened using a detailed health questionnaire to exclude any psychiatric or neurological disorders, vascular risk factors or any factors contraindicative of MRI scanning (e.g., claustrophobia, metal

implants, pacemaker, etc.). All participants gave informed consent approved by the Institutional Review Board at the National Taiwan University Hospital. Prior to the fMRI experiments, participants were administered the Graded Chinese Character Recognition Test (Huang, 2001) to evaluate their knowledge of Chinese characters. All participants performed the tasks for Study 2a first and then the tasks for Study 2b.

For the current study, they were randomly assigned into two groups ($n = 20$ and 21) and were asked to perform a similar event-related task but were given different instructions, i.e., lexical decision (LD) or lexical recognition (LR). Participants with large head movements over 1.1 mm during the fMRI tasks ($n = 3$ in the LD group and $n = 3$ in the LR group) and those whose behavioral task data were lost to technical mishaps ($n = 2$ in the LR group) were excluded. As a result, 17 and 16 participants were included in the LD group and the LR group for analysis, respectively. Participant demographics are summarized in Table 3-1. A two-sample t -test on the grade scores of the Graded Chinese Character Recognition Test (Huang, 2001) demonstrated that the participants in the LD group (all had the highest score of 10) were equivalent in their ability in Chinese character recognition as the participants in the LR group ($M = 9.98$, $SD = 0.054$), $t(15) = 1.38$, $p = .19$.

Task Stimuli, Paradigm, and Procedure

We designed an event-related task, which was adapted from the lexical decision/recognition task in Hue & Tzeng's (2000) study. An event-related design was thought to minimize strategic effects on behavioral responses and participants' expectation in the stimulus type. It also provided flexibility in data analyses, which allowed the identification of the hemodynamic response elicited by each type of character stimuli, as well as comparisons among them.

Table 3-1. *Summary of demographics.*

	Lexical Decision	Lexical Recognition
<i>n</i>	17 (6 males)	16 (8 males)
Age		
Range	18 – 29	19 – 29
<i>M (SD)</i>	21.88 (2.91)	23.69 (2.68)
Education		
Range	13 – 18	13 – 18
<i>M (SD)</i>	15.24 (1.44)	15.94 (1.34)
Handedness ^a		
Range	60 – 100	78.95 – 100
<i>M (SD)</i>	93.45 (10.45)	96.14 (6.45)

Note. *n*: number of participants.

^aHandedness was measured by the Edinburgh Handedness Inventory (Oldfield, 1971); the score of 100 means strongly right-handed and -100 strongly left-handed.

The event-related task consisted of four types of character conditions, high-frequency characters (HF), low-frequency characters (LF), pseudo-characters (PC), and non-characters (NC). Participants saw one visual character stimulus at each trial. The LD (lexical decision) group was asked to judge whether the stimuli were real characters (i.e., “is it a real character?”), and the LR (lexical recognition) group was instructed to respond whether they recognized the stimuli (i.e., “do you know the character?”). Forty characters were selected for each of the conditions (160 characters in total). To control for visual complexity, the radicals of all characters followed the left-right composition rule. HF and LF characters were selected from the Character-Component Analysis Toolkit software (C-CAT; see Lo & Hue, 2008) using the corpus prepared by the Chinese Knowledge Information Processing Group (CKIPG, 1993). The CKIPG corpus consists of 20 million Chinese characters (5656 different characters) sampled from the articles published in three major Taiwanese newspapers

and one magazine. According to the frequency of occurrence in the CKIPG corpus, the ranks of the selected HF characters ranged from 650 to 849 ($M = 743.93$; $SD = 59.10$) among 5656 characters, and those for LF characters ranged from 3022 to 3190 ($M = 3092.5$; $SD = 57.74$). The numbers of strokes for both HF and LF characters were controlled within the range from 8 to 19 (HF: $M = 12.78$, $SD = 3.17$; LF: $M = 12.72$, $SD = 3.10$). No significant difference was found between the two conditions, $F(1, 78) = .01$, $p = .94$. Pseudo-characters were composed of radicals and the composition of radicals followed the word form rules, but they were not real characters. Non-characters were also composed of radicals, but the composition of radicals was in violation with the word form rules. An illustration of the task paradigm with examples of the stimuli in each condition is shown in Figure 3-1.

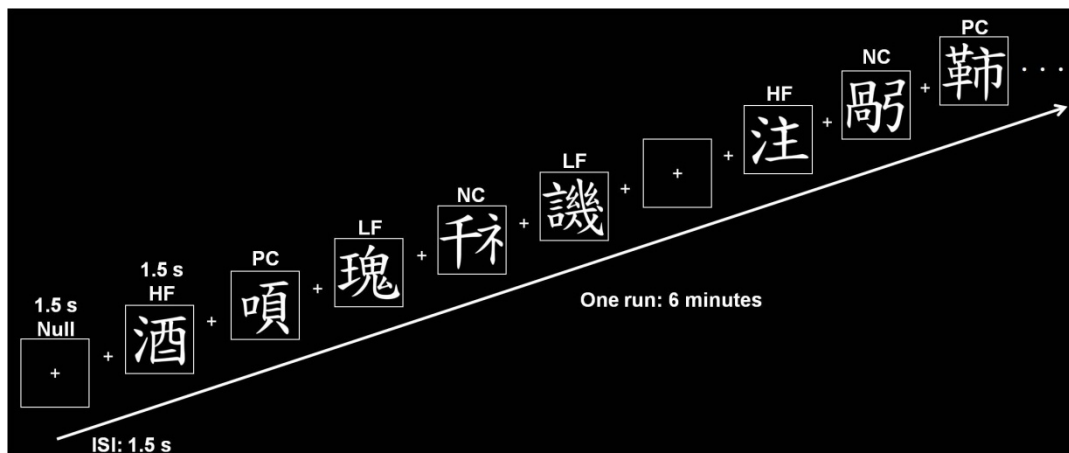


Figure 3-1. The paradigm of the even-related lexical decision/recognition task. HF: high-frequency character; LF: low-frequency character; PC: pseudo-character; NC: non-character.

The genetic algorithm provided by Wager and Nichols (2003) was applied to jitter the order of event presentation during the fMRI scan. In the algorithm, 80 null events were added to vary the inter-stimulus interval (ISI). The 160 events of

characters and 80 null events were designated to appear every 3 s: an event (either a character or a null event) was displayed for 1.5 s and the interval between two consecutive events was 1.5 s. A fixation cross was displayed during the intervals as well as the null events. When a null event appeared between two character events, it would appear as a longer interval between two character events. Consequently, the interval between the offset of one character event and the onset of the next character event (i.e., ISI) varied from 1.5 s to 4.5 s, and the interval between the onsets of two consecutive events of the same character condition (i.e., stimulus onset asynchrony, SOA) varied from 6 s to 69 s. The total series lasted for 720 s (240 events) and was divided into two runs to reduce fatigue effects. The order of two runs was counterbalanced across participants.

The tasks were presented using E-prime version 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). The stimuli were back projected onto a screen at the rear of the scanner bore and participants viewed the images via a mirror attached to the head coil placed directly above their eyes. They responded to the trials by a button press on a respond pad held in their right-hand.

Image Acquisition

Functional MRI data were acquired in a 3 Tesla MR scanner (TIM Trio, Siemens, Erlangen, Germany) using a 32-channel head coil. A T2-weighted image was first obtained as an anatomical reference using the following parameters: TR 6800 ms; TE 101 ms; flip angle 150°; FOV 220 mm; voxel size 0.86 × 0.86 mm; slice thickness 4.5 mm; 35 axial slices. A gradient-echo EPI sequence was used for functional images to measure blood-oxygen level-dependent (BOLD) contrast and they were obtained at the same location as the T2-weighted image by using the following parameters: TR 1800 ms; TE 24 ms; flip angle 90°; FOV 220 mm, voxel size 3.44 × 3.44 mm; slice

thickness 4.5 mm; 35 axial slices with no gap. A total of 200 functional images were acquired in each run. After the acquisition of functional images, a high-resolution T1-weighted 3D MP-RAGE scan covering the whole brain (TR 2000 ms; TE 2.97 ms; flip angle 15°; FOV 250 mm; isotropic voxels $1 \times 1 \times 1$ mm) was obtained to provide an additional anatomical reference.

Behavioral Data Analysis

The participants' behavioral responses on the task were divided into: Hit, Correct Rejection (CR), Miss, False Alarm (FA), and No Response. In the LD group, the hit and CR responses corresponded to events in which participants correctly responded “yes” to real characters and “no” to non-real characters, respectively. In the LR group, the Hit and CR responses referred to events where participants answered “yes” to real characters that they should have known and “no” to non-real characters that they should not have known. We assumed that all participants had sufficient lexical knowledge required for the tasks for the following reasons. First, they were native Chinese speakers with formal education in Chinese since childhood. Second, they performed fairly well in the Graded Chinese Character Recognition Test (Huang, 2001) and no significant difference in performance was found between the LD group (all had the highest grade score of 10) and the LR group (grade scores $M = 9.98$, $SD = 0.054$), $t(15) = 1.38$, $p = .19$. The Miss and FA responses in both groups were the opposites of Hit and CR. No response simply meant that no responses were recorded during the presentation of stimuli.

The accuracy rate (i.e., percentage of Hit and CR) and reaction time were analyzed for each participant. The No Response events were excluded from the computation of accuracy rate and reaction time. For the computation of reaction time, only events with expected responses, i.e., Hit and CR, were used to obtain the average

for each condition. The individual participant's accuracy rate and averaged reaction time for all four conditions were then analyzed using a mixed-design two-way analysis of variance (ANOVA) test, with the character condition as a within-subjects factor and the instruction group as a between-subjects factor. The effects of instruction and character condition were examined.

Image Data Preprocessing and Analysis

All functional images were preprocessed and analyzed using the SPM8 software (Statistical Parametric Mapping 8; Wellcome Department of Cognitive Neurology, London, UK). The high-resolution T1-weighted image was first segmented into different tissue types using the New Segment tool in SPM8, and the segmented gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were combined to generate a skull-stripped T1 image. Next, all functional images were slice-timing corrected to the middle slice acquired in time within a volume (Sladky et al., 2011) and then spatially realigned to the first volume of the image series to adjust for head movement. The estimated motion parameters were produced for each participant and retained as regressors in the individual-level analysis later. The skull-stripped T1 image, T1-weighted image, and T2-weighted image were coregistered with the mean functional volume. Subsequently, the skull-stripped T1 image was segmented into GM, WM and CSF, and the segmentation parameters were used to normalize all functional and anatomical images to the Montreal Neurological Institute (MNI) template space. The functional images were smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm full-width at half-maximum (FWHM).

After preprocessing, both runs, each containing four character conditions, were included into a design matrix in separate sessions in the same order for each participant. All events in the task were included in the analyses. To model condition-

specific effects, we employed a voxel-wise general linear model using the canonical hemodynamic response function with time derivatives as reference functions. The estimated motion parameters generated from realignment were included as covariates to control for the variances caused by head movement. The normalized gray matter from the segmentation of the skull-stripped T1 image was used as an explicit mask to ensure that only within-brain voxels were analyzed.

According to the behavioral performance, the LD group only had 48.2% accuracy rate for the PC condition (see the Results section for details). The chance level accuracy rate made it unclear what processes were going on for this particular condition and it might suggest that this condition was not well designed to examine the effect of interest. Thus, we decided to exclude the PC condition from the subsequent group-level analyses on the fMRI data. The lexicality effect would then be examined by comparing non-character with real character conditions. For the group-level analysis, the contrast images of the other three character conditions from both instruction groups were entered in a random-effects two-way ANOVA test with two factors, instruction (between-subjects) and character condition (within-subjects). The accuracy rate and averaged reaction time of each condition for every participant were included as covariates of non-interest to control for the effect of task difficulty. The effect of character condition was assessed by contrasting two conditions of both instruction groups (e.g., HF in both instructions vs. LF in both instructions, LF in both instructions vs. PC in both instructions, etc.). The effect of instruction was examined by contrasting all conditions in LD with all conditions in LR as well as by contrasting an individual condition in LD with the same condition in LR (e.g., HF in LD vs. HF in LR, LF in LD vs. LF in LR, etc.). The significant activation from the main effect of instruction LD > LR was thought to show regions that were likely involved in

orthographic analysis. The results of the ANOVA test were thresholded at $p < .005$ (uncorrected) with cluster volume ≥ 20 voxels. The justification for applying this threshold is referred to in Lieberman & Cunningham (2009) and described below.

Many researchers have attempted to use increasingly conservative statistical thresholding to correct for multiple comparisons in neuroimaging data analysis, such as applying family-wise error (FWE) correction procedure or false discovery rate (FDR) techniques. These approaches have been shown to effectively protect against Type I errors, i.e., diminishing the likelihood of claiming noises as true effects. However, while Type I errors are largely decreased, Type II errors are simultaneously increased, which causes a higher likelihood of treating real effects as spurious. Moreover, motor and sensory phenomena usually have a larger effect than more complex cognitive and affective phenomena, and thus using conservative thresholding methods will cause a bias toward measuring larger rather than smaller (but real) effects. Lieberman & Cunningham's simulation demonstrates that a threshold at $p < .005$ with a 20 voxel extent produces a threshold equivalent to FDR $p < .05$ with common neuroimaging parameters. Therefore, this thresholding method is recommended as it provides a good balance between Type I and Type II errors for studies examining more complex cognitive processes.

In addition to the whole-brain ANOVA test, we used the MarsBaR toolbox (Brett et al., 2002) in SPM8 to extract the BOLD percent signal change within the a priori ROIs defined in Study 1, namely the bilateral middle frontal gyri and ventral occipito-temporal cortices. We were interested in how the manipulation of lexicality and orthographic analysis had effects on these regions. Hence, two-way ANOVA tests were performed to examine the effects of instruction and condition on the BOLD signal in the ROIs.

Results

Behavioral Data

The averaged accuracy rate and reaction time for each condition in the LD and LR groups are summarized in Table 3-2 and shown in Figure 3-2. The 2×4 mixed-design ANOVA results revealed that the main effect of instruction was significant in terms of accuracy rate, $F(1, 31) = 22.4, p < .001$, indicating that the overall percentage of expected responses regardless of conditions differed between two groups; the main effect of instruction in reaction time was not significant, $F(1, 31) = .49, p = .49$. For the main effect of the within-subjects factor of character condition, since Mauchly's tests indicated that the assumption of sphericity was violated in both accuracy rate, $\chi^2(5) = 177, p < .001$, and reaction time, $\chi^2(5) = 48.7, p < .001$, the degrees of freedom were corrected using Greenhouse-Geisser estimates of sphericity ($\epsilon = .35$ and $.50$, respectively). For accuracy rate, the main effect of condition was significant, $F(1.04, 32.4) = 78.0, p < .001$, and so was the interaction effect, $F(1.04, 32.4) = 24.6, p < .001$. For reaction time, both the main effect of condition, $F(1.49, 46.2) = 185, p < .001$ and the interaction effect, $F(1.49, 46.2) = 13.0, p < .001$, were significant. Then pair-wise comparisons between conditions were computed in each instruction group with Bonferroni correction for multiple comparisons. For the LD group, the accuracy rate in PC was significantly lower than in the other three conditions ($p < .001$ for all); the reaction time in PC was the longest amongst all conditions ($p < .001$ for all), and NC was longer than HF ($p < .001$) and LF ($p = .001$). For the LR group, the accuracy rate in PC was significantly lower than in HF ($p = .016$), LF ($p = .038$) and NC ($p = .008$), and LF was lower than NC ($p = .005$); the reaction time was different in every pair of comparison ($p < .001$ for all) except that LF and NC were not significantly different ($p = 1.00$).

Table 3-2. *Summary of behavioral performance.*

	Accuracy Rate (%)				Reaction Time (ms)			
	HF	LF	PC	NC	HF	LF	PC	NC
LD (<i>n</i> =17)	98.8 (1.79)	98.7 (2.36)	48.2 (24.3)	98.5 (2.80)	625 (51.7)	650 (50.5)	960 (141)	723 (77)
LR (<i>n</i> =16)	98.6 (2.60)	96.4 (2.72)	83.8 (15.5)	99.5 (1.01)	663 (61.3)	742 (89.2)	894 (119)	735 (84.8)

Note. The averaged accuracy rate and reaction time for each condition in the LD

(lexical decision) and the LR (lexical recognition) groups. HF: high-frequency character; LF: low-frequency character; PC: pseudo-character; NC: non-character.

Values are presented in *M (SD)*.

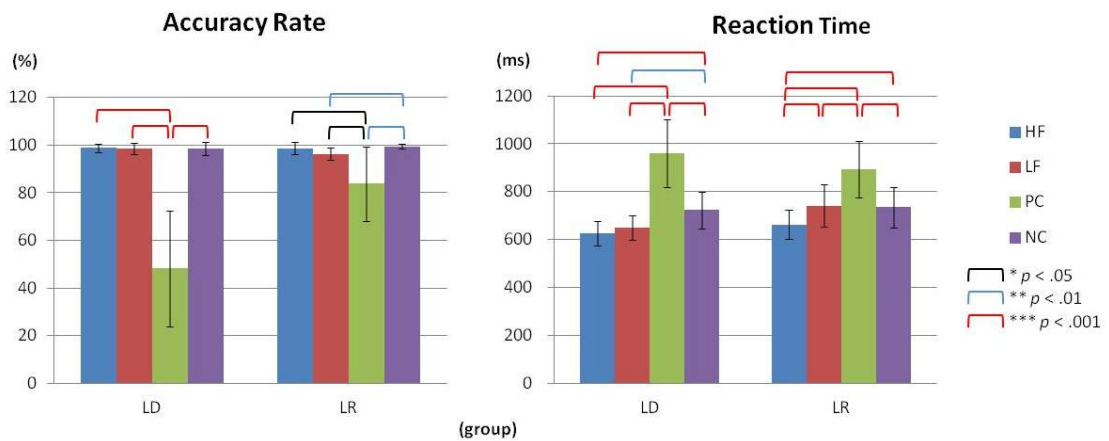


Figure 3-2. The averaged accuracy rate and reaction time for each condition in both the LD (lexical decision) and the LR (lexical recognition) groups with error bars representing standard deviations. HF: high-frequency character; LF: low-frequency character; PC: pseudo-character; NC: non-character.

Activation for Individual Conditions

The activation maps for individual conditions are shown in Figure 3-3. For both instruction groups, all three types of character conditions recruited a similar and large extent of activation in the bilateral occipito-temporal cortices, including the fusiform gyrus, the inferior occipital gyrus, and the middle occipital gyrus. Common activation was also found in the bilateral inferior parietal lobule (BA 40), the right precuneus (BA 7), the bilateral precentral gyri (BAs 4/6), the left postcentral gyrus (BAs 2/3/5), the right middle frontal gyrus (BA 9), the left insula (BA 13), and the bilateral cerebellar areas (including lobule VI and lobule IX). In general, the NC condition recruited a larger extent of activation than the other two conditions, and the LD group showed greater activation than the LR group.

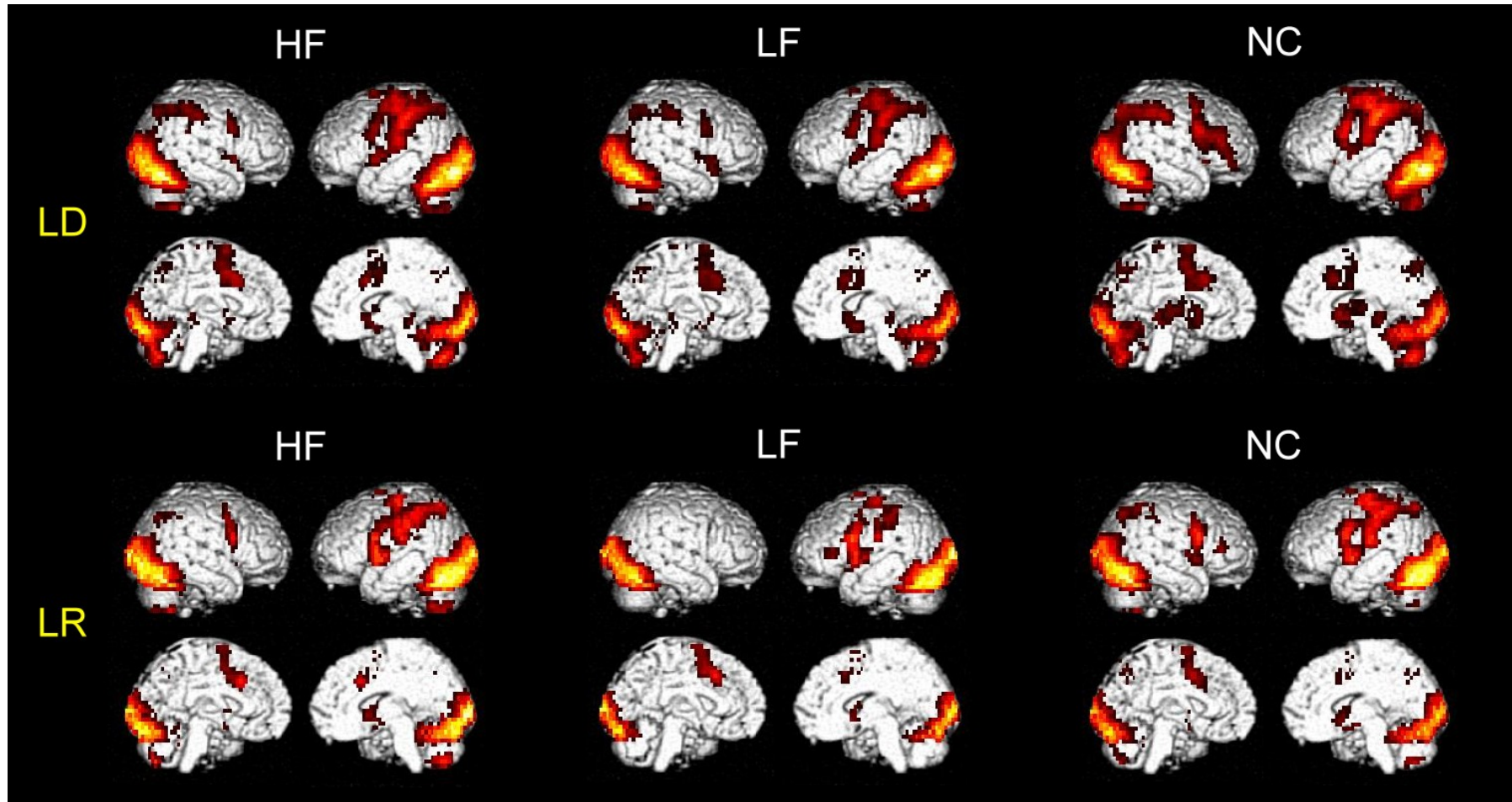


Figure 3-3. Activation maps of each condition within the LD (lexical decision) and the LR (lexical recognition) groups. HF: high-frequency character; LF: low-frequency character; NC: non-character. $p < .005$ (uncorrected) with clusters ≥ 20 voxels.

ANOVA Results

The ANOVA results are illustrated in Figure 3-4 and the activation coordinates are summarized in Table 3-3. The main effect of condition showed significant activation in the bilateral middle frontal gyri (BAs 6/8/9), the bilateral inferior parietal regions (BA 40), the left fusiform gyrus (BA 19), the left middle temporal gyrus (BAs 19/39), and the subcortical regions including the right parahippocampal gyrus and the left thalamus. The main effect of instruction revealed significant activation in the bilateral inferior occipital gyri (BAs 17/18), the right fusiform gyrus (BA 37), the right cerebellar lobule VI, and the right inferior parietal regions (BAs 7/40). The interaction effect was observed in the right inferior parietal lobule (BA 40).

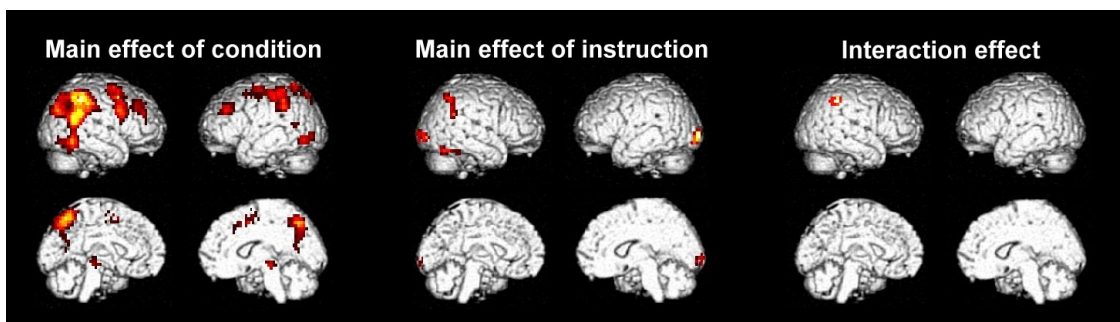


Figure 3-4. The activation results of the 3 (condition) x 2 (instruction) ANOVA test. $p < .005$ (uncorrected) with clusters ≥ 20 voxels.

Table 3-3. *Results of the ANOVA analysis.*

Voxel	Region	L/R	BA	x	y	z	F
(a) Main effect of condition							
402	Middle frontal gyrus	R	6	27	8	50	29.48
	Precentral gyrus	R	9	51	12	36	12.07
	Middle frontal gyrus	R	8	30	32	36	11.72
1648	Inferior parietal lobule	R	40	41	-44	45	28.98
	Precuneus	L	7	-8	-64	54	18.8
	Superior temporal gyrus	R	22	51	-54	18	17.23
58	Fusiform gyrus	L	19	-49	-74	-9	11.72
	Inferior occipital gyrus	L	18	-45	-81	-4	8.98
59	Middle frontal gyrus	L	9	-32	29	32	10.7
56	Supramarginal gyrus	L	40	-56	-44	36	10.65
28	Substantia nigra	R	-	13	-26	-9	10.01
	Parahippocampal gyrus	R	28	27	-26	-9	6.85
	Parahippocampal gyrus	R	36	27	-33	-14	6.84
21	Thalamus	L	-	-14	-26	-4	9.75
	Subthalamic nucleus	L	-	-8	-16	-9	6.7
23	Middle temporal gyrus	L	19	-38	-61	14	8.4
	Middle temporal gyrus	L	39	-38	-57	27	5.86
(b) Main effect of instruction							
45	Inferior occipital gyrus	L	17	-25	-98	-4	29.52
27	Cerebellum – Lobule VI	R	-	41	-64	-22	15.76
	Fusiform gyrus	R	37	41	-44	-22	12.25
34	Inferior occipital gyrus	R	18	27	-98	0	14.4
	Inferior occipital gyrus	R	18	34	-88	-4	14.02
	Lingual gyrus	R	17	17	-98	-9	9.13
54	Inferior parietal lobule	R	7	41	-57	50	13.08
	Supramarginal gyrus	R	40	44	-50	36	11.04
	Superior temporal gyrus	R	22	54	-54	22	9.28
(c) Interaction effect							
41	Inferior parietal lobule	R	40	41	-44	40	11.05

Note. The coordinates are in MNI space. BA: Brodmann area. L/R: left/right

hemisphere. Coordinates in bold are peak coordinates within the activation clusters. p

$< .005$ (uncorrected) with clusters ≥ 20 voxels.

Comparisons between Character Conditions

The results are illustrated in Figure 3-5 and the activation coordinates are summarized in Table 3-4. The HF condition showed greater activation than the LF

condition in the bilateral superior (BA 22) and middle temporal gyri (BAs 19/20/21), the right inferior parietal lobule (BA 40), the bilateral precuneus (BA 7), the left supramarginal gyrus (BA 40), the bilateral middle frontal gyri (BAs 6/8/9), the right hippocampal region, and the bilateral cerebellar lobule IX. As compared with NC, HF showed greater activation in the left anterior cingulate gyrus (BAs 24/32), the right supramarginal gyrus (BA 40) and the right middle temporal gyrus (BA 21). The LF condition did not show greater activation than the other conditions. As compared with real characters (HF and LF), NC showed greater activation in the bilateral fusiform gyri and inferior occipito-temporal regions (BAs 18/19/37), the right inferior frontal gyrus (BAs 44/45) and middle frontal gyrus (BAs 6/9), and the precuneus (BA 7). As compared with LF, NC also showed stronger activation in the bilateral inferior parietal lobule (BA 40), the right angular gyrus (BA 39), the thalamus, and the right cerebellar lobules IV and V.

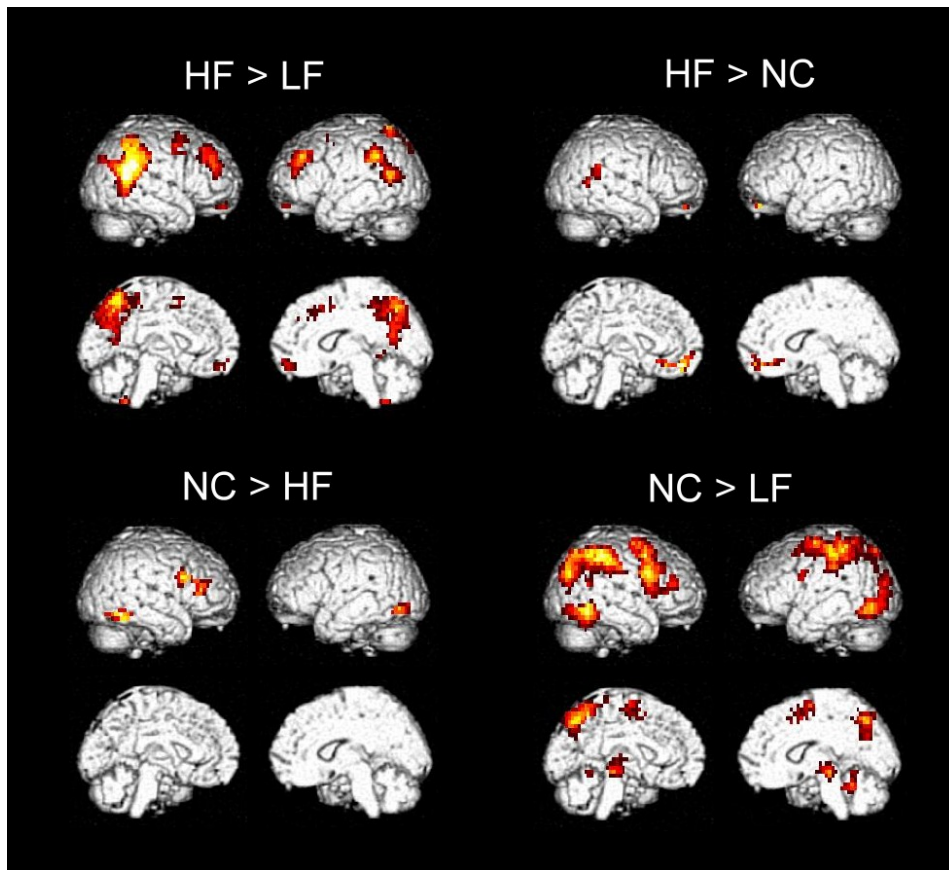


Figure 3-5. Effects of condition on both instruction groups. HF: high-frequency character; LF: low-frequency character; NC: non-character. Only contrasts showing significant activation are displayed. $p < .005$ (uncorrected) with clusters ≥ 20 voxels.

Table 3-4. Peak coordinates within the significant clusters for the effects of condition.

Region	BA	HF > LF				HF > NC			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>R</i> Middle frontal gyrus	6	27	8	50	5.15				
	8	30	32	36	4.71				
<i>L</i> Middle frontal gyrus	9	-32	29	36	4.41				
	9	-35	42	27	3.51				
	9	-45	46	18	3.21				
	6	-21	8	54	3.53				
	6	-28	1	45	3.44				
<i>R</i> Medial frontal gyrus	6	-21	8	45	3.22				
	32	23	18	40	4.71				
	10	6	53	-18	3.33				
<i>R</i> Inferior parietal lobule	40	54	-44	27	5.29				
<i>L</i> Supramarginal gyrus	40	-56	-44	36	4.58				
<i>R</i> Supramarginal gyrus	40					65	-47	27	3.14
<i>L</i> Precuneus	7	-8	-64	54	5.4				

(table continues)

Table 3-4 (*continued*)

Region	BA	HF > LF				HF > NC			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>R</i> Precuneus	7	10	-68	50	4.62				
	7	6	-61	54	4.59				
<i>R</i> Superior temporal gyrus	22	51	-54	18	5.58				
	22	65	-47	22	5.14				
<i>L</i> Middle temporal gyrus	19	-38	-61	14	4.09				
	39	-56	-68	18	3.56				
<i>R</i> Middle temporal gyrus	21					61	-54	9	3
<i>R</i> Fusiform gyrus	37	30	-54	-4	3.71				
<i>R</i> Hippocampus	36	34	-37	-9	3.39				
<i>R</i> Parahippocampal gyrus	28	30	-26	-14	3.24				
<i>R</i> Cerebellum – Lobule IX	-	6	-54	-58	3.5				
<i>L</i> Cerebellum – Lobule IX	-	-8	-50	-54	3.2				
<i>L</i> Anterior cingulate	32					-8	49	-14	3.77
	24					-4	32	-14	3.71
Region	BA	NC > HF				NC > LF			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>R</i> Inferior frontal gyrus	44	48	12	27	3.62	58	15	9	3.48
	45	44	32	14	3.28				
<i>R</i> Middle frontal gyrus	9	44	22	27	2.84	51	12	36	4.88
	6					27	8	50	6.62
<i>L</i> Precentral gyrus	4					-32	-13	54	4.94
	6					-56	5	22	3.14
	6					-56	5	32	3.12
<i>R</i> Precuneus	7	30	-61	32	3.34				
<i>L</i> Precuneus	7					-11	-68	50	4.99
<i>L</i> Inferior occipital gyrus	18	-45	-81	-4	2.82				
<i>R</i> Inferior parietal lobule	40					41	-44	45	6.87
<i>L</i> Inferior parietal lobule	40					-38	-44	50	5.07
<i>R</i> Angular gyrus	39					34	-61	36	5.06
<i>R</i> Inferior temporal gyrus	37					54	-54	-14	4.95
<i>R</i> Fusiform gyrus	37	51	-50	-14	3.9				
	19					51	-71	-14	4.08
<i>L</i> Fusiform gyrus	19	-49	-74	-9	3.15				
	19	-38	-68	-14	3.02				
<i>R</i> Superior occipital gyrus	19					37	-78	32	5.17
<i>L</i> Thalamus	-					-14	-26	-4	4.36
<i>R</i> Substantia nigra	-					13	-26	-9	4.18
<i>R</i> Parahippocampal gyrus	36					27	-33	-14	3.44
	28					27	-26	-9	3.1
<i>R</i> Cerebellum – Lobule V	-					17	-50	-22	3.63
	-					27	-47	-22	3.14
<i>R</i> Cerebellum – Lobule IV	-					6	-50	-14	3.13

Note. HF: high-frequency character; LF: low-frequency character; NC: non-character.
 $p < .005$ (unc.), voxels ≥ 20 .

Comparisons between Instruction Groups

The results are illustrated in Figure 3-6 and the activation coordinates are summarized in Table 3-5. When comparing all conditions in the LD group with all conditions in the LR group, we found that the LD group showed stronger activation than the LR group in the bilateral inferior occipital gyri (BAs 17/18), the right mid-fusiform gyrus (BA 37), the right inferior parietal lobule (BA 7), the right supramarginal gyrus (BA 40), the right superior temporal gyrus (BA 22), and the right cerebellar lobule VI. The activation was similar to the main effect of instruction. These regions might be related to the process of orthographic analysis that was required for lexical decision but not lexical recognition regardless of the types of character conditions. On the contrary, the LR group did not show significantly stronger activation than the LD group. For all individual comparisons between LD and LR within each condition, the NC condition showed the greatest differences, while the HF condition showed the smallest.

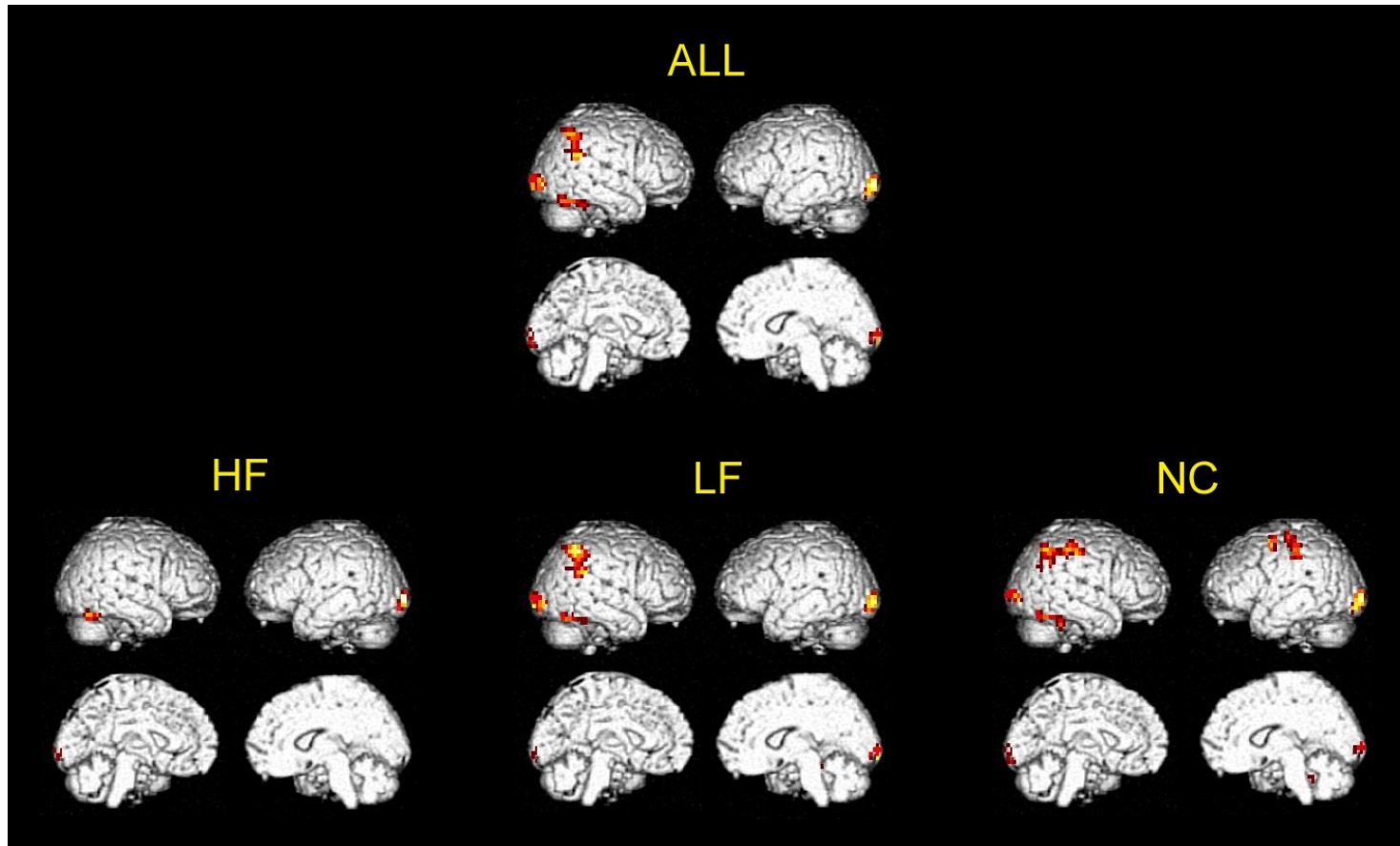


Figure 3-6. Effects of instruction on each condition for LD > LR (lexical decision > lexical recognition). Effects of instruction for LR > LD did not show significant activation. ALL: all character conditions; HF: high-frequency character; LF: low-frequency character; NC: non-character. $p < .005$ (uncorrected) with clusters ≥ 20 voxels.

Table 3-5. *Peak coordinates within the significant clusters for the effects of instruction on each condition for LD > LR.*

Region	BA	All conditions				High-frequency				Low-frequency				Non-character			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>Z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>L</i> Inferior occipital gyrus	17	-25	-98	-4	5.43					-25	-98	-4	4.77	-25	-98	-4	5
<i>R</i> Inferior occipital gyrus	18	27	-98	0	3.79					34	-92	-4	3.59	34	-88	-4	3.15
	18	34	-88	-4	3.74					27	-98	0	3.56				
<i>R</i> Fusiform gyrus	37	41	-44	-22	3.49					41	-44	-22	3.29				
<i>R</i> Middle occipital gyrus	18					-25	-98	0	4.64					27	-98	4	3.26
<i>R</i> Lingual gyrus	17	17	-98	-9	3.02					13	-98	-9	2.79				
<i>L</i> Lingual gyrus	18					-35	-92	-14	3.13					-32	-92	-14	3.66
<i>R</i> Calcarine fissure	17													20	-102	0	2.79
<i>R</i> Inferior parietal lobule	7	41	-57	50	3.61					41	-57	50	3.83	41	-57	50	3.48
	40									41	-47	45	3.62	54	-30	54	3.74
	40													44	-40	45	3.26
	40													-56	-26	40	2.96
<i>R</i> Supramarginal gyrus	40	44	-50	36	3.32					44	-50	36	3.56				
<i>R</i> Superior temporal gyrus	22	54	-54	22	3.04												
<i>R</i> Inferior temporal gyrus	37					44	-57	-22	3.3								
<i>L</i> Postcentral gyrus	40													-52	-26	54	3.79
<i>L</i> Precentral gyrus	4													-28	-23	54	3.67
	4													-35	-16	68	2.96
	4													-35	-2	58	3.24
<i>R</i> Cerebellum – Lobule VI	-	41	-64	-22	3.97	41	-68	-22	3.52	41	-64	-22	3.57	41	-64	-22	3.43
	-													37	-44	-27	3.41
	-													27	-47	-36	3.05
<i>R</i> Parahippocampal gyrus	36									27	-37	-18	3.11				

Note. The coordinates are in MNI space. BA: Brodmann Area. $p < .005$ (uncorrected), voxels ≥ 20 . Coordinates in bold are peak coordinates within the activation clusters.

ROI Analysis

The two-way ANOVA tests on the BOLD percent signal change within a priori ROIs revealed significant main effect of condition in the left middle frontal gyrus, $F(2, 62) = 4.04, p = .022$; the right middle frontal gyrus, $F(2, 62) = 30, p < .001$; the left vOT, $F(2, 62) = 24.7, p < .001$; the right vOT, $F(2, 62) = 19.4, p < .001$. Neither significant main effect of instruction nor interaction between condition and instruction was found. Pair-wise comparisons between conditions were performed for each ROI within each instruction group. The results are illustrated in Figure 3-7. In the right middle frontal gyrus ROI, the activity in NC was significantly greater than in HF ($p = .006$) and LF ($p = .001$) for the LD group, but no difference was found for the LR group. In the left vOT ROI, the activity in NC was greater than in HF and LF ($p < .001$) for the LD group, and NC also greater than HF ($p = .01$) and LF ($p = .018$) for the LR group. In the right vOT ROI, both instruction groups had greater activity in NC as compared with HF (both $p = .001$) and LF (LD: $p = .011$, LR: $p = .032$).

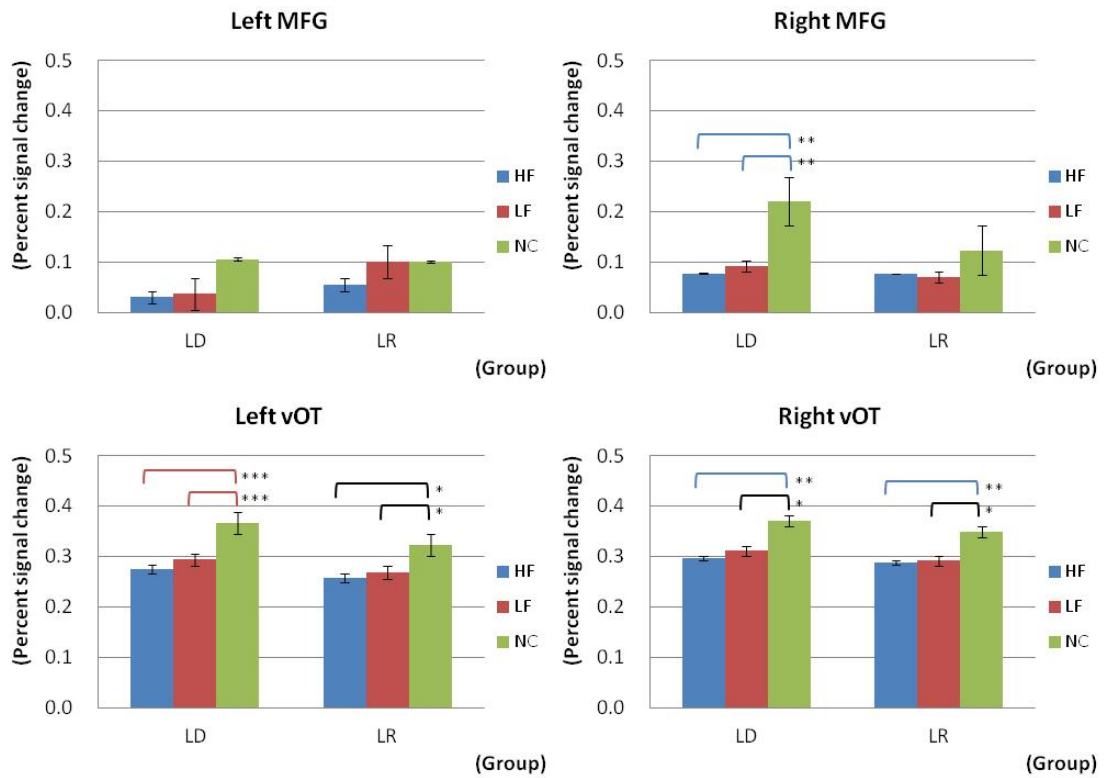


Figure 3-7. Average BOLD percent signal change in a priori ROIs. Asterisks indicate significant difference between conditions in each instruction group (* $p < .05$, ** $p < .01$, *** $p < .001$). Error bars denote standard errors. MFG: middle frontal gyrus; vOT: ventral occipito-temporal cortex; LD: lexical decision group; LR: lexical recognition group; HF: high-frequency characters; LF: low-frequency characters; NC: non-characters.

Discussion

In the current study, we investigated the involvement of the sub-network in orthographic processing of Chinese character reading. Orthographic processing may involve visuospatial analysis of characters, orthographic analysis, and mental lexicon search to help with character identification. While the majority of previous literature in neuroimaging that studied orthographic processing of Chinese characters implemented tasks that emphasized on the visuospatial analysis process, e.g., stroke analysis (C. C. H. Chan et al., 2007), physical identification judgment (S.-T. Chan et al., 2009; J. Liu et al., 2009; Wang et al., 2011; Zhao et al., 2010), font size judgment (C. Liu et al., 2008), the experimental paradigm of the event-related lexical decision/recognition task in our study allowed us to examine lexicality effect and orthographic analysis in orthographic processing.

One critical limitation in the current analysis, however, was the exclusion of the pseudo-character condition due to low accuracy rate. The chance-level (48%) accuracy rate of the PC condition in the lexical decision group indicated that the PC stimuli used in the current study were too difficult for lexical decisions and might induce certain strategies for systematically erroneous responses. Although over 50,000 Chinese characters are listed in the *Kang-Xi Dictionary*, it is estimated that a native Chinese-speaking college student only knows about 5,000 characters (Hue, 2003). It appears that the number of characters known is much small (approximately 10 %) relative to the number of characters existing in a dictionary. As the pseudo-characters conform to the composition rules and look very much like real characters, the participants may have mistaken the pseudo-characters as real characters that exist in the dictionary in a lexical decision task even though they were not able to retrieve the pronunciation and meaning associated with the pseudo-character. This response

strategy would unfortunately lead to many errors for lexical decision judgment to pseudo-characters. The chance-level accuracy rate also prevented us from only including correct responses of the PC condition into the analysis as the number of events was too small compared to the other conditions. Hence, we decided to eliminate the PC condition from the analysis. However, it would be interesting to compare pseudo-characters and non-characters to examine the effects of differential lexical access in the future studies. We suggest that a pilot behavioral study is essential to select the pseudo-characters that are easier to be recognized as non-real characters in lexical decision and to ensure the performance level is comparable across different character types.

Across all the other three conditions, the lexical decision task generally elicited strong activation in the bilateral inferior occipito-temporal cortices, the bilateral parietal cortex, and some less robust activation in the bilateral inferior and middle frontal regions. The overall activation pattern was consistent with Dong et al.'s (2005) findings when they contrasted the lexical decision condition on single-character Chinese words and non-words (the mirror images of real words) with fixation. On the other hand, the lexical recognition task showed a generally similar pattern but to a less extent of activation. In this section, we will discuss about the differential effects by the manipulation of lexicality and orthographic analysis based on the whole-brain and ROI analyses.

Lexicality Effect

We focused on the contrasts between non-characters and characters to examine lexicality effect, with a particular interest in the differential activation in the ventral occipito-temporal cortex. The results showed greater activity for NC in the bilateral vOT and the right inferior and middle frontal gyri than for HF and LF characters. Non-

characters also recruited greater activity in the bilateral inferior parietal lobule as compared with LF characters.

The non-characters created for the current study had a reversed left-right composition of phonetic and semantic radicals; in other words, the phonetic radical was placed on the left and the semantic radical on the right to form a non-character. As a phonetic radical was still embedded within a non-character, it might evoke a phonological representation that was associated with the phonetic component. Hence, although lexical access for a non-character was impossible, the components within the non-character might have induced sublexical processing as pseudowords in alphabetic languages do.

The higher activity in the ventral occipito-temporal cortex for non-characters than for real characters could be explained by the interactive account proposed by Price and Devlin (2011). In this account, the ventral occipito-temporal cortex is considered as an interface that integrates bottom-up sensory inputs and top-down predictions based on prior experience. When we see a word or word-like stimulus, in the forward connection the visual attributes are analyzed in the primary visual cortex and then accumulated in the ventral occipito-temporal cortex. In the backward direction, phonological or semantic representations based on prior experience predict the activity in the ventral occipito-temporal cortex. Differential activation to different types of characters could be explained by the interaction between bottom-up visual sensory inputs and top-down phonological prediction. Pseudowords are word-like, and both pseudowords and words automatically call for prediction from phonological areas. However, the activation in the ventral occipito-temporal region is higher for pseudowords because the prediction error is higher than for words. In the current study, we found higher activation in the bilateral ventral occipito-temporal cortex for non-

characters than for real characters (both HF and LF). According to the interactive account, higher activation for NC could be attributed to higher prediction errors. The sublexical components in non-characters might have engaged predictions from phonological areas. However, the predictions do not match with the visual inputs because non-characters do not have correct mental lexicons, which caused prediction errors and thus higher activation in the ventral occipito-temporal cortex.

In addition, previous studies have shown that higher activity for pseudoword reading than for word reading occurred in the posterior part of the left ventral occipito-temporal cortex, and this region was associated with sublexical processing in reading (Price & Devlin, 2011; Price & Mechelli, 2005). It was therefore hypothesized in the current study that the NC condition would recruit more activation in the posterior ventral occipito-temporal cortex. The prediction was confirmed by the ROI analysis with the pre-defined vOT masks from Study 1. The bilateral vOT ROIs were centered at (-40, -66, -12) and (40, -66, -12), within the posterior part of the vOT ($y = -60$ to $y = -70$ in MNI space) (Price & Mechelli, 2005). The ROI analysis revealed greater BOLD percent signal change for NC as compared with HF and LF in the bilateral vOT masks. Finally, it is worthwhile to note that we did not only find significant lexicality effect in the left vOT but also in the right counterpart. Our findings support bilateral involvement of the vOT in Chinese character identification.

While no lexicality effects were observed in the left middle frontal gyrus ROI, significantly higher activation for non-characters than real characters were found in the right middle frontal gyrus ROI for the lexical decision group. The left middle frontal gyrus has been suggested to play a role in Chinese language processing for mapping orthographic inputs onto phonological representations (i.e., orthography-to-phonology) at the lexical level (L. Liu et al., 2009; Tan, Liu, et al., 2001; Tan et al.,

2000). A whole Chinese character is mapped to a pronunciation at the mono-morphemic or syllabic level, and it has been shown that the left middle frontal gyrus contributes to syllabic processing while the left inferior frontal gyrus is associated with phonemic processing (L. Liu et al., 2009; Siok et al., 2003). In the current study, lexicality effects of higher activation for non-characters than characters were observed in the right middle frontal gyrus but not in the left middle frontal gyrus. Although a non-character does not have a corresponding pronunciation at the lexical level, mapping a pronunciation to the phonetic component within a non-character may be possible. Therefore, we propose that the right middle frontal gyrus might be associated with orthography-to-phonology transformation at the sublexical level for Chinese character processing. Nevertheless, the dissociation of lexical and sublexical orthography-to-phonology transformation for the left and right middle frontal gyri needs to be verified by further investigations.

Orthographic Analysis

As proposed by Hue & Tzeng (2000) that orthographic analysis is required for lexical decision but not for lexical recognition, comparing the two tasks may reveal brain regions that are involved in orthographic analysis. The direct contrast between LD and LR tasks regardless of character conditions showed that LD recruited stronger activation in a number of regions as compared with LR, including the bilateral inferior occipital gyri, the right fusiform gyrus, and the right inferior parietal lobule, whereas LR did not show any greater activity than LD.

The stronger activity of the bilateral inferior occipital cortices for LD might indicate that lexical decision demands more intensive visual processing of the visual character stimuli. Woollams et al. (2011) found higher activation for atypical words than for typical words in the left inferior occipital gyrus, posterior to the ventral

occipito-temporal region. The goal of orthographic analysis is to check orthographic typicality of a visual stimulus, i.e., familiarity of compositions of its components. Hence, the higher activation for the lexical decision group in the inferior occipital gyrus that was induced by the manipulation of orthographic analysis might be associated with orthographic typicality. Different from alphabetic languages again, significant activation was found in the inferior occipital gyrus bilaterally.

Higher activation in the right fusiform gyrus was also observed for the lexical decision group than the lexical recognition group. The right fusiform gyrus and the right inferior parietal regions might be related to the distinct ventral-dorsal streams for visual word reading. Accumulated converging evidence from cognitive studies and brain imaging studies has suggested that the ventral pathway (i.e., from occipital to inferior occipito-temporal cortex) is responsible for identifying the visual word forms (Cohen et al., 2002; Nobre, Allison, & McCarthy, 1994; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999), while the dorsal pathway (i.e., from occipital to posterior parietal cortex) plays a role in spatial encoding of letter positions (Pammer, Hansen, Holliday, & Cornelissen, 2006) and allocation of visuo-spatial attention in reading (Vidyasagar & Pammer, 2010). The ventral-dorsal pathways for reading corresponds to the visual domain hypothesis, which proposes that visual information is projected to the temporal lobe for identification of visual features (ventral pathway, the “what” pathway) and to the parietal lobe for spatial/motion analysis (dorsal pathway, the “where” pathway) (Goodale & Milner, 1992).

Inconsistent with our hypothesis, no greater activation in the middle frontal gyrus was found for the lexical decision group than the lexical recognition group. As the left middle frontal gyrus has been suggested to be responsible for visuospatial analysis of Chinese character forms (L. Liu et al., 2009; Tan, Feng, et al., 2001; Tan,

Liu, et al., 2001), we hypothesized that greater activation would be found in the lexical decision group for orthographic analysis. However, the lack of difference indicates that the middle frontal gyrus might not be involved in orthographic analysis and thus visuospatial analysis might not be the essential role of this region.

Finally, although this is not the major finding of the current study, it is worthwhile to note the extensive bilateral cerebellar activation observed in the various conditions. There were mainly two activation clusters in the cerebellum for each condition, one extended from the ventral occipito-temporal regions to lobule VI and Crus I in the superior cerebellum, and the other located near lobules VIIIA/VIIIB and IX in the inferior cerebellum. A meta-analysis on the functional topography in the cerebellum (Stoodley & Schmahmann, 2009) showed that the cerebellar lobule VI is associated with many higher-order cognitive functions such as language, verbal working memory, and spatial processing. In particular, language tasks were found to recruit the right lobule VI, Crus I/Crus II and a small cluster in the left lobule VI. In the current study, greater activation in the right lobule VI was shown in the LD group as compared with the LR group for all conditions. Although the cerebellar lobules VIIIA/VIIIB have been largely associated with sensorimotor functions, the posterior inferior lobule of VIIIA has been shown to reliably activate during verbal working memory (e.g., Durisko & Fiez, 2011; Stoodley & Schmahmann, 2009). In addition, the cerebellar lobule IX has been implicated in discriminative processes (Gao et al., 1996; Petacchi, Kaernbach, Ratnam, & Bower, 2011). These findings suggest the significance of the cerebellar involvement in the lexical decision/recognition task; however, to examine the specific functional roles of these cerebellar regions in language processing requires further investigations.

STUDY 2b

Phonological Processing in Reading Chinese Characters

Introduction

The meta-analysis in Study 1 identified a group of regions involved in phonological processing of Chinese characters, including the posterior dorsal part of the left inferior frontal gyrus, the left middle frontal gyrus, the left inferior parietal lobule, the right superior temporal gyrus, and the bilateral ventral occipito-temporal cortices (vOT). Particularly, the involvement of the posterior dorsal part of the left inferior frontal gyrus and the left inferior parietal lobule distinguished phonological processing from semantic processing. The meta-analysis also identified a sub-network that might be specific to Chinese character processing, which consists of the left middle frontal gyrus and the right ventral occipito-temporal cortex. In Study 2a, we examined the involvement of this sub-network in Chinese character identification and provided further evidence to support its role in character processing. The results suggest that the bilateral middle frontal gyri might be responsible for orthography-to-phonology transformation and the bilateral ventral occipito-temporal regions are involved in identification of visual character forms. In particular, the ventral occipito-temporal cortex is the interface that integrates visual sensory inputs with top-down phonological predictions, of which the amount of activation may be associated with the extent of prediction errors (Price & Devlin, 2011). In the current study, we aimed to further investigate the involvement of this sub-network, particularly the middle frontal gyrus, in phonological processing of Chinese character reading using a priori regions-of-interest (ROIs) defined in Study 1.

The ROIs of the middle frontal gyrus and the ventral occipito-temporal region were obtained from a conjunction between orthographic and phonological processing in the meta-analysis. While the center of the bilateral middle frontal gyri ROIs are located at the root of the middle frontal gyri, it is close to an intersection of several regions, including the dorsal part of the inferior frontal gyrus, the inferior frontal sulcus and the premotor cortex (see Figure 2-4). By Brodmann Area labeling, the ROIs include parts of BAs 9 and 44. It is plausible that this region may be involved in different functions because of the location. This could also explain why several functional roles have been attributed to the left middle frontal gyrus in Chinese language processing, such as visuospatial analysis of character forms (L. Liu et al., 2009; Tan, Feng, et al., 2001; Tan, Laird, et al., 2005; Tan, Liu, et al., 2001), orthography-to-phonology or orthography-to-semantics transformation (L. Liu et al., 2009; Tan, Liu, et al., 2001; Tan et al., 2000), articulatory rehearsal (Kuo et al., 2004). Regardless of languages, the bilateral middle frontal gyri are engaged in a dynamic network for processing sentence-level linguistic prosody (Gandour et al., 2004; Tong et al., 2005), and involved in metaphor processing depending on the factors of figurative, familiarity and difficulty (Schmidt & Seger, 2009). In addition, the border of the left inferior and middle frontal gyrus has been found to be activated for speech segmentation (LoCasto, Krebs-Noble, Gullapalli, & Burton, 2004).

The activation of the bilateral middle frontal gyri has been reported not only in language task but also in verbal and non-verbal working memory tasks (Rottschy et al., 2012; Veltman, Rombouts, & Dolan, 2003). The middle frontal gyrus has been suggested to be involved in “manipulation” and “monitoring” of information within working memory regardless of the nature of the information (i.e., verbal or spatial) (Owen et al., 1998; Zurowski et al., 2002), as well as in response selection (Rowe,

Toni, Josephs, Frackowiak, & Passingham, 2000), both of which are the essential correlates of the central executive system in working memory. Studies have found greater activation in the dorsolateral prefrontal cortex for manipulation than for maintenance tasks (D'Esposito, Postle, Ballard, & Lease, 1999; Veltman et al., 2003). According to a review by Corbetta & Shulman (2002), the right middle frontal gyrus and inferior frontal gyrus are involved in the ventral frontoparietal network of attention that is specialized for detection of relevant stimuli and orienting attention to salient stimuli. Moreover, the middle frontal gyrus ROIs specified from Study 1 overlapped largely with the inferior frontal junction (IFJ), a region that has been proposed to serve a crucial role in cognitive control (Brass, Derrfuss, Forstmann, & Cramon, 2005). The inferior frontal junction has been found to be involved in task switching, set shifting, and Stroop tasks (for reviews, see Brass et al., 2005; Derrfuss, Brass, Neumann, & von Cramon, 2005). As its location is at the junction of three functional neuroanatomical domains, i.e., the language, working memory, and premotor domains, it is thus suggested that the functional role of IFJ would be to integrate information from these domains (Brass et al., 2005). Due to its functional and neuroanatomical properties, it is thought that the middle frontal gyrus might play a domain-general role in language processing that manipulates and integrates information from different components, e.g., mapping orthography to phonology.

Phonological processing in Chinese has been studied using a variety of language paradigms, such as rhyming judgment (Booth et al., 2006; Cao et al., 2009; L. Liu et al., 2009; Tan et al., 2003), homophone judgment (Y. Chen et al., 2002; Dong et al., 2005; Kuo et al., 2004; Siok et al., 2003; Tan, Liu, et al., 2001), character naming (L. Liu et al., 2006; Tan, Feng, et al., 2001), and initial consonant judgment (Siok et al., 2003). These paradigms require the participants to retrieve phonological

representations given the orthographic inputs. Reading Chinese characters is different from reading alphabetic words in that grapheme-to-phoneme conversion is not possible in Chinese. Instead, it requires direct orthography-to-phonology transformation in which a phonological representation is retrieved from the cognitive network and mapped onto the character. Hence, the orthography-to-phonology transformation has been a process of major focus for studies investigating phonological processing of character languages such as Chinese.

In the past, the character stimuli used were monophonic characters, meaning each character is mapped to one pronunciation. Phonological processing was studied by directly contrasting a phonological task condition with a control condition, such as fixation or line orientation judgment. Even though the majority of Chinese characters are monophonic characters, there is an exception of about 10 % of the characters being heterophonic homographic characters, i.e., characters that have more than one pronunciation (see Hue, 1997, 2003; National Institute for Compilation and Translation, 1967). They have on average two to four alternative pronunciations, each of which is associated with a different meaning. The definitive pronunciation of a heterophonic homographic character is determined according to the context. Reading these characters might activate multiple possible pronunciations before a correct pronunciation is chosen. Therefore, reading heterophonic homographic characters might require more orthography-to-phonology transformation as compared with reading monophonic characters. Comparisons between reading heterophonic homographic characters and reading monophonic characters thus would provide a direct approach to investigating orthography-to-phonology transformation.

A similar approach was implemented in an fMRI study with Japanese kanji, the majority of which have multiple pronunciations. Matsuo et al. (2010) utilized this

characteristic in kanji and designed an event-related homophone judgment task to compare homophone judgment to heterophonic homographic kanji pairs with monophonic kanji pairs. The results showed that kanji pairs with multiple sound possibilities recruited greater activation in the posterior regions of the left inferior frontal gyrus (IFG) and the left middle frontal gyrus (MFG), the bilateral anterior insulae, and the left anterior cingulate cortex as compared with those with only one pronunciation. It was suggested that the left posterior prefrontal cortex plays a role in selection of language information from competing sources and that three sub-divisions in this region (posterior ventral IFG, posterior dorsal IFG, and the foot of MFG) correspond to selection of three types of language components (semantics, phonology, and written words, respectively). Hence, the stronger involvement of the left posterior IFG and the left MFG for heterophonic homographic kanji pairs may be responsible for increased demands in selection of phonological information corresponding to a character.

As compared with Japanese kanji, the number of alternative pronunciations for the heterophonic homographic characters in Chinese and the proportion of these characters are relatively small. Hence, one may argue that the difference between reading heterophonic homographic characters and monophonic characters might not be as strong in Chinese as in Japanese kanji. However, in the current study we selected the heterophonic homographic characters of higher occurrence to ensure that participants were familiar with the alternative pronunciations of the characters, and designed a homophone judgment task similar to that in Matsuo et al.'s (2010) study. In this task, participants were asked to think of any possible pronunciations of the characters in a pair and to judge if both characters had the same pronunciation. We think that explicitly requesting participants to retrieve as many possible sounds of the

characters could ensure participants' performance and allow us to examine different levels of orthography-to-phonology transformation between characters with multiple sounds and characters with only one sound.

The aim of the current study was to investigate the involvement of the sub-network in phonological processing, with a particular interest in the functional role of the middle frontal gyrus. The previous two studies provided us some hints to formulate the hypotheses for this study. In the meta-analysis (Study 1), we proposed that the middle frontal gyrus (BA 9) might be involved in visuospatial analysis of Chinese logographs regardless of the nature of the language task, and that greater involvement of this area for phonological and semantic processing might be responsible for orthography-to-phonology and orthography-to-semantics transformation. In Study 2a, we found significantly higher activation in the right middle frontal gyrus for non-characters than for real characters in the lexical decision group but no differential activation was found in the bilateral middle frontal gyri for orthographic analysis (lexical decision > lexical recognition). Based on the findings, we proposed that the middle frontal gyrus might not be associated with visuospatial analysis but rather orthography-to-phonology transformation. In addition, the left and right middle frontal gyri might be involved in lexical and sublexical orthography-to-phonology transformation, respectively. Therefore, in the current study, with the manipulation of different loadings of orthography-to-phonology transformation in the homophone judgment task, we are particularly interested in examining the involvement of the middle frontal gyrus for different types of characters. We hypothesize that the higher demands in orthography-to-phonology transformation for heterophonic homographic characters would lead to greater activation in the middle frontal gyrus. The ventral occipito-temporal cortex, on the other hand, is involved in visual word form

recognition. Thus, we expected no differential activation to be observed in the ventral occipito-temporal cortex due to the manipulation of orthography-to-phonology transformation loads.

Methods

Participants

After two runs of the lexical decision/recognition task in Study 2a, the same group of forty-one participants performed an event-related homophone judgment task designed for the current study. We excluded the participants with large head movements over 1.1 mm during the fMRI tasks ($n = 5$) and those whose behavioral task data were lost to technical mishaps ($n = 2$). As a result, thirty-four young participants (15 males; age range: 18 - 29, $M = 22.7$, $SD = 2.90$) were included for analysis. All were right-handed (range: 60 - 100, $M = 94.9$, $SD = 8.63$) measured by the Edinburgh Handedness Inventory (Oldfield, 1971), and the Graded Chinese Character Recognition Test (Huang, 2001) administered prior to the fMRI experiments demonstrated that all had excellent knowledge of Chinese characters (grade score $M = 9.99$, $SD = 0.038$).

Task Stimuli, Paradigm, and Procedure

The homophone judgment task consisted of 60 many-to-one (one heterophonic homographic character and one monophonic character) pairs and 60 one-to-one (two monophonic characters) pairs. Each type of character pairs was composed of 30 homophonic pairs (i.e., two characters in a pair had the same pronunciation) and 30 non-homophonic pairs (i.e., two characters in a pair had different pronunciations). Hence, all character pairs in the homophone judgment task could be categorized into four conditions: many-to-one homophonic pairs (MO_H), many-to-one non-homophonic pairs (MO_NH), one-to-one homophonic pairs (OO_H), and one-to-one

non-homophonic pairs (OO_NH). Examples of the character pairs are shown in Figure 3-8. All characters were selected from the Character-Component Analysis Toolkit software (C-CAT; see Lo & Hue, 2008) using the corpus prepared by the Chinese Knowledge Information Processing Group (CKIPG, 1993). The radical-composition (e.g., left-right, up-down, etc.), ranks and strokes of the characters were matched within every character pair and balanced across four conditions (see Table 3-6 for details of character attributes).

An event-related design of the homophone judgment task was conducted in the current study (Figure 3-9). During this task, one character pair was presented at a time for 2.5 s and participants were asked to judge whether the two characters had the same pronunciation. We applied the genetic algorithm provided by Wager and Nichols (2003) to jitter the order of event presentation during the fMRI scans. Sixty null events were added to vary the inter-stimulus interval (ISI). The 120 events of character pairs and 60 null events were designated to appear every 4 s: an event (either a character pair or a null event) was presented for 2.5 s and the interval between two consecutive events was 1.5 s. A fixation cross was displayed during the intervals as well as the null events. When a null event appeared between two events of character pairs, it would appear as a longer interval between two character pairs. Consequently, the interval between the offset of one character pair event and the onset of the next character pair event (i.e., ISI) varied from 1.5 s to 5.5 s, and the interval between the onsets of two consecutive events of the same character pair condition (i.e., stimulus onset asynchrony, SOA) varied from 8 s to 144 s. The total series lasted for 720 s (180 events) and was divided into two runs to reduce fatigue effects. The order of two runs was counterbalanced across participants.

	One-to-one pair	Many-to-one pair
Homophone	般 [ban1] 頒 [ban1]	著 [zhu4, zhuo2, zhao2, zhe0, zhao1] 卓 [zhuo2]
Non-homophone	嫌 [xian2] 填 [tian2]	惡 [e4, wu4, wu1] 賀 [he4]

Figure 3-8. Examples of character pairs in the homophone judgment task. For instance, the characters in the many-to-one homophonic pair, 著 and 卓, share the same pronunciation [zhuo2], so they are judged as a homophonic pair.

Table 3-6. Summary of character attributes.

	MO_H	MO_NH	OO_H	OO_NH
Number of pairs	30	30	30	30
Radical-composition ^a				
Left-right	18	17	18	17
Single	1	3	1	3
Surrounded	4	7	4	7
Up-down	7	3	7	3
Rank ^b				
Range	199 – 2947	39 – 2910	228 – 2700	88 – 1946
<i>M</i> (<i>SD</i>)	1384 (719)	1214 (671)	1349 (595)	1148 (478)
Stroke ^c				
Range	5 – 19	6 – 18	8 – 18	8 – 17
<i>M</i> (<i>SD</i>)	12.5 (3.35)	11.6 (2.88)	12.3 (2.64)	12.1 (2.65)

Note. Ranks and strokes of the characters were obtained from the Character-

Component Analysis Toolkit software (C-CAT; see Lo & Hue, 2008) according to the corpus prepared by the Chinese Knowledge Information Processing Group (CKIPG,

1993). MO_H: many-to-one homophonic pairs; MO_NH: many-to-one non-homophonic pairs; OO_H: one-to-one homophonic pairs; OO_NH: one-to-one non-homophonic pairs.

^aThe numbers of different types of radical-composition were matched within the homophonic conditions (MO_H and OO_H) and non-homophonic conditions (MO_NH and OO_NH).

^bThe ranks of heterophonic homographic characters in MO_H and MO_NH pairs were determined by the averaged ranks of all possible pronunciations for each character. A one-way ANOVA revealed no significant difference in ranks among four conditions, $F(3, 236) = 1.92, p = .13$.

^cA one-way ANOVA revealed no significant difference in strokes among four conditions, $F(3, 236) = 0.97, p = .41$.

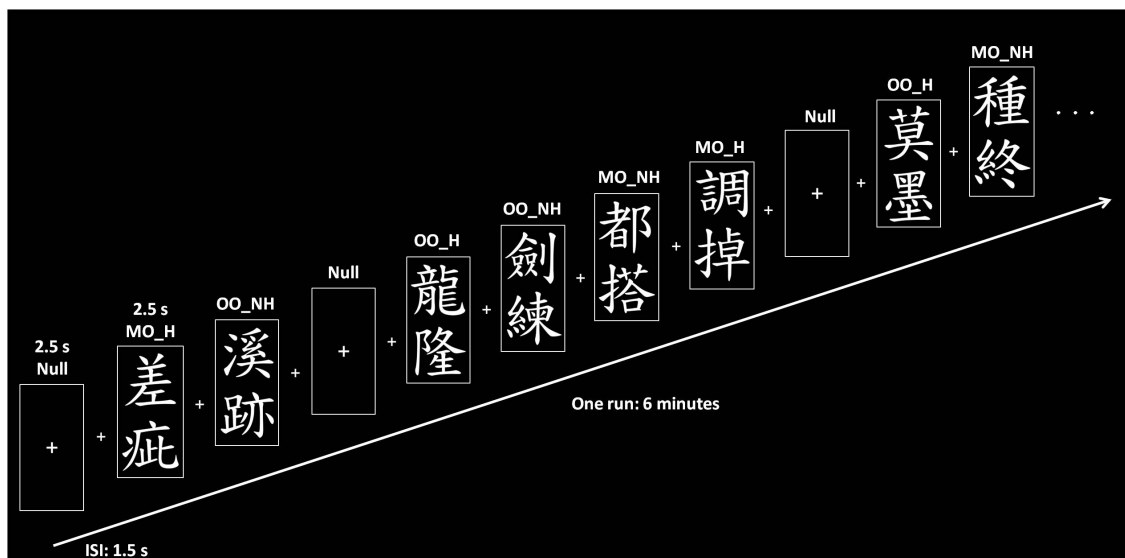


Figure 3-9. The paradigm of the even-related homophone judgment task. MO_H: many-to-one homophonic pairs; MO_NH: many-to-one non-homophonic pairs; OO_H: one-to-one homophonic pairs; OO_NH: one-to-one non-homophonic pairs.

The tasks were presented using E-prime version 2.0 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). The stimuli were back projected onto a screen at the rear of the scanner bore and participants viewed the images via a mirror attached to the head coil placed directly above their eyes. They responded to the trials by a button press on a respond pad held in their right-hand.

Image Acquisition

Functional MRI data were acquired in a 3 Tesla MR scanner (TIM Trio, Siemens, Erlangen, Germany) using a 32-channel head coil. Image acquisition parameters are as described in Study 2a in the Methods section on pages 59-60.

Behavioral Data Analysis

The participants' behavioral responses on the task were divided into: Hit, Correct Rejection (CR), Miss, False Alarm (FA), and No Response. Hit and CR responses corresponded to events in which participants correctly responded "yes" to homophonic pairs and "no" to non-homophonic pairs, respectively. On the other hand, Miss and FA responses were the opposites of Hit and CR. No response simply meant that no responses were recorded during the presentation of stimuli.

The accuracy rate (i.e., percentage of Hit and CR) and reaction time were analyzed for each participant. The No Response events were excluded from the computation of accuracy rate and reaction time. For the computation of reaction time, only events with expected responses, i.e., Hit and CR, were used to obtain the average for each condition. The individual participants' accuracy rate and averaged reaction time for all four conditions were then analyzed using two-way pronunciation (many-to-one/one-to-one) by judgment (homophonic/non-homophonic) analysis of variance (ANOVA) tests to examine if there was any difference between conditions.

Image Data Preprocessing and Analysis

All functional images were preprocessed and analyzed using the SPM8 software (Statistical Parametric Mapping 8; Wellcome Department of Cognitive Neurology, London, UK). The preprocessing steps were identical to those in Study 2a as described in the Methods section on page 61.

After preprocessing, both runs, each containing four conditions, were included into a design matrix in separate sessions in the same order for each participant. All events in the task were included in the fMRI data analyses. To model condition-specific effects, we employed a voxel-wise general linear model using the canonical hemodynamic response function with time derivatives as reference functions. The estimated motion parameters generated from realignment were included as covariates to control for the variances caused by head movement. The normalized gray matter from the segmentation of the skull-stripped T1 image was used as an explicit mask to ensure that only within-brain voxels were analyzed. Four contrasts were employed to obtain the activation evoked by each condition.

For the group-level analysis, the contrast images of the four conditions from individual analyses were entered in a random-effects two-way pronunciation (many-to-one/one-to-one) by judgment (homophonic/non-homophonic) ANOVA test. The accuracy rate and averaged reaction time of each condition for every participant were included as covariates of non-interest to control for the effect of task difficulty. The resulting activation maps are reported at a threshold of $p < .005$ (uncorrected) with cluster volume ≥ 20 voxels (Lieberman & Cunningham, 2009).

In addition to the whole-brain ANOVA test, we used the MarsBaR toolbox (Brett et al., 2002) in SPM8 to extract the BOLD percent signal change within the a priori ROIs defined in Study 1, namely the bilateral middle frontal gyri and vOT.

Two-way ANOVA tests were performed to examine the effects of pronunciation and judgment on the BOLD signal in the ROIs.

Results

Behavioral Data

The averaged accuracy rate and reaction time for each condition are summarized in Table 3-8 and shown in Figure 3-10. For accuracy rate, the main effect of pronunciation, $F(1, 33) = 236, p < .001$, and the interaction between pronunciation and judgment, $F(1, 33) = 4.54, p = .041$, were significant, but the main effect of judgment was not, $F(1, 33) = 2.77, p = .11$. For reaction time, the main effect of pronunciation, $F(1, 33) = 190, p < .001$, and the main effect of judgment, $F(1, 33) = 90.0, p < .001$, were significant, but the interaction was not, $F(1, 33) = .099, p = .755$. Pair-wise comparisons between conditions were computed with Bonferroni correction for multiple comparisons. For the accuracy rate, all pairs of conditions were significantly different ($p < .001$) except for MO_H vs. MO_NH ($p = .39$) and OO_H vs. OO_NH ($p = 1.00$). For the reaction time, all pairs of comparisons were significantly different ($p < .001$) except for MO_H vs. OO_NH ($p = 1.00$). As there were significant differences in behavioral performance between conditions, the accuracy rate and reaction time were added into the group-level fMRI analysis as covariates of non-interest to control for the effect of task difficulty.

Table 3-7. *Summary of behavioral performance.*

Accuracy Rate (%)				Reaction Time (ms)			
MO_H	MO_NH	OO_H	OO_NH	MO_H	MO_NH	OO_H	OO_NH
77.2	83.7	95.9	96.0	1363	1556	1147	1345
(12.7)	(11.3)	(3.97)	(4.03)	(188)	(213)	(193)	(166)

Note. Values are presented in *M (SD)* for each condition. MO_H: many-to-one

homophonic pairs; MO_NH: many-to-one non-homophonic pairs; OO_H: one-to-one

homophonic pairs; OO_NH: one-to-one non-homophonic pairs. *N* = 34.

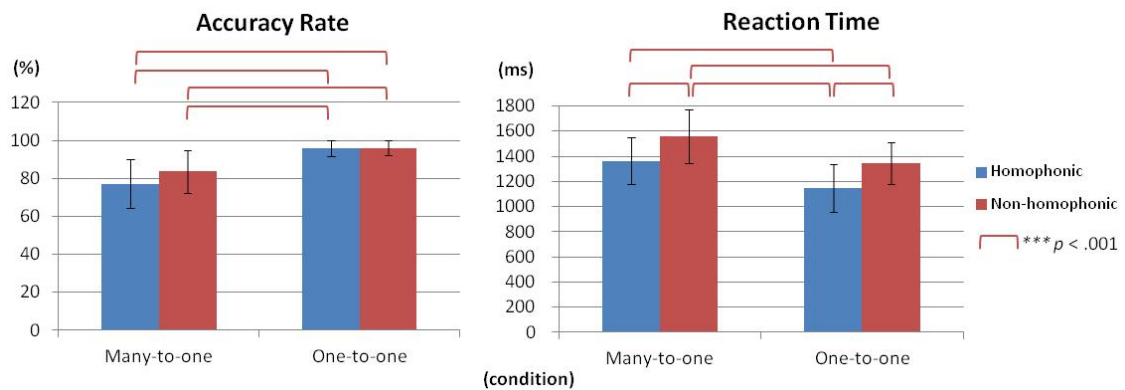


Figure 3-10. The averaged accuracy rate and reaction time for each condition. MO_H: many-to-one homophonic pairs; MO_NH: many-to-one non-homophonic pairs; OO_H: one-to-one homophonic pairs; OO_NH: one-to-one non-homophonic pairs. Asterisks indicate significant differences in pair-wise comparisons between conditions (***) $p < .001$). *N* = 34.

Activation for Individual Conditions

The overall activation patterns (see Figure 3-11) were very similar across the four conditions. All conditions recruited strong activation in the bilateral ventral occipito-temporal regions, bilateral inferior and middle frontal gyri, and the left parietal lobe particularly in the inferior parietal lobule.

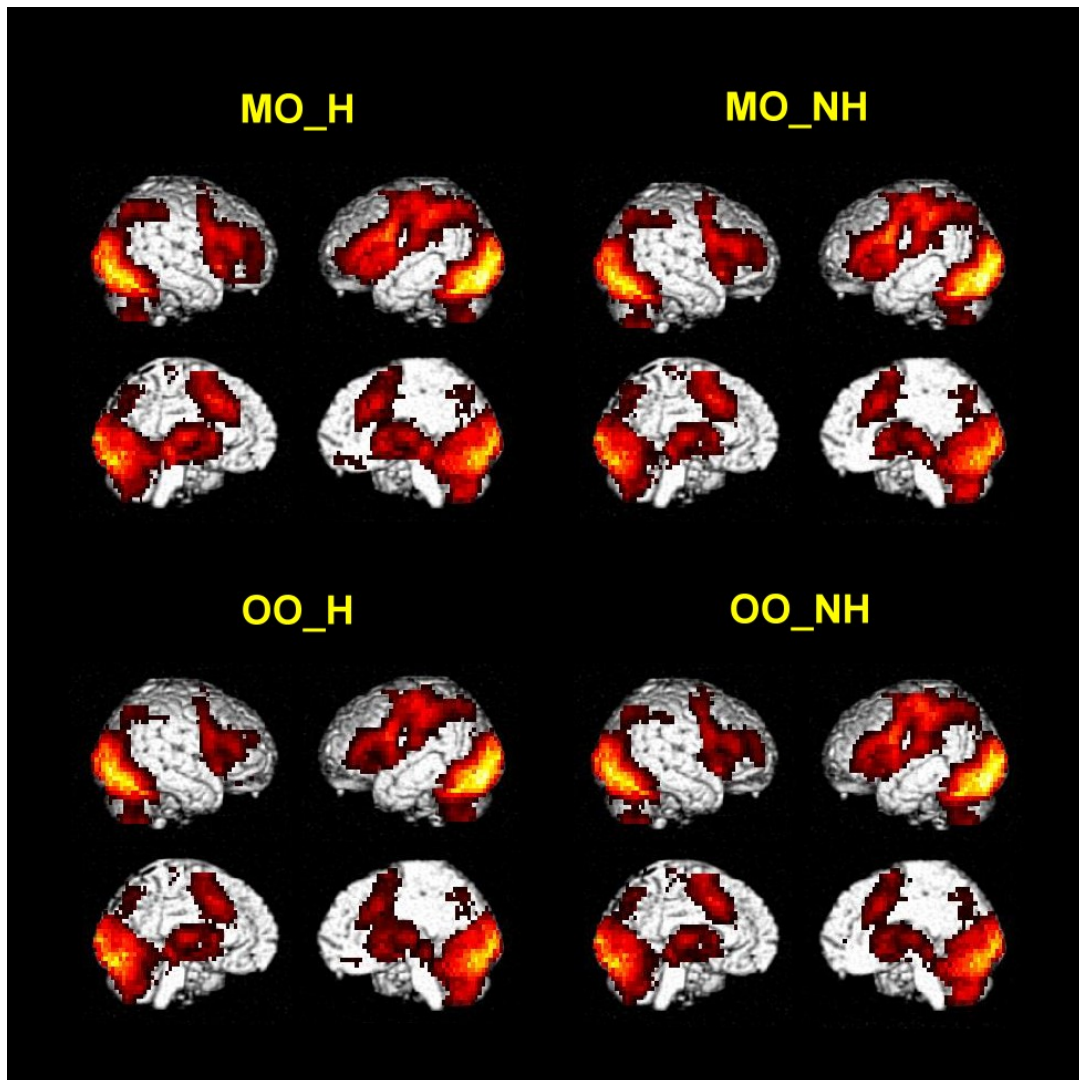


Figure 3-11. The activation maps for each condition. MO_H: many-to-one homophonic pairs; MO_NH: many-to-one non-homophonic pairs; OO_H: one-to-one homophonic pairs; OO_NH: one-to-one non-homophonic pairs. $p < .005$ (uncorrected), cluster volume ≥ 20 voxels, with task performance as covariates of non-interest.

ANOVA Results

The two-way ANOVA results are illustrated in Figure 3-12 and the peak coordinates of activation are summarized in Table 3-8. The analysis revealed significant main effect of pronunciation (many-to-one/one-to-one) in the bilateral medial frontal gyri (BA 8), the left insula (BA 47) and inferior frontal gyrus (BA 44),

the right superior parietal lobule (BA 7), the right inferior (BAs 44/47) and middle frontal gyri (BA 9), and the left inferior parietal lobule (BA 40). Significant main effect of judgment (homophonic/non-homophonic) was found in the angular gyrus (BA 39), the precuneus (BA 19), the superior (BA 6) and middle frontal gyri (BAs 6/8), the precentral gyrus (BA 4), the inferior parietal lobule (BA 40), the anterior cingulate gyrus (BA 32), and the medial frontal gyrus (BA 10) in the left hemisphere. No significant interaction effect was found.

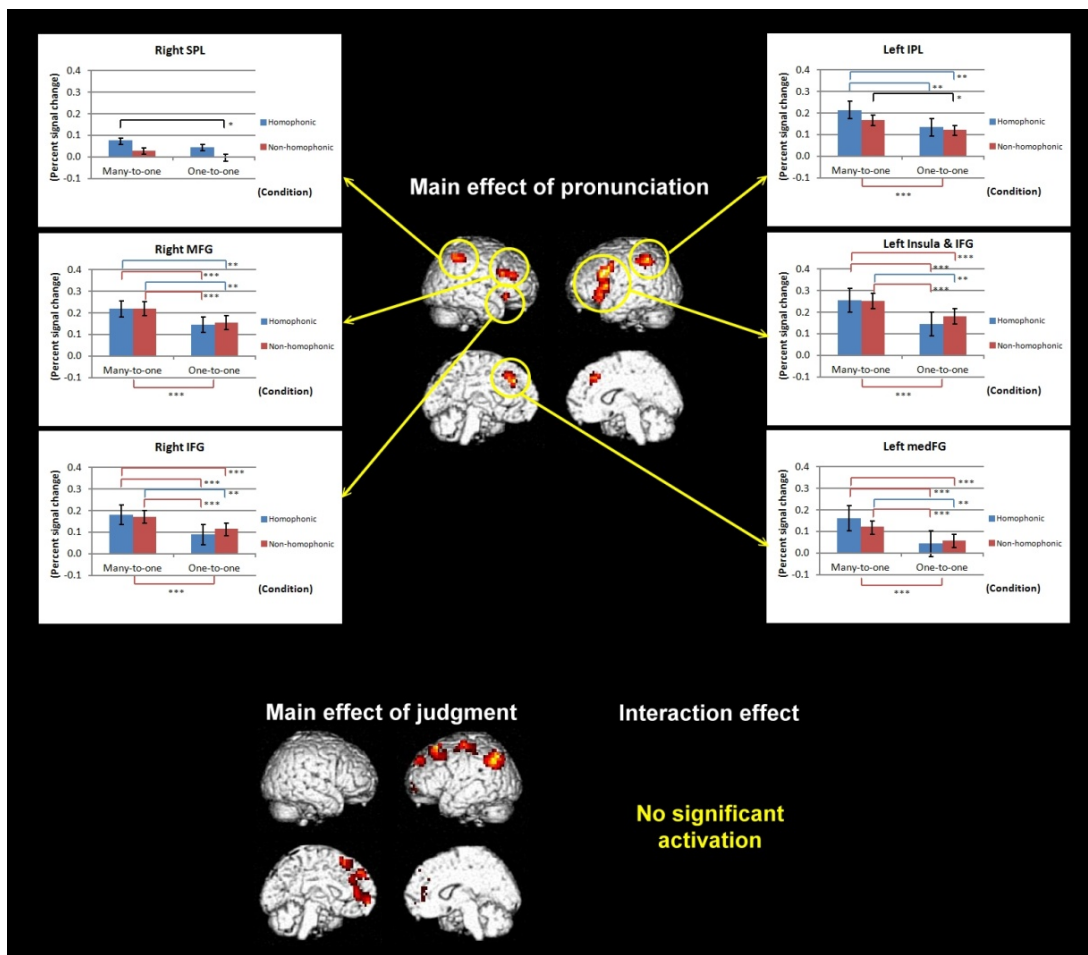


Figure 3-12. The activation maps of the 2 (pronunciation: many-to-one/one-to-one) x 2 (judgment: homophonic/non-homophonic) ANOVA results. Blue bars: homophonic conditions; red bars: non-homophonic conditions. $p < .005$ (uncorrected) with clusters ≥ 20 voxels.

Table 3-8. *Results of the ANOVA analysis.*

Voxel	Region	L/R	BA	x	y	z	F
(a) Main effect of pronunciation (many-to-one/one-to-one)							
66	Medial frontal gyrus	L	8	-4	29	45	19.41
	Medial frontal gyrus	R	8	3	32	40	16.54
258	Insula	L	47	-28	22	-9	18.37
	Precentral gyrus	L	44	-45	12	32	17.81
	Inferior frontal gyrus	L	44	-45	12	9	16.12
50	Superior parietal lobule	R	7	48	-57	54	16.22
35	Inferior frontal gyrus	R	47	34	25	-9	15.65
74	Middle frontal gyrus	R	9	48	36	22	14.28
				51	22	22	10.37
	Inferior frontal gyrus	R	44	44	15	27	13.06
91	Inferior parietal lobule	L	40	-59	-33	45	13.13
				-49	-47	50	12.56
				-38	-54	45	12.17
(b) Main effect of judgment (homophonic/non-homophonic)							
155	Angular gyrus	L	39	-49	-68	45	28.11
	Precuneus	L	19	-42	-68	50	26.99
111	Superior frontal gyrus	L	6	-18	25	58	25.84
	Middle frontal gyrus	L	6	-42	15	45	16.04
		L	8	-38	25	50	13.59
80	Precentral gyrus	L	4	-35	-16	63	15.93
	Inferior parietal lobule	L	40	-38	-33	63	11.92
				-38	-30	50	9.36
173	Superior frontal gyrus	L	8	-18	46	36	14.68
	Anterior cingulate	L	32	-4	42	9	14.59
	Medial frontal gyrus	L	10	-8	60	0	14.22

Note. The coordinates are in MNI space. Coordinates in bold are peak coordinates

within the activation clusters. BA: Brodmann area. L/R: left/right hemisphere. $p < .005$ (uncorrected) with clusters ≥ 20 voxels.

Many-to-one vs. One-to-one Pairs

The results are illustrated in Figure 3-13 Row A and activation coordinates are summarized in Table 3-9. As compared with one-to-one pairs, many-to-one pairs showed greater activation in many regions in the frontal lobe, including the bilateral medial frontal gyri (BAs 6/8), the left superior frontal gyrus (BA 6), the left insula

(BA 47), the left precentral gyrus (BA 44), the bilateral inferior frontal gyri (BAs 44/47), and the right middle frontal gyrus (BA 9). Many-to-one pairs also showed increased activity in the bilateral inferior parietal lobule (BA 40) and the right superior parietal lobule (BAs 7/19) in the parietal lobe. Separating the character pairs into homophonic pairs and non-homophonic pairs for the comparisons between many-to-one pronunciations and one-to-one pronunciation, we found that many-to-one > one-to-one comparison for the homophonic pairs (i.e., MO_H > OO_H) showed similar results to all many-to-one pairs > all one-to-one pairs, whereas the many-to-one > one-to-one comparison for the non-homophonic pairs (i.e., MO_NH > OO_NH) only showed activation in the middle frontal gyrus (BA 9), the inferior frontal gyrus (BA 44), the inferior parietal lobule (BA 40), and the superior parietal lobule (BA 7) in the right hemisphere. On the other hand, one-to-one character pairs did not show greater activation than many-to-one pairs.

Homophonic vs. Non-homophonic Pairs

Homophonic > non-homophonic pairs (Figure 3-13 Row B; Table 3-10).

Within many-to-one pairs, the homophonic pairs (MO_H) recruited greater activity in the superior frontal gyrus (BA 6), the medial frontal gyrus (BAs 8/10), the angular gyrus (BA 39), the inferior parietal lobule (BA 40), the inferior (BA 20) and middle temporal gyrus (BA 21), the parahippocampal region, and the amygdala in the left hemisphere as compared with non-homophonic pairs (MO_NH). For one-to-one pairs, the homophonic > non-homophonic contrast (OO_H > OO_NH) showed similar but a smaller extent of activation as that for many-to-one pairs, including significant activation in the angular gyrus (BA 39), the superior frontal gyrus (BAs 6/8), the middle frontal gyrus (BA 8), the medial frontal gyrus (BA 10), and the anterior cingulate (BA 32) in the left hemisphere.

Non-homophonic > homophonic pairs (Figure 3-13 Row C; Table 3-11).

The contrasts within many-to-one pairs and one-to-one pairs showed significant

activation in different regions. For many-to-one pairs, significantly greater activation for the non-homophonic pairs (MO_NH) as compared with the homophonic pairs (MO_H) was found in the left precuneus (BA 7), whereas for one-to-one pairs, greater activation for the non-homophonic pairs (OO_NH) as compared with the homophonic pairs (OO_H) was shown in the precentral gyrus (BA 4), the inferior parietal lobule (BA 40), the insula (BA 13), and the inferior frontal gyrus (BA 45) in the left hemisphere.

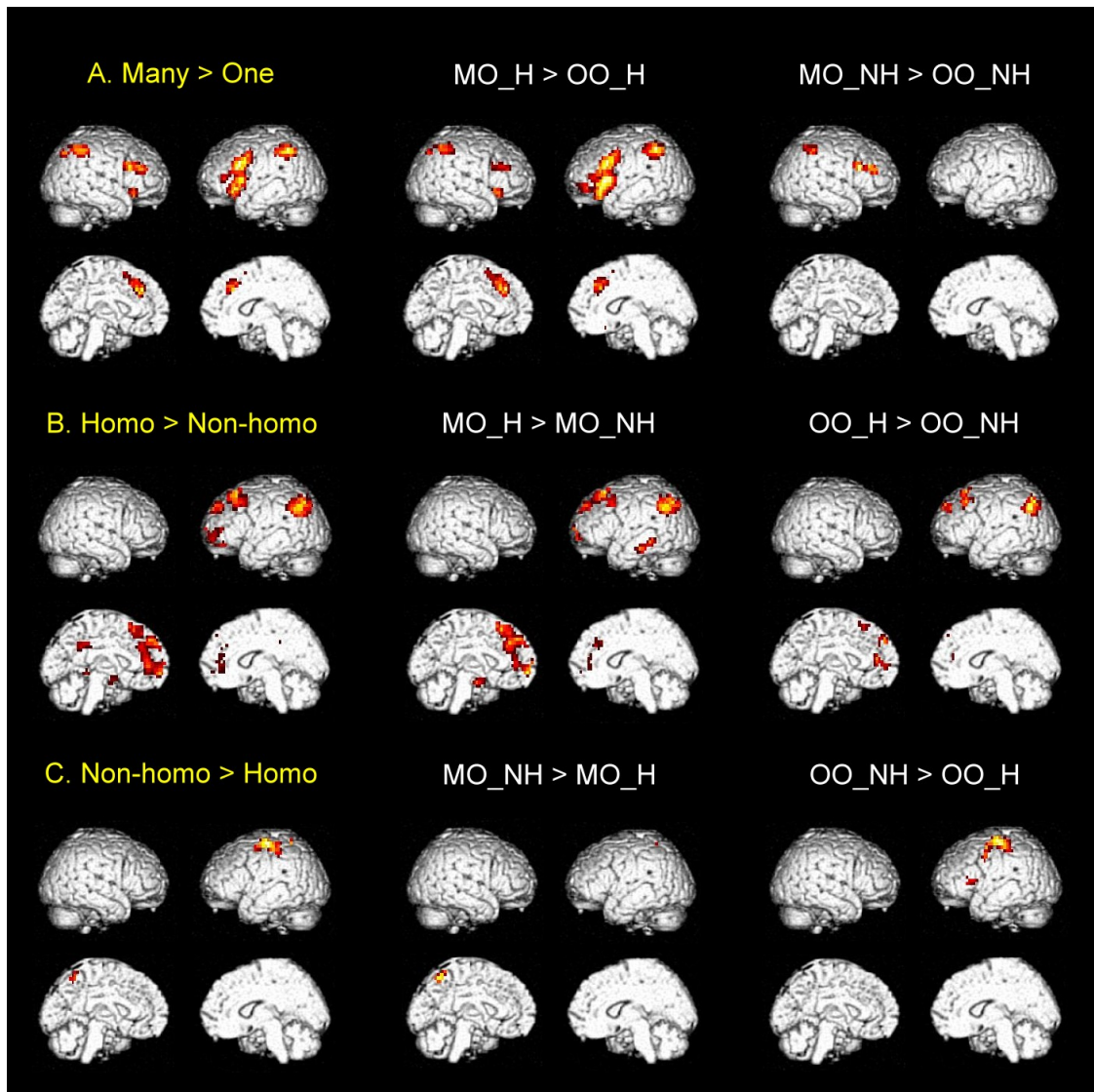


Figure 3-13. The activation maps of contrasts between conditions: (A) Many > One: all many-to-one pronunciation pairs (homophonic and non-homophonic) > all one-to-one pronunciation pairs (homophonic and non-homophonic); (B) Homo > Non-homo: all homophonic pairs (many-to-one and one-to-one pronunciation) > all non-homophonic pairs (many-to-one and one-to-one pronunciation); (C) Non-homo > Homo: all non-homophonic pairs > all homophonic pairs. MO_H: many-to-one homophonic pairs; MO_NH: many-to-one non-homophonic pairs; OO_H: one-to-one homophonic pairs; OO_NH: one-to-one non-homophonic pairs. $p < .005$ (uncorrected), cluster volume ≥ 20 , with task performance as covariates of non-interest.

Table 3-9. *Peak coordinates within significant clusters from man-to-one pairs vs. one-to-one pairs.*

Region	BA	Many > One				MO_H > OO_H				MO_NH > OO_NH			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>L</i> Medial frontal gyrus	8	-4	29	45	4.4	-4	29	45	4.82				
<i>R</i> Medial frontal gyrus	8	3	32	40	4.06	3	32	40	4.42				
<i>L</i> Superior frontal gyrus	6	-4	15	58	3.06	-4	15	54	3.42				
<i>L</i> Precentral gyrus	44	-45	12	32	4.22	-45	12	32	4.58				
<i>L</i> Insula	47	-28	22	-9	4.28								
	13					-42	22	4	4.5				
<i>L</i> Inferior frontal gyrus	44	-45	12	9	4.01	-42	15	9	4.4				
<i>R</i> Inferior frontal gyrus	47	34	25	-9	3.95	34	25	-9	3.89				
	44	44	15	27	3.61	44	15	27	2.95	44	15	27	3.37
<i>R</i> Middle frontal gyrus	9	48	36	22	3.78	48	32	22	3.14	48	39	22	3.57
	9	51	22	22	3.22								
<i>R</i> Superior parietal lobule	7	48	-57	54	4.02	48	-54	54	4.07	48	-57	54	3.03
	19	44	-71	45	3.26								
<i>L</i> Inferior parietal lobule	40	-59	-33	45	3.62	-38	-54	45	3.88				
		-49	-47	50	3.54	-49	-50	54	3.82				
		-38	-54	45	3.49	-35	-47	40	3.48				
<i>R</i> Inferior parietal lobule	40									51	-44	50	3.07
<i>R</i> Precuneus	19					37	-71	45	2.96				

Note. *L*: left hemisphere; *R*: right hemisphere; *x*, *y*, *z* coordinates are in the MNI space. Many > One: many-to-one homophonic and non-homophonic pairs > one-to-one homophonic and non-homophonic pairs; MO_H > OO_H: many-to-one homophonic pairs > one-to-one homophonic pairs; MO_NH > OO_NH: many-to-one non-homophonic pairs > one-to-one non-homophonic pairs. $p < .005$ (uncorrected), cluster volume ≥ 20 , with task performance as covariates of non-interest.

Table 3-10. *Peak coordinates within significant clusters from homophonic pairs vs. non-homophonic pairs.*

Region	BA	Homo > Non-homo				MO_H > MO_NH				OO_H > OO_NH			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>L</i> Angular gyrus	39	-49	-68	45	5.3	-45	-64	45	4.51	-49	-68	45	4.61
<i>L</i> Precuneus	19	-42	-68	50	5.19								
	31	-14	-47	36	3.39								
<i>L</i> Superior temporal gyrus	22	-42	-50	18	2.63								
<i>L</i> Middle temporal gyrus	21					-56	-40	-9	3.67				
	21					-66	-23	-18	3.41				
<i>L</i> Inferior temporal gyrus	20					-59	-26	-22	3.61				
<i>L</i> Superior frontal gyrus	6	-18	25	58	5.08	-14	25	58	4.99	-18	25	58	3.53
	8	-18	46	36	3.83					-21	46	36	3.37
	8									-4	53	40	3.34
	8									-14	53	40	2.78
<i>L</i> Middle frontal gyrus	6	-42	15	45	4	-42	12	45	3.88				
	8	-38	25	50	3.68					-38	25	50	3.47
	10	-42	56	0	3.85								
<i>L</i> Medial frontal gyrus	10	-8	60	0	3.77	-8	60	0	3.93	-8	56	4	2.78
	8					-4	36	32	4.06				
<i>L</i> Inferior parietal lobule	40					-52	-57	45	4.32				
<i>L</i> Anterior cingulate	32	-4	42	9	3.82					-4	42	14	3.13
<i>L</i> Cingulate gyrus	31	-4	-37	36	2.99								
<i>L</i> Hippocampus	-	-28	-23	-14	3.32								
<i>L</i> Medial globus pallidus	-	-14	-2	-14	3.29	-14	-2	-14	3.63				
<i>L</i> Parahippocampal gyrus	30	-21	-40	-4	3.13								
	35					-28	-23	-18	4.03				
<i>L</i> Amygdala	28					-21	-9	-18	3.51				

Note. *x*, *y*, *z* coordinates are in the MNI space. All coordinates are in the left hemisphere. Homo > Non-homo: many-to-one and one-to-one homophonic pairs > many-to-one and one-to-one non-homophonic pairs; MO_H > MO_NH: many-to-one homophonic pairs > many-to-one non-homophonic pairs; OO_H > OO_NH: one-to-one homophonic pairs > one-to-one non-homophonic pairs. $p < .005$ (uncorrected), cluster volume ≥ 20 , with task performance as covariates of non-interest.

Table 3-11. *Peak coordinates within significant clusters from non-homophonic pairs vs. homophonic pairs.*

Region	BA	Non-homo > Homo				MO_NH > MO_H				OO_NH > OO_H			
		<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i>
<i>L</i> Precentral gyrus	4	-35	-16	63	3.99					-35	-16	63	4.11
	4									-32	-9	54	3.53
	4									-52	1	45	3.48
<i>L</i> Inferior parietal lobule	40	-38	-33	63	3.45					-38	-30	50	3.18
	40	-38	-30	50	3.06								
<i>L</i> Precuneus	7	-14	-57	54	3.1	-11	-61	54	3.34				
	7					-14	-50	63	2.87				
	7					-21	-50	58	2.82				
<i>L</i> Superior parietal lobule	7	-28	-50	68	2.92								
<i>L</i> Insula	13									-38	18	9	3.46
<i>L</i> Inferior frontal gyrus	45									-45	25	4	3

Note. *x*, *y*, *z* coordinates are in the MNI space. All coordinates are in the left hemisphere. Non-homo > Homo: many-to-one and one-to-one non-homophonic pairs > many-to-one and one-to-one homophonic pairs; MO_NH > MO_H: many-to-one non-homophonic pairs > many-to-one homophonic pairs; OO_NH > OO_H: one-to-one non-homophonic pairs > one-to-one homophonic pairs. $p < .005$ (uncorrected), cluster volume ≥ 20 , with task performance as covariates of non-interest.

ROI Analysis

The average BOLD percent signal change for each condition in a priori ROIs are illustrated in Figure 3-14. The two-way pronunciation (many-to-one/one-to-one) by judgment (homophonic/non-homophonic) ANOVA tests revealed significant main effect of pronunciation in the left middle frontal gyrus ROI, $F(1, 33) = 38.3, p < .001$, and the right middle frontal gyrus ROI, $F(1, 33) = 11.8, p = .002$. No significant effects were observed in the bilateral vOT ROIs. Pair-wise comparisons between conditions were also computed in each ROI. In the left middle frontal gyrus ROI, the activity for MO_H was greater than OO_H and OO_NH ($p < .001$), and the activity for MO_NH was also greater than OO_H ($p < .001$) and OO_NH ($p = .007$). No significant pair-wise differences were found in the other ROIs.

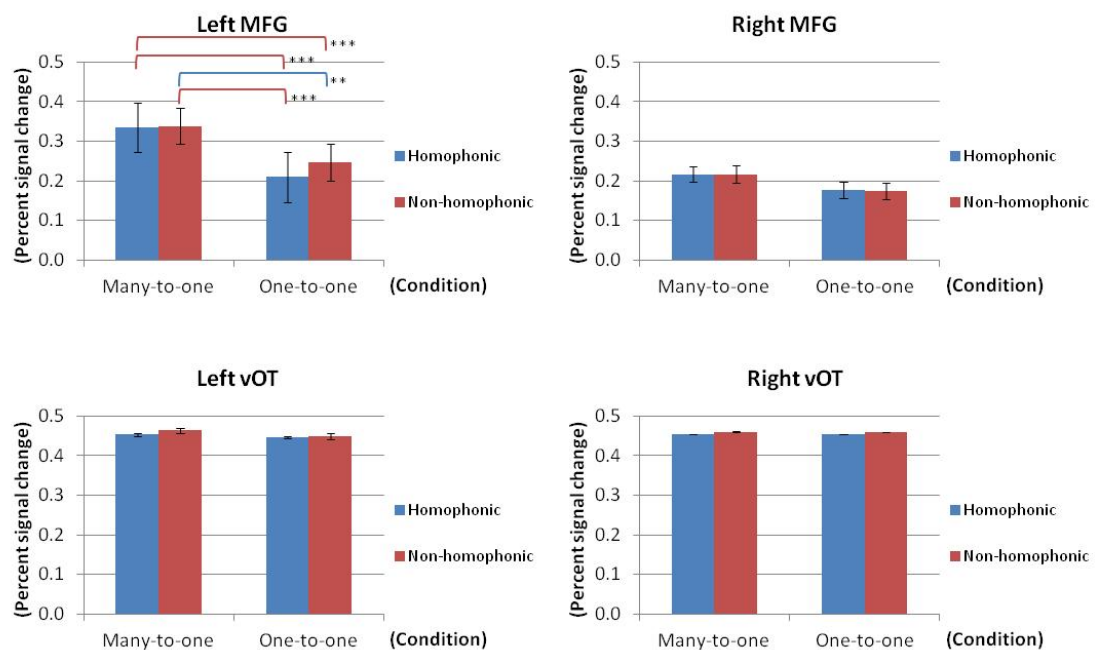


Figure 3-14. Average BOLD percent signal change in a priori ROIs. Asterisks indicate significant difference between conditions in each instruction group (** $p < .01$, *** $p < .001$). Error bars denote standard errors. MFG: middle frontal gyrus; vOT: ventral occipito-temporal cortex.

Discussion

In the current study, we manipulated the levels of demands in orthography-to-phonology transformation to examine the role of the middle frontal gyrus in phonological processing. Particularly, we hypothesized that increased demands in orthography-to-phonology mapping for reading heterophonic homographic characters would lead to greater activation in the middle frontal gyrus. Consistent with our hypothesis, stronger activation for many-to-one character pairs relative to one-to-one pairs was observed in the bilateral middle frontal gyri, the bilateral inferior frontal gyri and inferior parietal lobule. The results suggest that these regions might play an important role in phonological processing.

The four character conditions (MO_H, MO_NH, OO_H and OO_NH) yielded a very similar pattern of activation, including the bilateral ventral occipito-temporal regions, bilateral inferior and middle frontal gyri, and the left parietal lobe particularly in the inferior parietal lobule, and these regions are thought to reflect the cognitive processes required by the task. To perform the homophone judgment task, participants first needed to recognize the visual word forms, then match the orthographic inputs to phonological representations to recall the possible pronunciations of the characters, and finally compare the pronunciations of the two characters in order to judge whether they were homophonic or non-homophonic. According to the accumulated evidence, the bilateral ventral occipito-temporal regions might be responsible for the initial recognition of visual character forms (Cohen et al., 2002; Nobre et al., 1994; Price & Devlin, 2011; Tarkiainen et al., 1999). Notably, we again observed bilateral involvement of this region for Chinese character processing, which could be attributed to the increased demands in visuospatial decoding of the Chinese character forms (Bolger et al., 2005; Y. Liu & Perfetti, 2003; Tan, Laird, et al., 2005). Given the nature

of addressed phonology in reading Chinese, participants had to retrieve the phonological representations from the cognitive network to match with the recognized logographs. As suggested in previous literature, the middle frontal gyrus is involved in the coordination of different types of cognitive resources in the central executive system (D'Esposito et al., 1995), and thus might be responsible for the integration of orthographic and phonological representations in Chinese lexical processing, i.e., orthography-to-phonology transformation (Kuo et al., 2001; Kuo et al., 2003; Tan, Liu, et al., 2001). The inferior parietal lobule has been proposed to serve as the storage of phonological representations (Fiez et al., 1996). Hence, both regions would be activated when participants engaged in retrieving the possible pronunciations from the phonological storage to match the logographic inputs. In addition, the inferior frontal gyrus might play a role in further processing these phonological representations and phonological analysis (Poldrack et al., 1999). The overall activation elicited by the homophone judgment task demonstrates a network consisting of several regions that underlies phonological processing of Chinese character reading.

The results from the comparisons between many-to-one pairs with one-to-one pairs and between homophonic pairs with non-homophonic pairs showed a very similar pattern as the results in Matsuo et al.'s (2010) study that implemented a similar experimental paradigm with Japanese kanji characters. The similarity in results may indicate high resemblance between Chinese characters and Japanese kanji, both of which utilized the principle of addressed phonology in determining the pronunciations of characters. Notably, we observed a more bilateral recruitment of cortical activity in Chinese lexical processing, whereas a more left-lateralized activation was shown in Japanese kanji reading. It should be noted, however, that direct comparisons of the results are restricted because of the different magnetic strengths of the MRI scanners

(1.5 T in Matsuo et al.'s study) and the different activation thresholds used between the two studies. Although the averaged number of possible pronunciations for a heterophonic homographic Chinese character is smaller than a heterophonic homographic Japanese kanji, we were still able to observe the differences in phonological processing between reading heterophonic homographic characters and monophonic characters in Chinese, which was attributed to the phonological selection process by Matsuo et al. (2010). In the current study, we kept the attribution of phonological selection process in mind, and further extended our discussion in terms of the functional roles of the differential activation between reading heterophonic homographic characters versus monophonic characters.

When compared with one-to-one pairs that consisted of two monophonic characters, reading many-to-one pairs that were composed of one heterophonic homographic character and one monophonic character recruited greater activation in the bilateral middle frontal gyri, the bilateral inferior frontal gyri and bilateral inferior parietal lobule. Since the behavioral results showed that the many-to-one pairs were significantly more difficult than the one-to-one pairs, one may argue that the differences in brain activation were due to task performance. However, we excluded this potential confound of task difficulty by including the participants' behavioral performance into the fMRI analysis as covariates of non-interest, and thus the variances in brain activity possibly resulted from task difficulty were removed.

The regions obtained from the many-to-one > one-to-one comparison were similar to the regions observed in the activation elicited by individual conditions except for the bilateral ventral occipito-temporal regions. The absence of the bilateral ventral occipito-temporal regions in the comparison was as expected and was consistent with its role in recognition of visual word forms. Since visual character

inputs for both types of character pairs were similar in number, the demands in recognition of character forms should be equivalent. Thus reading both types of character pairs should not yield differential activation in the bilateral ventral occipito-temporal regions. On the other hand, reading many-to-one pairs exposed increased demands in orthography-to-phonology mapping through the search for phonological representations and perhaps furthering the processing of these phonological representations as well. Hence, the greater activation in the middle frontal gyrus, inferior parietal lobule, and inferior frontal gyrus observed may be due to the increased neural demands of the above functions involved respectively in reading the many-to-one pairs.

Consistent with our hypothesis, the ROI analysis showed higher activity for many-to-one pairs as compared with one-to-one pairs in the left middle frontal gyrus ROI, which may suggest that this region is associated with higher demands in orthography-to-phonology mapping for reading many-to-one pairs. On the other hands, although the main effect of pronunciation was significant in the right middle frontal gyrus ROI, no significant difference was found in the pair-wise comparisons. The ROIs were located at the more posterior portion of the middle frontal gyrus. On the contrary, from the whole-brain contrast between many-to-one and one-to-one pairs, we found significantly greater activation for many-to-one pairs in the middle portion of the right middle frontal gyrus. The middle portion of the dorsolateral prefrontal cortex has been implicated in verbal working memory (Owen et al., 1998) and direction of attention (Corbetta & Shulman, 2002). Therefore, the greater activation for many-to-one pairs than for one-to-one pairs in the middle portion of the right middle frontal gyrus might be associated with increased demands in general verbal working memory and attention induced by the task, which may not be specific to language processing.

The homophone judgment task activated a wide network of regions that are similar to the verbal working memory network; thus, we could also consider the greater activation observed for reading many-to-one pairs within the framework of verbal working memory. The homophone judgment task implemented in the current study is thought to tax heavily on verbal working memory. After successfully retrieving the pronunciations of the given characters, participants have to maintain the pronunciations of both characters and make comparisons between them. When one of the characters in a pair has more than one possible pronunciation, participants have to maintain the pronunciation and meanwhile continue to search for other possible alternatives. Thus, the many-to-one pairs would need a longer maintenance period and require more comparisons between pronunciations than the one-to-one pairs would (i.e., manipulation). Researchers have proposed that the inferior frontal gyrus is crucial for subvocal rehearsal and the inferior parietal lobule could be attributed to the phonological store, and both regions make up the articulatory loop in verbal working memory (Paulesu, Frith, & Frackowiak, 1993). Hence, the increased activation of the inferior frontal gyrus and inferior parietal lobule for many-to-one pairs could be attributed to subvocal rehearsal during maintenance and the phonological store of phonological representations that are both involved in verbal working memory. Moreover, the increased activation in the middle frontal gyrus may be involved in manipulating and integrating information from different domains, as the central executive system in working memory. While we think that the middle frontal gyrus might be a domain-general region, it responds differentially to the specific characteristics of Chinese characters. For instance, the left posterior middle frontal gyrus might show increased activation when the demands of orthography-to-phonology transformation in Chinese character reading increases.

In summary, our results support the functional role of the left middle frontal gyrus in orthography-to-phonology transformation in Chinese lexical reading, which could also be explained in terms of the components involved in verbal working memory. That is, the middle frontal gyrus is suggested to play a role in the central executive system in working memory that manipulates, monitors, and integrates information within working memory. This characteristic essentially contributes to the coordination of orthographic and phonological representations, which underlies the process of orthography-to-phonology transformation. Furthermore, our results show that although the involvement of the middle frontal gyrus is dominant in the left hemisphere, the right counterpart might also be recruited when task demands in verbal working memory and attention increase.

The Posterior and Anterior Networks for Reading

In Study 2a, the orthographic properties of Chinese characters were manipulated to induce different levels of demands in the lexical identification process. The lexical decision/recognition task required the participants to visually identify or recognize a given visual stimulus, and cortical activation was mostly observed in the posterior part of the brain including the parietal and occipital lobes. In Study 2b, the demands in orthography-to-phonology transformation were manipulated to evoke different levels of phonological processing. The homophone judgment task with visual presentation of characters required not only visual character form identification but also retrieval of phonological representations. Hence, it was shown to recruit both the posterior regions of the brain for visual character processing and the anterior regions for phonological processing. Taken together, the findings of Study 2a and Study 2b might suggest a hierarchical model for reading, which consists of a posterior network for initial recognition of visual character forms and an anterior network for retrieval

and analysis of higher-order information, such as phonological (Study 2b) or semantic representations. Understanding the temporal properties of the posterior and the anterior activations would help elucidate the order of information flow in the hierarchical pathway for reading. Future studies could test this hierarchical pathway using dynamic causal modeling (DCM) to investigate the dynamics within the hierarchical model for reading, e.g., the bottom-up and top-down interaction between the posterior and anterior regions.

CHAPTER IV: STUDY 3

The Integrity of the Specialized Sub-Network for Chinese Character Processing

Overview

Observations of direct evidence for the differential cortical recruitment for Chinese character processing in the previous studies have been presented so far. In Study 1, we summarized the networks underlying Chinese orthographic, phonological, and semantic processing by a meta-analysis on the existing empirical fMRI studies, and the findings consolidated the additional involvement for Chinese character processing in the left middle frontal gyrus and the right ventral occipito-temporal cortex as compared with the universal language network that has been based on alphabetic languages. Both regions are thought to form a sub-network that is specialized for Chinese character processing. In Study 2, the involvement of these differential regions in the processing of Chinese character identification and homophone judgment was empirically investigated with the aim to elucidate their functional roles in orthographic and phonological processing. The findings confirmed the bilateral recruitment of the ventral occipito-temporal cortex for complex visuo-spatial decoding and recognition of lexical and sublexical character forms. The consistent involvement of the middle frontal gyrus in Chinese lexical processing was found, suggesting this region to play a role in coordinating and mapping the orthographic information and phonological/semantic representations. Moreover, a more bilateral pattern of brain activity was observed in Chinese character processing.

The neuroanatomical mechanisms underlying language processing could be influenced by several factors, such as brain injuries, language impairments, age, gender, and handedness. In the following chapter, we looked at convergent evidence of the engagement of the sub-network specialized for Chinese character processing. Specifically, we studied the integrity of this sub-network in language processing in normal Chinese speakers, with particular interests in how it might be influenced by

individual characteristics such as age and handedness. Hence, Study 3 consisted of two studies that investigated Chinese character processing in terms of age-related effects across a wide age range (Study 3a) and hemispheric lateralization in right- and left-handed Chinese speakers (Study 3b).

STUDY 3a

Functional Changes in Word Retrieval during Healthy Aging

Introduction

Aging comes along with decline in a variety of cognitive functions, among which language ability is in fact relatively preserved as compared with other functions, such as memory. However, growing evidence has shown that language production impairments occur frequently in older adults, which are often observed in increased word-retrieval difficulties and reduced verbal fluency. One of the most prominent word-retrieval failures is the tip-of-the-tongue (TOT) experience, which is characterized by a failure to retrieve a word despite a strong feeling of knowing and being close to recalling the word. Behavioral studies have demonstrated that older adults experience more TOTs than younger adults (e.g., Burke, MacKay, Worthley, & Wade, 1991; James & Burke, 2000). Other behavioral studies have also shown that older adults make more errors than younger adults in naming pictures or objects, such as in the Boston Naming Test (e.g., Van Gorp, Satz, Kiersch, & Henry, 1986; Zec, Burkett, Markwell, & Larsen, 2007). Moreover, word retrieval deficits are also among the earliest signs of dementia (Henry, Crawford, & Phillips, 2004; Murphy, Rich, & Troyer, 2006).

A growing interest in studying the age-related changes in the neural mechanisms underlying word retrieval has emerged in the last decade. One line of research observed greater activation in the right inferior frontal region which resulted in less lateralization of frontal activity in older adults as compared with in younger adults. Meinzer et al. (2009) examined semantic fluency and phonemic fluency in young and old German speakers. They found a significant drop of performance in the

older group during the semantic fluency task, whereas the performance during the phonemic fluency task was comparable between the two groups but poorer than during the semantic fluency task for both groups. In addition, they observed greater activity in the right (inferior and middle) frontal regions in the older group during the semantic fluency task, which was negatively correlated with performance, but no differential activity between the two groups was found in the phonemic fluency task. The findings were replicated by Wierenga et al. (2008), who studied age effects on word retrieval in English speakers by using an overt picture naming task and observed that older adults showed a larger frontal network than young adults. They also correlated brain activity with performance on the task, and found that the increased involvement of the right frontal activity might not be universally compensatory as it was positively correlated with word retrieval accuracy only in high performing older adults but not in young adults or low performing older adults. Their results suggest that word-finding difficulties are likely due to problems with selection, retrieval and execution of the lexical-semantic information rather than deterioration of semantic knowledge.

The increased bilateral recruitment of the frontal regions with aging was consistent with the HAROLD (hemispheric asymmetric reduction in older adults) model (Cabeza, 2002), which proposes that under similar task circumstances, older adults seem to recruit more bilateral prefrontal activity during cognitive performance than younger adults. Many studies have concluded that the additional frontal activity is recruited to compensate for age-related deterioration in brain structures and function in order to achieve a cognitive goal (for review see Park & Reuter-Lorenz, 2009). Hence, the increased right frontal activity for older adults in language processing might help sustain behavioral performance. However, other evidence has shown opposite findings against the compensatory roles of the right frontal activity. For example, Meinzer et al.

(2009) and Meinzer, Seeds, et al. (2012) found that the increased right frontal activity in older adults was negatively correlated with semantic fluency.

Another line of research attributed word-retrieval difficulties in the TOT states to deficits in phonological retrieval rather than semantic retrieval (Burke & Shafto, 2004). According to the models of word production that postulate a network of interconnected nodes of semantic, lexical, and phonological representations, word production starts with activation of semantic representations followed by matching with a lexical representation and then retrieval of corresponding phonological representations (e.g., Levelt, 2001). The transmission-deficit model (Burke et al., 1991) proposes that TOTs occur when semantic and lexical representations are activated, causing a feeling of knowing, but phonological representations cannot be retrieved because the connections from lexical to phonological representations are too weak. Aging is one of the factors that may weaken the connections to phonological nodes. This model has recently been supported by neuroimaging evidence. In a structural MRI study, Shafto et al. (2007) found that the number of TOTs increased with age and correlated with gray matter atrophy in the left insula, an area implicated in word production. Later in another fMRI study using a picture naming task, it was shown that during TOTs the older adults showed less activity in the left insula compared to the younger adults, and the less TOT activity was affiliated with lower gray matter density in the left insula (Shafto et al., 2009). Both studies provided a neural account of TOTs being phonological retrieval failures.

While most studies have focused on age-related changes in the cortical activation induced by external cognitive tasks, others have found that older adults show less reduction in the task-negative network relative to younger adults (Damoiseaux et al., 2008; Grady et al., 2009; Grady, Springer, Hongwanishkul,

McIntosh, & Winocur, 2006; Lustig et al., 2003; Miller et al., 2008; Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). When a task condition is subtracted from a baseline condition (e.g., rest), a set of brain regions including the posterior cingulate/precuneus, medial prefrontal cortex, and the lateral parietal cortex show task-negative responses, i.e., these regions are more active during rest than during the task condition. These regions overlap with the regions in the default mode network (DMN). One of the current theories about DMN states that it consists of regions with increased activity during resting and reduced activity when people attend to an external task (Fox & Raichle, 2007). In other words, the DMN is often represented as task-induced deactivation. Studies have demonstrated the relationship between the DMN and language performance. For instance, Gauffin et al. (2013) found that people with generalized epilepsy had impaired language performance, which might be explained by inadequate suppression of the DMN during sentence reading. For individuals with aphasia, intensive semantic feature analysis therapy improved integration in the posterior regions of the DMN along with improvement in language performance (Marcotte, Perlberg, Marrelec, Benali, & Ansaldo, 2013). Moreover, reduced deactivation in the DMN regions was found in older adults and was associated with poorer language performance. In a recent study, Meinzer, Seeds, et al. (2012) implemented semantic fluency and phonemic fluency tasks and examined brain activity of word retrieval in young and older English speakers. They replicated the findings of a previous study by the same research group (Meinzer et al., 2009), demonstrating that older adults had increased activation in the right inferior frontal regions during word retrieval. In addition, they extended the analyses to age-related changes in the task-negative network. In particular, they found that older adults showed reduced task-induced deactivation during both semantic and phonemic fluency

tasks, and that the degree of task-negative responses was positively correlated with performance. That is, older adults who showed reduced task-negative responses performed poorer in the verbal fluency tasks. Overall, these studies suggest that it is important to take into account changes in the DMN while we examine age-related influences on the neural network for language processing.

To the best of our knowledge, no studies have examined the age effects on language processing in the Chinese population; thus, whether linguistic differences would modulate the age-related changes in neural activity for language processing remains unclear. As word retrieval difficulty is one of the most prominent language deficits in aging, the current study aimed to examine whether age had universal effects on the neural mechanisms underlying word retrieval in Chinese speakers as in alphabetic language speakers. Two tasks were selected to investigate the neural mechanisms underlying word retrieval: (1) semantic fluency and (2) homophone judgment tasks. A semantic fluency task was implemented to examine retrieval of lexical-semantic and phonological representations (Henry et al., 2004). Although it was a word generation task, it allowed us to indirectly examine the word retrieval process that was invoked during word generation. Previous studies showed that semantic fluency was vulnerable to aging and reduced semantic fluency for older adults was accompanied by pronounced changes in neural activity (Meinzer et al., 2009; Meinzer, Seeds, et al., 2012). In addition, a resting condition was included as the baseline condition in the semantic fluency task, which provided the possibility to examine task-negative networks in the same task. A homophone judgment task was implemented to directly examine retrieval of phonological representations. It allowed us to examine not only phonological retrieval but also visual character processing; thus it was possible to explore whether the sub-network specialized for Chinese character

processing would be affected across different age groups through the homophone judgment task.

Overall, the semantic fluency task and the homophone judgment task implemented in the current study allowed the feasibility to examine age effects on word retrieval in terms of lexical-semantic retrieval and phonological retrieval, as well as age effects on the task-negative network. We investigated age-related changes in the neural networks by whole-brain regression analysis, and also focused on age-related effects on the sub-network by ROI analysis. If the influence of age on language processing is a universal phenomenon, we would expect to see changes in the bilateral frontal activity for the semantic fluency task and changes in the brain regions related to phonological retrieval (e.g., insula) during the homophone judgment task as age increases (Meinzer et al., 2009; Meinzer, Seeds, et al., 2012; Shafto et al., 2009). According to the transmission-deficit model, declines in word retrieval are caused by weakened connections between lexical information and phonological information with increasing age (Burke et al., 1991). These connections are especially important for Chinese reading as it involves addressing of phonological representations onto visual orthographic inputs. In Study 2a and Study 2b, we have postulated that the orthography-to-phonology transformation is represented in the additional activation of the left middle frontal gyrus for Chinese character processing. Thus, we hypothesized that older adults would show decreased activation in the left middle frontal gyrus as the mappings from lexical to phonological representations are weakened by aging. In addition, as suggested in previous studies, we expected that the older adults would show reduced task-induced deactivation in the default-mode regions as compared with the young adults.

Methods

Participants

A total of 89 right-handed participants (age range: 19 – 79) were recruited and they performed two blocked-design tasks, semantic fluency task (SF) and homophone judgment task (HJ). All participants were screened using a detailed health questionnaire to exclude any psychiatric or neurological disorders, vascular risk factors or any factors contraindicated of MRI scanning (e.g., claustrophobia, metal implants, cardiac pacemaker, etc.). The participants above 35 years old (i.e., middle-aged and above) were administered the Chinese version of the Mini-Mental State Examination (MMSE; Guo et al., 1988) to ensure normal status of cognitive functioning, and none of them scored below 29 out of 33 ($n = 54$, $M = 32.2$, $SD = 0.98$). The participants gave informed consent approved by the Institutional Review Board at the National Taiwan University Hospital. The participants who had the following conditions were excluded: poor image quality ($n = 6$ for SF and 6 for HJ), large head movements with translation exceeding 1.3 mm along any axis ($n = 2$ for SF and 10 for HJ), missing behavioral data ($n = 2$ for SF and 7 for HJ), or outlier in behavioral performance ($n = 2$ for SF). As a result, 77 (37 males) and 66 (34 males) participants were included for analysis in the semantic fluency task and homophone judgment task, respectively.

The participants' demographics are summarized in Table 4-1. In the semantic fluency group, there was no gender difference in age, $t(75) = .00$, $p = 1.00$, handedness, $t(75) = -0.39$, $p = .70$, or education, $t(75) = 1.16$, $p = .25$. In the homophone judgment group, there was also no gender difference in age, $t(64) = 0.18$, $p = .86$, handedness, $t(64) = -0.19$, $p = .85$, or education, $t(64) = 1.59$, $p = .12$. However, age was negatively correlated with education level for both the semantic fluency group, $r(75) = -.56$, p

$< .001$, and the homophone judgment group, $r(64) = -.52, p < .001$. The negative correlation between age and education level in both groups indicated a tendency for the older participants to have a lower education level as compared with the younger participants. Thus, the education level was added into the fMRI data analysis as a covariate of non-interest.

Table 4-1. *Summary of demographics.*

	Semantic Fluency Task			Homophone Judgment Task		
	Male	Female	All	Male	Female	All
<i>n</i>	37	40	77	34	32	66
Age						
Range	19 – 79	22 – 71	19 – 79	19 – 79	22 – 71	19 – 79
<i>M</i>	44.7	44.7	44.7	40.6	39.9	40.2
<i>SD</i>	(16.9)	(15.3)	(16.0)	(16.3)	(13.8)	(15.0)
Handedness						
Range	42.8 – 100	65.2 – 100	42.8 – 100	42.8 – 100	65.2 – 100	42.8 – 100
<i>M</i>	92.1	93.1	92.6	90.9	91.5	91.2
<i>SD</i>	(11.7)	(10.5)	(11.0)	(14.1)	(11.2)	(12.7)
Education						
Range	6 – 25	6 – 24	6 – 25	8 – 25	6 – 24	6 – 25
<i>M</i>	15.9	14.9	15.4	16.8	15.3	16.1
<i>SD</i>	(3.94)	(3.77)	(3.86)	(3.50)	(4.00)	(3.79)

Note. *n*: number of participants; Handedness: Edinburgh Handedness Inventory

(Oldfield, 1971) scores ranging from -100 (strongly left-handed) to +100 (strongly right-handed); Education: years of education counted from the first year of elementary school to the highest education level. Age was negatively correlated with education level for both the semantic fluency group, $r(75) = -.56, p < .001$, and the homophone judgment group, $r(64) = -.52, p < .001$.

Task and Procedure

The participants performed two blocked-design tasks (semantic fluency and homophone judgment) within the scanner. The semantic fluency task (illustrated in Figure 4-1) consisted of five resting blocks alternating with five category blocks (including fruits, animals, home appliances, tools, and vegetables). During the resting condition, the participants were asked to rest with their eyes open, while during the category condition, they were presented one category in each block and were asked to covertly generate as many items as they could within that category. The homophone judgment task (illustrated in Figure 4-2) was adapted from the English rhyming task (Lurito, Kareken, Lowe, Chen, & Mathews, 2000), and it consisted of five line orientation judgment blocks alternating with five character homophone judgment blocks. During the line orientation judgment blocks, the participants were presented two sets of lines in every trial and were asked to judge whether they were in the same orientation. For the character homophone judgment blocks, they were required to judge whether a pair of characters had the same pronunciation. Each trial was presented for 2.5 s with an inter-stimulus interval of 0.5 s. In this study for the homophone judgment task, only monophonic characters were used. For each task, every block lasted for 30 seconds and the duration of the task was five minutes. All participants were given one run of the semantic fluency task and then one run of the homophone judgment task.

In order to prevent head movement during the scanning session and to familiarize the participants with the tasks, they were given a practice session before entering the scanner. The same categories were used in the practice session and the actual scan of the semantic fluency task. During the practice session, participants were asked to overtly generate the items while their responses were recorded. Their

responses were then used as their behavioral performance later for the analysis. The behavioral performance for the homophone judgment task was recorded during the actual scan while participants responded with a button-press to the task within the scanner. The stimuli used in the practice session were not used in the actual experiment.

The tasks were presented using E-prime version 1.2 software (Psychology Software Tools, Inc., Pittsburgh, PA, USA). The stimuli were back projected onto a screen at the rear of the scanner bore and participants viewed the images via a mirror attached to the head coil placed directly above their eyes. They were given a small response keypad to hold in their right-hand and responses for the homophone judgment task were recorded by a button press.

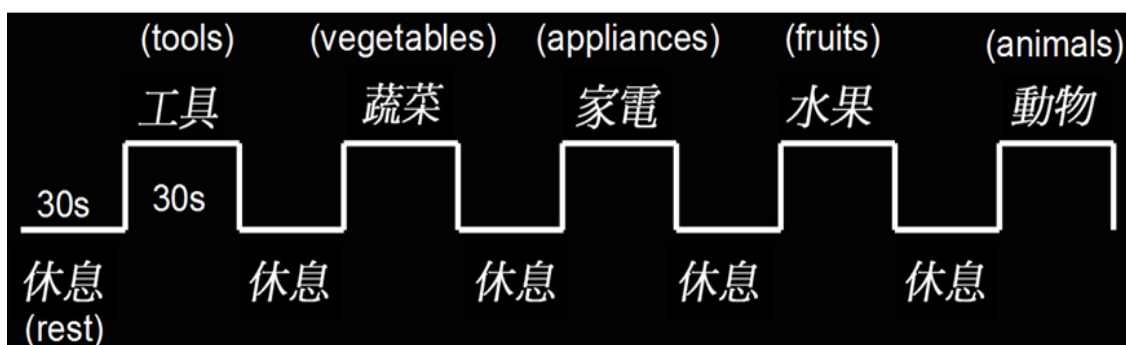


Figure 4-1. Experimental paradigm of the semantic fluency task.

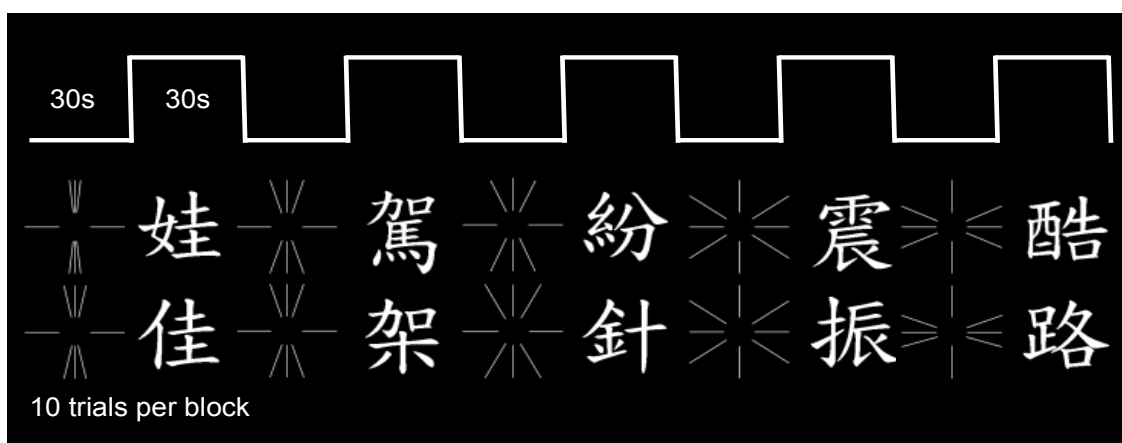


Figure 4-2. Experimental paradigm of the homophone judgment task.

Image Acquisition

Functional MRI data acquisition was performed in a 3 Tesla MR scanner (Trio, Siemens, Erlangen, Germany) using a CP head coil. A T2-weighted image was first obtained as an anatomical reference using the following parameters: TR 5920 ms; TE 102 ms; flip angle 150°; FOV 240 mm; voxel size 0.9×0.9 mm; slice thickness 3.8 mm; 34 axial slices. A gradient-echo EPI sequence was used for functional images to measure blood-oxygen level-dependent (BOLD) contrast and they were obtained at the same location as the T2-weighted image by using the following parameters: TR 2000 ms; TE 24 ms; flip angle 90°; FOV 240 mm, isotropic voxels $3.8 \times 3.8 \times 3.8$ mm; 34 axial slices with no gap. A total of 150 functional images were acquired in each run. After the acquisition of functional images, a high-resolution T1-weighted 3D MP-RAGE scan covering the whole brain (TR 1400 ms; TE 2.48 ms; flip angle 15°; FOV 256 mm; isotropic voxels $1 \times 1 \times 1$ mm) was also obtained to provide an additional anatomical reference.

Behavioral Data Analysis

For the semantic fluency task, the summation of the number of items participants generated in the five categories during the practice run was taken as their

behavioral performance. For the homophone judgment task, the participants' behavioral responses were divided into: Hit, Correct Rejection (CR), Miss, False Alarm (FA), and No Response. Hit and CR responses corresponded to events in which participants correctly responded “yes” and “no” to the stimulus pairs, respectively, e.g., “yes” to same-pronunciation character pairs, “no” to different-orientation line sets. On the contrary, Miss and FA responses were the opposites of Hit and CR. No response simply meant that no responses were recorded during the presentation of stimuli. The accuracy rate (i.e., percentage of Hit and CR) and reaction time were analyzed for each participant. The No Response events were excluded from the computation of accuracy rate and reaction time. For the computation of reaction time, only events with expected responses, i.e., Hit and CR, were used to obtain the average for each condition. As we were interested in the contrast between the homophone judgment and the line orientation judgment conditions, the differences of the accuracy rate and reaction time between the two conditions were computed.

Correlation analyses were conducted to examine the relationship between age and behavioral performance, and ANOVA tests were performed to investigate the differences in behavioral performance with respect to gender.

Image Data Preprocessing and Analyses

All functional images were preprocessed and analyzed using the SPM8 software (Statistical Parametric Mapping 8; Wellcome Department of Cognitive Neurology, London, UK). The high-resolution T1-weighted image was first segmented into different tissue types using the New Segment tool in SPM8, and the segmented gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were combined to generate a skull-stripped T1 image. To obtain the volumes of GM, WM and CSF, a voxel-based morphometry (VBM) analysis was performed on the estimated

segmentations from New Segment using the VBM8 tool in SPM8. All functional images were spatially realigned to the first volume of the image series to adjust for head movement, and estimated motion parameters were produced for each participant. The skull-stripped T1 image, T1-weighted image, and T2-weighted image were coregistered with the mean functional volume. Subsequently, the skull-stripped T1 image was segmented into GM, WM and CSF, and the segmentation parameters were used to normalize all EPIs and anatomical images to the Montreal Neurological Institute (MNI) template space. The functional images were smoothed with a Gaussian kernel of $8 \times 8 \times 8$ mm full-width at half-maximum (FWHM).

Statistical analysis was performed using a mixed effects model, fixed effects for individual-level analysis and random effects for group-level analysis. For individual participants, hemodynamic response was analyzed using the voxel-wise general linear model in order to model two conditions of interest in each task, i.e., resting and category conditions for the semantic fluency task; line orientation and character conditions for the homophone judgment task. The estimated motion parameters generated from realignment were included as covariates to control for the variances caused by head movement. The normalized gray matter from the segmentation of the skull-stripped T1 image was used as an explicit mask to ensure that only within-brain voxels were analyzed. Task-positive and task-negative responses were examined by contrasting the two conditions within each task, i.e., category > resting and resting > category for the semantic fluency task; character > line and line > character for the homophone judgment task. By the definition of DMN, however, it should be noted that the task-negative contrast in the semantic fluency task (resting > category) would be more suitable to examine the DMN activity as its control condition was resting. On the other hand, the control condition in the homophone

judgment task was line orientation judgment which involved a certain degree of cognitive demand and thus the task-negative contrast might reveal some processes related to the demand rather than purely the DMN.

For the group-level analysis, the obtained contrast images from all participants were analyzed using one-sample t-tests to generate the average group activation maps for the contrasts in each task. The t-maps were reported at a threshold of $p < .005$ (uncorrected for multiple comparisons) with cluster volume ≥ 20 voxels.

Regression analyses were performed on each contrast to examine the effect of age on the brain activation. In addition to the confounding effect from education level, possible confounding effects from gray matter atrophy due to aging (Peelle, Cusack, & Henson, 2012; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003) as well as from task difficulty were considered. We found that age was negatively correlated with gray matter volume in both the semantic fluency group, $r(75) = -.67, p < .001$, and the homophone judgment group, $r(64) = -.68, p < .001$. Behavioral performance for the semantic fluency task was based on the total number of items participants generated and for the homophone judgment task it was the difference in the accuracy rate and reaction time between the character and line conditions as the contrast between the two conditions was of interest. It was shown that age was negatively correlated with the total number of generated items in the semantic fluency group, but not significantly correlated with the difference in the accuracy rate and reaction time between the two conditions in the homophone judgment task (see the Results section for details). Therefore, for the regression analyses in the semantic fluency task, the GM volume obtained from VBM analysis, the participants' behavioral performance and education level were entered as covariates of non-interest; for the homophone

judgment task, the GM volume and the education level were added as covariates of non-interest.

In addition, within the regression analysis on a task-positive contrast with age, since the regions positively correlated with age may be contributed by increase in task-induced activation and/or decrease in task-induced deactivation as age increased, and similarly the regions negatively correlated with age may be contributed by decrease in task-induced activation and/or increase in task-induced deactivation as age increased, it is important to differentiate the sources (i.e., task-induced activation or deactivation) of the significant regions observed in the regression analyses. For example, suppose for the category > resting contrast, in one voxel a younger adult shows 10 % signal change and an older adult shows 20 % signal change (activation), and in another voxel the younger adult shows -20 % signal change and the older adult -10 % signal change (deactivation); a regression analysis on this contrast with age will show both voxels to have positive correlation with age, although the correlation is manifested by increased activation in the first voxel but decreased deactivation in the second voxel. It is conceivable that the same problem would occur for the regression analyses on a task-negative contrast with age. Therefore, the result from each regression analysis was inclusively masked by the averaged group activation (or deactivation) of the respective task-positive (or task-negative) contrast to ensure that the activation correlated with age was within the activation (or deactivation) induced by the contrast. For example in the semantic fluency task, the regression analysis on the category > resting contrast was masked by the group activation of the category > resting contrast, and the regression analysis on the resting > category contrast was masked by the group deactivation from the resting > category contrast. The results of regression analyses

were reported at a threshold of $p < .005$ (uncorrected for multiple comparisons) with a minimum cluster of 20 voxels (Lieberman & Cunningham, 2009).

Next, we examined if the age-related changes in brain activation are compensatory for behavioral performance. One criterion for a successful compensatory account for the age-related changes requires evidence to show that the age-related increase in activation is positively correlated with performance (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). From the whole-brain regression analyses with age described above, we identified the regions that showed age-related changes in the task-positive and task-negative contrasts in both tasks, and these significant clusters were extracted as the regions-of-interest (ROIs). Using the MarsBaR toolbox (Brett et al., 2002) in SPM 8, we obtained the average BOLD percent signal change within each ROI in each participant to represent the degree of activation of that ROI given the respective contrast. For each ROI, we correlated the percent signal change with behavioral performance.

In addition to whole-brain regression analyses, we specifically examined if there were any age-related changes in the sub-network using the a priori ROIs identified in Study 1, namely the bilateral middle frontal gyri and ventral occipito-temporal cortices (vOT). The values of average percent signal change within each a priori ROI in each participant were extracted using the MarsBaR toolbox. Subsequently, a hierarchical multiple regression analysis was performed for each ROI to examine whether percent signal change would be predicted by age with behavioral performance controlled. In step 1, the average percent signal change was the dependent variable and behavioral performance (i.e., the number of items generated in the semantic fluency task, and the accuracy rate and reaction time of the character condition in the homophone judgment task) was entered in as the independent variable.

In step 2, age was added into the model from step 1. We examined whether the proportion of variances in the percent signal change explained by age was significantly larger than zero.

Results

Behavioral Results

The behavioral results are summarized in Table 4-2. For the semantic fluency task, there was a significant negative correlation between age and the number of generated items, $r(75) = -.39, p = .001$, indicating that the older participants tended to perform poorer than the younger participants (see Figure 4-3). No gender difference was found, $t(75) = 0.35, p = .73$.

For the homophone judgment task (see Figure 4-4), age was negatively correlated with the accuracy rate in the character condition, $r(64) = -.37, p = .002$, but not correlated with the accuracy rate in the line condition, $r(64) = -.13, p = .29$, or the difference in accuracy rate between the two conditions, $r(64) = -.20, p = .11$. Age was positively correlated with the reaction time in the character condition, $r(64) = .40, p = .001$, and the line condition, $r(64) = .26, p = .038$, but not with the difference in reaction time between the two conditions, $r(64) = .19, p = .12$. No gender difference was found in behavioral performance except in the reaction time of the character condition, in which males responded slower than females, $t(64) = 2.39, p = .02$.

Table 4-2. *Summary of behavioral performance.*

	Male		Female		All
	Range	<i>M</i> (<i>SD</i>)	Range	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)
<i>Semantic Fluency Task</i>					
N of items	30 – 65	51.7 (8.59)	33 – 63	51 (7.93)	51.3 (8.21)
<i>Homophone Judgment Task</i>					
<u><i>Accuracy rate (%)</i></u>					
Character	76.7 – 100	95.0 (4.54)	71.7 – 100	92.6 (6.17)	93.8 (5.48)
Line	66.0 – 97.9	91.2 (6.23)	68 – 98	90.4 (6.43)	90.8 (6.29)
Difference	-7.26 – 32	3.77 (7.06)	-10 – 15.1	2.26 (4.79)	3.04 (6.07)
<u><i>Reaction time (ms)</i></u>					
Character	1021 – 1626	1372 (145)	939 – 1612	1277 (176)	1326 (167)
Line	883 – 1513	1179 (163)	762 – 1374	1114 (157)	1148 (162)
Difference	-83.7 – 466	193 (143)	-20.3 – 509	163 (117)	179 (131)

Note. Difference of accuracy rate/reaction time = accuracy rate/reaction time of the

character condition – accuracy rate/reaction time of the line condition. Males

responded slower than females in the character condition in the homophone judgment

task, $t(64) = 2.39$, $p = .02$.

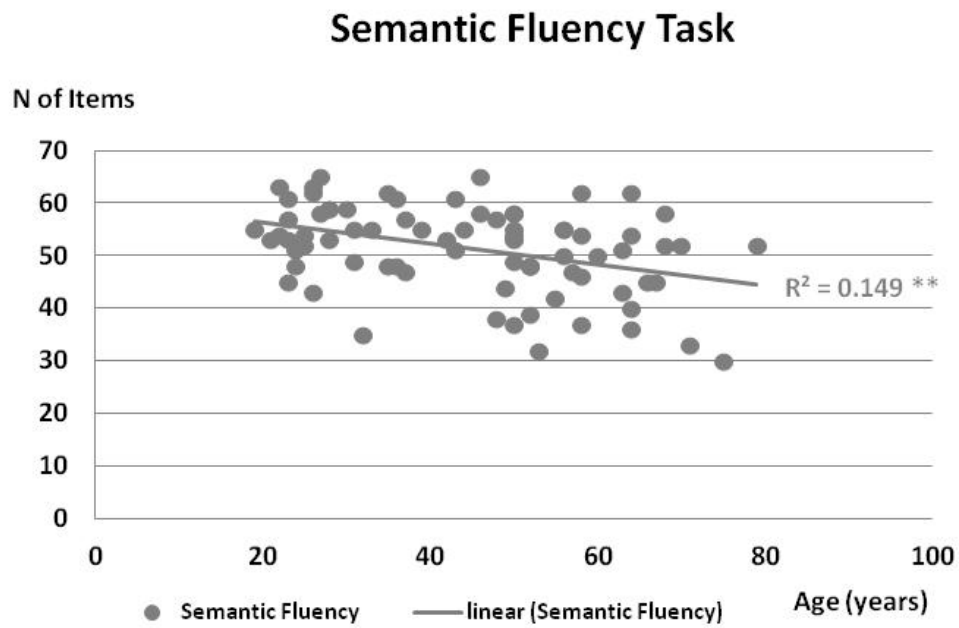


Figure 4-3. The distribution of the number of generated items by age in the semantic fluency task. Age was negatively correlated with the number of generated items, $r(75) = -.39, p = .001$. (** $p < .01$)

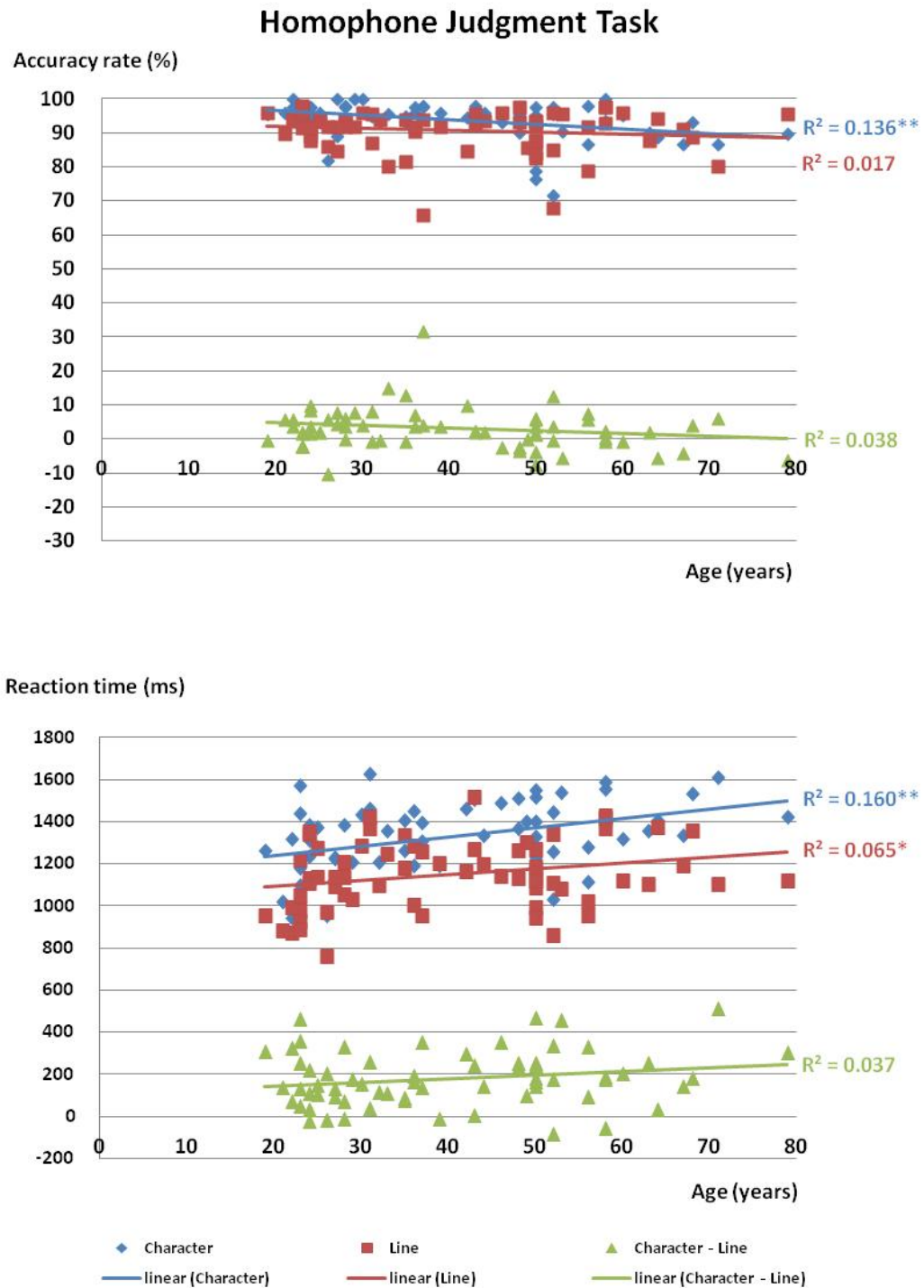


Figure 4-4. The distribution of accuracy rate and reaction time by age in the homophone judgment task. Age was negatively correlated with the accuracy rate in the character condition, $r(64) = -.37$, $p = .002$, and positively correlated with the reaction time in the character condition, $r(64) = .40$, $p = .001$, and the reaction time in the line condition, $r(64) = .26$, $p = .038$. (* $p < .05$, ** $p < .01$)

Group Activation

The group activation maps are illustrated in Figure 4-5. Both tasks showed a similar pattern of task-related positive activity in the anterior cingulate gyrus and the bilateral inferior and middle frontal gyri (dominant in the left hemisphere). In addition, the character > line contrast in the homophone judgment task also elicited strong activation in the left middle and superior temporal gyri and the bilateral ventral occipito-temporal regions.

For task-negative responses, the resting > category contrast in the semantic fluency task yielded strong deactivation in the medial prefrontal cortex, the posterior cingulate gyrus/precuneus and the posterior temporo-parietal junction bilaterally. The line > character contrast in the homophone judgment task activated the bilateral precuneus, the bilateral middle occipital gyri (dominant in the right hemisphere), the right inferior parietal lobule, and the right posterior lateral parietal cortex.

Regression Analysis

Task-positive responses (Figure 4-6 and Table 4-3). The regression analyses on both tasks revealed that there was age-related increase in task-related positive activity but no age-related decrease, indicating that adults showed greater activation in the task-positive contrasts as age increased. For the category > resting contrast in the semantic fluency task, the activation positively correlated with age was found in the right inferior frontal gyrus (BAs 44/45) and the right middle frontal gyrus (BA 6). For the character > line contrast in the homophone judgment task, increased activation with age was observed in the insular cortices, the hippocampus, and the parahippocampal gyrus bilaterally.

Task-negative responses (Figure 4-7 and Table 4-3). The regression analyses on the resting > category contrast in the semantic fluency task demonstrated

that as age increased, there was age-related decrease in task-induced deactivation in the bilateral precuneus, posterior cingulate gyri, medial prefrontal cortices, and middle temporal gyri (BAs 21/39), and the right superior frontal gyrus (BA 8). For the line > character contrast in the homophone judgment task, decreased task-induced deactivation with age was shown in the bilateral posterior cingulate gyri.

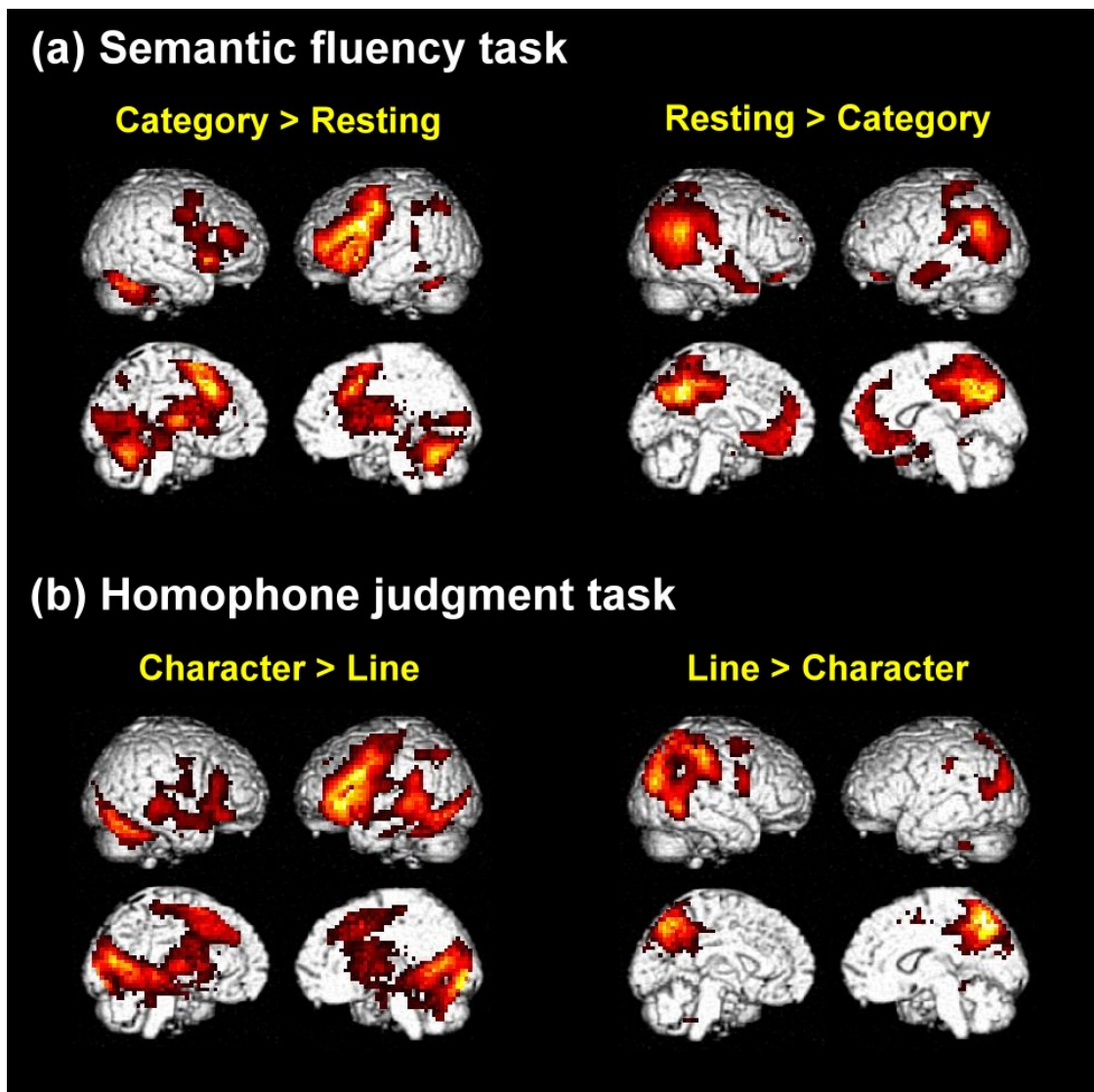
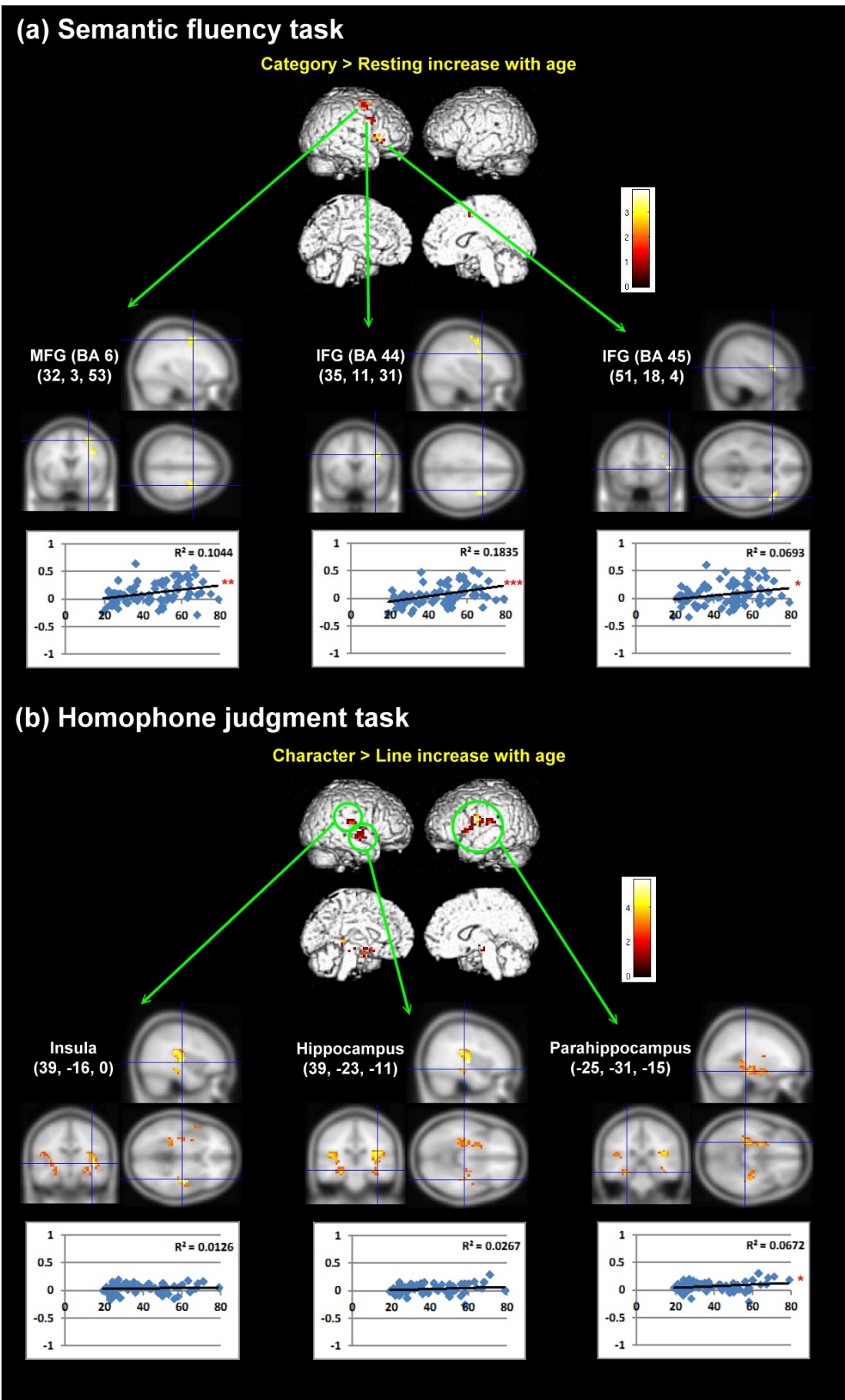


Figure 4-5. Group activation maps from (a) the semantic fluency task ($n = 77$): category > resting and resting > category contrasts and (b) the homophone judgment task ($n = 66$): character > line and line > character contrasts. $p < .005$ uncorrected, cluster ≥ 20 voxels.



(next page)

(Figure on previous page) *Figure 4-6.* The regression results on task-positive responses. The activated regions showed positive correlation with age, i.e., responses increased as age increased, in the task-positive contrasts in (a) the semantic fluency task (category > resting) and (b) the homophone judgment task (character > line). Both regression results were masked by the respective task-positive contrasts and thresholded at $p < .005$ uncorrected, cluster ≥ 20 voxels, with covariates of non-interest included (semantic fluency: GM volume, number of generated items and education level; homophone judgment: GM volume and education level). The scatter plots demonstrate the correlation between age and the percent signal change of BOLD activity extracted from each activation cluster. The crosshairs show the peak coordinates within each activation cluster. MFG: middle frontal gyrus; IFG: inferior frontal gyrus. Asterisks indicate the significance level of the correlation between age and percent signal change in the clusters (* $p < .05$; ** $p < .01$; *** $p < .001$).

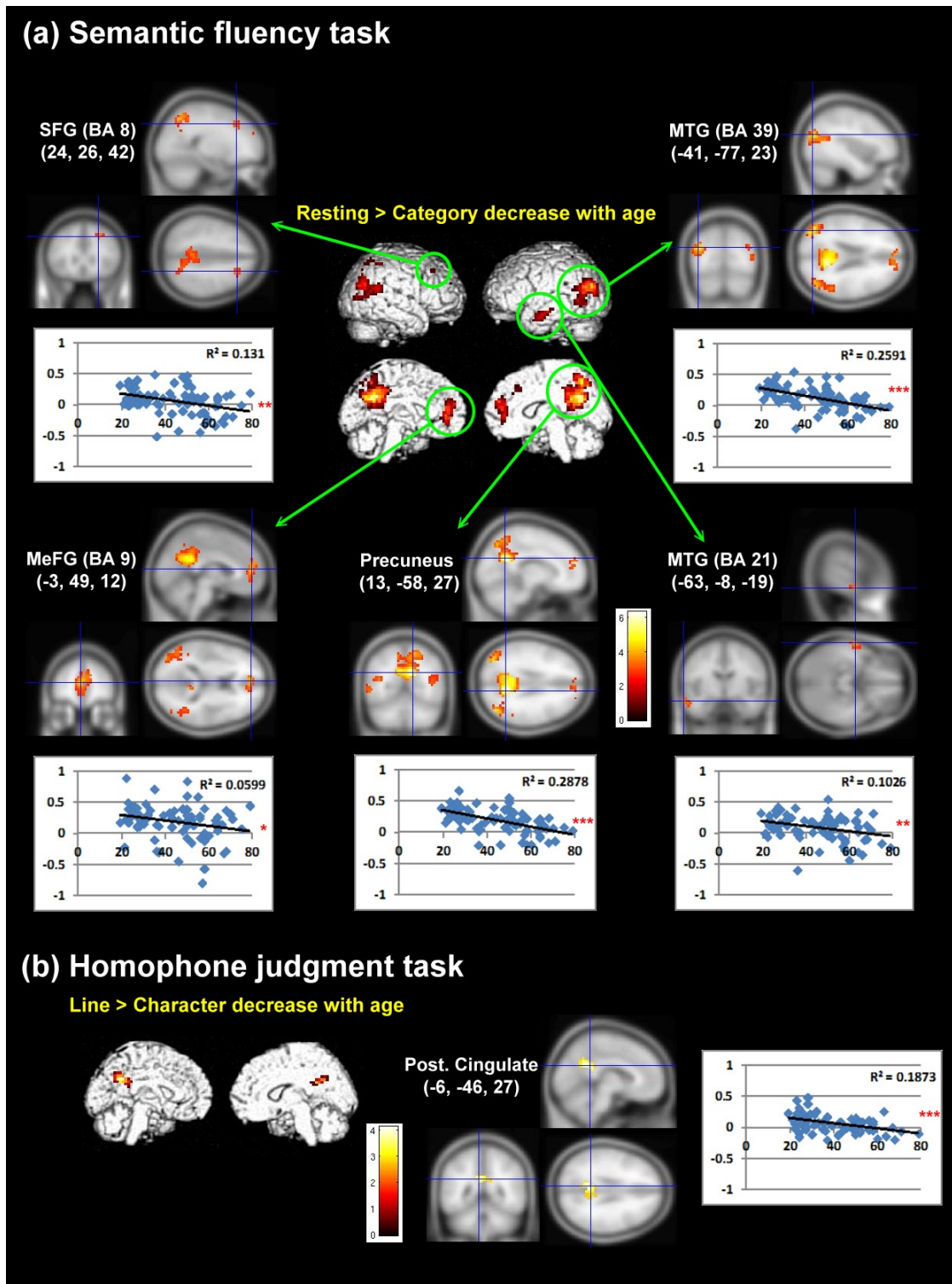


Figure 4-7. The regression results on task-negative responses. The activated regions showed negative correlation with age, i.e., responses decreased as age increased, in the task-negative contrasts in (a) the semantic fluency task (resting > category) and (b) the homophone judgment task (line > character). Both regression results were masked by

the respective task-negative contrasts and thresholded at $p < .005$ uncorrected, cluster ≥ 20 voxels, with covariates of non-interest included (semantic fluency: GM volume, number of generated items and education level; homophone judgment: GM volume and education level). The scatter plots demonstrate the correlation between age and the percent signal change of BOLD activity extracted from each activation cluster. The crosshairs show the peak coordinates within each activation cluster. SFG: superior frontal gyrus; MeFG: medial frontal gyrus; MTG: middle temporal gyrus; Post. Cingulate: posterior cingulate. Asterisks indicate the significance level of the correlation between age and percent signal change of BOLD activity in the ROIs (* $p < .05$; ** $p < .01$; *** $p < .001$).

Table 4-3. Results from the Regression Analyses.

Semantic Fluency						Homophone Judgment					
Region	BA	x	y	z	T	Region	BA	x	y	z	T
<i>Age-related increase in “category > resting”</i>						<i>Age-related increase in “character > line”</i>					
R Inferior frontal gyrus	44	35	11	31	3.89	R Insula	13	39	-16	0	5.62
	45	51	18	4	3.51		13	39	-27	19	4.99
	45	43	30	0	2.82	L Insula	13	-44	-27	19	4.05
R Middle frontal gyrus	6	32	3	53	3.29	R Claustrum	-	35	-20	8	4.7
R Precentral gyrus	4	39	-8	57	2.96	L Parahippocampal gyrus	35	-25	-31	-15	4.35
						L Hippocampus	-	-29	-39	-4	3.89
<i>Age-related decrease in “resting > category”</i>						R Hippocampus	-	39	-23	-11	3.87
R Precuneus	31	13	-58	27	6.35	R Medial globus pallidus	-	20	-12	-7	3.2
L Posterior cingulate	23	-3	-46	27	4.95						
L Cingulate gyrus	31	-10	-54	31	4.85	<i>Age-related decrease in “line > character”</i>					
L Middle temporal gyrus	39	-41	-77	23	4.71	L Posterior cingulate	23	-6	-46	27	4.12
	21	-41	-58	15	3.54	L Cingulate gyrus	31	-14	-54	31	4.02
	21	-63	-8	-19	3.9	R Cingulate gyrus	31	9	-54	31	3.15
	21	-56	-1	-26	3.49						
	21	-52	-16	-15	3.01						
L Middle occipital gyrus	19	-52	-61	-4	3.29						
L Medial frontal gyrus	9	-3	49	12	4.29						
	9	-3	53	23	3.65						
R Superior frontal gyrus	9	20	53	19	2.93						
	8	24	26	42	3.7						

Note. L/R: left/right hemisphere; x, y, z coordinates: MNI space. These regions were peak coordinates within the clusters that showed increased or decreased activation as age increased in each contrast. $p < .005$ uncorrected, voxels ≥ 20 , with covariates of non-interest included (Semantic fluency: GM volume, number of generated items and education level; homophone judgment: GM volume and education level). Coordinates in bold are peak coordinates within the activation clusters.

The relationship between age-related changes and performance. The regression analyses on the task-positive and task-negative responses revealed age-related activations that were not traditionally associated with language processing. To evaluate if these differential activations are compensatory, we examined the correlations of the activity of these regions with the respective performance. For the semantic fluency task, none of the clusters was significantly correlated with behavioral performance, i.e., the number of generated items ($p > .05$). For the homophone judgment task, the task-positive and task-negative clusters were also not correlated with behavioral performance, i.e., the accuracy rate and reaction time of the character condition ($p > .05$).

A Priori ROI Analysis

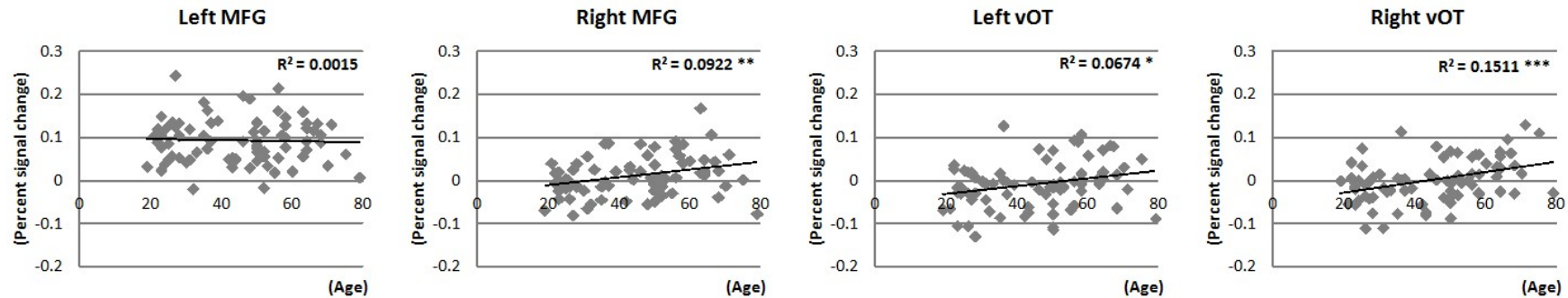
The correlations between brain activity in the ROIs with age and behavioral performance are illustrated in Figure 4-8 (semantic fluency task) and Figure 4-9 (homophone judgment task). The hierarchical multiple regression analyses were performed to examine if the activity in a priori ROIs was correlated with age while behavioral performance was controlled (see Table 4-4). For the semantic fluency task, significant results were found in the right middle frontal gyrus and the right vOT ROIs. In the right middle frontal gyrus ROI, the multiple regression analysis at step 1 showed that behavioral performance was not significantly correlated with percent signal change, $R^2 = .012$, $F(1, 75) = .94$, $p = .34$. When age was added at step 2, the second multiple regression analysis revealed that age significantly accounted for the amount of percent signal change in the ROI, R^2 change = .08, $F(1, 74) = 6.52$, $p = .013$, suggesting that older adults tended to show greater activity. In the right vOT ROI, the first multiple regression analysis showed that behavioral performance predicted percent signal change in the ROI, $R^2 = .089$, $F(1, 75) = 7.30$, $p = .009$, indicating that

participants who generated less items during the task showed greater activity in the ROI. At step 2, the second multiple regression analysis evaluated whether age predicted activity in the ROI over behavioral performance. The results showed that age significantly accounted for the amount of percent signal change in the right vOT ROI while behavioral performance was controlled, R^2 change = .088, $F(1, 74) = 7.90$, $p = .006$. The positive coefficient suggested that older adults had greater activity in the right vOT ROI.

For the homophone judgment task, significant results were only found in the right middle frontal gyrus ROI. At step 1, the multiple regression analysis revealed that the accuracy rate and reaction time of the character condition significantly predicted the amount of percent signal change in the right middle frontal gyrus ROI, $R^2 = .17$, $F(2, 63) = 6.23$, $p = .003$. The coefficients indicated that participants who performed worse (i.e., lower accuracy rate and longer reaction time) had higher activity in the right middle frontal gyrus ROI. At step 2, age also significantly accounted for the amount of percent signal change when behavioral performance was controlled, R^2 change = .15, $F(1, 62) = 14.0$, $p < .001$. This showed that when the behavioral performance was comparable, older participants tended to have greater activity in the right middle frontal gyrus ROI than younger participants.

Semantic Fluency Task

(a) Correlation between brain activity and age



(b) Correlation between brain activity and behavioral performance

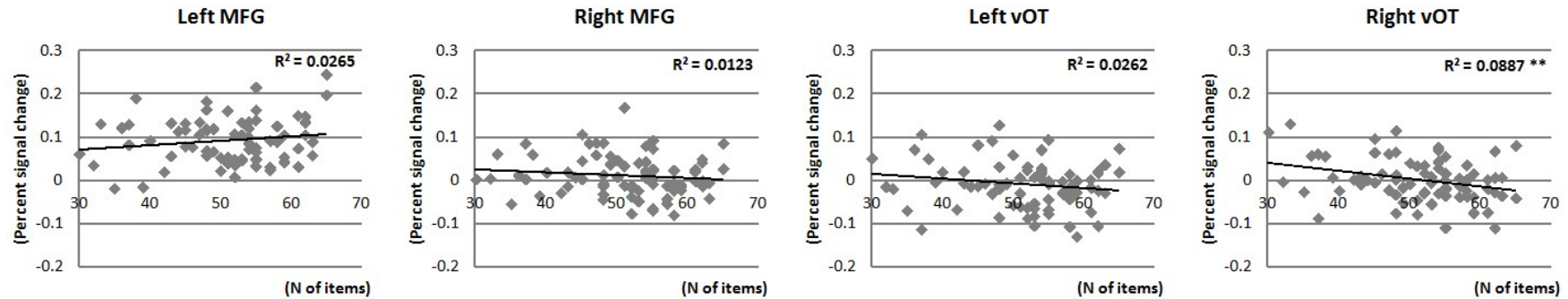
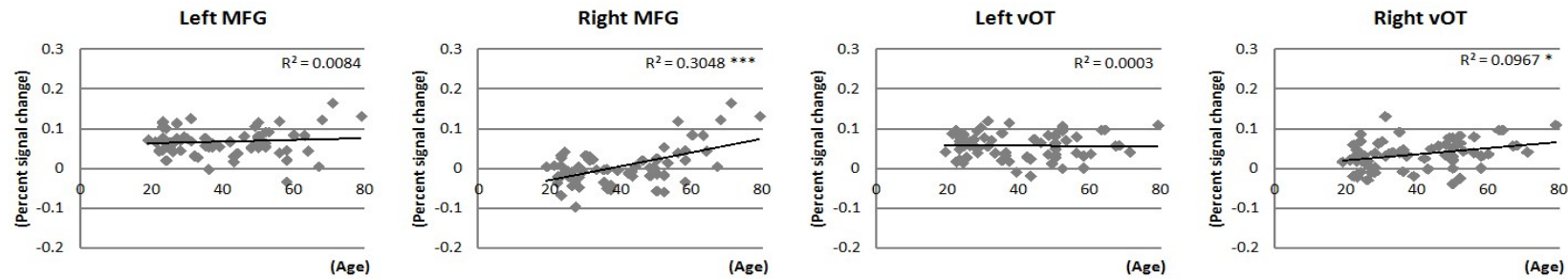


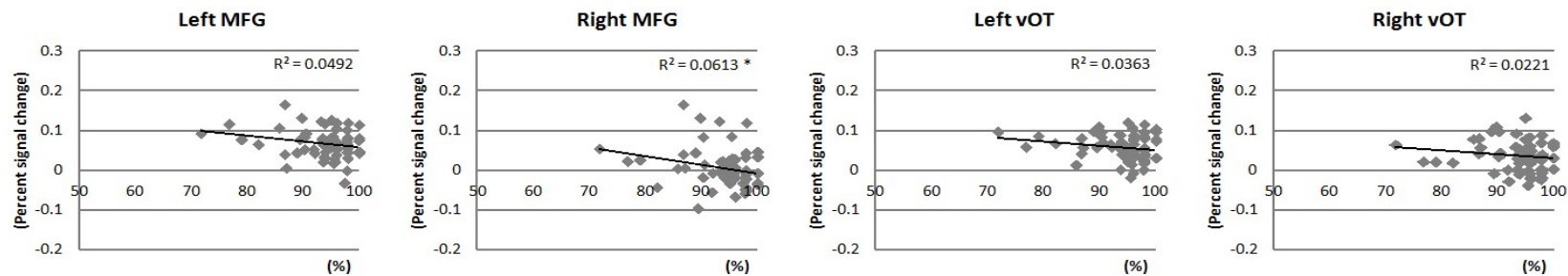
Figure 4-8. Correlation between (a) brain activity with age and (b) brain activity with behavioral performance (number of generated items) for the semantic fluency task. Asterisks indicate significance level of the correlations (* $p < .05$, ** $p < .01$, *** $p < .001$). MFG: middle frontal gyrus; vOT: ventral occipito-temporal cortex.

Homophone Judgment Task

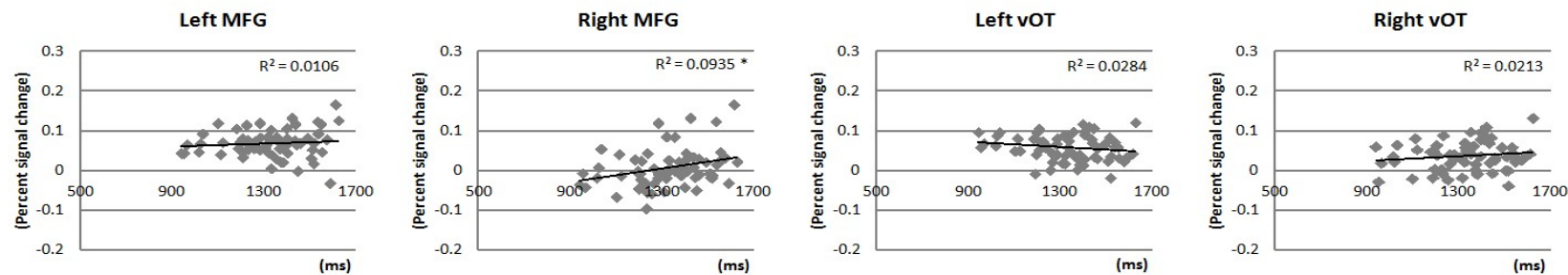
(a) Correlation between brain activity and age



(b) Correlation between brain activity and accuracy rate of the character condition



(c) Correlation between brain activity and reaction time of the character condition



(next page)

(Figure on previous page) Figure 4-9. Correlation between (a) brain activity with age, and brain activity with behavioral performance – (b) accuracy rate and (c) reaction time of the character condition for the homophone judgment task. Asterisks indicate significance level of the correlations (* $p < .05$, *** $p < .001$). MFG: middle frontal gyrus; vOT: ventral occipito-temporal cortex.

Table 4-4. *Summary of results from the hierarchical multiple regression analyses on a priori ROIs.*

ROI	Variable	Step 1						Step 2						R^2
		B	β	t	p	F	R^2	B	β	t	p	F	R^2	change
<i>Semantic fluency</i>														
Lt MFG	Intercept	.04		1.08	.28	2.04	.027	.033		.65	.52	1.03	.027	.001
	N of items	.001	.16	1.43	.16			.001	.17	1.40	.17			
	Age							9.19E-5	.028	.23	.82			
Rt MFG	Intercept	.044		1.30	.20	.94	.012	-.031		-.70	.49	3.76*	.092	.08*
	N of items	-.001	-.111	-.97	.34			4.36E-5	.008	.063	.95			
	Age							.001	.31	2.55	.013			
Lt vOT	Intercept	.046		1.18	.24	2.02	.026	-.02	.052	-.38	.71	2.87	.072	.046
	N of items	-.001	-.16	-1.42	.16			-4.78E-4	.001	-.59	.55			
	Age							.001	4.13E-4	1.91	.06			
Rt vOT	Intercept	.095		2.70	.009	7.30**	.089	.01		.23	.82	7.94**	.18	.088**
	N of items	-.002	-.30	-2.70	.009			-.001	-.17	-1.52	.13			
	Age							.001	.32	2.81	.006			
<i>Homophone judgment</i>														
Lt MFG	Intercept	.17		2.21	.031	2.12	.063	.18		2.18	.033	1.45	.065	.002
	ACC	-.001	-.23	-1.88	.065			-.002	-.25	-1.85	.069			
	RT	2.41E-5	.12	.96	.34			2.92E-5	.14	1.03	.31			
	Age							1.35E-4	-.059	-.40	.69			

(table continues)

Table 4-4 (*continued*)

ROI	Variable	Step 1						Step 2						R^2 change
		B	β	t	p	F	R^2	B	β	t	p	F	R^2	
Rt MFG	Intercept	.10		1.01	.32	6.23**	.17	-.034		-.35	.73	9.66***	.32	.15***
	ACC	-.002	-.27	-2.32	.023			-.001	-.080	-.69	.50			
	RT	9.09E-5	.32	2.80	.007			3.41E-5	.12	1.03	.31			
	Age							.001	.47	3.74	4.09E-4			
Lt vOT	Intercept	.20		2.72	.008	2.04	.061	.20		2.58	.012	1.35	.061	.001
	ACC	-.001	-.18	-1.48	.15			-.001	-.19	-1.41	.17			
	RT	-2.98E-5	-.16	-1.28	.20			-2.74E-5	-.14	-1.04	.30			
	Age							-6.22E-5	-.03	-.20	.84			
Rt vOT	Intercept	.089		1.09	.28	1.53	.046	.028		.33	.74	2.28	.099	.053
	ACC	-.001	-.16	-1.29	.20			-3.13E-4	-.048	-.36	.72			
	RT	3.33E-5	.16	1.26	.21			8.01E-6	.038	.28	.78			
	Age							.001	.28	1.91	.061			

Note. The dependent variable was the percent signal change within each a priori ROI. At step 1 the independent variable was behavioral performance (semantic fluency: N of items – number of generated items; homophone judgment: ACC – accuracy rate, and RT – reaction time); at step 2 the independent variables were behavioral performance and age. Asterisks indicate significance level in the regression models and significant R^2 change for adding age into the model at step 2 (* $p < .05$, ** $p < .01$, *** $p < .001$). B : unstandardized regression coefficient; β : standardized regression coefficient. MFG: middle frontal gyrus; vOT: ventral occipito-temporal cortex; Lt: left; Rt: right.

Discussion

The current study is the first fMRI study to date that investigates age effects on the neural substrates of language processing in native Chinese speakers across young, middle-aged, and old age. We implemented the semantic fluency task and the homophone judgment task to examine age-related changes in the neural activity underlying word retrieval. Semantic fluency was implemented to indirectly examine the retrieval process of lexical-semantic and phonological representations, and the homophone judgment task was used to directly explore phonological retrieval. The results are summarized as follows. First, in the semantic fluency task, as age increased, greater task-positive responses (category > resting) were found in the right inferior and middle frontal gyri, whereas reduced task-negative responses (resting > category) were observed in the bilateral precuneus, posterior cingulate gyri, medial prefrontal cortices, and middle temporal gyri, and the right superior frontal gyrus. Second, in the homophone judgment task, as age advanced, increased task-positive responses (character > line) were found in the insular cortex, the hippocampus, and the parahippocampal gyrus bilaterally, whereas decreased task-negative responses (line > character) were shown in the bilateral posterior cingulate gyri. Third, these age-related changes in brain activation were not significantly associated with behavioral performance. These findings will be discussed in detail below in terms of age-related changes in task-positive and task-negative networks. Finally, when behavioral performance was controlled, the older adults showed higher activation in the right middle frontal gyrus and the right ventral occipito-temporal ROIs in the sub-network during the semantic fluency task, and they also showed higher activity in the right middle frontal gyrus ROI during the homophone judgment task.

Two factors that may confound age-related changes in the BOLD activity must be considered before we interpret the observed functional changes with age effects. First, several studies have identified that aging comes along with gray matter volume decline in nearly all parts of the brain, with particularly rapid decrease in the inferior regions of the frontal cortex, e.g., the inferior frontal gyrus and the insula (Good et al., 2001; Grieve, Clark, Williams, Peduto, & Gordon, 2005; Peelle et al., 2012; Resnick et al., 2003; Tisserand et al., 2002). In the current study, we also found reduced whole-brain gray matter volume with advanced age in the participants for the tasks. Second, older adults tended to have a reduced level of performance in a variety of cognitive functions (for review see Glisky, 2007), and the declined functioning or increased task difficulty for older adults may be reflected in a differential pattern of brain activity as compared with young adults (e.g., Meinzer et al., 2009; Meinzer, Seeds, et al., 2012; Spreng, Wojtowicz, & Grady, 2010). In the current study, as age increased, the older adults generated fewer items in the semantic fluency task and generally responded slower to both the character homophone judgment and line orientation judgment conditions in the homophone judgment task as compared with the younger adults (although the differences of the accuracy rate and reaction time between the two conditions were not correlated with age). Both gray matter volume decline and impaired behavioral performance with normal aging even in the absence of neurological pathologies may be associated with changes in the functional activity. Also, decreased gray matter density has been found to be related to cognitive decline (Tisserand et al., 2004). Thus, it is clear that functional activity, gray matter density, and cognitive performance are intimately tied together, and their influences on each other in the context of aging must be taken into account. As the focus of the current study was on the functional activity, we included the gray matter volume and task

performance into the regression analyses as covariates of non-interest, intending to control for possible confounding effects while examining the relationship between functional activity and aging.

Age Effects on Task-Positive Network

Consistent with previous studies (Meinzer et al., 2009; Meinzer, Seeds, et al., 2012; Wierenga et al., 2008), the results showed increased task-positive responses with age for the semantic fluency task in the right inferior and middle frontal gyri. With behavioral performance factored out, the increased recruitment of the right frontal region was also consistent with the HAROLD model (Cabeza, 2002), demonstrating that under similar task circumstances older adults tended to recruit bilateral prefrontal activity during cognitive performance. For the fact that we controlled for possible variances due to task performance in our analysis, the increased activity in the right inferior frontal gyrus observed might suggest that older adults need to recruit greater activity in the right frontal regions in order to achieve an equivalent level of performance as young adults. Moreover, a negative correlation between whole-brain gray matter volume and age was identified, showing that older adults had reduced gray matter volume as age advanced. The increased activity in the right inferior and middle frontal gyri with increasing age was observed when the changes in gray matter volume were controlled, suggesting that greater activity in the frontal regions might be recruited to compensate for the functional loss due to deterioration of the gray matter volume. However, we did not find significant correlation between the activity in the right frontal regions and behavioral performance, so the current data did not provide direct evidence to support successful compensation of the increased right frontal activity.

In the homophone judgment task, increased task-positive responses were found in the bilateral insular cortices as age increased. Our result was not necessarily contradictory to Shafto et al.'s (2009) finding of reduced activity in the left insula in older adults during TOT states. Instead, our analysis provided supportive evidence of the age-related changes in the insular cortex from a different perspective, demonstrating that when behavioral performance was equated and gray matter atrophy was controlled, the older adults recruited greater activity in the bilateral insulae. The increased task-positive responses in the bilateral insulae with age were also consistent with the HAROLD model (Cabeza, 2002) and might suggest a compensatory role of the increased bilateral frontal activity. However, the increased activation in the bilateral insulae was not correlated with better performance, so the compensation hypothesis was not fully supported in the current data in terms of success. In addition, increased task-positive responses were also observed in the left limbic system including the hippocampus and parahippocampal gyrus. It has been shown that the limbic system has relative gray matter preservation with increasing age (Good et al., 2001; Grieve et al., 2005; Raz et al., 1997). However, the functional attribute of the increased activity found in the current study is not clear and may not be directly related to language processing. As the major focus was to explore age-related changes in the neural mechanisms underlying language processing, to interpret the findings in the limbic system may require more evidence beyond the scope of the current study.

Increased task-positive responses with advanced age were observed in different regions in the two tasks, suggesting that task demands might modulate age effects differently. Nevertheless, although different components in language processing might be affected, they were involved in the word retrieval process. The increased activity with age in the semantic fluency task was found in the right inferior frontal gyrus

(BAs 44/45), a region homologous to the Broca's area. The left inferior frontal gyrus has been suggested to be responsible for access and manipulation (Poldrack et al., 1999) or selection (Matsuo et al., 2010; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) of phonological and semantic representations, while the right inferior frontal gyrus has been implicated to be selectively upregulated in response to increased task demands in linguistic tasks (Meinzer, Flaisch, et al., 2012). As the semantic fluency task appeared to be more demanding for the older adults, the left inferior frontal gyrus activity alone might not be sufficient to deal with the demands in the access and selection process, and thus the older adults might require the upregulation of activity from the right inferior frontal gyrus to assist their performance. As the compensation hypothesis (i.e., greater activation predicts better performance) was not fully supported in the current data, the increased right inferior frontal activation might be associated with increased task difficulty but might not be necessarily beneficial for behavioral performance.

For the homophone judgment task, age-related changes were identified in the bilateral insulae, which was consistent with Shafto et al.'s (2009) results despite that a different task was used. The insula has been related to articulatory planning (Dronkers, 1996; Price, 2010; Wise et al., 1999). In addition, as suggested in Shafto et al.'s studies, reduced activity in the left insula during TOT states might indicate phonological retrieval deficits with aging. Thus, the increased activity in the bilateral insulae found in the older adults during the homophone judgment task might imply that because of the reduced efficiency of functioning in the insular cortex arising from declined gray matter volume, the older adults needed to recruit increased functional activity in order to achieve the equivalent level of successful phonological retrieval as the young adults. However, the increased insular activity was not associated with

better performance in the homophone judgment condition when age was controlled. Overall, the differential age-related changes between the two tasks suggest that age effects on language processing might not be limited to one single component or one single cortical region.

Age Effects on Task-Negative Network

The task-negative contrast in the semantic fluency task (resting > category) revealed significant deactivation in the bilateral posterior cingulate gyri, precuneus, medial prefrontal cortices, and bilateral lateral parietal lobes. These regions largely overlapped with the regions in the DMN (Fox & Raichle, 2007). On the other hand, the task-negative contrast in the homophone judgment task (line > character) also revealed significant deactivation in the bilateral precuneus, which might be part of the DMN. In addition, other regions were found to show greater activity during the line orientation judgment condition as compared with during the homophone judgment condition, including the bilateral middle occipital gyri (dominant in the right hemisphere) and the right posterior parietal cortex. These regions might be associated with spatial processing that was demanded by the line orientation judgment condition. As the task-negative contrast in the semantic fluency task served as a more suitable contrast to examine the task-negative network, the following discussion on age-related changes in task-negative responses will be based on this contrast.

When examining age effects on the task-negative network, we found a negative correlation between task deactivation and age, indicating that the older adults had attenuated task deactivation as compared with the younger adults. The reduced task deactivation was found in the regions that overlapped with the DMN, that is, bilateral precuneus, posterior cingulate gyri, medial prefrontal cortices, and middle temporal gyri, and the right superior frontal gyrus. Several studies have pointed out that both

normal aging (Grady et al., 2006; Lustig et al., 2003) and Alzheimer's disease (Lustig et al., 2003) are associated with reduced task deactivation in the DMN during the experimental tasks, which might signal a reduction in inhibitory processes or in the ability to direct attention properly. In addition, previous studies found that the reduced deactivation in the DMN was correlated with poorer performance on memory encoding (Miller et al., 2008) and slower reaction time in verb generation (Persson et al., 2007). The reduced task deactivation in the DMN regions with aging found in the current study was consistent with findings from previous studies (Grady et al., 2006; Lustig et al., 2003; Miller et al., 2008; Persson et al., 2007), suggesting that the reduced deactivation in the DMN during normal aging might hinder older adults from successful performance. Therefore, it is thought that in order to achieve the equivalent level of performance as the younger adults, the older adults needed to recruit additional activity from the frontal cortex (e.g., the inferior frontal gyrus) to compensate for the functional loss due to reduced deactivation in the DMN regions. However, our data did not show significant correlation between the DMN deactivation and behavioral performance when age was controlled (i.e., reduced deactivation was not predicted by poorer performance).

Age Effects on the Sub-network

The ROI analysis revealed further evidence regarding age-related changes specifically in the sub-network for Chinese language processing. For both semantic fluency and homophone judgment tasks, we found that when behavioral performance was controlled, the older adults showed higher activation in the right middle frontal gyrus ROI as compared with the young adults. On the contrary to our hypothesis that the older adults would show reduced activation in the left middle frontal gyrus as the connections from orthographic to phonological information were attenuated with

increasing age, our results showed increased activation in the right middle frontal gyrus for older adults. Similar to the reduced lateralization in the inferior frontal gyrus, we also observed more bilateral recruitment of the middle frontal gyrus for the older adults, which suggested a dedifferentiation process of aging. However, the increased activation for the older adults may not be compensatory as it was found to predict poorer performance in the homophone judgment task. As for the ventral occipito-temporal cortex, we did not expect to see age-related changes as this region was thought to be associated with lexical recognition process, which may not be affected by cognitive aging. However, we found significantly negative correlation between behavioral performance and the activity in the right vOT for the semantic fluency task, i.e., increased activity associated with poorer performance. The increased activation was also correlated with increasing age, indicating that the older adults had poorer performance in the semantic fluency task and they also had increased activation in the right vOT. As the semantic fluency task did not tax visual character processing as much as the homophone judgment task did, the increased recruitment of the right vOT for the semantic fluency task might not be attributed to visual character recognition. Instead, it might be associated with semantic memory and category recognition processes that are required in the semantic fluency task (Bruffaerts et al., 2013).

Is Age Effect on Word Retrieval Universal?

The findings of increased task-positive responses and decreased task-negative responses with age generally replicated findings in previous studies that investigated word retrieval in alphabetic language speakers, e.g., English and German (Meinzer et al., 2009; Meinzer, Seeds, et al., 2012; Shafto et al., 2009; Wierenga et al., 2008). However, although no age-related changes were found in the sub-network from the whole-brain regression analysis, the ROI analysis revealed increased activation in the

right middle frontal gyrus and the right vOT in older adults. The increased activation in the right middle frontal gyrus suggests a dedifferentiation process where older adults recruited a more distributed, but rather inefficient, network for orthography-to-phonology connections in word production. The increased activation in the right vOT for older adults might be associated with increased difficulty in retrieving semantic knowledge and category processing during the semantic fluency task. The age-related changes in the sub-network might suggest that aging has differential effects on the neuroanatomical representation of language processing because of different language experience. However, we could not deny the possibility that these changes were neglected in the previous studies simply because they were not revealed by whole-brain analyses.

One limitation regarding the methodologies needs to be considered. The same categories were used for the practice run and the actual experiment of the semantic fluency task. The purpose for using the same categories was to prevent head movement during the actual scan, so participants' performance was recorded during the practice. However, this could be a limitation in that it might cause differential practice effects on participants of different ages. Perhaps sparse imaging design could be considered for future studies. It could allow recoding of verbal responses during the scan, so it could be avoided to use repeated categories for the practice and the experiment of the semantic fluency task.

In summary, the current study revealed increased task-positive activation with age in the right inferior and middle frontal gyri for the semantic fluency task and the bilateral insulae for the homophone judgment task. Moreover, as age advanced, reduced task-induced deactivation was observed in a group of regions that overlapped with the default mode network. The reduced deactivation in the DMN regions during

the task conditions has been implied to be associated with the reduction in inhibitory processes or poorer allocation of attention, which might hinder participants from successful performance. The increased frontal activity with age has been suggested to play a compensatory role for the reduced efficiency of the task-related regions in older adults and/or to compensate for the impairment in performance caused by reduced deactivation in the DMN regions. However, it should be noted that the current data did not fully support the compensation hypothesis, which defines the age-related increase in brain activation as successful compensation for performance. Although there were correlations between age and the task-positive activation in the frontal regions as well as between age and the task-negative deactivation in the DMN regions, these regions were not correlated with behavioral performance. Thus, the absence of significant relationship with performance suggests that these age-related changes do not support successful compensation. Nevertheless, the current study identified the regions that showed age-related changes in word retrieval, and future investigations are required to further examine the compensatory mechanism. More studies need to elucidate the relationships among age, task performance, functional activity changes, and regional gray matter decline (in specific ROIs). Finally, the findings generally suggest a universal phenomenon for the influence of age on the neural substrates underlying word retrieval, but more bilateral recruitment of the sub-network was observed in older adults.

STUDY 3b

Language Lateralization in Chinese Speakers during Phonological Processing

Introduction

Language is one of the most lateralized functions in humans, and handedness (i.e., hand preference) is one of the factors that may influence hemispheric dominance of language processing. Although it has been established that the majority of right-handers have left-hemisphere dominance for language processing, a higher incidence of atypical language dominance (i.e., right or symmetrical) has been observed in left-handers. Understanding language dominance in individuals has important clinical implications for presurgical planning and treatment for language impairment due to brain insults. Nevertheless, most of the existing studies on language processing in Chinese speakers have been focused on right-handers, and little is known about the neural representations underlying language processing in left-handed Chinese speakers. Thus, the current study examined language lateralization in both right- and left-handed Chinese speakers with an aim to elucidate whether language dominance is universal irrespective of the spoken languages. In particular, the language dominance in the specialized sub-network for Chinese character processing was investigated to explore whether lateralization would modulate the involvement of the sub-network.

A number of studies on alphabetic language speakers have shown that left-hemisphere language dominance is more consistent in right-handers, whereas left-handers have a less consistent pattern of language lateralization (Hund-Georgiadis, Lex, Friederici, & von Cramon, 2002; Jorgens, Kleiser, Indefrey, & Seitz, 2007; Knecht, Deppe, et al., 2000; Knecht, Dräger, et al., 2000; Pujol, Deus, Losilla, & Capdevila, 1999; Springer et al., 1999; Szaflarski et al., 2002). We reviewed findings

of previous studies and presented a summary of the incidence of typical and atypical language dominance in left- and right-handers in Table 4-5. Although the incidence revealed in each study varied, generally in right-handers about 0 – 7.5 % showed right-hemisphere dominance, whereas the incidence of right-hemisphere dominance increased to 8 – 41 % in left-handers with a larger variance. Thus, the language hemispheric dominance in left-handers is less predictable than in right-handers. Moreover, Knecht, Dräger, et al. (2000) showed that the incidence of right-hemisphere dominance increased linearly with the degree of left-handedness, although no significant relationship between the two factors was found in the other study (Jorgens et al., 2007).

In many of the previous studies, the laterality index (LI) was computed based on the brain activation within a specific region-of-interest (ROI), usually the inferior frontal cortex (or Broca's area) (Hund-Georgiadis et al., 2002; Jorgens et al., 2007; Knecht, Deppe, et al., 2000; Knecht, Dräger, et al., 2000; Pujol et al., 1999), or based on activation in a more global region in the cerebral hemispheres (Springer et al., 1999; Szaflarski et al., 2002). However, other studies have highlighted the importance of considering the lateralization patterns within multiple brain regions that are related to language processing rather than focusing on one specific region or across the global hemisphere (Seghier, Kherif, Josse, & Price, 2011; Tzourio-Mazoyer, Josse, Crivello, & Mazoyer, 2004; Van der Haegen, Cai, & Brysbaert, 2011). Calculating laterality indices within multiple regions individually may provide a more comprehensive understanding of the cortical organization of language dominance for the following reasons. First, language processing involves a network of brain regions rather than the inferior frontal cortex only. Second, within the network of language processing, it has been shown that healthy individuals might have inconsistent patterns of lateralization

in two language-related regions, e.g., high left lateralization in the angular gyrus but low left lateralization in the ventral precentral gyrus (Seghier et al., 2011). Seghier et al.'s findings suggest that the directions of lateralization may reverse between regions within the same subject during the same task condition, and thus calculating the laterality index based on one single region or across the whole hemisphere may overlook spatial heterogeneity in language lateralization.

Previous literature has pointed out that handedness may influence language lateralization and that regional heterogeneity in language dominance needs to be taken into account. In the previous studies in this thesis, we have consistently found the additional recruitment of the left middle frontal gyrus and the right ventral occipito-temporal cortex (vOT), which were thought to form a sub-network specialized for Chinese character processing. Understanding the lateralization of this specialized sub-network in Chinese speakers will provide more information about the integrity of this sub-network with other universal language-related regions. Therefore, the final study in this thesis investigated language dominance particularly during phonological processing in native right-handed and left-handed Chinese speakers. The homophone judgment task was selected because it has been shown to elicit strong involvement of the inferior frontal gyrus (i.e., Broca's area – the universal language-related region), the middle frontal gyrus and the ventral occipito-temporal cortex in right-handers in Study 3a. The current study examined language dominance within this network with the aims to explore the following: (a) the whole-brain activation elicited by the homophone judgment task for the right- and left-handers; (b) the incidence of left-hemisphere, bilateral, or right-hemisphere dominance within the inferior frontal gyrus, the middle frontal gyrus, and the ventral occipito-temporal region in each handedness group; (c) the relationship between the degree of handedness and language

lateralization within each region; and (d) the couplings between the lateralization of different regions, e.g., whether the lateralization of the inferior frontal gyrus was consistent with the lateralization of the middle frontal gyrus. As suggested in previous literature, we expected that the majority of right-handers would show left-hemisphere dominance in the inferior frontal gyrus, the middle frontal gyrus, and the ventral occipito-temporal region, whereas more atypical hemispheric dominance would be observed in left-handers. The degree of handedness would show higher correlation with the hemispheric dominance of these regions for right-handers than for left-handers. As found in a previous study (Cai, Paulignan, Brysbaert, Ibarrola, & Nazir, 2010) that the ventral occipito-temporal activation was lateralized to the same hemisphere as the inferior frontal region during reading, we hypothesized that the lateralization of the inferior frontal activation would predict the lateralization of the middle frontal and ventral occipito-temporal activation in both handedness groups.

Table 4-5. *Incidence of typical and atypical language dominance revealed in previous studies.*

Study	Modality	Language	Task	Right-handers				Left-handers			
				<i>n</i>	L	Bi	R	<i>n</i>	L	Bi	R
Pujol et al. (1999)	fMRI	Spanish/Catalan	Word generation	50	96	4	0	50	76	14	10
Springer et al. (1999)	fMRI	English	Semantic decision	100	94	6	0	-	-	-	-
Knecht, Deppe, et al. (2000)	fTCD	German	Word generation	188	92.5	0	7.5	-	-	-	-
Knecht, Dräger, et al. (2000) ^a	fTCD	German	Word generation	107	-	-	4	37	-	-	27
				48	-	-	6	26	-	-	27
Hund-Georgiadis et al. (2002) ^b	DLT	German	Rhyme word discrimination	17	94	0	6	17	47	12	41
	fMRI	German	Word classification		94	0	6		53	6	41
Szaflarski et al. (2002) ^c	fMRI	English	Semantic decision	-	-	-	-	50	78	14	8
Jorgens et al. (2007)	fMRI	German	Sentence completion	11	100	0	0	11	55	27	18

Note. The studies are listed in chronological order. Handedness was determined by the Edinburgh Handedness Inventory (EHI; Oldfield, 1971).

fTCD: functional transcranial Doppler sonography. DLT: dichotic listening test. *n*: sample size. L, Bi, and R: left-hemisphere, bilateral, and right-hemisphere dominance; values indicate the incidence in percentage.

^aThis study only reported incidence of right-hemisphere dominance. The first row indicated the sample size and incidence of extreme right- or left-handers ($EHI > 99$ or < -99), and the second row for $75 < EHI \leq 99$ or $-99 \leq EHI < -75$.

^bThis study used both DLT and fMRI to examine language lateralization on the same group of participants.

^cThis study examined non-right-handed subjects, which included ambidextrous and left-handed participants with EHI scores ranging from -100 to 52. Lateralization of eleven ROIs was examined, but the incidence reported here was based on the whole hemisphere ROI.

Methods

Participants

Twenty-two right-handed (11 males; age $M = 24.9$, $SD = 2.92$) and twenty-two left-handed (11 males; age $M = 22.2$, $SD = 2.26$) native Chinese speakers were recruited. Handedness was determined by the Edinburgh Handedness Inventory (Oldfield, 1971). The mean handedness scores were 88.7 ($SD = 16.8$, range: 42.8 to 100) for the right-handers and -88.9 ($SD = 16.1$, range: -47.4 to -100) for the left-handers. Participants were screened using a detailed health questionnaire to exclude any psychiatric or neurological disorders, vascular risk factors or any factors contraindicated of MRI scanning (e.g., claustrophobia, metal implants, pacemaker, etc.). All participants gave informed consent approved by the Institutional Review Board at the National Taiwan University Hospital.

Task and Procedure

Participants were asked to perform a blocked-design homophone judgment task similar to the homophone judgment task implemented in Study 3a. The task consisted of five blocks of line orientation judgment condition alternating with five blocks of character homophone judgment condition (see the Methods section in Study 3a on pages 126-127 for detailed description of the task and procedure, and refer to Figure 4-2 for the illustration of the experimental paradigm). The participants were given a small response keypad to hold and were asked to respond to the task by a button press using their dominant hand, i.e., the right hand for right-handers and the left hand for left-handers.

Image Acquisition

Functional MRI data acquisition was performed in a 3 Tesla MR scanner (Trio, Siemens, Erlangen, Germany) using a CP head coil. Image acquisition parameters were the same as for Study 3a (see the Methods section on page 128).

Behavioral Data Analysis

The participants' behavioral responses were divided into: Hit, Correct Rejection (CR), Miss, False Alarm (FA), and No Response. Hit and CR responses corresponded to events in which participants correctly responded “yes” and “no” to the stimulus pairs, respectively. On the contrary, Miss and FA responses were the opposites of Hit and CR. No response simply meant that no responses were recorded during the presentation of stimuli. The accuracy rate (i.e., percentage of Hit and CR) and reaction time were analyzed for each participant. The No Response events were excluded from the computation of accuracy rate and reaction time. For the computation of reaction time, only events with expected responses, i.e., Hit and CR, were used to obtain the average for each condition. The accuracy rate and averaged reaction time of each condition for every participant in both groups were evaluated separately by two-sample t-tests to examine whether left- and right-handed groups performed differently on each condition. Because the brain activation of interest came from the contrast of character > line conditions, we also computed the differences of accuracy rate and reaction time between the conditions and examined whether the two handedness groups differed in the performance differences between the conditions.

Image Data Preprocessing and Analyses

All functional images were preprocessed and analyzed using the SPM8 software (Statistical Parametric Mapping 8; Wellcome Department of Cognitive Neurology, London, UK). The preprocessing steps were identical to those in Study 3a

as described in the Methods section on pages 129-130, except that the voxel-based morphometry (VBM) analysis was not necessary for the current study as no age-related gray matter atrophy was assumed in the group of young participants.

Statistical analysis was performed using a mixed effects model, fixed effects for individual-level analysis and random effects for group-level analysis. For individual participants, hemodynamic response was analyzed using the voxel-wise general linear model in order to model two conditions of interests, i.e., line orientation judgment and character homophone judgment conditions. The estimated motion parameters generated from realignment were included as covariates to control for the variances caused by head movement. The normalized gray matter from the segmentation of the skull-stripped image was used as an explicit mask to ensure that only within-brain voxels were analyzed. The contrast of character > line was obtained in each individual participant to examine the activation for language processing. The character > line contrasts for the participants in each group were then submitted to one-sample t-tests to generate the commonly activated regions within each group. Subsequently, a two-sample t-test was conducted to examine the activation difference between the groups. The results from both one-sample t-tests and the two-sample t-test were thresholded at $p < 0.005$ (uncorrected) with cluster volume ≥ 20 voxels (Lieberman & Cunningham, 2009).

A priori regions of interest (ROIs) were defined from the results in Study 1 (meta-analysis): (a) the inferior frontal gyrus (IFG): 10-mm spheres centered at (-47, 27, 11) and (47, 27, 11) bilaterally, located within the Broca's area; (b) the middle frontal gyrus (MFG): 10-mm spheres centered at (-48, 14, 32) and (48, 14, 32) bilaterally, a region overlapped with the posterior dorsal inferior frontal gyrus and middle frontal gyrus (BAs 9/44); (c) the ventral occipito-temporal region (vOT): 10-

mm spheres centered at (-40, -66, -12) and (40, -66, -12) bilaterally, located within the fusiform gyrus. Bilateral masks of these ROIs were obtained using the MarsBaR toolbox in SPM 8 (Brett et al., 2002)..

To examine hemispheric lateralization of brain activation within these ROIs, the laterality index (LI) was computed for each ROI in each participant. The AveLI approach (Matsuo, Chen, & Tseng, 2012) was selected for the computation of LIs. This method first obtains subordinate LIs (sub-LIs) by setting a threshold at the positive t-value in each voxel within the given ROI. At a particular t-value, from the highest to the lowest, the sub-LI is calculated as $(Lt - Rt)/(Lt + Rt)$, where Lt and Rt are the summation of voxel t-values at and above the given threshold within the left and the right ROIs, respectively. Suppose there are 200 voxels with positive t-values within the bilateral ROIs, we would obtain 200 sub-LIs. Next, the AveLI is simply the average of all sub-LIs obtained within the given ROIs, calculated as $\sum(sub - LI)/VN$, where VN is the total number of voxels with positive t-values within the given ROIs. Rather than adopting a pre-defined activation threshold, the AveLI uses all voxel t-values as thresholds to obtain the final LI. The non-thresholding nature of the AveLI allows for analyzing LIs in ROIs with minimal activation. Since the AveLI automatically assigns higher weightings to higher t-value voxels, it shows robustness against noise caused by lower t-values. In addition, the use of all task-related voxel t-values as thresholds and the average of all sub-LIs obtained from these thresholds make the AveLI resistant against outlier effects. Overall, the AveLI appears to be a moderate and balanced method as compared with other LI computing methods (e.g., Branco et al., 2006; Fernández et al., 2001). According to Matsuo et al.'s criteria, an AveLI close to 1 (or -1) indicates the activation within the given ROI is strongly left (or right) hemisphere dominant. Thus, based on the participants' AveLIs in each ROI,

they were categorized as left-hemisphere dominant ($0.2 < \text{AveLI} \leq 1$), symmetrical ($-0.2 \leq \text{AveLI} \leq 0.2$), or right-hemisphere dominant ($-1 \leq \text{AveLI} < -0.2$) for each region. The boundary for symmetrical dominance (between 0.2 and -0.2) was adopted from previous literature (Springer et al., 1999; Szaflarski et al., 2002) and has been suggested to be reasonable for attributing language dominance (Seghier, 2008).

The incidence of left-hemisphere, symmetrical, and right-hemisphere dominance was calculated for each ROI in each group. In addition, two-sample t-tests were conducted to investigate whether the two groups had different AveLIs in each ROI. Finally, Pearson correlation was performed to examine the relationship between handedness scores and the AveLIs of each ROI, as well as the relationship between the AveLIs of any two ROIs.

Results

Behavioral Results

The averaged accuracy rate and reaction time are summarized in Table 4-6 and illustrated in Figure 4-10. The independent two-sample t-tests revealed that the behavioral performance of the right-handed (RH) and the left-handed (LH) groups was comparable. For accuracy rate, no significant difference between the two groups was found in the line condition, $t(42) = 0.31, p = .76$, character condition, $t(42) = 0.62, p = .54$, nor the performance difference between the two conditions, $t(42) = 0.32, p = .75$. Similarly for reaction time, no significant difference between the two groups was found in the line condition, $t(42) = -0.65, p = .52$, character condition, $t(42) = -0.16, p = .88$, nor the performance difference between the two conditions, $t(42) = 0.64, p = .52$.

Table 4-6. *Summary of behavioral performance.*

	Accuracy rate			Reaction time		
	Line	Character	Difference	Line	Character	Difference
RH	93.1 (3.1)	95.7 (3.75)	2.5 (4.49)	1089 (173)	1246 (193)	157 (130)
	86 – 98	82 – 100	-10 – 10.1	762 – 1367	939 – 1626	-27.0 – 460
LH	92.8 (3.59)	94.9 (4.49)	2.08 (5.18)	1120 (136)	1255 (168)	135 (95.0)
	84.8 – 98.0	86 - 100	-7.88 – 14.6	912 – 1333	970 – 1571	3.96 - 410

Note. The values are presented as *M (SD)* in the first rows and range in the second

rows for each group. Difference of accuracy rate/reaction time = accuracy rate/reaction time of character homophone judgment condition – accuracy rate/reaction time of line orientation judgment condition.

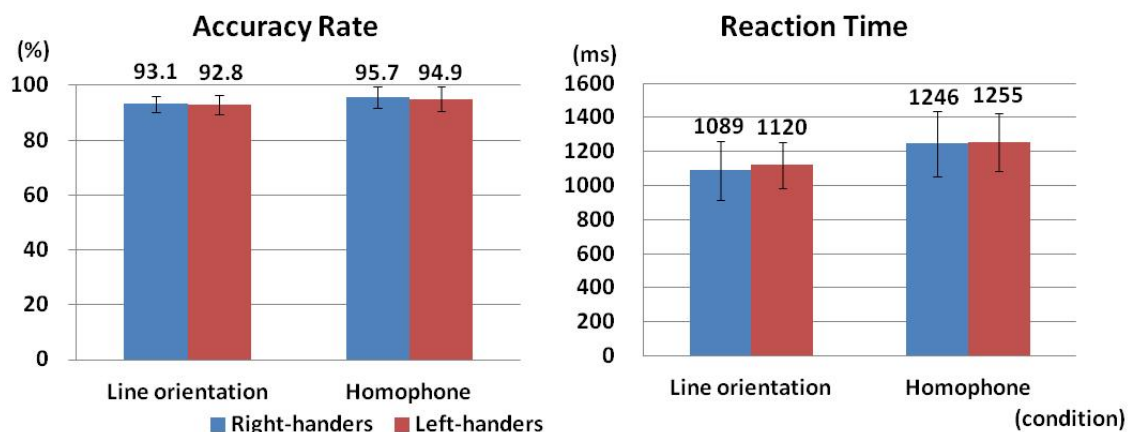


Figure 4-10. The mean accuracy rate and reaction time of the right-handed and left-handed groups for each condition. The error bars represent standard deviations.

Group Activation Results

The individual group activation maps and the group comparison result based on the character > line contrast are displayed in Figure 4-11. Under the same threshold, the right-handed group showed a larger extent of activation than the left-handed group. Both groups showed activation in the bilateral inferior frontal gyrus and the bilateral ventral occipito-temporal regions. The right-handed group also activated the left

angular gyrus (BA 39) and the right middle and superior temporal gyri (BAs 21/22), while the left-handed group did not. The two-sample t-test revealed that the right-handers had stronger activation in the inferior frontal gyrus (BAs 44/47), the middle frontal gyrus (BA 46), the superior parietal lobule and the precuneus (BA 7), and the angular gyrus (BA 39) in the left hemisphere as compared with the left-handers, and no significant activation was found in the reversed comparison.

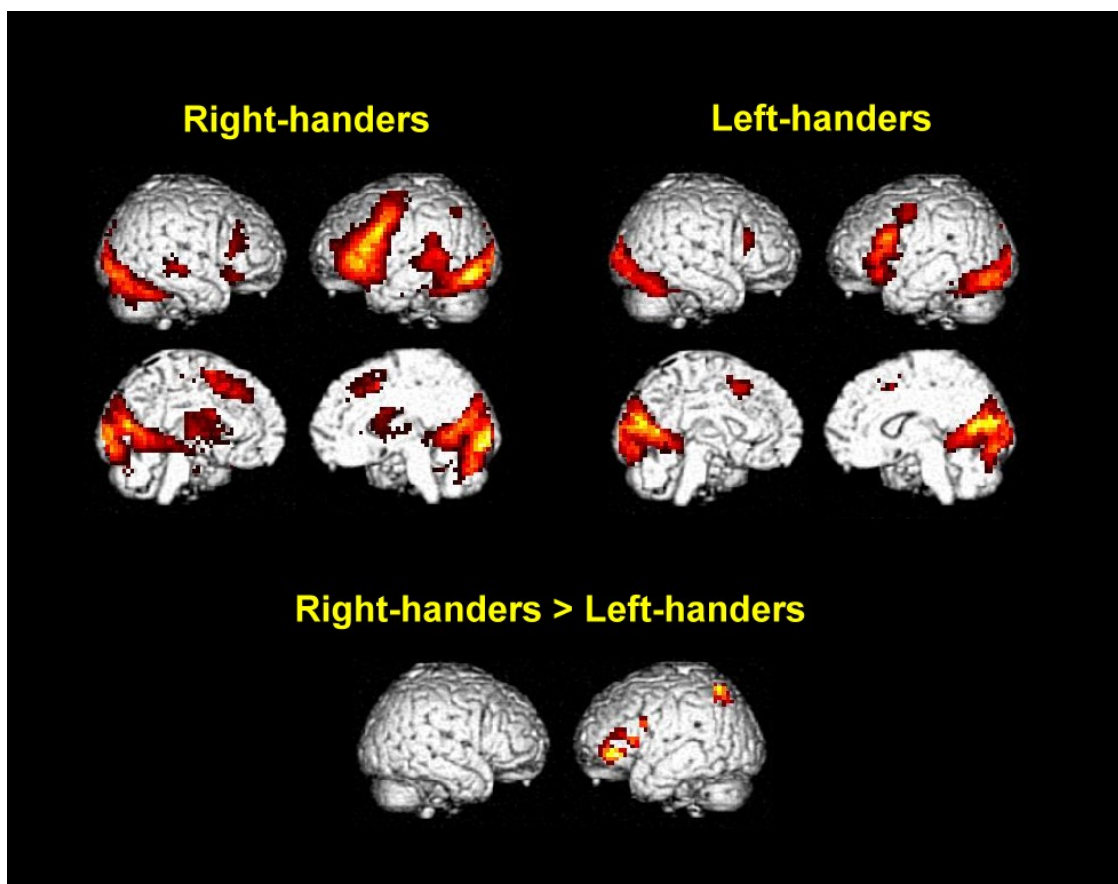


Figure 4-11. The group activation of the character > line contrast in the right-handed and the left-handed groups. The bottom panel shows the differential activation that was stronger in the right-handed group than in the left-handed group. The activation was thresholded at $p < .005$ (uncorrected) with a cluster volume ≥ 20 voxels.

Regional Language Dominance

All the participants' AveLIs for each ROI were plotted in Figure 4-12. It was observed that the left-handers showed higher incidence of right-hemisphere dominance for all three ROIs than the right-handers. Also, higher incidence of inconsistent lateralization patterns across the ROIs was found in the left-handers as compared with the right-handers.

The averaged AveLIs within each ROI for each group are summarized in Table 4-7. Levene's test indicated unequal variances in all ROIs, so the number of degrees of freedom was adjusted. Two-sample t-tests revealed that the AveLIs of the right-handed group was significantly greater than that of the left-handed group in the inferior frontal gyrus, $t(26) = 3.27, p = .003$, the middle frontal gyrus, $t(23) = 3.47, p = .002$, and the ventral occipito-temporal region, $t(35) = 2.36, p = .024$.

The participants were then categorized into left-hemisphere, bilateral, or right-hemisphere dominance for each ROI according to their AveLIs. The number of cases and the incidence of lateralization are summarized in Table 4-8. For the inferior frontal gyrus, almost all right-handed participants (95.5%) and 59.1 % of the left-handers showed left-hemisphere dominance, whereas one right-hander showed bilateral dominance (4.55%) and the other left-handers showed either bilateral (13.6%) or right-hemisphere dominance (27.3%). For the middle frontal gyrus, all right-handers showed left-hemisphere dominance. In the left-handers, the majority (68.2%) showed left-hemisphere dominance, whereas the others showed right-hemisphere (27.3%) or bilateral (4.55%) dominance. For the ventral occipito-temporal region, a more varied pattern of hemispheric dominance was observed. The majority of participants showed left-hemisphere dominance (right-handers: 90.9%; left-handers: 59.1%). In the rest of the right-handers, 4.55% showed bilateral and 4.55% right-hemisphere dominance; in

the rest of the left-handers, 18.2% and 22.7% showed bilateral and right-hemisphere dominance, respectively.

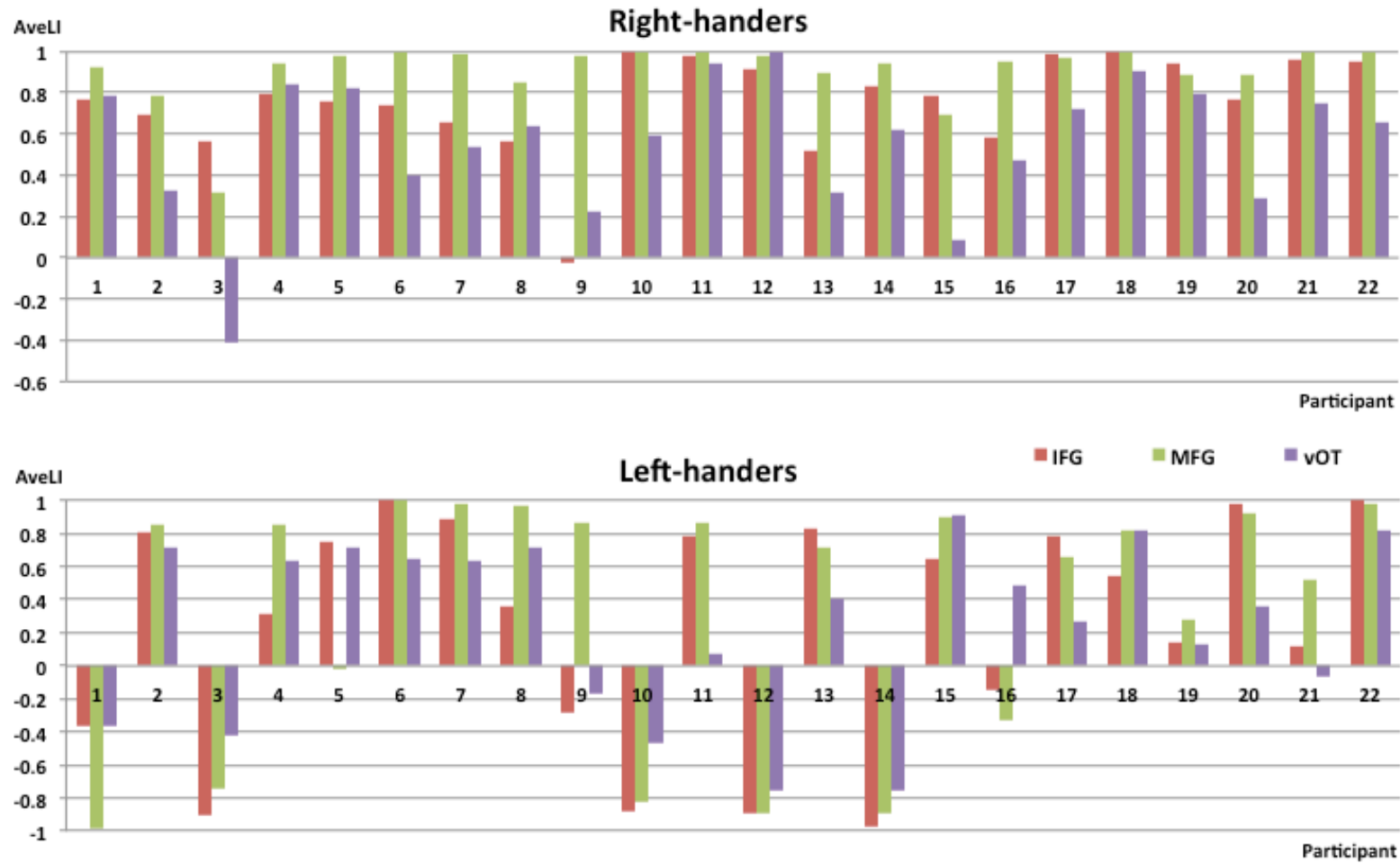


Figure 4-12. Plot of all participants' regional AveLIs. IFG: inferior frontal gyrus; MFG: middle frontal gyrus; vOT: ventral occipito-temporal region.

Table 4-7. *Summary of the AveLIs.*

	Right-handers			Left-handers		
	IFG	MFG	vOT	IFG	MFG	vOT
<i>M</i>	0.76	0.91	0.56	0.25	0.34	0.24
<i>SD</i>	0.23	0.15	0.33	0.69	0.75	0.53

Note. $n = 22$ for each group.

Table 4-8. *Lateralization incidence.*

	Right-handers			Left-handers		
	IFG	MFG	vOT	IFG	MFG	vOT
L	21 (95.5)	22 (100)	20 (90.9)	13 (59.1)	15 (68.2)	13 (59.1)
Bi	1 (4.55)	0	1 (4.55)	3 (13.6)	1 (4.55)	4 (18.2)
R	0	0	1 (4.55)	6 (27.3)	6 (27.3)	5 (22.7)

Note. The values are presented in the format of “number of participants (incidence in percentage)”. L, Bi, and R: left-hemisphere, bilateral, right-hemisphere dominance. $n = 22$ for each group.

Correlation between Handedness and AveLI

When both right-handers and left-handers were grouped together, the correlation analyses (Figure 4-13) revealed significant correlations between handedness and the AveLI of all ROIs. Handedness was positively correlated with the AveLI of the inferior frontal gyrus, $r(42) = .47, p = .001$, the middle frontal gyrus, $r(42) = .49, p = .001$, and to a less extent with the ventral occipito-temporal region, $r(42) = .36, p = .017$. When the correlation analyses were performed separately in each handedness group, no significant correlation was found (all $p > .05$).

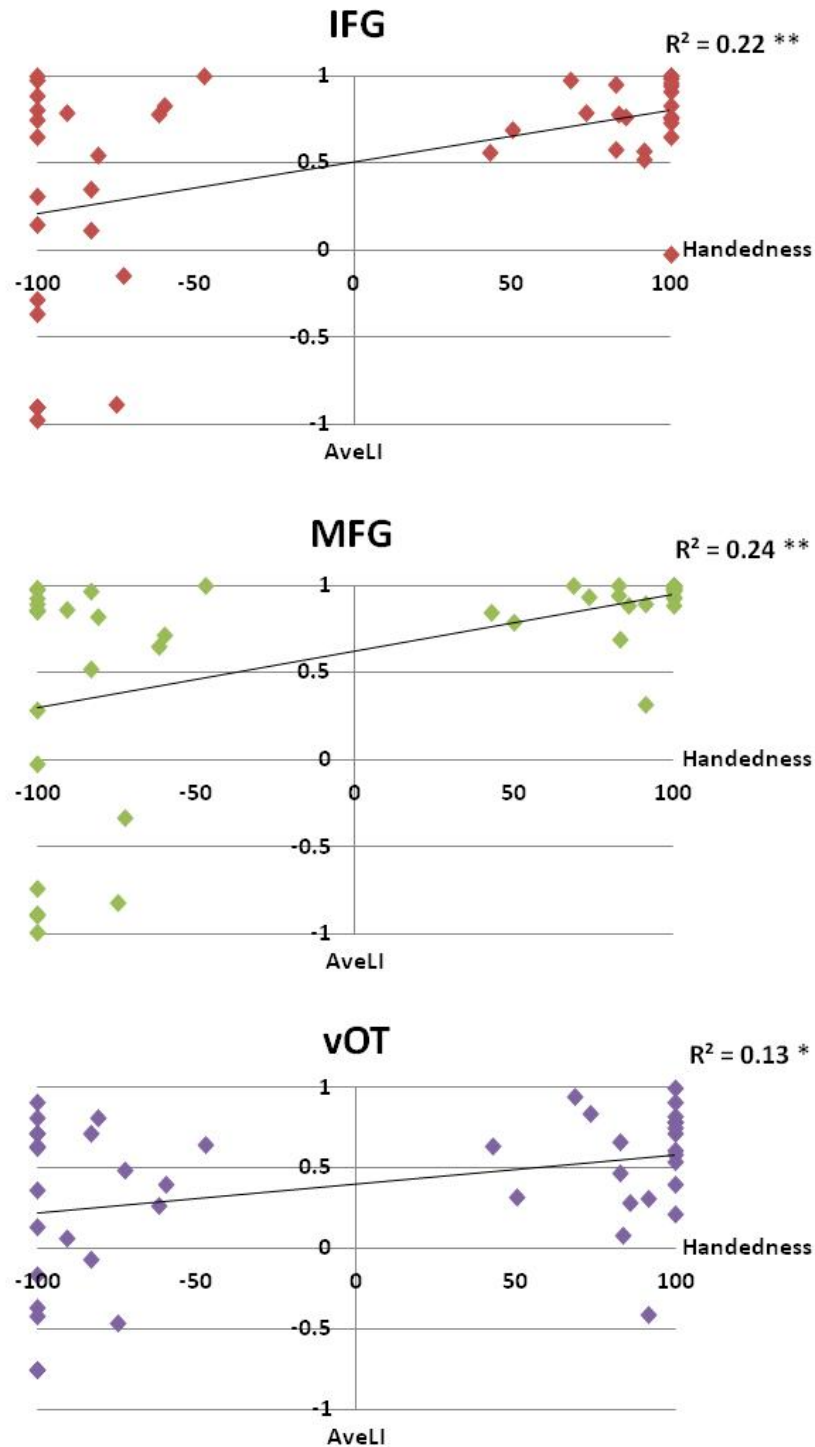


Figure 4-13. Correlation between handedness (x-axis) and AveLI (y-axis) within each ROI. Inferior frontal gyrus (IFG): $r(42) = .47, p = .001$; middle frontal gyrus (MFG): $r(42) = .49, p = .001$; ventral occipito-temporal region (vOT): $r(42) = .36, p = .017$. Asterisks indicate significance level of the correlations ($^{*} p < .05, ^{**} p < .01$).

Correlation between ROIs

When both right-handers and left-handers were grouped together (Figure 4-14), strong positive correlations were observed between the AveLIs of the inferior frontal gyrus and the middle frontal gyrus, $r(42) = .85, p < .001$, between the AveLIs of the middle frontal gyrus and the ventral occipito-temporal region, $r(42) = .77, p < .001$, as well as between the AveLI of the inferior frontal gyrus and the ventral occipito-temporal region, $r(42) = .81, p < .001$. When the correlations were examined separately in each group, significant correlations for the right-handers were observed between the AveLIs of the inferior frontal gyrus and the ventral occipito-temporal region, $r(20) = .56, p = .007$, as well as between the AveLIs of the middle frontal gyrus and the ventral occipito-temporal region, $r(22) = .78, p < .001$, but not between the inferior frontal gyrus and the middle frontal gyrus, $r(22) = .25, p = .27$. For the left-handers, significant correlations were found in all three pairs of ROIs: IFG and MFG, $r(22) = .86, p < .001$; MFG and vOT, $r(22) = .78, p < .001$; IFG and vOT, $r(22) = .85, p < .001$.

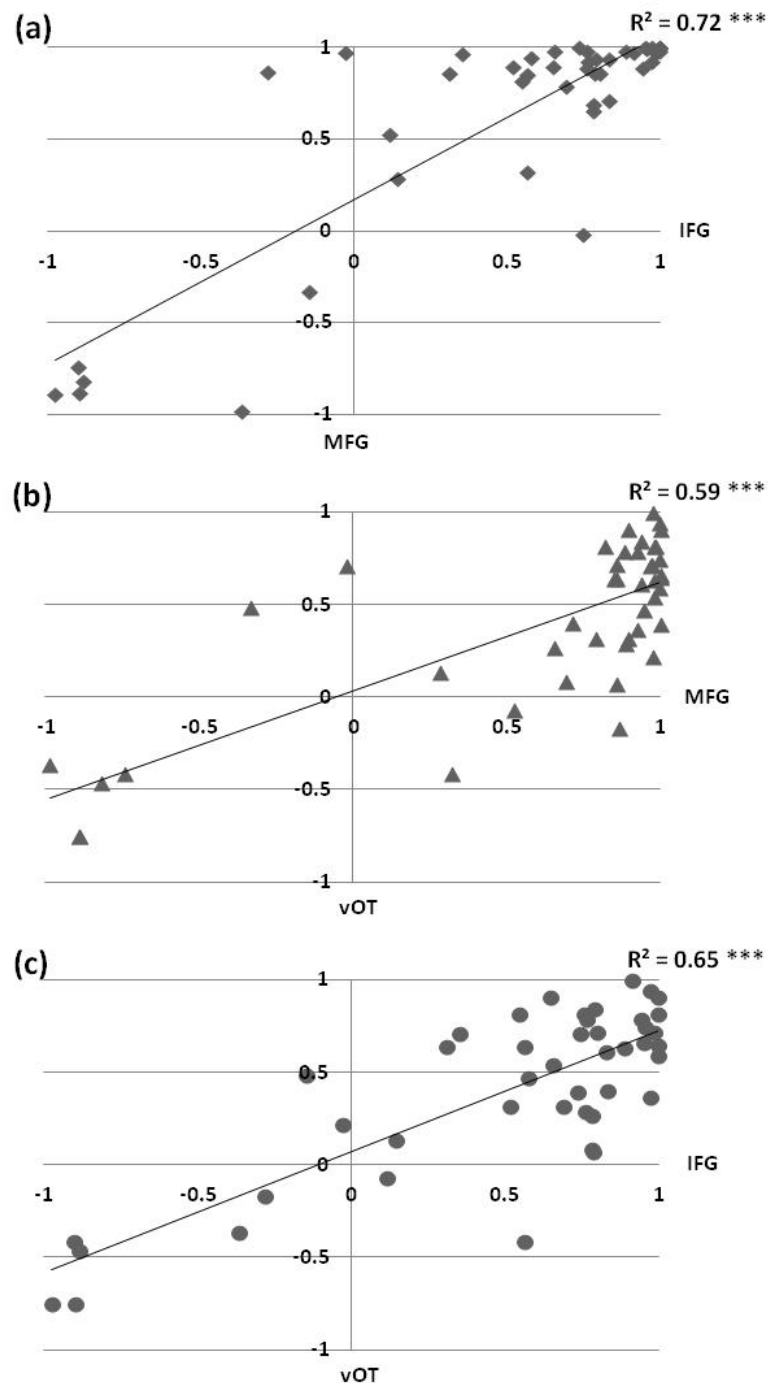


Figure 4-14. Correlations between the AveLLs of ROIs. (a) A positive correlation between IFG (x-axis) and MFG (y-axis), $r(42) = .85$, $p < .001$. (b) A positive correlation between MFG (x-axis) and vOT (y-axis), $r(42) = .77$, $p < .001$. (c) A positive correlation between IFG (x-axis) and vOT (y-axis), $r(42) = .81$, $p < .001$. IFG: inferior frontal gyrus; MFG: middle frontal gyrus; vOT: ventral occipito-temporal region.

Discussion

The current study investigated language dominance in both right-handed and left-handed Chinese speakers in three ROIs, including the inferior frontal gyrus, the middle frontal gyrus and the ventral occipito-temporal region. The results are summarized as follows. (a) Group activation: Both groups showed activation in the left inferior frontal gyrus and bilateral ventral occipito-temporal cortices, and the right-handed group also activated the bilateral middle frontal gyri. (b) Regional language dominance: Regional AveLIs revealed that left-hemisphere dominance was prominent in the majority of right-handed participants within all three regions, whereas for left-handers approximately 60% had left-hemisphere dominance, one fourth right-hemisphere dominance, and the rest bilateral dominance within the ROIs. Twenty right-handers (90.9%, all left-hemisphere dominance) and eighteen left-handers (81.8%; 13 left- and 5 right-hemisphere dominance) showed consistent lateralization to the same direction within all ROIs, whereas the other participants showed crossed lateralization among the ROIs. (c) Correlation between handedness and AveLIs: A positive correlation was observed between handedness and the AveLIs of all three regions. (d) Correlation between ROIs: The AveLIs of the inferior frontal gyrus, the middle frontal gyrus, and the ventral occipito-temporal region were found to be positively correlated with each other. These findings will be discussed in detail below.

Group Activation

The significant activation of the inferior frontal gyrus, the middle frontal gyrus and the ventral occipito-temporal cortex at the group level was consistent with our findings in Study 3a, suggesting the reliability of the homophone judgment task in activating these language-related regions. It also provided justification for using the homophone judgment task to examine lateralization in the three ROIs. The right-

handed group seemed to recruit a larger extent of activation as compared with the left-handed group, although direct comparisons only revealed greater activation in the left inferior frontal region and the left lateral parietal cortex for the right-handed group. Since one-sample t-tests reveal the regions that are commonly activated among the group, the greater activity for the right-handed group could be attributed to the more consistent lateralization patterns among the right-handed participants. By contrast, the less consistent lateralization patterns among the left-handed participants might be the reason for the smaller extent of group activation. Similarly, the average AveLI for each ROI showed that the AveLIs for the inferior frontal gyrus (0.76) and middle frontal gyrus (0.91) were strongly left-lateralized for the right-handers as compared to the left-handers (inferior frontal gyrus: 0.25, middle frontal gyrus: 0.34), whereas the AveLI for the ventral occipito-temporal region for both groups were less left-lateralized (right-handers: 0.56, left-handers: 0.24). This could also explain why the right-handed group had greater activation in the left inferior and middle frontal gyri as compared with the left-handed group.

Regional Language Dominance

Rather than focusing on language dominance in a single region or on global hemispheric dominance, the current study examined regional language dominance within a set of regions activated by the language task as well as the collateralization between these regions. As language processing is a complicated process that involves a network of regions, investigating language dominance within each region could prevent biased information based on a pre-defined region and could also account for spatial heterogeneity in language dominance. Indeed, although the majority of participants showed consistent lateralization among the regions selected in the current study, for the other participants (especially left-handers) the lateralization in one

region was not always indicative of the similar lateralization in another region during the same task conditions. This observation was consistent with findings of previous studies (Seghier et al., 2011; Tzourio-Mazoyer et al., 2004; Van der Haegen et al., 2011).

The incidence of typical and atypical language dominance varied between the groups as well as amongst the ROIs. In the inferior frontal gyrus, 95.5% of the right-handed participants showed left-hemisphere dominance, while 27.3% of the left-handed participants showed right-hemisphere dominance. This finding was quite consistent with Knecht, Dräger, et al.'s (2000), which found right-hemisphere dominance in 4-6% of the right-handers and 27% of the left-handers by using functional transcranial Doppler sonography. While many studies found a small portion (less than 7.5%) of right-handers showing atypical dominance (i.e., right-hemisphere) in the inferior frontal gyrus, no such case was observed in the current study. The absence of atypical dominance in right-handers and the differential distribution of lateralization in left-handers observed in the current study from that in other studies (e.g., Hund-Georgiadis et al., 2002; Pujol et al., 1999; Szaflarski et al., 2002) might be attributed to the limited number of participants (i.e., only 22 in each group), the different computation methods for laterality index, and (to a lesser extent) the different cutoff criteria for lateralization categorization.

For the middle frontal gyrus, the incidence of typical and atypical language dominance was similar to that for the inferior frontal gyrus. All right-handed participants had left-hemisphere dominance; for left-handed participants, 68.2% had left-hemisphere dominance and 27.3% had atypical dominance in the right hemisphere. This was a novel finding as no studies have examined the lateralization of the middle frontal gyrus in right-handed and left-handed Chinese speakers. The current study

showed high consistency in hemispheric dominance for both the inferior and middle frontal gyri. In Study 2 and Study 3a, the results consolidated the additional recruitment of the middle frontal gyrus (usually bilaterally) in Chinese character processing, and we proposed that it might be responsible for lexical and sublexical orthography-to-phonology transformation. It was postulated in Study 2a that the left middle frontal gyrus might be specialized for lexical orthography-to-phonology transformation, while the right counterpart might be related to sublexical orthography-to-phonology transformation. The current study did not directly examine the functional dissociation of the left and right middle frontal gyri. Nevertheless, the observation that some participants (especially left-handers) showed right-hemisphere dominance may suggest that the proposed functional dissociation for the left and right middle frontal gyri might not be definitive but rather determined by handedness. Future studies are necessary to directly investigate the functional roles of the middle frontal gyrus in individuals who show different patterns of dominance.

While a previous study revealed bilateral activity in the visual word form area (overlapped with the ventral occipito-temporal cortex) without a clear dominance in the left or right hemisphere in more than half of their left-handed participants (Van der Haegen et al., 2011), our data demonstrated left-hemisphere dominance in the ventral occipito-temporal ROI in 90.9% of the right-handers and 59.1% of the left-handers. Our results replicated the findings in previous studies on Chinese character processing in that bilateral recruitment of the ventral occipito-temporal regions was observed in the group activation. However, the assessment of lateralization at the individual level showed that the bilateral activity in the vOT was left-lateralized in a large portion of the participants, especially for right-handers. For the other participants, either symmetrical dominance or right-hemisphere dominance was observed. The results

thus suggest that Chinese character processing would recruit bilateral vOT for visual character recognition with a tendency toward left-hemisphere dominance for right-handers and a less predictable lateralization for left-handers.

The examination of the collateralization among all ROIs revealed that 20 right-handers (90.0%, all left-hemisphere dominance) and 18 left-handers (81.8%; 13 left- and 5 right-hemisphere dominance) showed consistent lateralization to the same direction, whereas the other participants showed crossed lateralization among the ROIs. Among the participants who had crossed lateralization, the left-handers seemed to have a more variable lateralization pattern than the right-handers. The high incidence of crossed lateralization indicated spatial heterogeneity in language dominance and highlighted the importance of examining regional language dominance, especially in left-handers.

Correlation between Handedness and AveLI

The positive correlation between the degree of handedness and the AveLIs of the inferior frontal gyrus, middle frontal gyrus, and ventral occipito-temporal region indicated that an individual's handedness might be indicative of the lateralization of language-related regions in the brain. This significant correlation replicated Knecht, Dräger, et al.'s (2000) findings, which demonstrated that the incidence of right-hemisphere dominance in the inferior frontal region increased with the degree of left-handedness. When the correlations were examined separately in each group, however, the significant correlation between handedness and the AveLIs disappeared. The increased incidence of right-hemisphere dominance in the left-handers might contribute to the significant correlation when both groups were examined together.

Correlation between ROIs

The positive correlation between the AveLIs of the inferior frontal gyrus and the middle frontal gyrus as well as the positive correlation between the inferior frontal gyrus and the ventral occipito-temporal region indicated that the lateralization of the inferior frontal gyrus might be indicative of the lateralization of the middle frontal gyrus and the ventral occipito-temporal region. When the correlations were examined separately in each group, significant correlations for the right-handers were observed between the AveLIs of the inferior frontal gyrus and the ventral occipito-temporal region as well as between the AveLIs of the middle frontal gyrus and the ventral occipito-temporal region, but not between the inferior frontal gyrus and the middle frontal gyrus. For the left-handers, significant correlations were found between any pair of regions. As the inferior frontal gyrus and the middle frontal gyrus ROIs are closely located, the strong collateralization between these two regions might increase the efficiency of their interaction to handle the rapid process of language production. The positive correlation between the lateralization of the inferior frontal gyrus and the ventral occipito-temporal region replicated the findings in Ven der Haegen's (2011) study. Furthermore, it was consistent with the findings in event-related potentials studies that demonstrated the posterior occipito-temporal areas involved in visual word processing were lateralized to the same hemisphere as the inferior frontal regions for language production (Cai, Lavidor, Brysbaert, Paulignan, & Nazir, 2007; Cai et al., 2010). The collateralization might be beneficial for efficient bottom-up and top-down processing during reading, from visual character form recognition to the access of phonological representations based on the given orthographic inputs. The degree of correlation between the lateralization of two regions may be reflected in the strength of direct or indirect connections between the regions, and the assessment of couplings

between two regions would require future studies by examining effective connectivity or structural connectivity.

In conclusion, we observed higher incidence of atypical language dominance and crossed lateralization among language-related regions in the left-handers. The examination of regional laterality indices also confirmed spatial heterogeneity in language dominance, especially for left-handers. In terms of the integrity of the specialized sub-network for Chinese character processing, it was shown that the lateralization of the inferior frontal gyrus was indicative of the lateralization of the middle frontal gyrus and the ventral occipito-temporal region, and the lateralization of the two regions within the sub-network was also correlated. These results have important implications for pre-surgical planning in native Chinese speakers, especially in left-handers. Examining regional laterality indices within the language network, particularly at the site of intended surgery, is recommended for the determination of language dominance. The current study also suggests that more empirical studies using the Wada (intracarotid amobarbital) Test (Wada, 1949) which has been considered as the clinical gold standard for examining language laterality may be necessary to examine language lateralization for patients who speak Chinese.

CHAPTER V: GENERAL DISCUSSION

Most of the existing models of language have been based on alphabetic languages, and thus the proposed universal language network seems to be biased toward alphabetic languages. However, the substantial discrepancies between the linguistic features of Chinese characters and alphabetic words have led cognitive neuroscientists to investigate whether these linguistic differences are represented by differential neural activity. Although previous literature has provided some supportive evidence of differential neural representations for Chinese character processing, most of them had a small number of participants (less than 20) and the functional roles of the differential representations still remain to be determined. The current thesis used fMRI to examine the neural substrates underlying Chinese character processing, with the aims to elucidate the functional roles and integrity of the language-related regions. The activation evoked by the Chinese language tasks were compared with the existing findings from studies investigating alphabetic language processing.

This thesis investigated the neural mechanisms underlying Chinese character processing through three lines of research. Study 1 helped set the stage for investigation by consolidating the existing findings from previous research; Study 2 aimed to elucidate the functional roles of the cortical regions involved in Chinese orthographic and phonological processing; Study 3 examined the integrity of the language network under the influence of age and handedness. This series of research provided direct and converging evidence with regard to the differential neural representations for Chinese character processing.

Summary of the Findings in Each Study

The investigations in this thesis began with a meta-analysis on the existing fMRI studies on Chinese character processing (Study 1). This study summarized the brain regions consistently involved in Chinese orthographic, phonological, and

semantic processing independently. While many of the regions overlapped with the universal language network that has been based on alphabetic languages, additional recruitment of the left middle frontal gyrus and the right ventral occipito-temporal cortices was identified and suggested that they might form a specialized sub-network for Chinese character processing. In addition, the convergent and divergent regions involved in orthographic, phonological, and semantic processing were identified. All three language-processing components showed convergent activation in the left middle frontal gyrus, left superior parietal lobule and left ventral occipito-temporal cortex. When compared with other components, phonological processing also involved the posterior dorsal part of the left inferior frontal gyrus, the left inferior parietal lobule and the left insula, and semantic processing recruited the anterior ventral part of the inferior frontal gyrus and the left middle temporal gyrus. Both phonological and semantic processing showed recruitment of the bilateral ventral occipito-temporal regions.

Next, two Chinese language tasks that utilized the unique characteristics of Chinese characters were applied to further elucidate the functional roles of the sub-network in orthographic and phonological processing. In Study 2a, the left-right composition properties of Chinese written characters were manipulated to form pseudo-characters and non-characters. By the design of a lexical decision/recognition task, we examined the neural mechanisms associated with lexicality effect and orthographic analysis. The ventral occipito-temporal cortex was suggested to be an interface integrating bottom-up visual sensory inputs and top-down phonological predictions. As compared with real characters, the non-character condition was found to show higher activation in the bilateral ventral occipito-temporal cortices because of higher prediction errors. Non-characters also recruited greater activation in the right

middle frontal gyrus, which might be attributed to sublexical orthography-to-phonology transformation for the phonetic components in non-characters. The comparison between the two types of instruction revealed a dual-stream network of visual spatial processing that might underlie orthographic analysis, which was thought to be required for lexical decision but not for lexical recognition. This network consisted of a ventral pathway from the occipital to the ventral occipito-temporal regions for identification of partial and global visual character forms and a dorsal pathway from the occipital to posterior parietal regions for spatial decoding of radical positions. The dual-stream network was observed in the right hemisphere in this study.

In Study 2b, the heterophonic homographic Chinese characters were utilized to manipulate the loads of orthography-to-phonology transformation and phonological retrieval during a homophone judgment task. Reading many-to-one character pairs was found to show greater activation in the bilateral middle frontal gyri, inferior frontal gyri and inferior parietal lobule as compared with reading one-to-one pairs. The increased activation in the left posterior middle frontal gyrus for many-to-one pairs was thought to reflect increased demands in orthography-to-phonology transformation, and the increased activation in the middle portion of the right middle frontal gyrus might be recruited due to increased demands in verbal working memory and attention. The bilateral inferior frontal gyri and inferior parietal lobule might reflect the increased demands in accessing and manipulating the phonological representations retrieved from the phonological storage for reading many-to-one pairs.

While Study 2 directly investigated the involvement of the specialized network in Chinese character processing, Study 3 examined how it might be influenced by individual characteristics such as age and handedness. Study 3a focused on age-related changes in the neural representations underlying word retrieval. A semantic fluency

task was applied to indirectly examine the word retrieval process invoked during word generation, and a homophone judgment task was implemented to directly investigate phonological retrieval. Generally consistent findings with previous studies were observed, showing increased activation in the right inferior frontal gyrus for the semantic fluency task and in the bilateral insulae for the homophone judgment task, both accompanied by reduced deactivation in the default mode network regions as age advanced. The age-related decreases in deactivation of the default mode network might be associated with reduction in inhibitory processes or poorer allocation of attention that could impair older adults' performance. Thus, it was thought that more activation in the bilateral frontal regions were recruited to compensate for the reduced efficiency of the frontal language-related regions and/or for the impairment in performance caused by reduced DMN deactivation. However, the hypothesis for successful compensation was not fully supported in this study and future investigations are required to verify the mechanism. While this study suggests that age effects on the neural mechanisms underlying word retrieval is generally a universal phenomenon, age-related changes were also observed in the sub-network using an ROI approach. For the older adults, increased activation was found in the right middle frontal gyrus for both tasks and in the right ventral occipito-temporal cortex for the semantic fluency task. As these age-related increases in the right hemisphere were negatively correlated with behavioral performance, it might suggest a dedifferentiation process of aging in the sub-network that deteriorates performance.

Study 3b explored regional language dominance within the specialized network for Chinese character processing (the middle frontal gyrus and ventral occipito-temporal cortex) and the universal language-related area, Broca's area (in the inferior frontal gyrus ROI), with respect to handedness. The results showed predominant left-

hemisphere dominance for all regions-of-interest in the majority of right-handed participants but a relatively varied lateralization pattern for the left-handers. Handedness was indicative of the lateralization of the inferior frontal gyrus and the middle frontal gyrus, and correlated to a less extent with the lateralization of the ventral occipito-temporal cortex. The lateralization of all three regions was indicative of the lateralization of one another. More importantly, although many participants showed a consistent lateralization among different language-related regions, we observed spatial heterogeneity in language dominance among the regions and this variance was greater in left-handers. The study revealed a consistent lateralization pattern in the inferior frontal gyrus as observed in studies on alphabetic language speakers, and moreover shed light on language dominance in the specialized network for Chinese character processing.

The Involvement and Integrity of the Sub-Network

The meta-analysis in Study 1 provided a general understanding of which cortical regions were involved in Chinese orthographic, phonological, and semantic processing as revealed in the existing research. Compared with the language networks proposed in other review papers or meta-analyses on alphabetic languages, the findings in the meta-analysis consolidated the additional recruitment of the left middle frontal gyrus and the right ventral occipito-temporal cortex, and both regions were proposed to constitute a sub-network that might be specialized for Chinese character processing.

Next, the involvement of this sub-network particularly in Chinese orthographic and phonological processing was directly investigated, with the aim to elucidate the functional roles of these regions in language processing. In particular, we examined how task manipulation would influence the activation in the ventral occipito-temporal

cortex and the middle frontal gyrus in orthographic processing and phonological processing, respectively. The activation in the bilateral ventral occipito-temporal cortices was found consistently in our language tasks that required visuo-orthographic processing of characters, such as lexical decision/recognition and homophone judgment tasks, but no significant activation was found in the semantic fluency task that did not require intensive visuo-orthographic processing. The bilateral recruitment is consistent with previous findings on Chinese character processing (e.g., Bolger et al., 2005; Tan, Laird, et al., 2005) and different from the left-dominant activation for alphabetic word reading (e.g., Cohen et al., 2000; Cohen et al., 2002; Jobard et al., 2003). Through the manipulation of lexicality as well as task requirement in the lexical decision and lexical recognition tasks, from the findings we conclude that the bilateral ventral occipito-temporal cortices are involved in visual character form recognition. The amount of activation in the ventral occipito-temporal cortex may be influenced by the integration of bottom-up visual sensory inputs and top-down phonological predictions. For example, higher activation would be expected for character-like stimuli that do not have a matched mental lexicon (e.g., pseudo-characters and non-characters) as the automatic phonological predictions do not match with the written orthographies. Higher activation would also be expected if increased orthographic analysis on the visual inputs is required, such as during the lexical decision task as compared with the lexical recognition task. Moreover, according to the hemispheric specialization for local/global visuospatial processing based on observations in patients with brain damage (Delis, Robertson, & Efron, 1986; Robertson & Lamb, 1991; Robertson, Lamb, & Knight, 1988) as well as in healthy individuals (Christie et al., 2012; Martinez et al., 1997), there may be a hemispheric specialization in the functional roles of the left and right ventral occipito-temporal cortices. It is suggested

that the left ventral occipito-temporal cortex is responsible for recognition of local visual character forms (i.e., radicals) and the right counterpart is sensitive to radical arrangement in recognition of the global visual character forms. However, the current studies did not directly manipulate local and global visual form recognition, so the hemispheric specialization needs to be verified in future studies.

As for the middle frontal gyrus, it was found to be involved to a greater extent in homophone judgment on many-to-one character pairs during phonological processing. In light of the role of the middle frontal gyrus in coordinating, integrating, and monitoring information within the central executive system in working memory, it is thought that this region might be responsible for coordinating orthographic information with phonological and/or semantic representations during Chinese lexical processing. This inference agrees with its role in orthography-to-phonology and orthography-to-semantics transformation as suggested by previous studies (Siok et al., 2008; Siok et al., 2004; Tan, Laird, et al., 2005). On the other hand, the middle frontal gyrus did not show significant effect by the manipulation of orthographic analysis, so visuospatial analysis of Character forms might not be the essential role of this region.

To understand the integrity of the sub-network, we examined whether age and handedness had similar effects on the sub-network as on other universal language-related regions such as the inferior frontal gyrus. For age effects on word retrieval, while age-related changes were found in the inferior frontal regions and the default mode network regions as shown in previous studies on alphabetic language speakers, subtle changes were also observed in the sub-network. Our findings suggest that although age effect on the neuroanatomical mechanisms underlying language processing is generally a universal phenomenon, aging also has differential effects on language-specific regions that are tuned by language experience. Finally, for the effect

of handedness on language hemispheric dominance, while the right-handers generally showed left-hemisphere dominance among the language-related regions, a less consistent lateralization correspondence was observed in the left-handers. The spatial heterogeneity in language dominance highlights the importance of taking into account hemispheric dominance of the sub-network in Chinese speakers, especially in left-handers.

Overall, the direct evidence from Study 1 and Study 2 confirmed the additional involvement of the sub-network in Chinese character processing as compared with the universal language network that has been based on alphabetic languages. The converging evidence in Study 3 has shown that the functional roles of the sub-network could be affected by aging and that language dominance within this sub-network has higher heterogeneity in left-handed Chinese speakers.

While the left middle frontal gyrus and the right ventral occipito-temporal cortex are proposed to form a sub-network that might be specialized for Chinese character processing, how these two regions communicate with each other and with other language-related regions in the brain is not clear. To the best of our knowledge, no studies have focused on mapping structural connectivity between the left middle frontal gyrus and the right ventral occipito-temporal cortex and how the white matter tracts contribute to language processing in Chinese. Nevertheless, these regions, together with other regions, form a network supporting Chinese character processing, and thus they might communicate to each other via direct or indirect connections through some of the major white matter tracts. For instance, if we look at the left hemisphere only, the white matter tract that is most proximal to and likely to connect the left middle frontal gyrus and the left ventral occipito-temporal cortex may be the inferior fronto-occipital fasciculus (IFOF), which has been shown to connect the

ventral occipital lobe and the inferior frontal gyrus and is possible to be involved in reading (Catani & Thiebaut de Schotten, 2008; Vandermosten, Boets, Poelmans, et al., 2012; Vandermosten, Boets, Wouters, & Ghesquière, 2012). The left ventral occipito-temporal cortex might communicate with the left middle frontal gyrus by sending signal through the IFOF to the inferior frontal gyrus, which might then be connected to the middle frontal gyrus via small tracts in the frontal lobe. Another possible connection between the left middle frontal gyrus and the left ventral occipito-temporal cortex is through the superior longitudinal fasciculus (SLF) and the vertical occipital fasciculus (VOF). The SLF connects the inferior parietal cortex and the dorsolateral prefrontal cortex (Catani & Thiebaut de Schotten, 2008; Makris et al., 2005), and the VOF seems to connect the ventral occipito-temporal cortex and the lateral occipital parietal junction (Yeatman, Rauschecker, & Wandell, 2013). The ventral occipito-temporal cortex might connect to the middle frontal gyrus via indirect connections through VOF to the lateral parietal lobe first and then through SLF to the dorsolateral prefrontal cortex. Inter-hemispheric communications may be achieved via white matter tracts that cross over both hemispheres, such as the occipital callosal projections (Ben-Shachar, Dougherty, & Wandell, 2007; Damasio & Damasio, 1983; Dejerine, 1892; Geschwind, 1965; Molko et al., 2002). Whether the projections of the abovementioned white matter tracts cover the middle frontal gyrus and the ventral occipito-temporal cortex specified in our sub-network needs to be verified in future studies, such as using diffusion MRI and fiber tracking techniques. Comparing the white matter tracts involved in the language network for Chinese speakers and alphabetic language speakers would also shed light on how differential language experience shapes the neuroanatomical architecture. Furthermore, effective

connectivity analysis could also be used to examine how tasks modulate the couplings between regions in the language network.

Limitations and Future Directions

Some limitations regarding research methodologies specific to each study have been mentioned in the previous three chapters. Here the discussions will be focused on the issues that this thesis has yet to address and thus require future investigations.

First of all, the role of the middle frontal gyrus in orthography-to-semantics transformation was not examined. In Study 1, the convergent activation across orthographic, phonological, and semantic processing in the left middle frontal gyrus suggests that it might be coordinating orthographic information with phonological and semantic information. In Study 2b, a paradigm with load manipulation of orthography-to-phonology transformation was used to directly examine the involvement of the middle frontal gyrus in phonological processing. However, we did not examine the role of the middle frontal gyrus in terms of orthography-to-semantics transformation. A paradigm with load manipulation of orthography-to-semantics transformation could be used in future studies to examine the involvement of the middle frontal gyrus. Moreover, if a comparable paradigm is established, comparisons between the two tasks could then elucidate whether there is functional dissociation for orthography-to-phonology and orthography-to-semantics transformation within the middle frontal gyrus.

Second, future studies to investigate both character language processing and alphabetic language processing (e.g., Chinese and English) simultaneously in the same study would make direct comparisons between the two languages more legitimate and reliable. As the current investigations focused mainly on Chinese character processing aiming to provide deeper understanding of the neural language networks, we did not

study alphabetic language processing empirically but compared the results with findings from other review papers, meta-analyses, and empirical studies on alphabetic language processing. There are limitations in such cross-study comparisons, such as lack of control in scanning environment, imaging parameters, subject characteristics, comparability of fMRI tasks, analysis methods, etc. However, based on the approaches established in the current investigations, future studies could be extended to include alphabetic language tasks that are comparable to the tasks implemented in the current studies, and then direct comparisons between two language processing would be possible.

Third, while the current thesis focuses on whether Chinese character processing recruits differential task-positive neuroanatomical representations as compared with alphabetic language processing, it is important to take into account how the task-induced deactivation (i.e., the DMN) might be associated with Chinese and alphabetic language processing differentially. As it has been shown that the DMN regions are differentially sensitive to different types of language processing (e.g., semantic matching, naming) (Seghier & Price, 2012), it is an intriguing question whether the DMN regions exhibit differential patterns in Chinese and alphabetic language processing. Understanding task-negative networks during processing of different languages will help to elucidate how underlying neural mechanisms might be shaped by language experience differentially and whether the differences are limited to task-positive (i.e., language-related) networks. However, the majority of the existing studies that investigated linguistic differences in the neuroanatomical networks have focused on task-positive or task-induced activity in language tasks. Although a few studies also examined the interaction between task-positive and task-negative networks in language processing, these studies focused on alphabetic language

processing (Koyama et al., 2010; Meinzer, Seeds, et al., 2012; Seghier & Price, 2012).

Hence, more studies are required to examine the DMN in Chinese language processing.

Fourth, the regions within the network underlying Chinese character processing have been identified, but the connections between the regions and how they work together to accomplish character processing remain unclear in the current studies. Diffusion MRI and fiber tracking techniques can help unravel the structural connectivity between regions in the language network, especially how the middle frontal gyrus and the ventral occipito-temporal cortex within the sub-network communicate with each other. Effective connectivity analysis by techniques such as Dynamic Causal Modeling (DCM) can be used to investigate the influence of one region on the other within a pre-defined network based on fMRI data, and thus it can reveal causal relationships between regions (i.e., the direction of influence). It can also test how external task conditions modulate the activation of a certain region or the connections between two regions. It would be essential to study effective connectivity within the Chinese language network in future studies because it would shed light on how the specialized sub-network for Chinese character processing is integrated and how it interacts with other universal language regions.

Fifth, fMRI suggests associations between the activation in a region and a cognitive process, but it does not imply the definite causal relationship between the activation and the cognitive process, nor does it confirm that the activation is necessary for the cognitive process (Matthews et al., 2003). Transcranial magnetic stimulation (TMS) can be used as a complementary tool to transiently and reversibly interrupt the neural activity in a specific region for characterization of behavioral effects. Future studies can employ TMS to verify the functional roles of specific

regions suggested by fMRI. For example, with an elaborated experimental design, TMS can be applied to transiently interrupt the activity in the left middle frontal gyrus to verify whether it would interfere with orthography-to-phonology transformation during phonological processing as manifested by slowed reaction time and/or decreased accuracy rate.

Finally, while Study 3a provided novel insight to age-related changes in the neural network underlying Chinese character processing, the interpretation of the findings may be limited by the cross-sectional design. As participants with a wide age range were recruited, the observed variation in brain activation across the participants could simply be attributed to individual differences, which were contributed by several characteristics in addition to age. Despite trying to control for several factors in Study 3a (i.e., gray matter volume, behavioral performance, and education level), we must admit that it is barely possible to consider all potential factors that might contribute to individual differences in one study. With this inevitable limitation of the cross-sectional design, we would not be able to completely distinguish the changes in brain activation that were caused by the effect of aging from those arising from other individual differences. This limitation could be better overcome by a longitudinal design, in which the same group of participants are followed up for several years at a pre-defined interval and neural responses to language processing as well as behavioral measures are acquired at each time point. The structural and functional changes in the brain could be examined along the course of aging while individual differences across groups could be controlled. Although a longitudinal study could take several years, it provides more direct evidence as to how the neural networks change during aging. Therefore, the age-related changes found in Study 3a as well as in other cross-sectional studies need to be verified by longitudinal studies in the future.

The studies listed above may not cover all future directions, but they provide interesting possibilities for future investigations. For example, not many studies have been conducted to examine effective connectivity in the Chinese language network or to use TMS to characterize the neural activity observed during Chinese character processing. However, both techniques can provide very essential information in establishing the neural networks underlying Chinese character processing.

Conclusions

The current fMRI investigations consolidated the additional recruitment of the left middle frontal gyrus and the right ventral occipito-temporal cortex for Chinese character processing, which might form a specialized sub-network. The functional roles of the sub-network were directly examined in the processes of character identification and homophone judgment. The integrity of the sub-network was investigated in terms of age-related effects on its activity and handedness effect on hemispheric dominance. The last set of studies provided novel insights into age-related functional changes in older adults and hemispheric dominance in left-handers during Chinese character processing because no studies have investigated these issues on native Chinese speakers.

Identifying the differential recruitment for Chinese character processing provides very important implications for pre-surgical planning in native Chinese speakers. These differential regions suggest that neurosurgeons should not fully generalize the existing models of language based on alphabetic languages to the Chinese speaking population. Rather, as brain organizations are shaped by linguistic features and language environment, the differences in language systems must be taken into account. Furthermore, understanding the neural mechanism underlying Chinese character processing in the normal population also helps us to establish models for

intervention in language disorders, such as dyslexia in reading characters. More investigations integrating fMRI with other techniques such as DCM, Diffusion MRI, and TMS would be a great asset in the establishment of the Chinese language network.

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