Fine motor control in using pen for writing and copying: in the impaired and healthy brain

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Abstract

The central issue of the dissertation is to investigate the neural-cognitive basis of writing and copying figures focusing on fine motor abilities. The neuronal recycling hypothesis is used as the theoretical framework, assuming that the ability to use pen emerged from other closely related cognitive abilities. The thesis contained four independent studies with either ischemic stroke patients or healthy participants. Chapter 2 describe the general methods used in our study. Chapter 3 is a neuropsychological study that utilizes principle component analysis and voxel-based morphometry. It explores the neural-cognitive basis underlying complex figure copying (CFC). It demonstrates the involvement of different processing stages that supports figure copying along the dorsal pathway, from visual through eye-hand coordination to the motor associative cortex. Chapters 4-6 focus on writing abilities, across two different systems: phonological and logographic. Chapter 4, is a neuropsychological study that utilized machine learning to explore the latent relationship between writing with other cognitive tasks in English and Chinese. Across the two-writing systems impairment in writing skills could be reliably classified using the same features. These cognitive features were related to CFC, attention, reading, memory and age. Chapter 5 presents two neuropsychological studies that examine the neuro-cognitive makeup of the ability to write words (phonological) and numbers (logographic). The first study is a detail comorbidity analysis of writing deficits of words, numbers, language and motor deficits. It demonstrates

that pure writing deficits are very rare, with the majority of writing deficits overlapping with motor (CFC) or language impairments. The second study in this chapter is a VBM study focus on writing numbers and words. We identified two dissociable networks that have been specifically evolved to support writing: a visual-manual motor ability to use pen mediated by right angular and middle frontal gyri; and an ability to transform symbolic representations grapheme to manual programs for use with the pen. Chapter 6 is an fMRI study with healthy participants investigating the neural substrates associated with writing English, Chinese and Pinyin. The study identifies different brain networks that support writing abilities across writing systems: visual information perception and visual motor transformation, semantic component. Chapter 7, summarize and compare the main finding of the four studies. Overall, the studies demonstrate the close relations between the sue of pen and other more basic cognitive functions, such as control of hand movement, language, attention. As predicted by the neuronal recycling hypothesis there were minimal pure deficits of writing or copying; and for proficient writers, the same neural structures supported different writing systems.

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Table of Contents

List of Illustrations

List of Tables

List of supplementary tables and figures in Appendix

Chapter 1

Introduction

The presentation of writing and copying figure have epoch-making significance in human history. These activities changed our way of transforming information, using visual marks as a mean of communicating ideas that overcome the boundaries of time and space. One other landmark skill of human culture is the ability to make and use tools, which can date back millions of years in our family tree. Pen, as a tool of writing and drawing, is a testimony of the human culture.

Human's history of using pen dates back to 5000 years ago. Steven Roger Fischer in his books 'History of Writing' suggests that the first kind of reed pen has been used for writing on parchment as long ago as the First Dynasty or about 3000 BC (Fischer, 2001). While in the eastern Asian, Chinese Brush was invented in around 2000 BC. In contrast to spoken language or other activities, using pen in writing or copying figures is a relatively recent addition to the human behavior repertoire. It is not an essential ability for human basic survival needs. Therefore, it is not commonly used or practiced by all human cultures (Dehaene & Cohen, 2007). As these activities are far too recent to have exerted any evolutionary pressure on brain evolution, it is unlikely that there were evolutionary dedicated brain regions specific to these activities (Dehaene,

2004). How the human brain evolved to adapt these abilities is still debated.

1.1 neuronal recycling hypothesis

Neuronal recycling hypothesis is often referred to as cultural recycling hypothesis to differentiate it from the evolutionary neural repurposing hypothesis (Parkinson & Wheatley, 2015).

Recent neuroimaging and neuropsychological studies suggest that the adult human brain houses dedicated neural structures that support ‘recent’ activities like reading and arithmetic (Dehaene, 2004). As these activities are not practiced by all humans and require learning, it is unlikely that the brain has evolved to accommodate these processing within universal neuro-anatomical foci. Dehaene (2009) suggest instead that the universal cortical specialized areas emerge through learning and practice to accommodate the acquisition of a new skill. The anatomical location of these regions is constrained by the functional architecture of the brain and therefore develops within the same anatomical foci across adults. The theory claimed that recent cognitive activities occupy neural basics initially devoted to different, but similar or related functions. (Dehaene, 2009).

The concept of neuronal recycling assumes that cognitive processes of recent skills recycle the ancient biological mechanisms that occur as a result of brain plasticity (Dehaene & Cohen, 2007). The neuronal recycling explained the acquired of abilities process takes place at a shorter time scale of weeks,

months or years, through epigenetic mechanisms that do not require any change in the genome (Dehaene, 2004). This takes much less time compare to evolution (Dehaene, Stanislas, Hauser, Duhamel, & Rizzolatti, 2005).

Dehaene and colleague's hypothesis is based on the following assumptions: 1. Brain structures' adaption to new cognitive abilities is restrained by its evolved function. 2. To develop skills like writing, original brain regions contributing to similar functions should be plastic enough to adapt to enable the accommodation of the new skills. 3. what can be learned is strongly influenced by the original organization of the cerebral cortex (Dehaene, Stanislas et al., 2005). Based on these assumptions, Dehaene and his colleagues predicted the following: i) Human's cognitive abilities should be associated with specific cortical areas; ii) Neural constraints restrain the acquisition of cognitive processes; iii) Cultural variability (such as different writing system) should be limited causing strong cross-cultural invariants (Changizi & Shimojo, 2005; Changizi, Zhang, Ye, & Shimojo, 2006; Dehaene, Stanislas et al., 2005).

Support for this hypothesis has been demonstrated in the visual associative cortices for reading. Similar to writing and copying figures, reading has a relatively short history of around 5400 years. Therefore many scholars conclude that the presence of reading is too modern to be a result of evolution (Dehaene, Stanislas et al., 2005; Dehaene, 2009; Szwed, Cohen, Qiao, & Dehaene, 2009). Previous studies consistently reported among a wider reading

network, a brain region in the left ventral visual stream consistently associated with reading (Bolger, Perfetti, & Schneider, 2005; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Petersen, Fox, Posner, Mintun, & Raichle, 1988). This region, termed the visual word form area (VWFA), is considered to comprise reproducible and specific neural mechanisms for recognizing written characters (Cohen et al., 2000). It shows higher activations to strings of letters relative than rest or to low-level stimuli (L. Cohen et al., 2000; Laurent Cohen et al., 2002; Jobard et al., 2003). Other studies showed within ventral occipital-temporal associated cortices preferential activation was recorded for faces, houses (Ben-Shachar, Dougherty, Deutsch, & Wandell, 2007; Ferber, Mraz, Baker, & Graham, 2007; Hasson, Levy, Behrmann, Hendler, & Malach, 2002; Puce, Allison, Asgari, Gore, & McCarthy, 1996). The VWFA is assumed to specialize in perceiving and reading visual symbols, independent of the writing systems (Dehaene and Cohen, 2007). Therefore, the neuronal recycling hypothesis proposed that the visual word recognition is a result of recycling cortical structures whose initial functions were for object recognition.

The major criticism of the neuronal recycling hypothesis concerns the existence of the visual word form area (Price & Devlin, 2003). To recap, neuronal recycling hypothesis postulate that the emergent of regions specialized for a newly acquired ability (e.g. word form area for reading) is constrained by the similarities to core processes (in the case of reading, processing fine detail of complex visual stimuli). In contrast Price and

colleagues (Price & Devlin, 2003), argue that newly acquired abilities do not lead to the emergent of specialized regions, and reading is accomplished by existing available processes (i.e. analyzing of complex visual stimuli). Similarly, Anderson (Anderson, 2010), propose that newly acquired function re-use rather than re-cycle existing brain circuit.

Taken the metaphor used in each hypothesis to indicate meaning, the neuronal re-cycling hypothesis argues that neurons will change their structure to adapt to a new function, while the neural re-use hypothesis argues that the structure will remain but new connections will allow support of new ability.

One way to understand the differences between these two hypotheses is suggested by Vogel and colleagues (Vogel, Petersen, & Schlaggar, 2014). Neuronal recycling hypothesis argues that the brain is organized based on the type of input stimuli (e.g. words or faces); while Price and Vogel argue that the brain is organized based on the type of processing applied for each stimulus (e.g. fine details for words as opposed to holistic configural processes for faces). The challenge is that often different stimuli are naturally associated with different processing types, which make it difficult to distinguish between the two hypotheses. It is also unclear whether a change (or what extent of a change) of neural connections due to plasticity, should be consider as a structural change (re-cycling) or structural preservation (re-using). Finally in the context of an experiment, conclusion of ‘specificity’ can only be made in the relation to the tested comparisons (Pernet, Schyns, & Demonet, 2007).

The current thesis concerned with identifying the cognitive-neural correlates of writing and its relations to other tasks. The neuronal recycling hypothesis is used as a framework, rather than as an overall hypothesis to be tested. The thesis specifically examined two predictions explicitly made by the neuronal recycling hypothesis (the re-use hypothesis is silent on these issues): 1) the cultural invariant predictions; 2) the relations between underlying 'core' cognitive processes and recently acquired abilities. Both of these predictions can be accommodated with the neural re-use hypothesis, or the process-based understanding of the brain.

Most of the work, supporting the neuronal recycling hypothesis has been carried out with functional MRI focusing on reading, where perception and recognition of symbols are required. Here we assumed that similar to VWFA in reading, we should able to observe overlap in the motor-related neural substrates of writing and copying figures. Like reading, we expect limited cultural variability across different writing systems.

1.2 Cognitive model of copying figure

Human beings use various drawing instruments to leave marks on paper or other two-dimensional mediums. Here we restrained our study on copying figure with the figure left in front of them. Figure copying, involving stimuli as the Rey-Osterrieth Figure (Rey, 1941), is a widely used clinical test to detect various kinds of cognitive abilities.

Copying figures need a series of evolved basic cognitive activities (Grossi, Angelini, Pecchinenda, & Pizzamiglio, 1993; Roncato, Sartori, Masterson, & Rumiati, 1987; Senese, De Lucia, & Conson, 2015). A model proposed by Angelini and Grossi (Angelini & Grossi, 1993) suggested that there are four steps to complete a figure copying task. First the single elements of the figure and their mutual spatial relations are identified based on a visual analysis; In the next step, a drawing plan was built up by defining procedural strategies to copy the figure; In a third step, participants would translate the constructional plan to specific graphomotor actions sequences (execution) using pen; In the fourth step, the executive processes of drawing would be continuously monitored by comparing the reproduced figure with the original one (control process) (Angelini & Grossi, 1993; Senese et al., 2015).

Poor performance in copying figures may reflect a number of different impaired cognitive functions including visual information perception, visuo-constructional ability, visual memory, executive functions (Shin, Park, Park, Seol, & Kwon, 2006; Watanabe et al., 2005) and processes associated with eye-hand coordination (Tchalenko & Chris Miall, 2009), planning and comparing (Grossi et al., 1993; Senese et al., 2015).

1.3 Cognitive model of writing

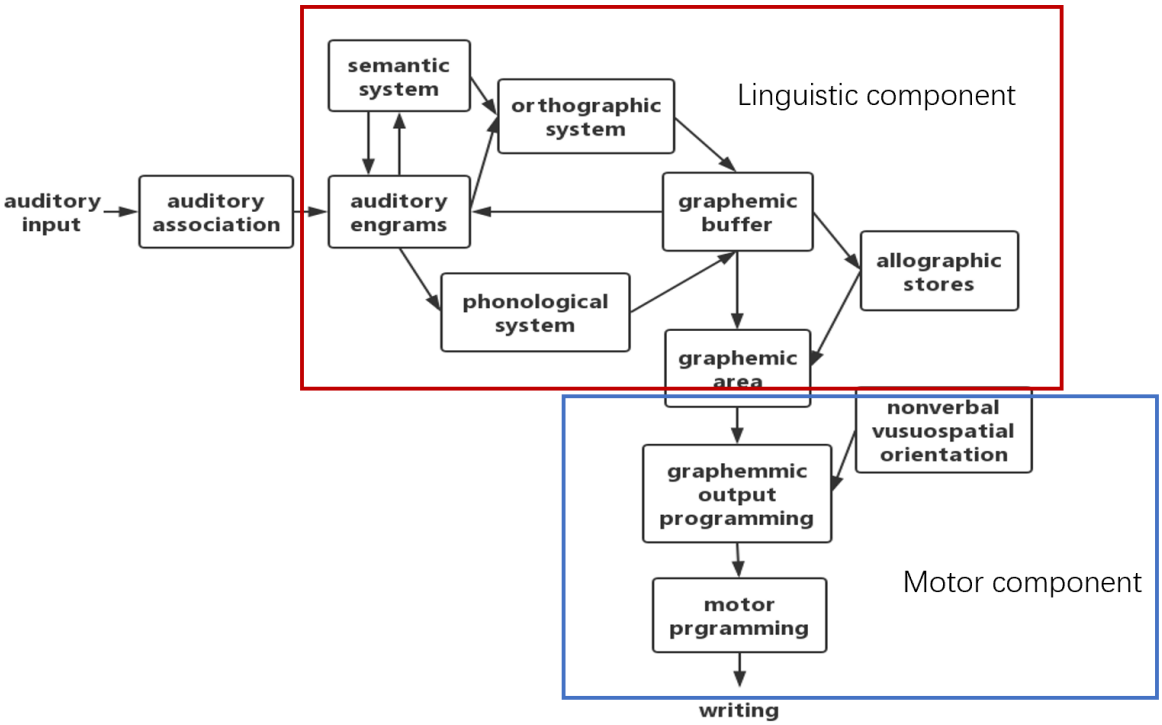
Writing may broadly refer to all the activities involved in hand writing, printing, cursive writing, and typing, that are in responding to various kinds of

input including visual, auditory, and one's own verbal and nonverbal thoughts. In our study, we explored writing processes in a narrow sense, focusing on the handwriting using a pen for single words or numbers in response to an oral cue, a dictation.

Writing involves multifaceted cognitive processes including but not limited, to linguistic related processes including assignment of meaning to visual-symbolic representations, and high-level motor control including eye-hand coordination. Goldstein (Goldstein, 1948) proposed one of the first models for writing which is still accepted today. It suggests that two cognitive components including linguistic and motor components contribute to handwriting (D P Roeltgen & Heilman, 1984; David P. Roeltgen & Lacey, 2013; David P Roeltgen & Heilman, 1985) (Figure 1). There are simplified two ways of transforming the auditory information to motor output (writing), sound-letter conversion (phonological system) and the visual word images (lexical system), and the latter one is influenced by the semantics factor. (D P Roeltgen & Heilman, 1984; David P. Roeltgen & Lacey, 2013) Patients having deficits in either motor or linguistic components may show impairment in writing diagnosed as agraphia. Due to the error type, agraphia may divide into peripheral and central agraphia separately. Peripheral agraphia typically shows errors related to poor motor or visualization abilities (Magrassi et al., 2010; Sinanovic et al., 2011). And central agraphia suffers problems in linguistic components including phonological agraphia, lexical agraphia, and semantic agraphia.

Other researchers have claimed some similar writing model. Such as Ardila (2004) proposed that writing is based on different basic cognitive abilities. Impairment in linguistic, motor and spatial might cause agraphia (Alfrede Ardila, 2004). He suggested the following intact knowledge were needed in writing including a knowledge of the language codes (phonemes, words), an ability to convert language sounds in graphemes, a knowledge of the graphemic system (alphabet) (linguistic component in Roeltgen's model), an ability to perform fine movements, and an appropriate use of the space for distributing, joining and separating letters (motor component in Roeltgen's model) (Alfrede Ardila, 2004). And he argued that since writing relies on some basic abilities that existed long before writing was invented, there is no brain area specialized for writing (Alfrede Ardila, 2004).

Figure 1 Cognitive model of writing (adopted from David P. Roeltgen & Lacey, 2013)



There are also some computational models emphasizing the distributed network that underpins writing. Most of them adopt the generic cognitive architecture of writing, though they mostly focus on theoretical sub-component of it. For example, a computational model is proposed to explained cursive hand writing (Schomaker, Lambert RB Thomassen & Teulings, 1989). The module goes into details of generating the motor output, starting by planning steps that includes retrial of graphemes, then allographs and connector codes, transforming these to stroke parameters and executing the actions by moving the pen. Then a feedback is initiated by comparing the output to the retrieved symbolic letter description.

1.4 Neural correlates of copying figure

Most of the studies showed that multi-brain regions contribute to figure copying. Function-lesion mapping studies indicate that both left and right hemisphere lesions contribute to deficits in copying complex figures (Guérin, Ska, and Belleville, 1999). For example, consider the postmortem structure-function study of Nielson and colleagues (Nielson, Cummings, and Cotman, 1996), who examined the association of each lobe (occipital, parietal, frontal and temporal) with figure copying in Alzheimer patients. Neural degeneration in the bilateral occipital lobe, best predicted CFC performance. Similarly, in studies using PET with Alzheimer patients (Melrose et al., 2013), deficits in performance in CFC tasks were associated with decreased metabolism in bilateral occipital cortices, plus also bilateral temporal–parietal regions and the right frontal lobe.

More recent studies have attempted to identify the roles of specific brain areas in drawing complex figures (Biesbroek et al., 2014; Chechlacz et al., 2014; Possin, Laluz, Alcantar, Miller, & Kramer, 2011). Focusing on the right hemisphere, Possin and colleagues (Possin et al., 2011) tested the neural degeneration that correlated with the ability to copy a figure in frontal-temporal dementia (FTD) as well as patients with Alzheimer's disease. Cortical degeneration was assessed in different lobes. They reported that right parietal damage predicted CFC performance in Alzheimer patients and the extent of damage to right middle frontal gyrus (MFG) predicted CFC performance of FTD

patients. Using additional tasks, the authors dissociated the functional role of the parietal and MFG. Specifically, they suggested that poor visuo-spatial perception is associated with degeneration in the right parietal cortex. In contrast atrophy to the right MFG correlated with deficits in spatial planning and visual working memory. However, as this study focused on pre-determined region of interests in the right hemisphere, it is difficult to infer the contribution of other regions to CFC.

A different approach to isolate unique cognitive processes underlying CFC was used by Biesbroek and colleagues (Biesbroek et al., 2014). The authors compared lesion associated with impairment in CFC to those associated with impairment in the judgment of line orientation (Benton, Varney, and Hamsher, 1978). The sample included stroke patients who during the test showed no signs of hemianopia, visual neglect and hemiparesis for the dominant hand. Lesions were manually delineated from different types of imaging (CT, MRI) and different types of sequences (MR-T1, MR-flair). Only lesions to the right hemisphere showed reliable associations with both tasks. Specifically, lesions to a large frontal-inferior parietal network extending to superior temporal lobe were correlated with impairment in both tasks. The involvement of these regions potentially reflects visual processing and selective attention. Lesions in the right superior parietal lobe, angular gyrus and middle occipital gyrus were associated reliably with poor performance on the Rey-Osterreich complex figure copy test (ROFC) and not on the orientation task (Biesbroek et al., 2014). However,

performances on the two tasks were not directly contrasted, which precluded direct inference on function-lesion dissociations. Using similar function-lesion mapping method Tranel and colleagues (Tranel, Rudrauf, Vianna, & Damasio, 2008) tested the neuroanatomical correlate of the Clock Drawing Test (CDT) with focal brain damage. The authors delineated lesion affecting two types of visual-spatial errors: lesions in right parietal cortices (supramarginal gyrus) were associated with increase in shape errors (impaired spatial organization, usually together with impaired number placement and/or omission of numbers, usually associating with impairment in the spatial information perception); while lesion to left inferior frontal-parietal opercular cortices lead to increase in 'arm' position errors (impaired time (hand) setting, in the context of a relatively well drawn clock that had all the numbers in approximately the correct spatial locations, which related to deficits in language processing) (Tranel et al., 2008).

Chechlacz and colleagues used whole brain voxel-based morphometry (VBM) with stroke patients focusing on specific visuo-spatial deficits interfering with CFC (Chechlacz et al., 2014). The authors looked at the type of errors generated by the patients when copying a complex figure of Birmingham Cognitive Screen (BCoS). They reported that lesions to the right thalamus and basal ganglia were associated with overall impairment in CFC. Lesions to right inferior parietal lobule and right middle frontal gyrus were associated with the amount of detail missed on the contralateral (left) side, potentially reflecting visuo-spatial biases typically observed in egocentric neglect. Misplacements of

elements in the figure were associated with lesions to the early visual cortex and the insula. Lesions to these latter regions also impaired the ability to copy small elements in the figure, suggesting a problem with local feature processing. Lesions to the right middle temporal gyrus, on the other hand, were associated with the inability to reproduce large elements, consistent with a deficit in global processing (Chechlacz et al., 2014).(We described more detail of the CFC in BCoS in Chapter 2).

Taken together these studies highlight the multi-faceted neural processing required by the CFC task. Lesion-symptom mapping studies (Biesbroek et al., 2014; Chechlacz et al., 2014; Possin et al., 2011) have emphasized the important role of right parietal, middle frontal and middle occipital cortices in visuo-spatial aspects of CFC – either mediating spatial attention particularly on the contra-lesional side (Biesbroek et al., 2014; Chechlacz et al., 2014) or spatial planning (Possin et al., 2011). However, the role of other factors such as high-level motor functions and the transformation of visuo-to-motor representations remains unclear and is debated (Gross and Grossman, 2008).

Visuo-motor transformation, required by figure copying and writing such as transcription, is hypothesized to involve two main steps, visual perception and eye-hand coordination (Sanghavi and Kelkar, 2005). Eye-hand coordination has been studied at different levels including object manipulation tasks (Johansson et al., 2001), target reaching actions (Carey, Della Sala, and Ietswaart, 2002), and visually guided tracing and drawing/copying (Gowen and

Miall, 2006, 2007; Ogawa and Inui, 2009). Deficits in target reaching actions may be seen in optic ataxia patients (Battaglia-Mayer and Caminiti, 2002), and are frequently associated with lesions in the left superior parietal lobule (Auerbach and Alexander, 1981). Deficits in eye-hand coordination may lead to tracing and drawing difficulty typically associated with constructional apraxia (CA) (Ferber et al., 2007; Guérin, Ska, and Belleville, 1999). Given that co-ordination is most frequently required with the patient's right hand, and maybe mediated by the left hemisphere, then the previous emphasis on right hemisphere processes may fail to address coordination problems.

The neuro-cognitive processes supporting eye-hand coordination in pencil-paper tasks such as CFC has previously been investigated using functional imaging (Gowen and Miall, 2007). Participants were required to either 'draw' with their finger a simple geometric shape (based on a verbal probe) or trace the lines of these shapes. Regions activated when drawing or tracing a figure included the cerebellar vermis, an area surrounding the left central sulcus including the pre and post central gyri, the superior medial frontal cortex and the right precuneus and superior parietal cortex. These cortical regions along with the inferior and superior occipital and right cerebellum showed a stronger response when the task required drawings as opposed to simply tracing a line. Another fMRI study asked healthy participants to copy or trace a figure using a computer mouse (Ogawa and Inui, 2009). Copying requires the reproduction of the figure at a separate location. In contrast to tracing, copying a figure requires

the participant to create and hold (at least for a short time), an analogue mental representation of the figure or parts of it. Similarly, to the study reported above (E. Gowen & Miall, 2007), regions around the central sulcus were activated more for copying relative to tracing. In addition, copying induced a larger spread of activation in the occipital cortex including bi-lateral lingual and middle occipital cortices and bilateral intraparietal sulcus. The authors suggested that these latter regions supported the generation of an analog visual representation (Ogawa and Inui, 2009). Both studies suggested that regions surrounding the left central-sulcus, potentially supported motor-sensory processes and regions in occipital and parietal cortices contribute to visuo-motor transformation. The involvement of the inferior parietal cortex in eye-hand coordination and visuo-motor transformation is also supported by physiological data (see review Colby, Duhamel, and Goldberg, 1995) and data on the effects of transcranial magnetic stimulation (e.g. Van Donkelaar, Lee, and Drew, 2002).

Visual motor transformation tasks involve high-level motor control. In neuropsychology, deficits to high-level motor functions are often referred to as praxis deficits. Apraxia is defined as an inability to perform complex actions and carry out skilled motor acts despite preserved sensory and motor abilities (Gonzalez Rothi, Ochipa, and Heilman, 1991). The symptoms of apraxia can include a failure to process gestures, a failure to interact with objects, failures to complete sequenced daily tasks and (more arguably) also the ability to build and construct figures (Gross and Grossman, 2008). The precise relations

between these different aspects of apraxia, however, are not well understood. For example, poor gesture performance is typically associated with damage to left parietal and middle frontal cortices (Koski, Iacoboni, and Mazziotta, 2002) and the basal ganglia (Leiguarda and Marsden, 2000), whereas CFC performance can be disrupted after right hemisphere lesions (Biesbroek et al., 2014; Chechlacz et al., 2014; Possin et al., 2011).

Moreover, impairments in CFC are also reported to co-occur with aphasia (Perren, Clarke, and Bogousslavsky, 2005; De Witte et al., 2008), spatial neglect (Linden et al.,, 2005), visual agnosia(Paterson and Zangwill, 1944) and sustained attention (Seidman et al., 1997). While the prevalence of these comorbidities is unknown, given the complexity of CFC, it is important to extract the covariant effects of these cognitive functions when investigating lesion-symptom mapping in relation to CFC. This was not done in previous studies (Biesbroek et al., 2014; Chechlacz et al., 2014; Possin et al., 2011).

1.5 Neural correlates with Writing

1.5.1 Neuropsychological studies

The classical reference for agraphia localization is attributed to Exner (Exner, 1881; F.-E. Roux, Draper, Köpke, & Démonet, 2010), who identify the left middle frontal gyrus (MFG) as the writing area, also known as the Exner's area. Few additional case studies supported the role of left MFG in writing ability

(Henderson, 2008; Hillis, 2008; Marcus, 1937). It is assumed that Exner's area contributes to the motor programs for generating letters (Exner, 1881). Though a recent careful examination of the evidence provided by Exner challenged the idea that Exner's area is the focus of writing control (F.-E. Roux et al., 2010). Roux and colleagues argued that Exner described a very small number of patients with agraphia symptoms in his work. And, only one of them had a limited lesion in the posterior part of the middle frontal gyrus. Furthermore, none of the case studies described by Exner had pure agraphia symptoms (Exner, 1881; F.-E. Roux et al., 2010).

Another classic autopsy study described agraphia patients with lesion to left angular gyrus (AG) despite intact left MFG and Broca's area. (Henschen, 1922) The involvement of this region in writing was supported by some later case reports. (Alfredo Ardila, Concha, & Rosselli, 2000; Iwata, 1986; H Tohgi et al., 1995) However, Henschen as well reported only a few numbers of patients with selective involvement of angular gyrus lesions and none of the patients had pure agraphia symptoms. More recent case studies reported the importance of other brain regions in writing, including the supplementary motor area (SMA) within the superior frontal gyrus (Pai, 1999), supramarginal gyrus (SMG) (D P Roeltgen & Heilman, 1984), insula (Marien, Pickut, Engelborghs, Martin, & De Deyn, 2001; D P Roeltgen & Heilman, 1984), the basal ganglia (Damasio et al., 1982) and the left posterior inferior temporal cortex (PITC) (Kawamura, Hirayama, Hasegawa, Takahashi, & Yamaura, 1987; Mochizuki &

Ohtomo, 1988; Sakurai, Sakai, Sakuta, & Iwata, 1994). Presumably, lesion to the left IT disrupted the function of the previously mentioned VWFA (Dehaene, Stanislas et al., 2005), suggesting this area also play a rule in writing and not just reading. On the whole it is worth noting that, most of the agraphia cases above often suffered from comorbidities of aphasia, reading disorder (alexia) or naming disorder (anomia); while motor deficits in these cases were not consistently reported.

Scarone and colleagues (Scarone et al., 2009) reported 15 cases of post-operative agraphia but intact speech. The authors argued that at least five brain regions in the dominant hemisphere contributed to the writing network, including the superior parietal, the supramarginal, the middle and inferior frontal (2nd and 3rd frontal convolutions), the superior frontal gyrus (i.e. SMA) and the insula. At follow up, only patients with superior frontal (SMA) lesion did not show a recovery in writing abilities (Scarone et al., 2009). Interestingly, their results indicated that agraphia could occur despite preserved speech and language abilities and is primarily associated with the functions of the left superior frontal gyrus.

Intra-operative cortical electric stimulation in two patients, report disruption to writing following the stimulation of the left superior parietal gyrus (Magrassi, Bongetta, Bianchini, Berardesca, & Arienta, 2010). Impairment of writing affecting both central and peripheral processes was observed despite preserved oral spelling ability. The authors argued that some of the central

processes specific for typing and handwriting converge with motor processes at the superior parietal gyrus (Magrassi et al., 2010). Roux and colleagues (F. E. Roux et al., 2009) observed that intra-operative stimulating the left SFG in 6 out of the 12 patients led to interference with writing abilities but did not affect language and motor abilities (F. E. Roux et al., 2009). Similar result was found by applying TMS to SFG (Vidaković et al., 2015).

While not surprisingly, many case reports highlight the important contribution of lesions to the dominant left hemisphere to agraphia. There are also case studies that suggest the right hemisphere contribute to writing in right-handed patients. Pure agraphia (with no symptoms of alexia or aphasia) was reported following a lesion to the right midline occipital and parietal lobe (Lee, et al,. 2015; Ozeki et al., 2008). Two other cases of agraphia patients, with aphasia or alexia symptoms are reported following lesion to the right parietal (David P. Roeltgen & Heilman, 1983), or right temporal occipital (Davous & Boller, 1994a). Ardila and Rosselli (a Ardila & Rosselli, 1993) studied 21 patients with right hemisphere lesions all showing agraphia symptoms. The authors divided the patients into two groups: pre-rolandic (frontal) and retro-rolandic (temporal, parietal, occipital) lesions. Using a special writing test, they found that patients with right frontal damage would more likely to make omission and addition of features or letters, which the authors associated with the motor component of language. Whereas spatial errors (e.g. inappropriate distribution of written material in the space, grouping of letters belonging to

different words, and splitting of words) were more likely to be detected in patients with posterior right hemisphere damage (a Ardila & Rosselli, 1993).

1.5.2 Neuroimaging studies

With the development of functional magnetic resonance imaging (fMRI), recent studies used fMRI to detect the neural correlates of writing in healthy subjects. These results were summarized by a meta-analysis that used “Activation Likelihood Estimation” with 18 published neuroimaging studies (Planton, Jucla, Roux, & Démonet, 2013). The authors suggested that 12 brain regions, including cortical and subcortical were involved in writing: left superior frontal area (middle frontal gyrus, MFG; superior frontal sulcus, SFS); primary motor and sensorimotor cortex, left superior parietal area (inferior parietal lobule, IPL; superior parietal lobule, SPL; intraparietal sulcus, IPS: 3 peaks), pre-supplementary (pre-SMA) motor areas, supplementary (SMA), right anterior cerebellum, left posterior nucleus of thalamus, left precentral gyrus (preCG) /inferior frontal gyrus (IFG), right posterior cerebellum, right superior frontal cortex, right inferior parietal lobule, left fusiform gyrus and left putamen (Planton et al., 2013).

To explore the differential role of the motor and language contribution to writing, the author analyzed separate data that controlled for motor output or for linguistic processes. When contrasting writing with non-writing motor tasks (tracing, finger tapping, imagining) the meta-analysis detected five areas of

interests: left MFG/SFS area, left ventral premotor/IFG region, left IPL and right cerebellum. When contrasting writing to language tasks (e.g. sub verbal naming task) the authors reported seven peaks located in the following regions, left MFG/SFS area, M1/SM1 area, SMA, left IPL, anterior and posterior cerebellum, and thalamus (Planton et al., 2013).

The authors observed that irrespective of the contrast and controls used, writing was always associated with increased responses of the left superior frontal sulcus/MFG area, left intraparietal sulcus/superior parietal area and the right cerebellum. These regions were suggested to be specifically involved in supporting writing (Planton et al., 2013).

An earlier meta-analysis (Purcell, Turkeltaub, Eden, & Rapp, 2011) of 11 writing studies aimed to isolate central and/or peripheral processes of word spelling found that a network of left hemisphere frontal, parietal, and temporal sites that are reliably and consistently associated with written word production. The most continuous brain regions associated with the central processes including the Fusiform gyrus/inferior temporal gyrus and the left inferior frontal gyrus. And the left precentral gyrus and SFG/SFS were identified as the most primary regions associated with peripheral processes (Purcell et al., 2011).

Considering the functional imaging and neuropsychological evidence, the left SFG (SMA) extending to the MFG (Exner's area) is repeatedly reported in relation to writing tasks. However, additional regions within the bilateral parietal and occipital are also suggested to play a rule in writing. Though reports of their

involvement are less consistent. (see Figure 2)

Figure 2 Neural substrates associated with writing in the previous neuroimage studies

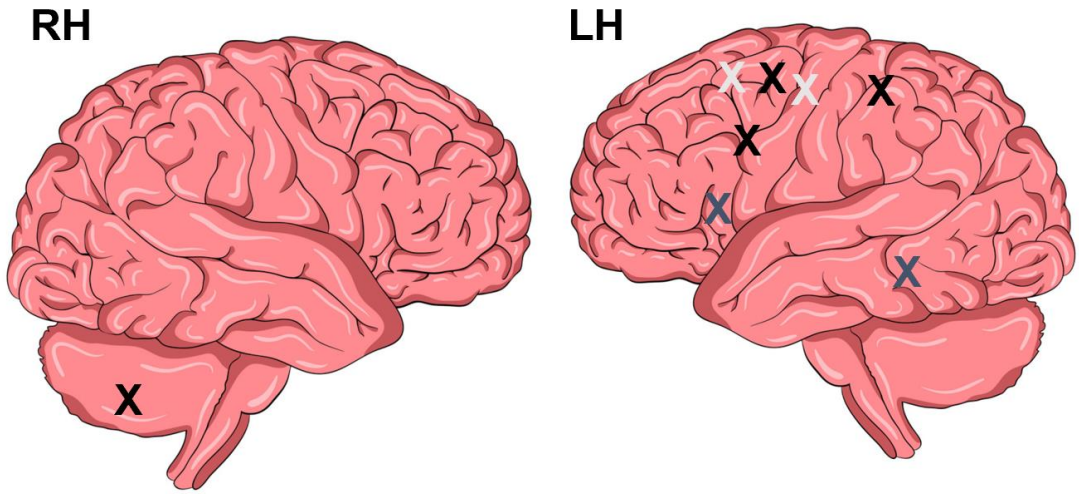


Fig 2: The black 'X' show brain regions showed correlation with writing irrespective of the contrast and controls used, and blue 'x' show brain regions associating with the central processes in writing while the white 'x' was associated with the peripheral processes of writing (Planton et al., 2013; Purcell et al., 2011).

The variety of writing systems raised another question, whether these different writing systems share a similar writing network such as between alphabetic language (e.g., English word) and logographic language (e.g., Chinese character, numbers).

Based on the presented cognitive models for writing above it can be postulated that different language systems will be based on some shared processing. These shared processes include visual (or auditory) input or one's own thinking, eye-hand coordination, visual-motor transformation, higher-level

motor control (motor output). However, Alphabetic language and logographic language are different in morphologies and mappings among orthography, phonology, and semantics (L. Zhu, Nie, Chang, Gao, & Niu, 2014). While most of the alphabetic languages used a phonemes to grapheme transformation based on a serial left to right structure of letter strings (Perfetti, Liu, & Tan, 2005), characters are the basic writing units and encode no clear phonological information at the sub-syllabic level in logographic language (L. Zhu et al., 2014). Thus, while various writing systems can utilize writing through the lexical-semantic route, only the phonological system can also use a phoneme to grapheme conversion route.

Bolger and colleagues (Bolger et al., 2005) reported a meta-analysis that examined the impact of writing systems on the neural-correlates of reading a single word. The analysis included 25 studies (published before 2005) in English and other Western European languages that use an alphabetic writing system (phonological), 9 studies of native Chinese reading (Character=logographic/Pinyin=logographic), 5 studies of Japanese Kana (syllabic, phonological) reading, and 4 studies of Kanji (morpho-syllabic, logographic) reading. All the included studies used similar contrasts such as comparing word reading or naming to a resting baseline, reading phonological vs. logographic (e.g. Chinese character contrasting to Pinyin). The study showed a network of common regions activated across different language systems. These regions included the left superior posterior temporal gyrus, the

left inferior frontal gyrus, the left occipitotemporal region. This study also indicated that the right-hemisphere in the inferior occipital and posterior fusiform regions contributing mainly to logographic language. The authors argued that these regions may provide additional support for the character's spatial arrangement of the radicals (Bolger et al., 2005).

Another meta-analysis by Tan (Tan, Laird, Li, & Fox, 2005) and his colleagues, used the activation likelihood estimation (ALE) method focusing on phonological processing in reading between the Chinese and alphabetic language. Their studies include 6 Chinese studies employing an explicit phonological judgment task. (e.g. Homophone judgement to font size decision or fixation, rhyme judgment to font size decision) and 13 studies with English or German utilizing an explicit phonology-related judgment task (e.g. Rhyme judgment to spelling or letter case decision, letter sound decision to letter spatial decision). Their result showed converge activation between the two languages around the left fusiform gyrus and the left inferior frontal gyrus and the left inferior parietal regions. Their studies also showed while the left posterior sites of temporoparietal regions were important for alphabetic languages only, the posterior neural system contributing mainly to the phonological processing of Chinese. (Tan et al., 2005)

A relatively recent meta-analysis (L. Zhu et al., 2014) summarized fMRI studies from 2005-2012, included 19 experiments for alphabetic (phonological) languages and 13 for logographic languages. These were all fMRI studies that

compared phonological judgment tasks (e.g. Rhyming judgment) to line other tasks (e.g. judgment or visual detection, phonological matching to fixation or orthographic decision). The authors reported that logographic languages significantly activated the left middle-superior frontal lobe, the right middle occipital gyrus, and the left fusiform gyrus, while the alphabetic languages led to significant activations in the left inferior/medial frontal gyrus, left middle temporal gyrus, left angular gyrus, cerebellum, bilateral superior frontal gyrus, and left lentiform nucleus.

To summarize, the above meta-analyses explore the difference in the neural basis between alphabetic languages and logographic language. Their results showed largely identical neural networks supporting reading across language but with minor differences between the two writing systems (Bolger et al., 2005; Tan et al., 2005; L. Zhu et al., 2014). It is worth noting that these analyses summarized across a variety of studies using different word-processing tasks. Hence their findings cannot provide direct evidence regarding particular functions such as phonological and lexical/semantic processing. These analyses only examined reading tasks mainly focusing on the linguistic components. There are relatively fewer studies that focus on writing across different languages and phonemes to grapheme conversions. (see Figure 3)

Figure 3 the main similarities and differences of neural substrates between reading in alphabetic and logographic language

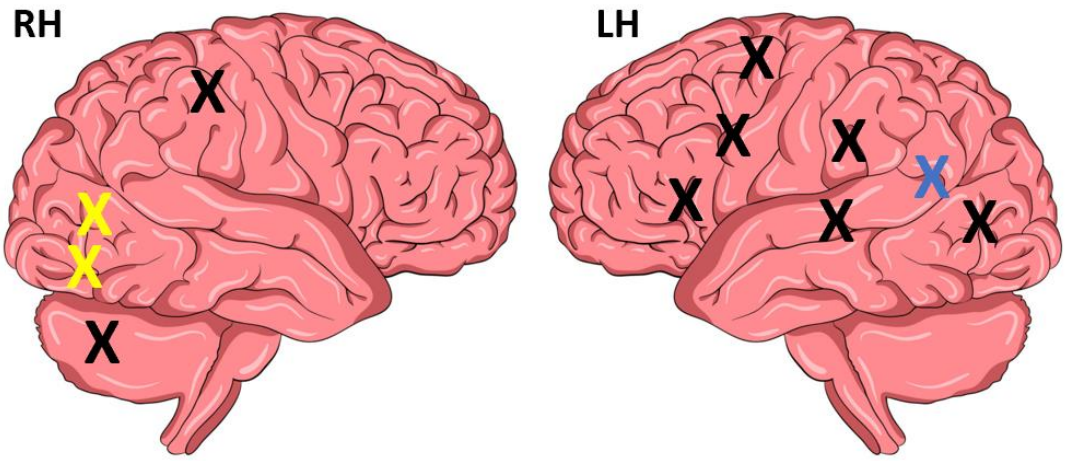


Fig 3: The black 'X' show overlapped regions contributing to reading both logographic and alphabetic language, with yellow for logographic and blue for alphabetic language(Bolger et al., 2005; Tan et al., 2005; L. Zhu et al., 2014).

Similar to the Chinese character, writing number is based on a logographic conversion of units of meaning-to-symbols. And there aren't many studies focus on the neural substrate associated with number writing. And little research directly compared the shared and dissociation of these two cognitive activities. Whether words writing and number writing are processed in conjunct cognitive and neural systems remained unclear.

Number writing requires ability to use the prior knowledge to produce meaningful graphic signs, like any logographic writing system. Hence writing

words in English (Western language) and writing numbers are not based on the same writing system. Words are based on the alphabetic system that uses phonological rules to map sounds to letter (graphic signs). While writing Number relies on a logographic system, in which the mapping of sounds to graphemes is mediated by prior semantic knowledge.

Some case reports support a dissociation between writing numbers and words. Anderson (S. W. Anderson, Damasio, & Damasio, 1990) and colleagues reported a case of a well-educated right-handed woman who suffered a circumscribed surgical lesion in the left premotor cortex (Exner's area). The patient had a severe problem in writing words, while she could easily write numbers and perform written calculations without difficulty. (S. W. Anderson et al., 1990). Starrfel reported a case that showed selective agraphia with a spared ability to write numbers. The patient suffered from head trauma in a car accident and his brain image (CT and MRI) showed no abnormalities. His letter writing is impaired while number writing and written calculation are spared. The study indicated dissociation in letter and number processes. The author argued that a deficit in visual-motor networks related to the physical shape of letters might account for the impairments (Starrfelt, 2007). However, high comorbidities of number writing deficit and word writing impairments support large neuro-cognitive overlaps between the two systems (De Luccia & Ortiz, 2016; Lopes-silva, Moura, Júlio-costa, Wood, & Horner, 2016).

1.6 The current thesis

The neural basis of copying figure and writing has been a source of inquiry and controversy. Previous studies showed multi brain regions contributed to copying figure and writing. More recent studies tried to explore different substrates associated with copying figure or writing. However, few of them focus on the motor output. Besides, based on the neuronal recycling hypothesis, the neural substrates of recent abilities like writing are constrained by the functional architecture of the brain. There should be large overlapped in the neural substrates among writing and its related general cognitive abilities. Previous studies supporting this neural cultural hypothesis mostly focus on the linguistic and visual perception component of these tasks. There remained few studies focus on the neural basics associated with the motor components of copying figure and writing.

The current thesis first aimed to explore the neural-cognitive basics of these two tasks by using different method in both stroke patients and healthy participants. We tried to identify the roles of specific brain areas and cognitive processes in different component of copying figure and writing, mainly focusing on the motor output supporting the use of pen. We assume that different writing systems would share similar cognitive model. And similar to VWFA reflecting invariance across different reading systems, there should be some motor regions specifically contributing to copying figure and writing. Converging evidences would be used in our studies.

In chapter 2, I introduce the general method used in our study.

Chapter 3 explored the neural basis of the factors underlying complex figure copying (CFC), using data from the BUCS trial(Humphreys, Bickerton, Samson, & Riddoch, 2012), which used the Birmingham Cognitive Screen (BCoS) in a large group of sub-acute, ischemic stroke patients (239). Two analyses were performed: we first assessed the contribution of co-morbid deficits (i.e. in gesture processing, object use, visual neglect, pictures naming and sustained attention) to the lesions associated with CFC. Secondly, we combined a Principle Component Analysis (PCA) and VBM analysis, to isolate different underlying task components and to link them to clinical neuroimaging scans. The idea of this chapter is to isolate different component especially the motor component of figure copying and related it to the neural correlates.

Chapter 4 explores the underlying cognitive processes of writing. Data of ischemic stroke patients form both the UK and China was analyzed. The cognitive profile of each patients was assessed using the BCoS (BCoS-En Humphreys, Bickerton, Samson, et al., 2012), BCoS-M (陈浩博 et al., 2017) and BCoS-C (Pan et al., 2015)). Support vector machine (SVM) was used to classify patient with and without writing deficits, based on their cognitive profile. The study aimed to determine whether reliable group differences exist on performance of cognitive tasks or on a combination of tasks between stroke patients with and without deficits in word writing. The analysis aimed to reveal intrinsic connection between word writing and other cognitive tasks. And to

explored whether there were differences in the cognitive pattern in patients with writing deficits between the two writing systems (Chinese and English).

Chapter 5 investigated the cognitive and neural substrates that underpin writing ability of words and numbers. As in chapter 3, two analyses were performed. The first explored comorbidity pattern between writing words/number and other language and motor deficits (N>700), using only data from the UK. The second tested similarities and differences in writing numbers and words and compare these to language and manual actions in a large group of sub-acute, ischemic stroke patients (n=267). We then used principle component analysis of the behavioral data to identify the writing components. By combining PCA and VBM analysis, we aimed to explore whether different writing system rely on overlapping cognitive and neural functions.

Chapter 6 reports an fMRI study, aimed to investigate the neural substrates associated with writing in two different language systems, alphabetic (phonological) and logographic. 20 young healthy undergraduate and postgraduate participated. All the participants perform writing or tracing (word and nonword) tasks in three different types of languages (simplified Chinese characters, Chinese Pinyin and English). We aimed to explore the neural substrates associated with different cognitive processes of writing and compared the difference between different language systems as well.

In chapter 7, we discussed the results of the study and their implications for the neuronal recycling hypothesis and the motor components of pen using

relating to writing and copying figures.

Chapter 2

Method

Current research recruited both stroke patients and healthy participants using different kinds of methods in four studies. To avoid repetition, the general research methods and database was introduced in this chapter.

2.1 Participants

We used sub-samples from the BUCS database in three of our studies. The BUCS trial recruited nine hundred and six patients after being admitted to the hospitals for stroke across the West Midlands (United Kingdom) (see Bickerton et al., 2015 for details). The inclusion criteria were as follows: the patient should 1) be within 3 months of a confirmed stroke; 2) be judged by the clinical team to be able to concentrate for at least 30 min to enable the tests to be administered; 3) have sufficient command of English to follow the instructions, and 4) have given written consent to participate. The study was approved by the National and local NHS ethical committees.

The BUCS study was approved by the UK National Research and Ethics Advisors' Panel (NHS REC 08/H0301/6) and by the local Trust's Research and Development departments in each hospital the patients were recruited from. According to guideline and regulation all patients were informed on the purpose of the study and signed a consent form. The data is held anonymously and stored on secure servers (see for more details on the BUCS

trial: http://www.bucs.bham.ac.uk/sites.php).

2.2 Behavioral measures

2.2.1 General introduction of BCoS

We assessed the patients' cognitive profile using the Birmingham Cognitive Screen (BCoS) battery (Humphreys et al., 2012). *BCoS is a cognitive screening instrument that assesses performance across a broad range of cognitive abilities. It takes about 1 hour to administer and generates cognitive profiles of individuals within 5 cognitive domains: (1) Attention and executive functions, (2) Language, (3) Memory, (4) Number Skills and (5) Action planning and control (Praxis). Importantly, the test is designed to maximize inclusion for stroke patients whilst generating test results that are less biased by the co-occurrence of language or spatial attention problems, which can otherwise have a co-varying impact on performance (e.g., avoiding contamination by aphasia and neglect by using forced-choice tests and vertical layouts) (Humphreys et al., 2012).*

The patients were assessed in a quiet room within the hospital. At the time of testing the patients and the examiners were blind to the area affected by the stroke.

The main aim of BUCS study (NHS study designed to develop the BCoS, Birmingham Cognitive Screen) was to establish a screen that can provide a detail cognitive profile of a stroke patient in a fairly limited amount of time. The

creators of the BCoS (Humphreys, Samson, Riddoch and Bickerton) design it to cover five main domains of cognition: memory, language, attention and executive functions, number and praxis. The tasks for each domain were designed based on the following criteria: 1) based on existing neuropsychological standardized tasks assessing this domain. For example, the complex figure copy task was design to be similar in its complexity to the Rey-Osterrieth Complex Figure test. The praxis tasks are similar to the Test of Upper Limb Apraxia (Vanbellingen et al., 2010). Picture naming test is a commonly used tool in most standardized assessment of aphasia. 2) New tasks and selection of task for each domain were devised based on theoretical knowledge and prior research. 3) The details of administrating and collecting results for each task was designed to maximize their sensitivity to a specific domain. The creators of the screen farther attempted to minimize overlaps between task requirements, to avoid confounding of a domain measurement. However, as the tasks are complex, overlaps are often unavoidable. For example, difficulty in language comprehension or sustained attention is likely to affect all tasks. The process of creating and validating the BCoS is reported in depth in the screen manual (G. W. Humphreys, Bickerton, Sampson, & Riddoch, 2012).

To test the internal structure validity of the BCoS, Humphreys and his colleagues (G. W. Humphreys, Bickerton, Sampson, et al., 2012) performed an exploratory factor analysis (using Principle components analysis, PCA with

oblique rotation and applying Kaiser's criterion) in 595 of the patients recruited in BUCS. The PCA results of the patients' cognitive profiles cluster the BCoS tests into seven groupings (see Table 9 in BCoS user manual): (1) spatial attention, (2) long-term memory, (3) language, (4) general orientation and comprehension, (5) controlled attention/working memory, (6) praxis/sequential processing, and (7) other (incorporating right-side attentional deficits in individuals with left hemisphere lesions). These components are mostly aligned with the theoretical driven domain structure of the BCoS. Though note that the number tasks fall within the language and controlled attention domain, while attention and executive function is divided to 4 separate components.

The BCoS external validity was further assessed by comparing it to standardise screens (Humphreys, Bickerton, Samson, et al., 2012). For all the language tasks, correlations with standardized tests were high ($r > .74$), apart from writing words which was $r = .68$. For the praxis tasks, the correlations with standardized tests were high ($r > .7$), apart from the multi-step object use which was $r=.41$.

To test the correlation among each task in BCoS, I performed correlation tests in 560 patients from the entire sample. A color-coded correlation matrix was showed in the figure 4. Only patients with no missing values were included. The asymmetry neglect score was reverse such that high score means better performance.

The correlation matrix suggested high (yellowish) within domain

correlations between tasks, for the memory, language and number domains. The correlations between tasks assessing the praxis domain were medium (greenish). While in the attention and executive function domain, the tasks appear to be clustered to spatial attention tasks and sustain and control attention. There were also medium strength correlations between tasks across domains, though of note most of the tasks assessing attention and executive function did not correlate (blueish) with tasks in other domains – though they did correlate with complex figure copy. As expected, the ability to sustain attention correlated with performances on most other tasks.

Figure 4 correlation matrix of each task in BCoS

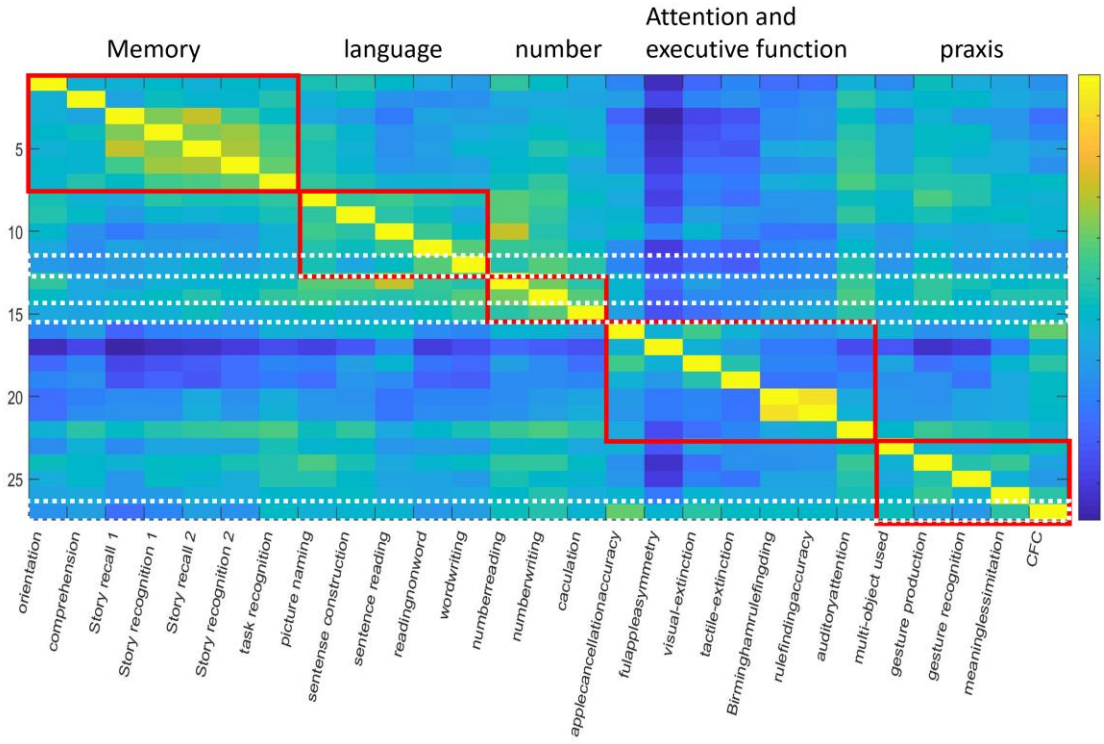


Fig 4 Red rectangles highlight the cluster of pre-assigned tasks for each domain based on the screen's manual. Dotted rectangles mark the three tasks of interest for the current thesis: word writing, number writing and the complex figure copy task.

2.2.2 Cut-off of BCoS

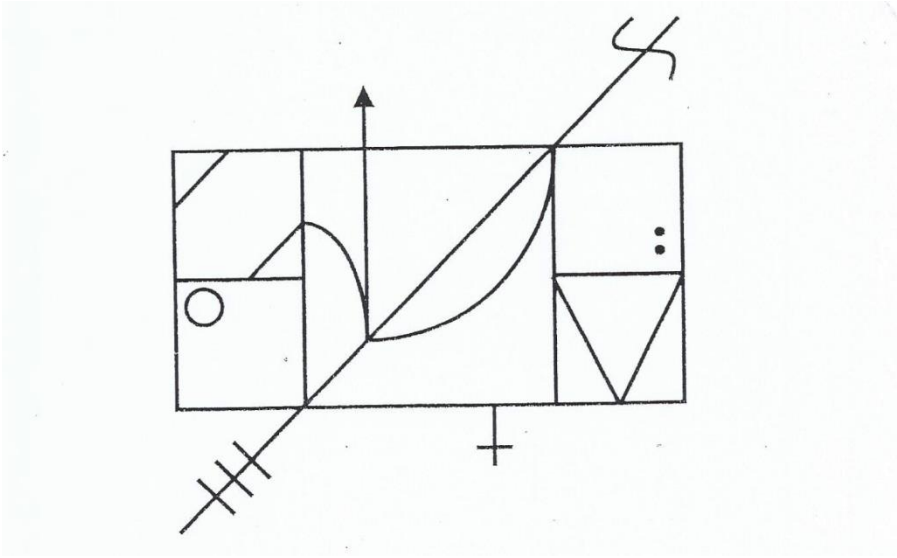
The BCoS cut-off value was based on the performance of 100 healthy controls. These participants all aged above 50 and without a history of a brain lesion. A sampling plan was developed to include representative proportions of adults according to selected demographic variables. Cut-off scores were set at 5th percentile for scores indicating abilities (e.g., reading accuracy) and 95th percentile for scores indicating difficulties (e.g. neglect), see details in (Humphreys, Bickerton, Sampson, et al., 2012)

2.2.3 Cognitive tasks in BCoS

Complex Figure Copy: In Complex figure copy test, patients were asked to copy a complex figure (CFC, Figure 5) as accurately as possible. The CFC task is scored based on soring each feature of the figure. The figure had total of 15 features, divided equally between the right, center and left side of the figure. In details: the figure has five left elements (diagonal end/three bars, rectangle, horizontal bar, double oblique bars/parallel, and circle), five right elements (diagonal end/one curved line, rectangle, horizontal bar, double oblique/triangle shape, and double dot), and five middle elements (arrow, right curve, left curve, middle cross, and main diagonal line). Each feature was scored on the dimensions: its presence/omission (1 point each), its shape/proportion (1 point each), and its placement (1 point each). Given the

size a prominence of the middle square its presence and shape/proportion is assigned 2 points. Thus, the maximum achievable score is 47 points (3*14 + 2) for the completed task. Participants who achieved an overall score of fewer than 42 points (age group of <64 years), 41 points (age group of 65–74 years), and 37 points (age group of >75 years) were classified as impaired in this task. (see Figure 6 for error type example in this task)

Figure 5 CFC task in BCoS



(Fig 5: The figure in BCoS contains a middle structure and additional structures to the left and right. There are in total 16 features. Each feature is scored on 3 criteria: presence, shape and placement (except for the Middle Square which consists the former 2 criteria). The final score is the sum of the accurate reproductions of features, achieved with a maximum of 47.)

(PS: Chechlacz and colleagues (Chechlacz et al., 2014) explored the neural substrates associated with CFC by dividing the errors to Global and Local Processing. They defined global features as the larger parts of the figure and included the middle square, the left rectangle, the right rectangle, the left double bar (inside the top left square), the right triangle, and the long main diagonal line. Local features were defined as details that further refined the figure. The local features included the top left diagonal bar, the parallel bar below it, the left horizontal bar, the left circle, the left diagonal end/three parallel bars, the left curve (inside the middle square),the arrow, the right curve (inside the middle square), the cross, the right double dot, the right side of the triangle,

the left side of the tri- angle, the right horizontal bar, and the right diagonal end/ curved line (“S” shape).)

Figure 6 example of the error made in CFC task

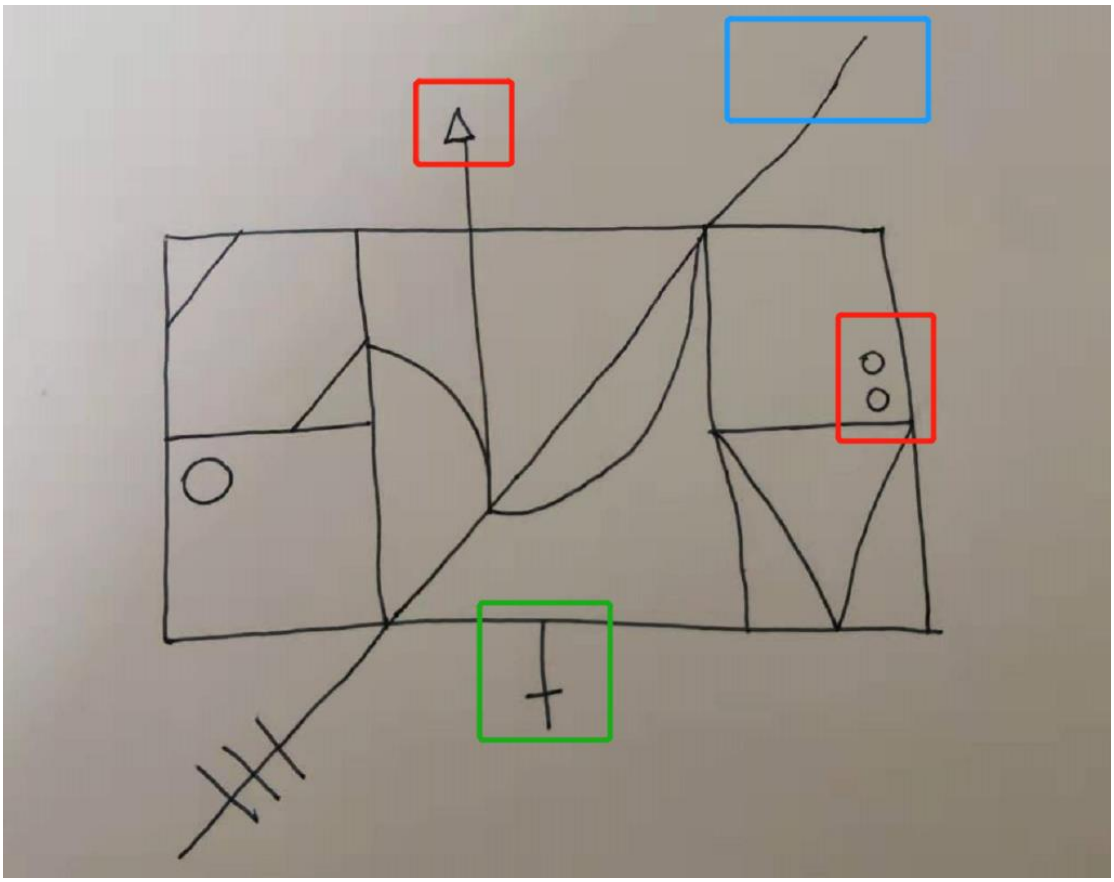


Fig 6: The above figure showed different error types in CFC, with red rectangle to shape error deduct 1 in scoring, green associated with position error deducting 1in scoring and blue with missing error which deducted 3.

Word Writing task: In the UK version BCoS, patients are asked to write four familiar words and one non-word. There are two exception words – one concrete (‘scissors’) and one abstract (‘although’) – and two regular words, one concrete (‘mustard’) and one abstract (‘thinking’) and one non-word (‘troom’). Similarly, there are four characters in the Chinses version of word writing task.

There are two concrete word ’物’ and ‘眼’ in Chinese Cantonese version (‘纹’ and ‘眼’ in Chinese Mandarin version), two abstract word ‘怎’ and ’授’ in Chinese Cantonese version (‘帮’ and ‘怎’ in Chinese Mandarin version). These Chinese characters include different types of structure, namely left-right structure and up-down structure. The test assesses the ability to write with correct spelling based on phonological and lexical knowledge and the ability to control a pen. In the current study, we considered the writing performances across all words. The maximum score is 5 in English and 4 in Chinese, meaning that only words that were spelled (or wrote) with no errors and recognizable scored 1 point, as correct. Patients who failed to response to the Word Writing test due to linguistic or motor deficit were scored 0. Participants who achieved an overall score of ferer than 3 points in UK version and 1 point in Chinese were classified as impaired in the task separately. (see Figure 7 for error type example in this task)

Figure 7 example of errors made in word writing task

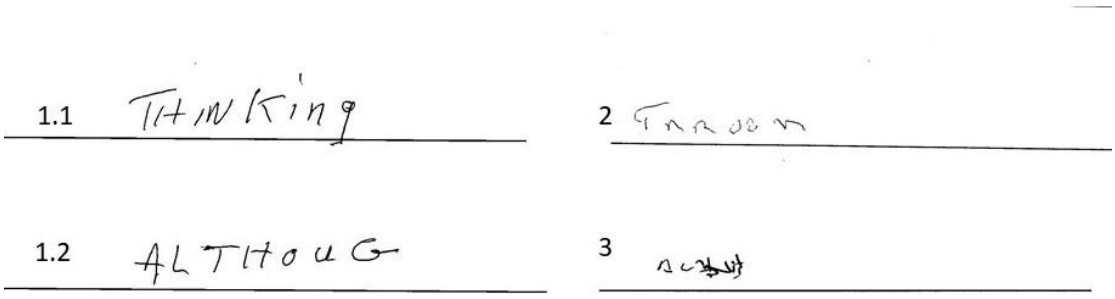


Fig 7: 1.1 & 1.2 Recognized without effort, writing quality score 2. 1.1 spelled correct and recognizable in 'thinking', scored 1 in this word. 1.2 spelled incorrectly with correct pronunciation. (phonological error), scored 0. 2. recognized with effort, writing quality scored 1. (wrong spelling scored 0) 3. unrecognizable, scored 0.

Number Writing task, the patients are asked to write down two multiple digits numbers (e.g. 807) and three prices (£5.99). For the price writing, participants are required to present it clearly with a price symbol, i.e. '£'. They scored a point only for complete correct output, with a maximum score of 5. Participants who achieved an overall score of fewer than 3 points when aged 75 and older, or less than 5 when younger than 75, were classified as impaired in the task.

Language correlated covariates

Picture Naming (PN) assesses the object naming ability (Lau et al., 2015): The task consists of 14-line drawings of seven living things and seven non-living things. The maximum score was 8.

In the **Sentence Construction** (SC) task, the patients are instructed to construct a sentence using two constraints: (1) the sentence must describe what a person is doing in the photograph shown; and (2) the sentence should contain two given words. The test measures whether the examinee has problems in semantic and syntactic processes. The maximum score was 8.

Sentence Reading task requires the reading of two sentences allowing the examiner to test the examinee's ability to read different word classes (verbs, nouns, pronouns, adjectives, adverbs and prepositions). There are both regular and exceptional words, as well as words with suffix and prefix in each

sentence. Maximum score was 42.

Number Reading task requires the reading of three multi-digit numbers (e.g. 2,304), three prices (£109.50) and three digital times (e.g. 9:30). The maximum score was 9 points.

Motor related covariates

Like the writing task, these tasks were performed with the patient preferred hand, or the one that was least affected by the patients' stroke.

In the **Multi-Step Object Use Test** (MOT) the patients are required to perform a sequence of actions with two objects (a battery and a torch, presented along with distractors) to complete a goal: light the torch. The task assesses patients' ability to select the correct object, correctly interact with them and follow the sequence actions ending with the goal. The scoring discounted problems due to primary motor deficits. The maximum score was 12.

In the **Meaningless Gesture Imitation** (MI) test, the patients are required to mimic four meaningless manual gestures (including a sequence of two hand positions in relation to the head and two involve a single finger position). The maximum score was 12.

In the **Gesture Production** (GP) task, the patient has to demonstrate six gestures based on verbal commands, 3 were transitive (e.g. 'combing hair') and 3 intransitives (e.g. 'hello').

In the **Gesture Recognition** (GR) test the patient has to recognize 6

gestures demonstrated by the examiner.

In the Meaningless Gesture Imitation (MI) test the task was to mimic four meaningless gestures with the less affected hand.

Other cognitive covariates

Orientation: the patient was asked to reply to 8 open verbal questions to test access to personal information.

Comprehension: A rating score based on the clinical judgment of the examiner, concerning language comprehension during the whole assessment.

Egocentric Neglect: A measure of spatial attention biases, assessed primarily by the spatial asymmetry score on the Apple cancellation test (Humphreys et al., 2012) (205 patients) but in some cases by a key cancellation task (cross all the keys on the page (85 were assessed on both) (see Bickerton et al., 2011). Egocentric neglect was measured by comparing performance for targets in the left and right visual fields. The scores on the key cancellation task were transformed to match the Apple cancellation task using linear regression estimated from 198 patients in our database who performed both tasks. The conversion formula was: egocentric neglect score in the Apple cancellation test =0.6088*(egocentric neglect scores in key cancellation test) +0.5078. The final scores represented the extent of the spatial attention bias, ignoring its direction.

Auditory attention: The task consists of 6 pre-recorded words including 3 target words ('no', 'hello', 'please'), each with a closely related distractor ('yes', 'goodbye', 'thanks'). The words are presented in random order, each word being preceded an equal number of times by a 2 s, 3 s or 4 s silence gap. The task is performed in three blocks, providing a measure of how well examinees can sustain their attention across the blocks. The participant had to selectively detect three target words and ignore distractors, with 54 stimuli presented across 2 min.

Barthel index: This used ten variables describing activities of daily living and mobility. A higher number indicates a greater likelihood of being able to live at home independently (Mahoney and Barthel, 1965)

More details about the Birmingham Cognitive Screen are described in (Humphreys, Bickerton, Samson, et al., 2012)

2.2.4 Dealing with the missing data

Missing data is a common problem for large and complex databases (Graham, 2009), such as the BUCS. As often the cases with clinical data, in the current study missing data is not random and was more associated with case severity. In the BUCS it typically emerged due to patient fatigue (e.g. there were lots of data points missing in CFC as this is the last task in the BCoS), or examiner evaluation that the patient cannot complete the task due to comprehension or other problem (e.g. patients with visual loss will not able to

complete any task that relies on visual stimuli). The way missing data is treated affect the results and may bias the interpretation. The decision on how to replace missing data reflect a trade-off between type I (finding an effect that is false, or boosting the chances of finding an effect) and type II error (missing to find an effect that is true, or reducing the chance of finding an effect).

In the current study I selected a conservative approach for dealing with missing data. The rationale was to reduce the chances for type I error (false discovery) and increasing the chance of type II errors. I used two approaches to deal with missing data. If the data was missing from the main variable of interest (chapter 3 - CFC, chapter 5 – writing tasks), I removed the whole case from the analysis, what is called listwise deletion. Similarly, in chapter 4 (machine learning chapter), where all variables carried equal importance for the research question, cases with missing data were deleted (this was applied to all variable apart from the visual neglect measure in the UK-BCoS, see below). This results in reducing the overall power of the study.

In the remaining cases, the missing data in other tasks was relatively low (< 5%) and was distributed across the tasks. To avoid biasing the results by missing data, missing data were replaced by the mean group. As all statistical analysis were based on linear regression, the mean of the group ensure that the results were unaffected by the missing data. Though I acknowledge that this method makes any true relations that exist more difficult to detect.

In the UK-BCoS database, the cancelation task (the task measuring visual

spatial neglect) was changed after data collection for about one quarter of the cases. The task changed from a key cancelation task to an apple cancelation task. Around 100 cases were assessed on both tasks during the transition period. Therefore, around quarter of the sample have missing data for the apple cancelation task. To replace these missing values, I used regression analysis to maps the key cancelation to the apple cancelation task in those patients who had both. The parameters obtained from this later procedure were used to replace the apple cancelation missing data when the results for the key cancelation were known.

Why not use more ‘modern’ approach to replacing missing data? More ‘modern’ approaches broadly rely on other sources of data to provide a good ‘guess’ for the missing data. These typically include some forms of multiple regression analysis with some optimization algorithm(Graham, 2009). These procedures assume that there is some redundancy in the measured data, and that pattern in the data are consistent across participants. While there is some correlation between the BCoS tasks (see above correlation matrix); these correlations are mostly moderate to weak. Furthermore, as the questions we asked were directly about co-morbidities, replacing missing data, using information from other tasks will artificially inflates the overlap between tasks in the data.

2.3 Principle component analysis (PCA)

We performed Principle component analysis (PCA) to tease apart the various cognitive components underlying CFC and Writing performance and its relations with other cognitive measures. We used VBM to identify the neural correlate of the latent variables identified by the PCA. The PCA was computed in SPSS, the data was scaled before the PCA was applied. We included the target tasks (CFC or Writing tasks) with other relative cognitive tasks in the PCA. The PCA teased apart the differential and shared components of the target tasks with the relative cognitive functions. PCA aims to reveal latent variables by projecting the data onto a new space defined by the components. Each new component is a linear combination of the weighted original scores. Higher loading (weight) means a larger contribution of a specific task to this component. The directional sign (+/-) of the loading is only meaningful when comparing the contribution of each task to the component. If all signs point to the same direction (+/-) this means that component reflects a shared latent variable underlying all tasks. If the signs are opposite, it means that the component dissociates the two tasks. Based on our research, for simplicity we ensured that when reporting the loading of the CFC (chapter3) or Writing (chapter 5) are always positive, hence when needed we flipped the loading signs in the component if the loading were negative in the target tasks.

Instead of using the Cattel's criterion to choose the components. All the components were extracted and put into the VBM models. It is because of the

following 2 reasons. Firstly, we want to increase the study power in VBM (by reducing unexplained variability). It was important to use a transformation that accounts for all variability in the data. Hence all the PCA components were included in the VBM model. Secondly, neuropsychological studies are often based on case studies, or pre-selected cases. These cases are at the tail of the distribution when considering the entire stroke population. Hence, they are likely to explain small amount of variability in the data, when considering the entire stroke sample. As the PCA is likely to be driven by outliers (the tail of the distribution) it hinders the ability to generalise the current results beyond the current sample. Such as in our writing VBM study only the first shared component had an eigenvalue > 1, the first four components had eigenvalue > .5. Thus, conventional criterion-based amount variable explained (>1) would have masked the relation between the writing and other pen using task (component 2), or the writing task versus other pen using tasks.

2.4 Neuroimaging assessment

All the patients in our study (BUCS trail) performed CT scans when they were admitted to the hospital by using Siemens Sensation 16, GE Medical System Light Speed 16 and Light Speed Plus with an in-plan resolution of 0.5 x 0.5mm and a slice thickness between 4 and 5 mm. The average days that CTs were acquired 2.8 days post-stroke，with a standard deviation of 4.85.

2.4.1 Pre-processing of brain images

The data were processed using an identical procedure to the one reported in previous studies using the same database (Chechlacz et al., 2014; Lau et al., 2015). We used SPM12 (Statistical Parametric Mapping) to preprocess the data. DICOM files were first converted to NIFTI format. Consequently, we normalized the data by transforming images into the MNI space. Following this, we applied the unified segmentation algorithm (Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). The unified model is used to draw the deformable tissue probability maps (also called priori tissue class). The a-priori tissue maps indicate the probability of the voxel belonging to one of the six types of signals expected in a brain: GM (grey matter), WM (white matter), CFS (cerebrospinal fluid), bone, fat and air. As a consequence of stroke, a 7th abnormal tissue type representing the lesion was also proposed to be present. To account for this we followed Seghier and colleagues' approach (Seghier et al., 2008) and added an additional a-priori map. We estimated that there would be 10% probability that either GM or WM consist of abnormal tissue; We estimated that there would be 10% probability that either GM or WM consist of abnormal tissue. The 10% probability for an abnormal voxel (lesion-voxel) within the GM and WM was estimated based on the ratio between average lesion size (computed for 160 patients; Chechlacz et al., 2012) and the number of voxels in GM plus WM tissues. It is a rough estimate. The exact number for a probability of a lesion in any given voxel does not make much difference; as the unified-segmentation

algorithm is primarily relying on the signal intensity when images are segmented. Finally, we applied a single Gaussian normal distribution to classify the intensity of the grey and white matter and two Gaussian distributions to classify for the intensity of abnormal tissue. To accommodate the random field theory, we smoothed the segmented GM and WM by using a 12mm3 FHWM Gaussian Kernel.

2.4.2 Voxel-based morphometry (VBM)

To compute the correlation between the behavioral results to grey matter lesions, we used random effects analyses within the general linear model framework (Ashburner and Friston, 2001). Voxel-based morphometry (VBM) is a computational approach to neuroanatomy that measures differences in local concentrations of brain tissue, through a voxel-wise comparison of multiple brain images. GLM model is used for modelling and statistical hypothesis testing in the VBM analysis. In equitation form, the GLM can be expressed as: $Y = X \beta + \varepsilon$; where Y represents the data from one voxel (which is the density of a voxel in our study); X is known as the design matrix or model, and its columns are known variously as regressors, covariates, independent variables or explanatory variables (EVs); β is a vector (i.e., a set of numbers) that consists of all the individual scaling parameters; and ε is the residual error (Ip, 2007). The dependent variable of VBM is grey matter probability of a given voxel. This is the product of the unified segmentation algorithm used to classify

the images to the different tissue types based on their configuration and applied on the signal intensity. In the case of CT, the signal intensity reflects the tissue density.

VBM uses the general linear model for statistical inferences. Multicollinearity, the correlation between variables is an important issue to consider in the context of GLM, especially when the main aim is to assess the reliability of a single variable as predictor, as is the case in most VBM. This is because high correlation between variables (regressors) leads to unstable estimation of the impact of individual variables. Variance inflation factor (VIF) expressed sometime as the GLM tolerance (1/(1-Ri2) is one measure to assess multicollinearity and whether it is a problem. As a rule of thumb, VIF of 10 and above which is equivalent to R2 of .9 between variables is assumed to indicate a problem (though this threshold has been challenged as been over conservative(O'Brien, 2007). In the case of the BCoS data, the highest correlation between two variables is between the various language tasks with R2 = .49, given a VIF of 1.96, which is within the acceptable range.

2.4.3 region of interests

In the current thesis ROIs were extracted for two reasons: for description purposes and for additional analysis outside the imaging analysis package, SPM (e.g. structural equation modelling). As the main aim was to further the description/understanding of the observed findings, the ROIs were defined

based on the group result (the finding: reliable blob) as opposed to some a-priori assumption (e.g. anatomical location).

A reliable blob is described using a peak voxel, representing the point by which the grey matter probability is best explained by the behavioral predictor; and a cluster extent, the number of voxels showing reliable relations above a given threshold (e.g. p<.001, uncorrected). Interpretation of the results in the current thesis was based on cluster level corrections. Hence the peak voxel may provide a biased representation of the cluster pattern which is inconsistent with the level of inference. As a compromise we selected a 6mm sphere cluster. These ensured: 1) all ROIs have the same size and 2) the voxels primarily reflect grey matter tissue probabilities (given the cortical sheet is fairly thin, <5mm).

SPM uses the first Eigen-variate to summarize the pattern of results across multiple voxels of an ROI (i.e. summary statistics). Other ways, for providing a summary statics over voxels will be mean or median. Eigen-variate is advantageous as it optimizes for explaining/retaining most of the variability in the data.

分页符

Charter 3

Lesion-symptom mapping of a complex figure copy task: A large-scale PCA study of the BCoS trial

This character has been published in the journal of Neuroimage: Clinical (The introduction has been shorted to avoid repetition)

Foreword

Copying figures is composed of a series of related basic abilities such as spatial visual perception, high level motor control and tool (pen) using abilities. In this chapter, we aimed to explore the neural substrates associated with copying figures. Previous studies showed multi brain regions in bilateral hemisphere contributed to figure copying. However, despite the high comorbidities of figure copying with other cognitive function, there is few studies account for the comorbidities effect. In our study, we account the comorbidities effect by taking them as covariates in the VBM models. And as most of the previous studies exploring the cognitive component mainly focus on the perception part, the second aim of this chapter was to delineate the motor component of figure copying and explore their neural basics. This is accomplished through a PCA recruiting figure copying and other praxis tasks.

3.1 Abstract

Complex figure copying is a commonly used neuropsychological test. Here we explored the neural basis of the factors underlying complex figure copying (CFC), using data from the Birmingham Cognitive Screen (BCoS) in a large group of sub-acute, ischemic stroke patients (239). We computed two analyses: in the first we assessed the contribution of co-morbid deficits (i.e. in gesture processing, object use, visual neglect, pictures naming and sustained attention) to the lesions associated with CFC. In a second analysis, a Principle Component Analysis (PCA) was used to isolate different underlying task components and to link to clinical neuroimaging scans. A voxel-based morphometry (VBM) analysis showed that poor CFC performance was associated with lesions to bi-lateral thalamus, lingual, right fusiform and right inferior parietal cortices (rIPC). The latter association with the posterior parietal cortex was diminished after controlling for neglect. Follow up analysis showed the neglect partially mediated the correlation of CFC and rIPC. The PCA revealed three main underlying components: (1) a component associated with high-level motor control common to different measures of apraxia and linked to the left postcentral gyrus, the right thalamus and middle frontal gyrus; (2) a visuo-motor transformation component unique to the CFC and associated with lesions to the posterior occipital and sensory cortices; (3) a component associated with multistep object use tasks which was correlated with lesions to the left inferior frontal orbital gyrus, the right fusiform and cerebellum. Using

clinical symptoms, cognitive profiles and lesion mapping we showed that beyond visual perception, CFC performance is supported by three functional networks: one for high-level motor control, a visuo-motor transformation component, and multistep object use network.

3.2 Introduction

Complex figure copying (CFC) is a widely used clinical test. In this task, participants are asked to copy a figure (e.g. Figure 5), with the figure either left in front of them or removed to load visual memory. Our study involved only the situation with the figure left in front of the participants. The CFC task is usually used to detect different kinds of cognitive impairment such as constructional apraxia (Chechlacz et al., 2014; Possin et al., 2011) and executive function disorder (Ogino et al., 2009).

To date, function-lesion mapping studies have focused primarily on the processing supporting the visual and attentional aspects of complex figure copy (Chechlacz et al., 2014; Possin et al., 2011). The motor output of complex figure copying is seldom mentioned in the literature. In the present study, we revisited the question regarding the lesion–correlates of CFC, focusing now on how these relate to high-level motor deficits, and other cognitive co-morbidities. We used a sub-set (~2/3) of the patients reported in Chechalcz et al., 2014. All patients were assessed using the Birmingham Cognitive Screen (BCoS) (G. W. Humphreys, Bickerton, Samson, et al., 2012). To ensure homogeneity of

lesions we included only ischemic stroke patients and patients who were originally right-handed. To reduce potential effects of cognitive rehabilitation and post-stroke plasticity we included only patients tested within 1 month of the stroke. To create function-lesion mapping, the behavioral data were combined with clinical neuroimaging (CT) using VBM. We first systematically assessed the impact of potential cognitive co-morbidities on the mapping of lesion to CFC. This was done by controlling for different cognitive covariates in the general linear model. All the data was extracted from the BCoS (G. W. Humphreys, Bickerton, Samson, et al., 2012). We specifically examined the potential neural overlaps of the following deficits with CFC: 1) high-level manual processes (assessed by gesture tasks), 2) motor sequenced task requiring interaction with object (assessed by a multi-step object task), 3) visual spatial neglect (assessed by the Apples cancellation task), 4) sustained attention (the auditory attention task), and 5) high-level visual deficits, object agnosia (assessed by a picture naming task). To assess the validity of this comorbidity we counted single cases that demonstrate overlap of deficits. We further formally compared the different models focusing on specific regions of interests (ROIs).

Our main interest in this study was to investigate processes associated with the motor output in copying figures, which supporting high-level motor control, visuo-motor transformation and action sequencing aspects of CFC. Therefor a follow up analysis explored the neural structures underlying CFC in relation to sensory-motor cognitive components as measured by tasks such as

multi-step object use, gesture production, gesture recognition and meaningless gesture imitation. Principle component analysis (PCA) was used to tease apart the various cognitive components underlying CFC performance and its relations with other praxis measures. We used VBM to identify the neural correlate of the latent variables identified by the PCA.

3.3 Method

3.3.1 Participants

We used a sup-sample from the BUCS database (see detail in chapter 2). In this study, we first excluded patients with hemorrhagic lesions (N=43), patients who were left-handed (N=76), and patients not assessed on the CFC due to fatigue or other reasons (N=123). Furthermore, there was an exclusion of patients for whom all BCoS assessments took place more than one-month post-stroke (N=209) or had CT scans taken more than one-month post-stroke (N=155). This was done to increase homogeneity and reduced the potential effects of rehabilitation.

Finally, to prevent artifacts in the neuroimaging analyses, we removed patients who either did not have a CT scan or had enlarged ventricles or poor-quality CT scans (N=61). Our final sample included a total of 239 ischemic stroke patients (Chechalcz et al., 2014 included 358 patients, including left-handed, hemorrhage and more than 1-month post-stroke).

The study sample comprised of 103 males and 136 females. The average age was 70.67±12.88 years, and the average years of education were 12.50±2.87. Table 1 shows the demographic and clinical data for the patients.

3.3.2 Behavioral measures

We assessed the patients' cognitive profile using the BCoS battery (Humphreys et al., 2012). Besides the complex figure copy tasks, the following tasks in BCoS were used as covariates in the analysis including Multi-Step Object Use Test (MOT), Gesture Production (GP), Gesture Recognition (GR), Meaningless Gesture Imitation (MI), Orientation, Comprehension, Egocentric Neglect, Picture, Auditory attention and Barthel index (see details in chapter 2).

3.3.3 Neuroimaging assessment

All the patients in our study performed CT scans when they were admitted to the hospital. Pre-processing of brain images was performed in SPM12 (Statistical Parametric Mapping) (see details in chapter 2).

3.3.4 Behavioral Data analysis

Missing data for all covariates were replaced by the group average. The amount of missing data for each task ranged from 0% to 7.1% with an average of 1.79%. To estimate the relation between the CFC and demographic data

along with all the other covariates, Pearson's correlation (two-tailed) analyses were performed. All together we computed 16 correlations, and the results were corrected for multiple comparisons using Bonferroni correction.

To identify underlying cognitive components of the CFC we used a PCA analysis. Before the PCA analysis, a KMO and Bartlett's test was performed across the four praxis tasks (MOT, GP, GR, MI) and CFC. The KMO value is 0.786 (over 0.6) and the significance level for Bartlett's test (332.274) with 10 degrees of freedom is below 0.001. This result indicated that there was a correlation in the data selected and the distributions of data meet the assumptions of multivariate analysis. We re-scaled the raw scores of each task linearly to range between 0 and 20 to account for the difference of the maximum scores of the five tests. A PCA analysis then was computed on the rescaled data. The PCA teased apart the differential and shared components of the CFC with the four other praxis tests (See more details of PCA in chapter 2).

3.3.5 Voxel-based morphometry (VBM)

VBM analysis was used in our study to relate patients' behavior performance to the brain imaging data (see details in chapter 2). We set up the following models in our study.

Models using the CFC raw scores: Model 1 included the CFC raw data with no additional cognitive covariates. Model 2 added the 4 praxis tests from BCoS as covariates (CFC + Praxis). It included the following tests: Multi-step Object

Use, Gesture Production, Gesture Recognition, and Meaningless Gesture Imitation. Similarly, Model 3 added the scores for Egocentric Neglect (CFC + Praxis + Neglect). Mode 4 accounted for Auditory Attention Neglect (CFC + Praxis + Neglect + Attention) and model 5 controlled as well for Picture Naming (CFC + Praxis + Neglect + Attention +Picture naming).

To formally compare the impact these models had on the lesion pattern we computed the log evidence of each model in a region of interest, using the SPM function (spm.vb_regionF.m). The difference between the log evidence was used to infer which model fits the data best (a difference larger than 3 assume sufficient evidence to support one model over another). This was computed for regions that showed different levels of association with CFC as depending on the specified model (rIPC, aCG, see results), as well as on a region that was not affected by the models (rFFG). For these analyses, we extracted the probability of grey matter values in each patient from each ROI. This was represented as an Eigen variate of 6mm sphere centered around the peak (Supp Table 2 in appendix 1).

When the associations of the lesion and CFC were affected by the inclusion of specific covariates (rIPC, aCG), we run further analysis to establish the type of relations between the CFC, the brain region and the cognitive covariate. This was done using structural equation modeling implemented in SPSS-AMOS. We used the difference between AIC to compare between the models and infer the relation pattern. Detailed of compared model and results

are presented in the supplementary materials (Supp Table 3 in appendix 1).

Finally, we designed a model that included all the PCA components but did not include the cognitive covariates above. The analysis of the PCA-VBM focused on components that are most clearly and meaningfully (CFC loading > 0.4, and explained more than 10% variability) linked to latent variables associated with variability in CFC.

We focus on results that survived cluster level family wise error correction with voxel reliability of $p < .005$ uncorrected. This was done due to the nature of the data and the expected result pattern. The data was segmented grey matter images of patients with relatively large lesions. These images were smoothed to 12x12x12 FWHM, as recommended for VBM to adhere to the continuity assumption of the random field theory. Given this data, we anticipated that behavior would correlate with relatively large lesions (cluster size), rather than with focal peaks. The choice of $p<0.005$, uncorrected at the voxel level, was done as software typically relying on cluster level correction, tend to use a more lenient voxel threshold. For example, FSL, which relies on cluster threshold correction and by default, uses $p < .01$ uncorrected for the voxel threshold. For completeness we report in the tables all clusters that had more than 150 voxels, this is equivalent to $p < 0.003$ uncorrected at cluster level; the expected number of voxels by chance per cluster was 14.

3.4. Results

3.4.1 Behavioral Results

Complex Figure copy - The patients recruited in our study had an average score of 35.20 (SD: 11.30) in the CFC task; performance varied with 14 patients scoring less than 10, and 94 of them scoring higher than 40 (see Figure 8, for the distribution). Compared to the cut-off points established from the age-matched healthy controls (G. W. Humphreys, Bickerton, Samson, et al., 2012), 117 were classified as impaired.

Figure 8: the distribution of performance in the CFC task.

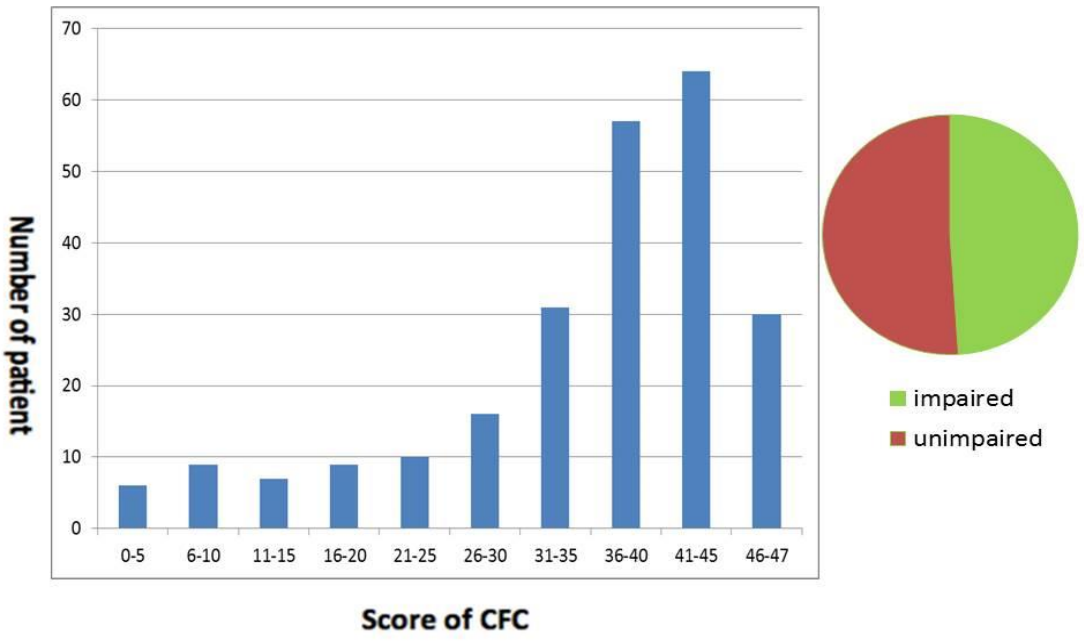


Fig 8. Participants who achieved an overall score of fewer than 42 points (age group of <64 years), 41 points (age group of 65–74 years), and 37 points (age group of >75 years) were classified as impaired in this task. About half of the patients got impaired in the CFC test.

Correlation of CFC with the demographic data - The correlation results are reported in Table 1. Gender and education did not affect performance on the CFC. Age had a weak negative impact, with older individuals performing worse than younger ones. The date from the stroke to the test was also weakly negatively correlated with CFC impairments. This may reflect a sampling bias, in which the more severe patients are likely to be assessed in the rehabilitation wards at a later time point after the stroke. As expected, the Barthel index and task comprehension had significant weak correlations with CFC, indicating that patients with worse performance in activities of daily living and worse understanding were likely to have a lower score in the CFC test. There were no significant correlations between CFC and whether the patient copied figures using their dominant hand or not.

Correlation of CFC with performance in other cognitive domains - Not surprisingly in the current study, CFC showed positive weak to moderate correlations with all the four praxis tasks: MOT, GP, MI, and GR.

CFC also correlated with visual spatial neglect. Patients who had page-based asymmetrical spatial attention (ego-centric neglect) were poorer at copying the complex figure (see Table 1), consistent with neglect impacting on performance on the CFC test. Finally, CFC also correlated with orientation, sustained attention and picture naming. These results demonstrated the prevalence of comorbid cognitive deficits in stroke patients (see also Bickerton et al., 2015). In order to describe in more detail, the prevalence of comorbidities

in our sample, we computed how many patients who were classified as impaired in CFC were also impaired in other cognitive domains. Of the 117 patients who showed a deficit in performing the CFC, the most common (56%) comorbidity was sustained attention assessed by the auditory attention task (Humphreys et al., 2012). In addition, 43% were also impaired in picture naming, suggesting the presence of object agnosia or aphasia. Visual neglect was observed in 39.3% of the patients impaired on CFC. Concerning the other apraxia tests, 39.9% of the patients were impaired at imitating meaningless gestures, 33.3% failed the multi-object use task, 26.5% the gesture production and finally 22.2% the gesture recognition tasks. These relatively high comorbidities highlight the importance of controlling for potential covarying cognitive deficits in lesion-symptom mapping. We also presented the inter-correlations of the cognitive data in supplementary table 1 in appendix 1.

Table 1: Demographic and clinical data on the patients. (n=239)

Demographic data			
Variables	Descriptive(mean/median or number of patients)	Range (SD)	Correlation with CFC
Gender (M/F)	103/136	N/A	0.120~
Using the Dominant Dand - CFC (yes/no)	210/26	N/A	0.066~
Age	70.67/73.00	12.88	-0.255**
Education Year	11.50/11.00	2.87	0.090
Scan Tme Since Stroke Days	2.80/1.00	4.85	0.002
BCoS in Days	12.32/11.00	8.23	-0.250**
Barthel Index	14.66/16.00	5.14	0.333**
Cognitive data			

Orientation (max=8)	7.52/8	1.34	0.264**
Auditory Attention (max=54)	43.17/50.00	14.08	0.414**
Comprehension (max=3)	2.85/3	0.39	0.294**
Multi Step Object Use (max=12)	10.26/12.00	3.33	0.318**
Gesture Production (max=12)	10.60/12.00	2.53	0.382**
Gesture Recognition (max=6)	4.98/5.00	1.19	0.226**
Meaningless Imitation (max=12)	9.76/10.00	2.58	0.489**
Picture Naming (max=14)	10.74/12	3.42	0.413**
Ego Centric Neglect (max=20)	2.47/1	3.78	-0.303**
Complex Figure Copy(max=47)	35.20/39.00	11.30	N/A

Table 1: ** P<0.003(after Bonferroni correction p<0.05/16)
~using point biserial correlation test

Given the potential relations between the various aspects of apraxia and poor performance on CFC, plus the relatively high correlation of the praxis tasks and CFC, we used PCA to identify the underlying cognitive components of CFC. We applied a PCA to the re-scaled raw scores of the five praxis tests to identify the shared and differential components between CFC and other praxis tests. We focused on the components that involved CFC.

Three components, involving the CFC explained 86% of the variability (Table 2). As PCA is a data-driven approach, interpretation of the component's meaning is speculative to a degree. Here we offered one possible interpretation but discussed alternatives interpretations of the components in the discussion. The first component was shared among all the 5 tests (all the tasks loading ranged from the absolute value of 0.34 to 0.56) and explained 53% of the variability. The least contributing variable was the gesture recognition task. We

assumed that this component represented high-level motor control, required by all praxis tasks. The second component differentiated primarily the CFC from the MOT (score high in CFC and impaired on MOT). This component explained 18% of the variability. We assumed that component 2 represented the cognitive process correlated to visuo-motor transformation. Finally, the third component was representative of the shared process underlying CFC and MOT and accounted for 15% of the variability. These two tasks required interaction with objects and planning of sequence actions, which suggests that component 3 represents interacting with objects and action planning. We note that component 4, is loaded primarily on the gesture recognition task (0.61) but also on CFC (.34), dissociating both from meaningless imitation (-0.71). This component explained only 8% of the variability in the data. We did not include component 4 in any further analysis, as we believe it primarily represent dissociation between the two gesture tasks. Besides, the contribution of CFC was smaller than our threshold, as well as the amount of variability explained by this component.

Table 2: PCA results on the re-scaled raw scores of the five praxis tests

Tasks	PC1: high-level motor control	PC2: visuo-motor transformation in drawing	PC3: interacting with objects and planning,	PC4	PC5
CFC	0.42	0.62	0.57	0.34	0.02
MOT	0.56	-0.74	0.36	0.04	0.06

GP	0.42	0.16	-0.45	-0.10	0.76
GR	0.34	-0.03	-0.57	0.61	-0.45
MI	0.46	0.21	-0.13	-0.71	-0.47
Exp. Var.	**53%**	**18%**	**15%**	**8%**	**6%**

Table 2: Abbreviation: CFC: complex figure copy; MOT: multi-step object use; GP: gesture production; GR: gesture recognition; MI: meaningless imitation.

In a supplementary analysis, we included the other cognitive tests picture naming, neglect, auditory attention in the PCA (Supp Table 4 in Appendix 1). The first two components were similar to the ones observed when including only the praxis tests. While the third component, which linked CFC and MOT and differentiated them from the other tasks, also loaded on neglect. This suggests that the cognitive mechanism underlying this third component may also support visual attention processing. Taken together when considering the 2nd component dissociating CFC from MOT in both PCA analyses; we suggest that this component is more likely to reflect visual motor transformation processes rather than visual-spatial processing (as neglect was loaded on the 3rd component).

3.4.2 Neuroimaging Results

We related the behavioral measures to the neuroimaging data to explore the lesion-symptom correlates with the CFC.

3.4.2.1 VBM based on raw scores of the CFC

VBM analysis results are reported in Table 3 and Figure 9. Based on the raw scores of the CFC, with no additional cognitive covariates, there was a significant positive relationship between performance and voxels in the right inferior parietal lobe, right fusiform, bilateral lingual gyrus, and bilateral thalamus (model 1). The significant correlations between worse performance in CFC and lesions in bilateral thalamus, bilateral lingual gyrus and right fusiform were observed even after we controlled for the other four praxis tests (model 2), egocentric neglect (model 3), verbal working memory, selection and sustained attention (the auditory attention test from BCoS) (model 4) and picture naming (model 5). Interestingly, after including the praxis covariates (model 2-5) voxels in the right anterior cingulate gyrus also correlated with CFC performance. In summary, the results suggest that bilateral thalamus, lingual, right anterior cingulate and right fusiform lead to an impaired ability to copy a complex figure even after controlling for various cognitive co-morbidities.

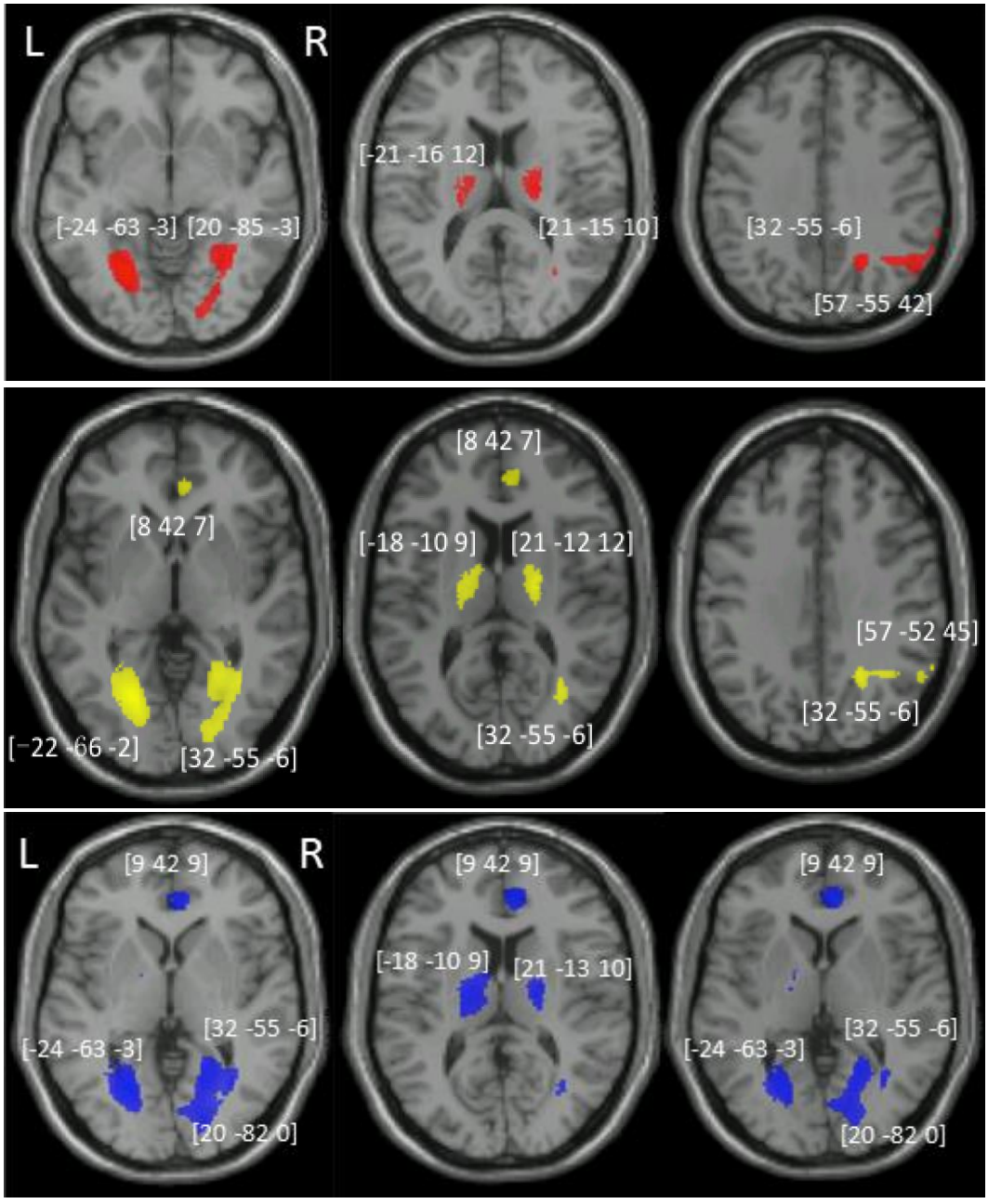
Table 3: VBM analysis based on the raw CFC scores after controlling for other correlated tests.

			Successively control for other cognitive tests				
Anatomy	BA		No cognitive covariate	Praxis	Neglect	Attention	Pictures Naming
Parietal lobe							
R IPG	39	Cluster	1040**	934**	NA	NA	NA
		Peak	4.01	4.29			
		x,y,z	[57 -55 42]	[57 -52 5]			
Occipital lobe							
R fusiform (extend to precun)	37	Cluster	448**	1810**	2698**	3185**	3062**
		Peak	3.46	4.02	4.29	4.34	4.29
		x,y,z	[32 -55 -6]	[32 -55 -6]	[32 -55 -6]	[32 -55 -6]	[32 -55 -6]
R Lingual	18	Cluster	210	NA	%	NA	%
		Peak	2.95				
		x,y,z	[20 -85 -3]		[22 -82 -2]		[20 -82 0]
L Lingual	19	Cluster	1071**	1435**	1365**	1658**	1555**
		Peak	3.81	4.00	4.03	4.32	4.19
		x,y,z	[-24 -63 -3]	[-22 -66 -2]	[-22 -66 -3]	[-22 -66 -3]	[-24 -63 -3]
Subcortical							
R Thalamus		Cluster	437**	380**	224**	165	305*
		Peak	3.69	3.64	3.48	3.40	3.65
		x,y,z	[21 -15 10]	[21 -12 12]	[21 -12 12]	[21 -12 12]	[21 -13 10]
L thalamus		Cluster	270	783**	750**	437**	1363**
		Peak	3.31	3.48	3.57	3.47	3.78
		x,y,z	[-21 -16 12]	[-18 -10 9]	[-18 -10 9]	[-18 -10 9]	[-18 -10 9]
Frontal							

R aCG		Cluster	NA	380**	393**	994**	961**
		Peak		3.30	3.39	3.80	3.74
		x,y,z		[8 42 7]	[8 42 7]	[8 42 7]	[9 42 9]
Cerebellum							
R cerebellum - vermis		Cluster	NA	NA	178	NA	NA
		Peak			3.22		
		x,y,z			[4 -52 -42]		

Table 3: FWE-correction at cluster level, *p < 0.05; **p < 0.01. % right lingual cluster was part of the R FFG cluster reported in the row above it Abbreviation: R: right; L: left; IPG: inferior parietal gyrus; aCG: anterior cingulate gyrus; Cluster: Cluster size; Peak: Peak Z; x,y,z: x,y,z(mm)

Figure 9: The VBM results on the CFC and after controlled for other correlated tests.



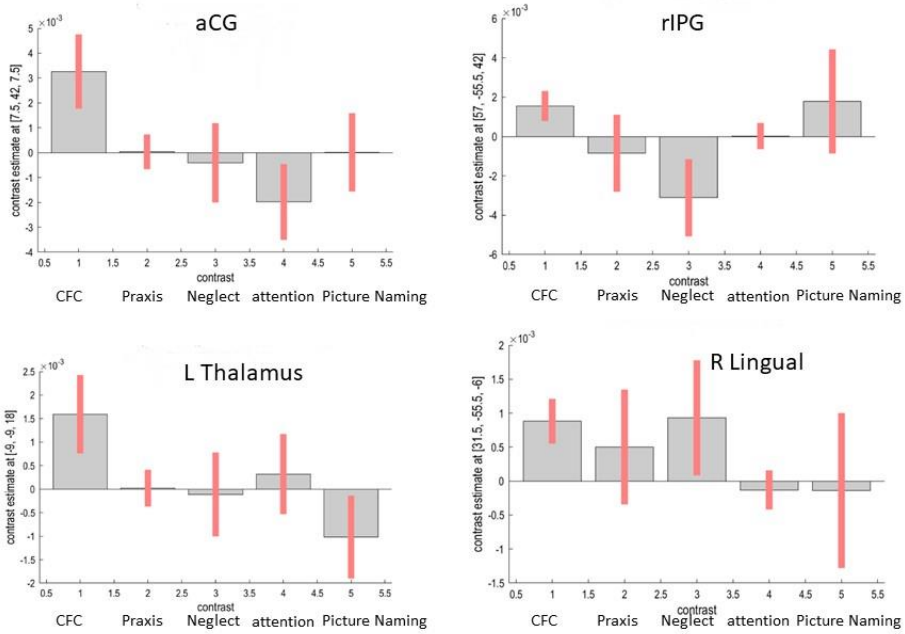


Fig 9: VBM results showing voxels corresponding to grey matter damage in (red) CFC only, (yellow) after controlling for the other four praxis tasks, (blue) after controlling for the praxis task, egocentric neglect, auditory attention and picture naming task. The function-lesion maps are overlaid on axial T1-weighted MRI slices of the single subject canonical template provided by SPM. The numbers in brackets represent the peak of the clusters given in MNI coordinates. Notice that lesion in aCG was reliably associated with CFC impairment only after we added the four praxis tests as covariates; while lesion to right IPG became unreliable after we added egocentric neglect as a covariate.

The charts representing effect size (beta) for complex figure copy task and the average effect size for the praxis (gesture and MO), visual neglect, visual attention, and picture naming tasks. Note that visual neglect variable, indicate higher score is equated with poorer performance which is opposite than all the other variables. Therefore, negative beta shows the expected grey matter pattern of less grey matter poorer performance. The error bars are 90% confidence interval of the effect size.

3.4.2.2 Model Comparison using log evidence

We formally compared the five models in three regions of interest (ROIs) using log evidence. 1) The fusiform gyrus was least affected by the changes in the model covariates. For this region the best model was the 3rd model where

we included the four praxis tasks and the neglect scores. 2) The right IPC that showed below threshold association with CFC once we added the neglect covariate. For this region the best model was also the 3rd one which included praxis and neglect; 3) The aCG which showed above threshold association with CFC after we controlled for the praxis tasks. Here the best model was the 1st one, where there was no control for any cognitive tasks (apart from orientation). These results demonstrate that the best-fitted model varies depending on the region selected and there is no one correct answer that fits all (Supp Table 2 in appendix 1).

3.4.2.3 Comparing the relations between the CFC, ROI and cognitive covariates

We used SEM to investigate in more details the relations between CFC, neglect and right IPC. We used the AIC values to select the best fitting model, which take into account the fitting accuracy and model complexity (number of parameters). We established three different models to described the relations between the three variables: 1) rIPC independently supports neglect and CFC, 2) rIPC involvement in CFC is fully mediated by neglect, and 3) rIPC involvement in CFC is partially mediated by neglect. Based on the value of AIC, the analysis suggested that the best model is the 3rd one, in which the correlation of rIPC and CFC are partially mediated via neglect.

A similar analysis was performed to explore the relation between aCG, CFC and the praxis tasks. The result indicated that the best model was that aCG and Praxis tasks independently explain CFC performances. In other words,

variability in CFC that cannot be accounted for praxis deficits was associated with aCG lesion. (see more details in Supp Table 3 in appendix 1).

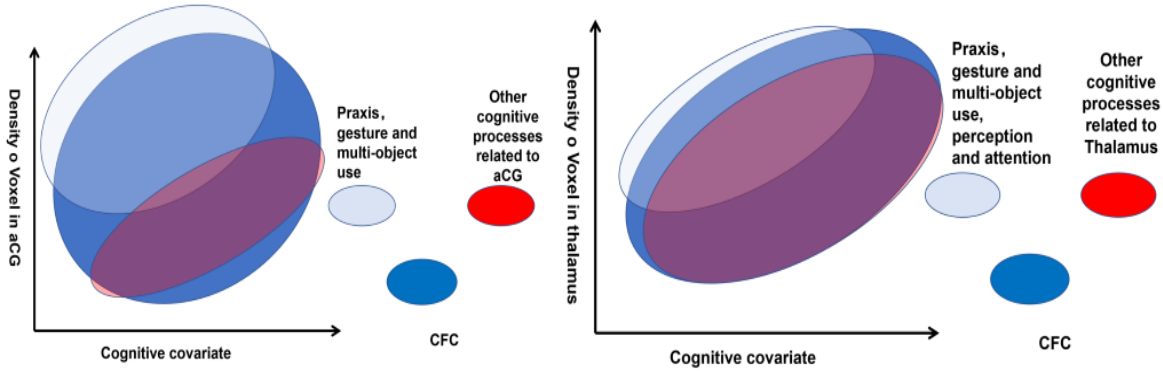
We display two schematic figures (Figure 10) to help better understand the correlation between patients' performance of CFC and the brain regions, one for the thalamus and one for the aCG. First, it is important to note that the cognitive covariates (gesture, MOT and attention) correlated with the CFC. Hence these are not orthogonal measures.

In the aCG (left), when considering CFC as a whole, there were no relations between density and CFC performances (dark blue circle). This lack of relations may emerge because aCG contributes little to the part of CFC which is also shared with the gesture and the object use tasks (light blue circle). But once removing variability due to these praxis related tasks the relation between aCG density and CFC are revealed (oval like). Removing variability due to other cognitive processes (especially attention and agnosia) further removed noise from the unexplained variance.

In the thalamus, the relations between the CFC and thalamus exist before and after controlling for the other cognitive tasks. This might be because (i) the thalamus also contributes to these gesture and object use tasks (figure on the right); or (ii) the strength of the correlation with CFC is strong enough to detect despite the large 'noise'. Examining the statistical measures of left and right thalamus, it appears that by accounting for gesture, object use perception and attention the correlations slightly weakens; suggesting the contribution of the

right thalamus to CFC is partly driven by these other cognitive covariates. While in the left thalamus the relation actually strengthens, similar to aCG. As these are just informal observations, interpretation should be made with cautious.

Figure 10. Correlation between patients' performance of CFC and the brain regions



3.4.2.4 VBM based on PCA scores for complex figure copy.

These results are presented in Table 4 and Figure 11. The analysis focused on the first three components (PC1, PC2, PC3), each explained more than 10% of the variability in the data. As the main aim of the current study was to map lesion associated with CFC, we selected components that had a clear and meaningful association with CFC. We further focused on contrasts linked to latent variables in CFC. In other words, we mapped lesions that predict poorer performances of CFC.

Table 4 VBM analysis based on the three components indicated by the PCA.

Table 4a CP1 shared component (motor control)

Anatomy	BA	cluster size	peak Z	x,y,z
R thalamus	NA	**405****	**3.36**	**22 -33 16**
L IPG	40	**172**	**3.33**	**-52 -43 40**
R MFG	6	**398****	**3.17**	**28 9 48**
L postcentral G	4	**272***	**3.25**	**-51 -10 40**

Table 4b CP2: CFC > MOT (visuo-motor transformation)

Anatomy	BA	cluster size	peak Z	x,y,z
R MOG extending to R fusiform	19	**1885****	**3.98**	**30 -81 3**
L LG	19	**1031****	**3.75**	**-26 -63 -2**
L Rolandic Oper	48	**433****	**3.66**	**-39 -30 27**

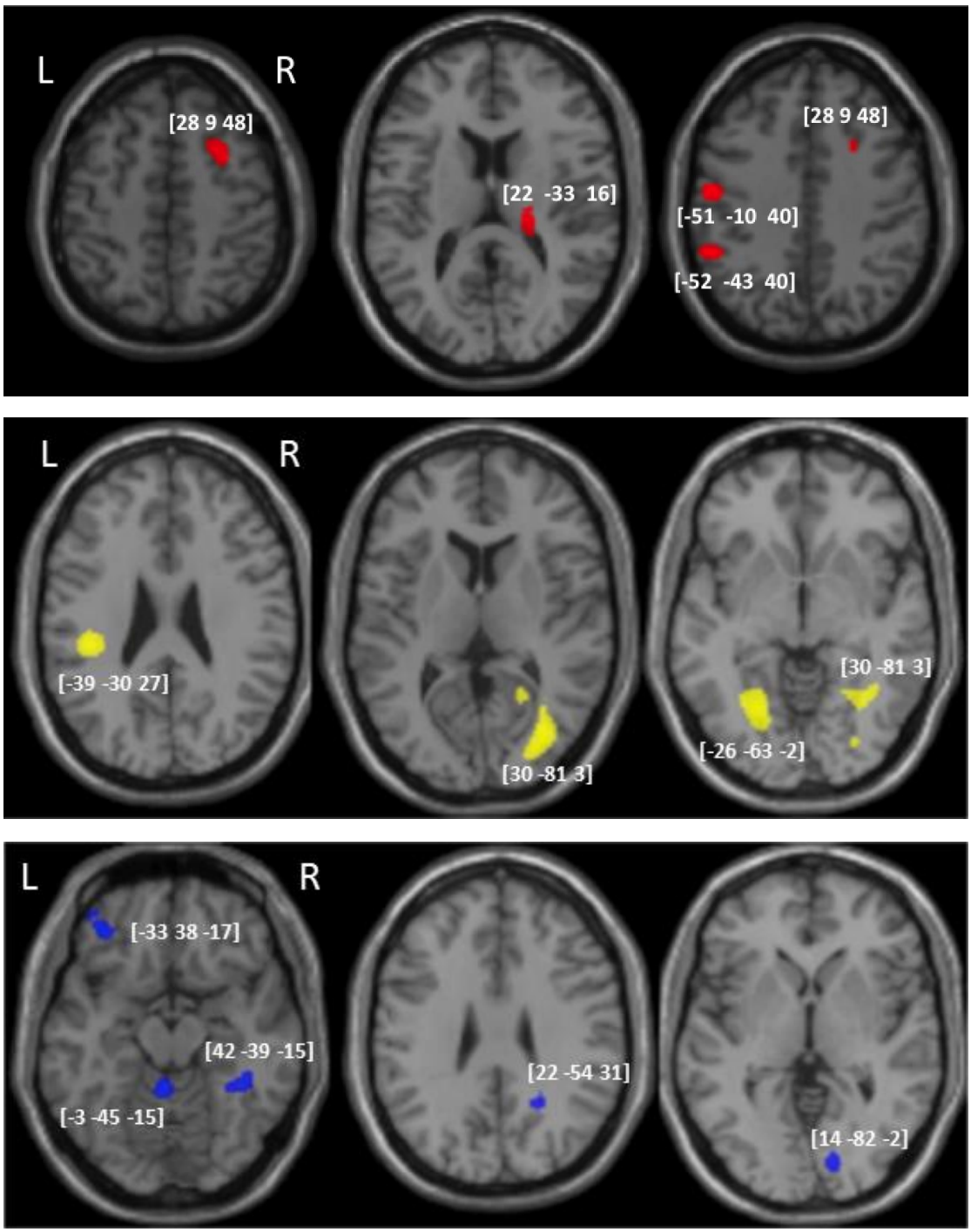
Table 4C CP3 CFC + MOT > Gesture task (interacting with objects and planning)

Anatomy	BA	cluster size	peak Z	x,y,z
L inf_frontal orb	47	**260***	**3.97**	**-33 38 -17**
R LG	18	**190**	**3.04**	**14 -84 -2**
R precuneus		**163**	**3.24**	**22 -54 31**
R fusiform	37	**399****	**3.25**	**42 -39 -15**
cerebellum	NA	**298***	**3.39**	**-3 -45 -15**

Table 4: FWE-correction at cluster level, *p < 0.05; **p < 0.01. Acronyms: R: right; L: left; BA: brodmann area; IPG: inferior parietal gyrus; MFG: middle frontal gyrus; MOG: middle occipital gyrus; aCG: anterior cingulate gyrus; LG: lingual gyrus; Rolandic Oper: rolandic operculum; inf_frontal orb: inferior frontal orbital gyrus; Cluster: Cluster size; Peak: Peak Z; x,y,z: x,y,z(mm)

Based on the loading pattern of the first shared component, we suggest that it represents high-level motor control. These were associated with reduced density in GM of the right thalamus, the right medial frontal cortex, and the left postcentral gyri. The second component, we identified with visuo-motor transformation, poorer CFC performances on this component were associated with reduced GM in the right lateral occipital, right fusiform, left lingual and right rolandic operculum gyri within the inferior parietal lobe. Finally, we observed that the third component associated with object interactions/neglect linked to lesions to the left inferior frontal orbital, right fusiform and cerebellum.

Figure 11 VBM analysis based on the first three components from PCA result



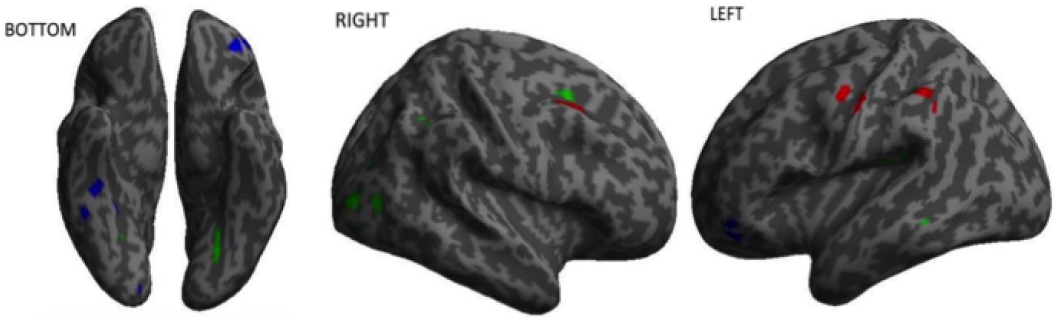


Fig 11: VBM results showing voxels corresponding to grey matter damage in (red) the first shared component refereeing to high-level control, (yellow) the second component indicating visual-motor transformation, and (blue) the third component representing interacting with objects and planning in multi-step task. The function-lesion maps are overlaid on axial T1-weighted MRI slices of the single subject canonical template provided by SPM. The numbers in brackets represent the peak of the clusters given in MNI coordinates.

A supplementary analysis (Supp Figure 1, Supp Table 5 in appendix 1) included the PCA components that were derived from all the eight cognitive tasks. The lesions associated with the shared (PCA1) and the drawing (PCA2) components were similar to the one reported above - though the right thalamus was no longer reliably associated with shared deficits across tasks. More interestingly, as component 3 was now loaded on the CFC, MOT and neglect, it was primarily associated with lesions to the right inferior parietal cortices, suggesting that this component reflecting spatial attention and not only being unique to the visuo-motor transformations associated with drawing.

3.5 Discussion

The current study aimed to reveal the underlying cognitive-neural components associated with copying a complex figure, as routinely tested in neuropsychological batteries. We first observed high comorbidities of failure to copy a complex figure with sustained and visual attention deficits. High comorbidities were also observed with picture naming and the various praxis tasks. The behavioral results are consistent with the idea that CFC performance depends on common high-level motor coding, shared with other praxis tasks, as well as spatial attention, assessed using visual cancellation.

The VBM results showed that CFC was associated with lesions to bi-lateral thalamus and lingual gyri, the right inferior parietal lobe, and fusiform gyrus. Interestingly, after controlling for spatial neglect, the right inferior parietal lobe showed no significant correlation with CFC. Further SEM analysis showed that lesion to the rIPC correlated with deficits of neglect and CFC; with the later deficits being partly mediated by the neglect deficits. In contrast, lesions to the anterior cingular gyrus (aCG) were associated with CFC performance after we controlled for the four praxis tests. Further SEM analysis showed that aCG explained variability in CFC that was not accounted for the four praxis tasks.

Focusing on aspects of the CFC linked to high-level motor control, we next applied PCA to dissociate underlying cognitive components that contributed to poor CFC performance. There were three main components when CFC

performance was considered alongside performance on the praxis tests. The first component explained variability across the five praxis tasks, representing shared involvement of high-level motor control. Low scores in this shared component correlated with lesions to the left postcentral gyrus, the right thalamus, and the middle frontal gyrus. The second component was unique to figure copy and dissociated it from the multi-step object task, suggesting that it reflects the visuo-motor transformations required specifically for drawing. Impairments in this process were associated with lesions to the right middle occipital gyrus, the left lingual gyrus, and rolandic operculum. Finally, a third component linked the CFC and the multistep object tasks separate from the gesture tasks. Without spatial attention taken into account, deficits were predicted by lesions to the left inferior frontal orbital gyrus, the right fusiform and cerebellum. We discuss each of these findings separately next.

3.5.1 Incidence and comorbidity of deficit in CFC

Within one month post an ischemic stroke, about half of the patients in our study showed impairments in the CFC task from the BCoS battery (G. W. Humphreys, Bickerton, Samson, et al., 2012). Considering that the analysis excluded patients who were unable to concentrate for at least 30 minutes or had severe limb paralysis, the incidence of CFC impairment maybe even higher.

The ability to copy a complex figure was found to be associated with

several cognitive functions, revealed by both correlation analysis and the prevalence of comorbid impairments. Significant and positive relationships with CFC were found with the four praxis tasks, neglect, picture naming, and auditory attention tests. The relatively high-level of symptom-association may not be surprising given the multifaceted processes required for successfully copying a figure (Sommers, 1989). The high prevalence of deficits in complex figure copy and the other praxis tasks was also evident in the PCA analysis which revealed that most of the variability in patients' performance could be explained by a single shared component. We interpreted this component to reflect high-level motor control. As it was more weighted on the tasks that involved manual action compared with the gesture recognition task. However, we cannot rule out the possibility that this component also reflects stroke severity. Or any other potential shared latent variables that affect all five tasks.

The PCA analysis also revealed dissociations between CFC and the other praxis task. Specifically, one component dissociated CFC from the gesture and object use task that we propose reflects visuo-motor transformation processes in drawing. Could that component be related to visual-spatial processing primarily? Visuo-motor transformation is hypothesized to involve two main steps, visual perception and eye-hand coordination, including the processes of visuospatial perception. Complex figure copying is a visually guided copying task requiring not only visuospatial processes but also eye-hand coordination. Furthermore, in the supplementary analysis, we included neglect (assessing

visuospatial processing) in the PCA analysis. In this analysis, we again observed a component that primarily dissociated CFC from MOT, with minimal contribution from neglect. This component was associated with a similar lesion map as the one in our main analysis (see below). Taken together, we therefor interpreted this component to primarily depict visual-motor transformation processing.

A third relevant component grouped CFC performance with performance on the multi-step object use tasks, distinguishing them from the gesture tasks. We suggest that this reflects interaction with objects and the planning of sequenced actions. As the gesture tasks are a single action step task compared to CFC and multi-step object used which are multi-step action, and the latter two tasks involving using tools (pen or torch). Taken together the findings suggested that deficits in CFC were linked to a general higher order motor deficit, but they also demonstrated an involvement of spatial-visual attention, organization and planning processes. The relation between the different praxis tasks and CFC is also manifested in the imaging data, which we described below.

The analysis of the behavioral results suggests sustained attention as potentially contributing to performance on the CFC. This is consistent with sustained attention being a basic resource for maintaining a cognitive set (Sommers, 1989). For example, beyond planning and organization, patients need to be able to maintain their focus and concentration on the task to enable

successful task completion. However, we did not observe a specific component related to the shared variability of sustained attention and CFC in the PCA results (Supp Table 4 in appendix 1). Furthermore, none of the identified clusters associated with CFC were modulated by performance in the sustained attention task. This may reflect the fact that sustained attention underpins success in any cognitive task, and is not a unique requirement for CFC.

As predicted, visual neglect was prevalent in patients who failed the CFC task. Spatial neglect deficits may hinder CFC due to poor visual spatial scanning and spatial representation (Behrmann and Plaut, 2001; Chechlacz et al., 2014). We also observed a high prevalence of comorbidity of CFC and picture naming deficits. As mentioned before, picture naming impairments are found in both aphasia and agnosia. Praxis deficits are commonly reported together with aphasia (Goldenberg and Spatt 2009; though see Roby-Brami et al., 2012). On the other hand, no clear link between CFC and agnosia has been found (Humphreys and Riddoch, 1987), despite having visual input analysis as a common basis for both tasks. The current imaging analysis suggests that CFC relies on processing at posterior and ventral parts of the occipital cortex (see below), similar to picture naming (Lau et al., 2015).

Clinical comorbidities may potentially be explained in two ways. Firstly, different tasks may rely on the same underlying cognitive processes. Secondly, it is possible that these tasks utilize different cognitive processes but the neural structures supporting them share the same vascular territory and hence

ischemic stroke is likely to affect both tasks together. To test these two explanations, we used two approaches. At the neural level we tested the impact of the different cognitive tests (used as covariates) on the mapping of CFC to lesion structure. We also computed a principle component analysis identifying shared and dissociated neural components of CFC and the 4 praxis tasks.

Our results suggest that the co-morbidity of gesture tasks and CFC can be explained by shared cognitive processes that support high-level motor control and are associated with lesions to frontal motor associated cortices (see Table 4). Similarly, spatial neglect and CFC both rely on intact spatial attention processing mediated via the right inferior parietal cortex (see Table 3 and Supp Table 5 in appendix 1). Co-morbidity of the multi-step object task and CFC can be explained by the involvement of motor schemas, interaction with objects and the need for planning and attentional control in both these tasks. Finally, neither the VBM nor the PCA results were affected by the inclusion of picture naming and sustain attention in the analyses. We therefore suggest that co-morbidities of these two tasks and CFC cannot be explained by the shared underlying specific neural-cognitive mechanisms that we have identified here. In such cases, the data could be driven by large lesions affecting neighboring regions, or shared cognitive components that were not identified here.

3.5.2 Neural structures correlated with CFC

From the VBM results, we found that bilateral thalami and lingual gyri, the right inferior parietal lobe and fusiform were correlated with the CFC raw score. The correlation of the raw CFC score and the right inferior parietal lobe disappeared after we controlled for neglect. Supplementary analyses also revealed that damage to the right IPC also correlated with the shared cognitive component that associated deficits in spatial neglect and CFC. To further explore the relation between CFC, neglect and rIPC, we set up three structural equation models that differ in their relation structure. Formal model comparison revealed that the best fitting model describes the correlation of rIPC and CFC as partially mediated via neglect (see details in Supp Table 3 in appendix 1).

This result expanded on findings reported by Biesbroek et al., 2014. The later authors report that the right inferior parietal lesion was associated with CFC deficits even after excluding patients who showed spatial neglect. Furthermore, using partially overlapping patients' samples of the same dataset, Chechlacz et al. (2014) reported that lesions within the right inferior parietal lobe were associated with left omission errors in CFC task (see also Tarnel et al., 2008 for clock drawing task). The right inferior parietal cortex is often reported to be associated with spatial biases(Chechlacz et al., 2014, 2010; Chechlacz, Rotshtein, Hansen, et al., 2012; Chechlacz, Rotshtein, Roberts, et al., 2012; Mort et al., 2003; Possin et al., 2011). Taken together, we suggest that deficits in CFC following damage to right inferior parietal emerged from

impairment to attentional and hand-visual coordination processes. The observed pattern was similar to the pattern of the right thalamus, where the addition of the attentional covariate weakened the relations between CFC and the brain structure (Table 3). I discuss this point below in more detail.

Interestingly, when including the four praxis tasks in the model we also observed that lesions to the aCG reliably predicted performance in CFC. To further investigate the relation between aCG, CFC and the praxis tasks, we use SEM (see above). The results indicated that the best fitting model describes aCG contribution to CFC but not to praxis, and independently praxis is associated with CFC. In other words, variability in CFC that cannot be accounted for by praxis deficits was associated to aCG lesion.

This matches the previous case study reports that damage to the aCG leads to impairments in CFC (Peru, Pavesi, and Campello, 2004). Lesions of the aCG are associated with impairments of executive functions, including planning a sequence of processes, which may cause worse performance in CFC (Peru, Pavesi, and Campello, 2004).

We also found that reduced grey matter integrity in bilateral lingual gyri, bilateral thalamus and right fusiform was associated with poor performance in CFC even after considering deficits in picture naming, spatial and auditory attention, and praxis. This suggests that these structures specifically contribute to processes underlying figure copying that cannot be explained by deficits in other cognitive functions. The involvement of the lingual gyri (Ogawa & Inui,

2009) and ventral occipital structures (Gowen & Miall, 2007; Ogawa & Inui, 2009) is in agreement with activation foci reported for a drawing task. The lingual lesion has also been reported to be associated with misplacing local elements (Chechlacz et al., 2014) and to be involved in tasks requiring the encoding of complex visual pictures, but without drawing (Machielsen et al., 2000). Taken together our data indicate that these posterior ventral occipital cortices may support the visual analysis of the elements and their relations in complex figures.

The association between damage to the bi-lateral thalami, which are part of the basal ganglia, observed here and also in Chechlacz et al. (2014), is in agreement with previous observations of the central role of this region supporting praxis (Leiguarda & Marsden, 2000). It has been argued that the basal ganglia support action sequencing and interactions with objects (Leiguarda & Marsden, 2000). We note too that the thalamus can also modulate attentional functions more generally (Brown, Schneider, and Lidsky, 1997).

We next used the components identified in the PCA, to better understand the different neuro-cognitive processes associated with CFC. The first shared component was associated with reduced density in grey matter in the right thalamus, the right middle frontal gyrus (MFG) and the left postcentral gyrus. The observation that these regions support all tasks requiring higher-level motor function is in line with previous neuropsychological reports and functional imaging studies (Leiguarda & Marsden, 2000). These further strengthen the

argument that deficits in CFC associated with lesions to these regions should be viewed as a praxis problem of higher-level motor control.

The second component loaded on the CFC alone and differentiated CFC from the MOT. This component correlated with lesions in the right middle occipital gyrus (extending to the fusiform gyrus), the left lingual gyrus and the left Rolandic operculum. As mentioned above, the lingual and middle occipital gyri have previously been found to be specifically important to drawing as opposed to simple tracing of a figure (Ogawa & Inui, 2009); while the Rolandic operculum has been reported to be involved in eye-hand coordination involved in drawing(E. Gowen & Miall, 2007). We therefore conclude that these regions support visuo-motor transformations that are required for drawing, use of pen, and not for other processes required when manually interacting with objects

The third component dissociated the CFC and MOT from the three other gesture tasks. This component was associated with lesions to the left inferior frontal orbital gyrus, right anterior fusiform and the cerebellum-vermis. The cerebellum-vermis is frequently involved in tasks that rely on tracing and drawing eye-hand coordination (E. Gowen & Miall, 2007). The cerebellum (Higuchi, Imamizu, and Kawato, 2007) and right FFG (see review Beauchamp and Martin, 2007) are assumed to form part of the tool use network. The inferior frontal gyrus has been implicated in construction tasks (such as drawing) that specifically rely on memory (Ogawa & Inui, 2009).

Previous studies (Chechlacz et al., 2014; Possin et al., 2011; Biesbroek et

al., 2014) highlight the importance of the visual perception process in CFC. Beyond visual perception, our data support three main neuro-cognitive networks associated with CFC. A shared motor schema network associated with lesions to frontal motor cortices and thalamus; a network linked to visuo-motor transformation in occipital and inferior parietal-sensory cortices; and processes of planning and sequential organization of action associated with cerebellum-vermis and fusiform gyrus lesions.

3.5.3 Methodological Considerations

The current study used a sub-set of the data reported by Chechlacz's study (Chechlacz et al. 2014;) and also a different analyses approach. It is therefore, worthwhile considering the impact of these changes on the observed and reported results. In the first model, using CFC raw scores Chechlacz linked CFC only to subcortical lesions within the right hemisphere. In the current study, however, we observed a larger network that included the right basal ganglia and thalamus, but also highlighted the contribution of the left thalamus, bi-lateral lingual, right fusiform and right inferior parietal to CFC. The difference between these two analysis approaches is puzzling. We note that the threshold used in Chechalcz et al. (2014) was very conservative (FWE of $p < 0.001$) which potentially may have led to increasing in type II error, where potentially reliable lesions failed to rich significance. Furthermore, it could be that the more

homogenous patient sample used here reduced the overall variability and led to an increase in the statistical power.

Nevertheless, the two studies using different analysis approaches provide complementary results. Chechalcz and colleagues conducted a detailed analysis of error types primarily reflecting visuo-perceptual deficits; in contrast here, the analysis used a data-driven approach and an analysis of symptom comorbidity to reveal the lesion associated with high-level motor processing, visuomotor transformation and object use/action sequencing.

Interesting, in line with Chechlacz et al. (2014) both analyses highlighted the importance of right parietal cortex for visuo-spatial processing in CFC. Chechlacz et al. demonstrated this using an analysis of different error types while in the current study it was shown by using performance on an independent spatial attention task. Our results indicated that the correlation between rIPC and CFC are partially mediated via neglect. In contrast to Chechlacz et al.'s analysis, we showed that the increase in misses reported to be associated with the right MFG, is potentially driven by a high-level motor deficit (here derived in the analysis of the first component).

Both analyses also highlighted the importance of the lingual gyrus and ventral visual stream to CFC; Chechlacz et al., demonstrated that these regions affected the ability to correctly position a feature within the figure. In the current study, these regions were associated uniquely with CFC, and associated with visuo-motor transformation. Linking the results, we can suggest the process of

positioning features in objects relies on visuo-motor transformation processes specific to drawing.

In this study, we used PCA analysis to identify latent variables associated with complex figure copy. We note that PCA is a data-driven approach. Therefore, interpretation of the component's meaning is speculative to a degree. Interpretation is done based on the weighting of the tasks on the component and the assumption regarding the processes required to complete each task. the structure of the observed components, we reported the number of cases showing the dissociation observed by the PCA analysis. However, we acknowledge that these interpretations should be made with cautious.

3.6 Conclusion

The current study identified dissociable networks supporting different aspects of visuo-motor performance for copying complex figures. Specifically, we identified three networks: sensory-motor cortex for high-level motor control, posterior occipital and operculum for visual-motor transformation, and cerebellum-temporal and IFG for multi-step tasks that require interaction with objects.

Afterword

In this study, we first observed high comorbidities and significant correlation of failure to copy a complex figure with related cognitive tasks. These behavioral results are consistent with the neuronal recycling hypothesis that CFC performance depends on common high-level motor coding, shared with other praxis tasks, as well as spatial attention, assessed using visual cancellation.

Our study showed that after controlled for other related cognitive tasks, patients' performance in CFC was associated with lesions to bi-lateral thalamus and lingual gyri, the right fusiform gyrus and the anterior cingular gyrus (aCG). However, since we didn't include all the cognitive tasks in the models, such as other pen using task (writing), we could not say it supports the existence of a pure specific figure copying region (region that only contributing to figure copy).

This chapter also tried to delineate different components of copying figures mainly focused on the motor aspect. Combining PCA and VBM we found three motor networks contributing to writing. (1) a component associated with high-level motor control common to different measures of apraxia and linked to the left postcentral gyrus, the right thalamus and middle frontal gyrus; (2) a visuomotor transformation component unique to the CFC and associated with lesions to the posterior occipital and sensory cortices; (3) a component associated with multistep object use tasks which was correlated with lesions to

the left inferior frontal orbital gyrus, the right fusiform and cerebellum. According to the neuronal recycling hypothesis, the neural basis of fine motor control should be similar for both writing and copying figures which both require using a pen. We will look into a similar component in word and number writing tasks in the fourth chapter.

Charter 4

Cognitive features that dissociate stroke patients with impaired and intact writing abilities

Foreword

The high comorbidities and correlation in figure copy with other relative tasks supported the idea that copying figures rely on related basic abilities. And it raised a question that if these recent activities rely on general cognitive activities, then it would be possible to predict patients' performance by their basic cognitive abilities. To verify this assumption, we used all the cognitive features extracted from the Birmingham Cognitive Screen to set up classification model. We assumed that basic general cognitive function can be assessed by other relative cognitive tasks. Then the classification model should be able to predict patients' ability to writing. Machine learning was used to assess whether writing impairment can be reliably classified patients with or without writing deficits in two countries, China and the UK. We explored the sensitivity and specificity of these models in our study. Another aim of this chapter is to explore the difference between the two language systems. We will compare their top-ranking features in the classification model separately.

4.1 Abstract

Agraphia is an acquired symptom that related to loss or impairments in producing written language. Here we explored the possibility of using cognitive features to dissociate stroke patients with and without impaired writing abilities in a large group of sub-acute, ischemic stroke patients. We recruited patients from both China and the UK. We assessed their different domain of cognitive abilities using Birmingham cognitive screen and use the technique of classification in machine learning to categorize behavioral data between patients with and without writing deficits. A total of 38 features were recruited in our studies. We use Laplacian score to rank features and then put the top-ranked features in linear support vector machine (SVM) for classification. Our results showed that models including 6 features effectively classified patients with writing deficits from those without. And the two dissociated models represented similar between the Chinese patient and the UK patient group. The top-ranking features in our study indicated that writing in either Chinese or English relies on similar basic abilities. Besides linguistic component, there are some other features needed in writing including visual spatial, eye-hand coordination, fine motor control with using a pen, delay memory, sustained attention and auditory information perception.

4.2 Introduction

Agraphia is an acquired symptom related to loss or impairments in

producing written language. It is commonly observed in patients with brain damage such as stroke (Marien et al., 2001; Sinanovic, Mrkonjic, Zukic, Vidovic, & Imamovic, 2011), cerebral trauma (Alfredo Ardila & Surloff, 2006) and neural degenerated diseases (Lambert et al., 2007). Pen-paper tests are widely used to detect the presence of agraphia. However, it should always keep caution about the diagnosis of agraphia because of its high comorbidities. Educational level and prior abilities to write need to take into account as well (Fine & Darkhabani, 2009).

The first case report of agraphia dated back to more than 100 years ago (Exner, 1881; F.-E. Roux et al., 2010). Since then, researchers display a consistent exploration of the writing cognitive model and its neural basis. Multi brain regions mainly on the dominant hemisphere have been linked to writing abilities (Damasio et al., 1982; Henderson, 2008; Henschen, 1922; Kawamura et al., 1987; Magrassi et al., 2010; Marien et al., 2001; Pai, 1999; Hideo Tohgi, Saitoh, Takahashi, Takahashi, & Utsugisawa, 1995). Nevertheless, there is still no confirm conclusion about the neural basis associating with writing.

Due to its cognitive processes, it is not surprising that most of the patients with writing deficits in previous reports showed impairments in other cognitive abilities. And this raised a question about the existence of pure agraphia and whether there is cognitive activity specific for writing.

Pure agraphia represents a selective impairment in writing with intact abilities in language and motor and may relate some specific brain regions.

Though there are some case studies reporting patients with pure agraphia (Auerbach & Alexander, 1981b; Croisile, Laurent, Michel, & Trillet, 1990; Rosati & De Bastiani, 1979), still some of them showed comorbidities with optic ataxia or other cognitive dysfunctions (Auerbach & Alexander, 1981b; Rosati & De Bastiani, 1979).

Some researchers argued that since writing relies on basic abilities that existed long before writing was invented, there is no brain area specialized for writing (Alfrede Ardila, 2004). The existence of specific writing abilities is still debated.

Based on a neuronal recycling hypothesis claimed by Dehaene (Dehaene, 2004; Dehaene & Cohen, 2007), universal cortical specialized areas emerge to accommodate the acquisition of a new skill. The neural basis of writing should be restrained with its relative cognitive activities. Brain lesions causing agraphia therefor may cause deficits in its relative basics cognitive function. Therefore, we assume that it would be possible to predict patients' performance in writing based on their general cognitive functions.

The neuronal recycling hypothesis predicts a shared cognitive mechanism for writing (like reading) across cultures. The neuronal recycling hypothesis is silent regarding the linguistic components that are involved in the transformation of orthography to meaning. This appears opposite to predictions made by linguistic models for writing. Linguistic models are mostly concerned with the aortography to meaning transformation (see figure 1), stressing the

different conversions pathways phonological or logographic (i.e. lexical). Specifically, it is argued that alphabetic language (e.g. English) and logographic language (e.g. Chinese) have different morphologies. (Zhu et al., 2014). Most of the alphabetic languages used a grapheme to phonemes transformation based on a serial left to the right structure of letter strings (Perfetti et al., 2005), characters are the basic writing units and encode no clear phonological information at the sub syllabic level in the logographic language. (Zhu et al., 2014) Hence, Linguistic models predict different underlying cognitive structures across culturally different writing systems.

Previous research compared the two language systems mainly on reading tasks showed largely identical but with minor differences in the two languages. (Bolger et al., 2005; Tan et al., 2005; L. Zhu et al., 2014) However, these studies used reading tasks mainly reflect the linguistic components of writing. There are relatively much fewer studies focus on the motor component of writing or directly comparing the difference in writing tasks.

In our study, we used machine learning to classify patients with or without writing deficits in the two countries, China and the UK. Our study aimed to explore whether reliable group differences existed on the performance of cognitive tasks or a combination of tasks between stroke patients with or without deficits in word writing. We aimed to answer the following questions. Should all the cognitive processes in writing can be described by a series of basic functions reflecting in a set of cognitive assessment screen? And what

basic cognitive abilities were required in the writing processes? Another objective of our study is to explore the exitance of different cognitive model of the two language systems.

4.3 Method

4.3.1 Participants

The data of ischemic stroke from the BUCS trial (Bickerton et al., 2014) which was run in the UK and the BCoS-C trial (Pan et al., 2015; 陈浩博 et al., 2017) which was run in south China were analyzed. Patients were recruited in acute and rehabilitation stroke units. The Chinese dataset used the same inclusion criteria as the British (see detail in the method chapter). This study was approved by the National and local NHS ethical committees in the UK, approved by the local research ethics committee in China, and all participants gave informed written consent.

Our study recruited a total of 237 Chinese patients from Guangzhou First People's hospital in China and 906 British patients around the West-midland area from the UK. Of the Chinese group, we excluded 46 patients without any record in word writing tasks and 21 patients who didn't complete at least one of the other cognitive tasks in Birmingham cognitive screen and finally got 170 patients in the Chinese group. Base on the cut-off, 127 of them were classified as normal in word writing tasks, while 43 of them were considered as having deficits in word writing. In the UK group, we successively deleted 43 with a

hemorrhagic lesion, 338 patients without a clear medical record of their stroke type, 83 patients not taking part in the writing tasks, and 148 patients who didn't complete at least one of the other cognitive tasks in Birmingham cognitive screen. We finally recruited 294 patients in the British group, including 209 without deficits in word writing and 85 the opposite based on the cut-off. See Table 5 for demographic details.

These data were used to set up two datasets in our study as follows.

Database A (CHN) includes 170 Chinese stroke patients that were dived into two groups. group A1 recruited 43 patients having deficits in writing. Group A2 recruited 127 without deficits in writing. Writing deficits were classified using standardize cut off scores from aged-matched healthy controls.

Database B (UK) includes 294 British stroke patients. Patients are dived into two groups the same way with database A including 85 patients impaired in word writing in Group B1 and 209 without in group B2.

4.3.2 Behavioral measures

The patients' cognitive profile was assessed using the BCoS (G. W. Humphreys, Bickerton, Samson, et al., 2012) and the two Chinese versions (Pan et al., 2015; 陈浩博 et al., 2017). (see the detail of cognitive tasks in BCoS in the method chapter)

See Table 5 for the list of tasks and measured used.

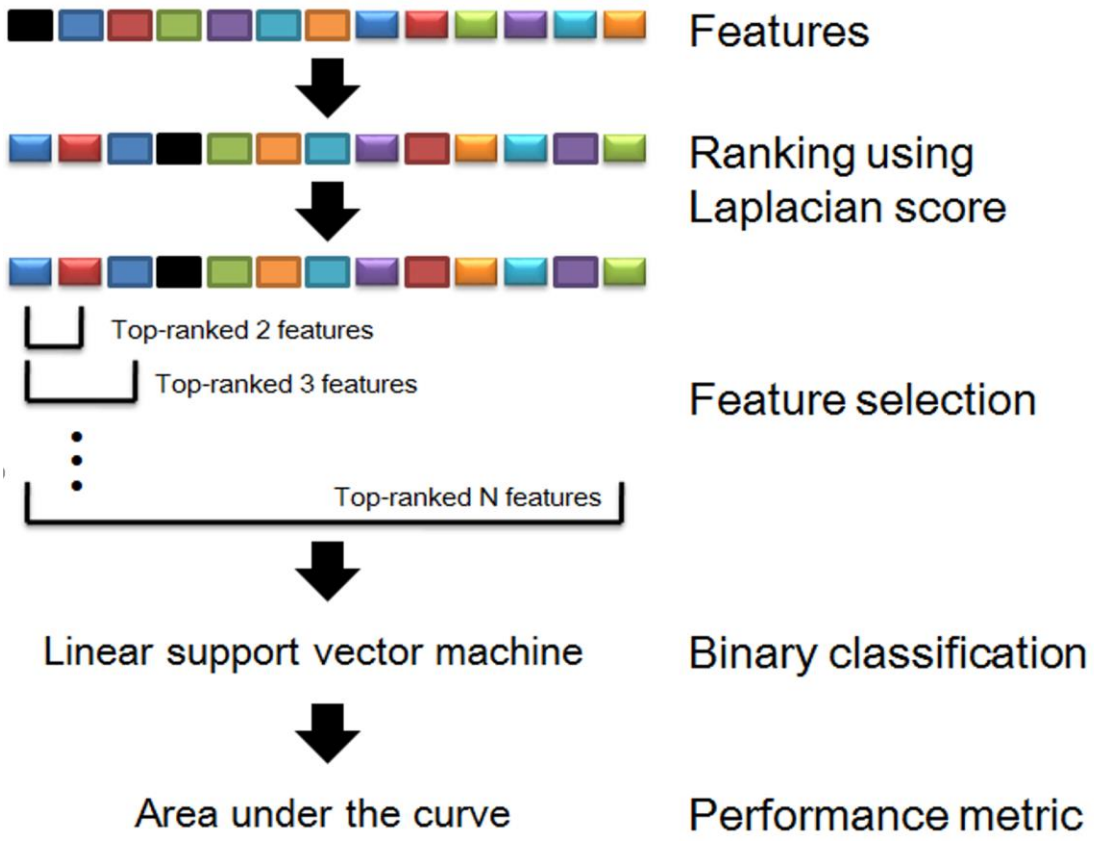
4.3.3 Features in Machine learning

32 cognitive measured extracted from the 23 tasks of BCoS and 6 demographic data were used as features; for a total of 38 features. The 6 demographic features included age, gender, education year, dominant hand, lesions side (left, right and bilateral) and tested language (this feature included only in the analysis of the Chinese data as two tested languages were used in this group Mandarin and Cantonese). 32 of them are cognitive features using their scores in related BCoS tasks (See Table 5).

4.3.4 The analysis framework

The analysis framework is demonstrated in Figure 12. It uses the Laplacian score to rank the above 38 features. Then top-ranked features are incrementally added as the input of linear support vector machine (SVM) to differentiate patients with deficits in writing words (Group A; Group B). The analysis was performed separately for each data set (Chinese (group A), UK group B)).

Figure 12: Semantic diagram of the framework used in this study



The analysis used the approach proposed in 2005 by He and his colleagues (He, Cai, & Niyogi, 2005). Specifically, based on each database, the steps in Figure 12 can be described as below:

1. We selected randomly subgroup of intact and impaired to train the classifier. For the China data, the training was done on 60 (30 in A1, 30 in A2) and for the UK data, the training was done on 118 (59 in B1, 59 in B2). The rest instances were used for testing.

2. Based on the training instances, the Laplacian score was used for

features ranking and the 38 features were sorted in descending order according to their Laplacian scores.

3. Features were incrementally added one by one, the SVM was optimized based on these training instances.

4. The trained model was evaluated on the testing instance and the area under the curve (AUC) was computed.

5. Step 1 to step 4 is repeated 1000 times and thereby, 1000 AUC values and 1000 times of feature ranking are obtained.

We note that the entire sample included 170 patients, of which only 43 had deficit in writing. It is often the case that the experimental group (i.e. impaired) is less prevalent in the population than the controls. We opted to keep the ratio and number of the two samples as observed and not to generate artificial data to increase the sample size and balanced the group. This is because the output is more ecologically valid and is more likely to be generalized beyond the current study. The cross-validation test which was achieved through multiple iterations confirmed the reliability and robustness of the results. This cross-validation test is used to confirm the reliability and robustness of the results through multiple iterations.

Please note that: (a) the training instances were randomly picked up; (b) the top-ranked 1 feature to the top-ranked 10 features were evaluated; (c) AUC assessed the effectiveness of machine learning classifier in patient

differentiation; (d) The classifier, linear SVM, was embedded in MATLAB. We used the function ‘fitcsvm’ for model training and the function ‘predict’ to predict the testing instances.

Our model is simple and easy to explain (several features and linear SVM). In addition, the study design accounted for the unbalance of the positive and negative samples.

Support Vector Machine (SVM) is a discriminative classifier, formally aimed as defining a hyperplane that will separate between two stimuli classes. In other words, given labelled training data (supervised learning), the algorithm outputs an optimal hyperplane which categorizes new examples. In a two-dimensional space, this hyperplane is a line dividing a plane in two parts where each class lay in either side.

The main interest of this chapter was not the classification accuracy per se, but the features that support an accurate classification. In the literature there are two methods for selecting features: “wrapper” and “filter”(Z. Zhu, Ong, & Dash, 2007).

“Wrapper” describes a family of algorithm that select the feature with the aim of maximising the accuracy of the classification algorithm. They are therefore tightly depended on the learning algorithm used.

‘Filter’ is a family of procedures were feature selection (dimensionality reduction) is done prior of the learning (classification training). As such feature

selection is independent of the classification algorithm used. ‘Filter’ methods used the structure of the data to reduce the dimensions and to select the most informative features.

Data reduction methods can be divided to supervised and unsupervised algorithms. In supervised methods the algorithm selects feature to maximise the different between the classed and the similarities within the classes. Fisher score is one example for such an algorithm, which is used in linear discriminate analysis. On the other hand, unsupervised algorithms are blind to the classes, and select features that best represent the data structure. PCA is one method for unsupervised dimension reduction. PCA select features based on their ability to explain variability in the data. Laplacian score is another ‘Filter’ method to select features prior to the training phase. It can be used supervised and unsupervised.

Laplacian score is given for each feature by combining information from the Laplacian Eigenmap and Locality Projection. In contrast to PCA, Laplacian map reduces dimension, while preserving the geometrical shape of the data. It uses graph theory to present data points (as nodes) and their similarity (as connection strength). Low dimensional space is constructed to ensure that points that are closed to each other in the high dimensional space retain these relations in the low dimensional space. Locality Projection of a feature reflects the feature ‘usefulness’ in preserving the neighborhood relationship of each data point.

The main interest of the current study was to examine the cognitive structure underlying writing abilities and the relations between different cognitive core functions. Therefore, Laplacian score appears an appropriate method for feature reduction.

Laplacian score for each feature was obtained from the training samples (70%), and was the averaged of the 1000 iteration.

To establish the number of relevant features for classifying patients to impaired vs. no impaired in writing words, support vector machine was used. In each phase another feature was added, starting from the feature with the highest Laplacian score (the feature that was most useful in retaining neighborhood relations in the original data) toward the one with the lowest.

The area under the curve (AUC, the relation between hits, true positive, and false alarms, false positive) of the classification of the test data was used to estimate the classification performances. By examining the AUC curve, the point where it asymptote, or the highest AUC results were selected, with the constraint that it will be comparable across the two samples.

4.4 Results

4.4.1 Behavior result of the two datasets

The demographic and cognitive results of each group are presented in Table 5. There was no age, gender, handedness differences between patients

who were impaired or intact in writing. Patients who were impairment in writing spend less time in education compared to their counterparts in both countries. Surprisingly, no difference was found in the lesion side. And for most, all the cognitive tests, patients with writing deficits performed worse than those without.

Figure 13 and 14 showed correlation patterns of the two datasets separately. The correlations between variables where primarily weak to moderates.

Table 5: Demographic and behavioural data of patients in both groups

FEATURES	DATABASE A (CHN)		COMPRISON	DATABASE B (UK)		COMPRISON
	A1(N=43)	A2(N=127)	T/P	B1 （N=85）	B2 （N=209）	t/p
	Mean±SD	Mean±SD		Mean±SD	Mean±SD	
AGE	67.94±11.60	66.30±9.23	-0.844/0.402	69.91±13.90	67.53±14,15	-1.311/0.191
GENDER	1(23/43)	1(70/127)	0.034/0.853#	1(36/85)	1(94/209)	0.169/0.681#
HANDEDNESS	1(1/43)	1(8/127)	NA/0.452#	1(14/84)	1(20/209)	2.942/0.086#
EDUCATION YEAR*	5.38±4.12	8.91±2.84	5.211/0.000	10.64±2.41	11.90±3.01	3.796/0.001
TESTED LANGUAGE	1(18/43)	1(48/127)	0.224/0.636#	NA	NA	NA
LOCATION SIDE (L/R)^	16/8	30/29	1.728/0.189#	25/30	51/78	0.557/0.455#
ORIENTATION	7.70±0.83	7.95±0.28	1.974/0.055	7.36±1.31	7.86±0.74	3.261/0.001
PICTURE NAMING*	11.14±2.88	12.54±1.70	3.011/0.004	9.76±3.58	12.24±1.85	6.051/0.000
SENTENCE CONSTRUCTION*	5.84±2.62	7.39±1.21	3.765/0.000	6.60±2.08	7.62±0.89	4.355/0.000
SENTENCE READING*	30.72±16.95	42.61±7.79	4.445/0.000	34.48±11.64	40.67±3.67	4.802/0.000
NONWORD READING*	4.09±2.30	5.52±1.14	3.911/0.000	3.22±2.20	5.22±1.38	7.799/0.000
MEMORY FREE	3.78±2.76	5.64±2.37	4.270/0.000	5.37±3.15	7.22±2.96	4.767/0.000

RECALL*						
MEMORY RECOGNIZE*	8.70±4.07	11.29±2.47	3.941/0.000	5.37±3.15	7.22±2.96	4.871/0.000
APPLE CANCELATION TEST*	3.93±18.62	42.00±13.02	2.959/0.005	35.68±16.15	42.84±10.89	3.752/0.000
ALLOCENTRIC NEGLECT	0.33±4.02	0.19±2.41	-0.267/0.790	0.82±4.23	1.24±3.83	0.829/0.408
EGOCENTRIC NEGLECT	0.12±2.22	0.24±2.49	0.281/0.779	0.81±4.54	0.89±4.56	0.142/0.887
VISUAL EXTINCTION(LU)	3.65±1.04	3.95±0.40	1.850/0.071	3.66±1.02	3.78±0.83	0.935/0.352
VISUAL EXTINCTION(RU)	3.67±1.04	4.00±0	2.053/0.046	3.84±0.61	3.86±0.69	0.247/0.805
VISUAL EXTINCTION(LB)	7.42±2.06	7.89±0.819	1.460/0.151	6.47±2.94	7.27±2.10	2.278/0.025
VISUAL EXTINCTION(RB)	7.19±2.35	7.98±0.13	2.224/0.032	7.58±1.38	7.65±1.47	0.400/0.690
TACTILE EXTINCTION(LU)	3.77±0.87	3.89±0.52	1.850/0.071	3.66±1.02	3.78±0.83	0.302/0.763
TACTILE EXTINCTION(RU)	3.72±0.88	3.97±0.18	2.053/0.046	3.84±0.61	3.86±0.69	0.979/0.329
TACTILE EXTINCTION(LB)	7.28±2.07	7.69±1.23	1.214/0.230	6.66±2.49	7.41±1.83	2.512/0.013
TACTILE EXTINCTION(RB)	7.63±1.35	7.94±0.24	1.498/0.141	7.41±1.69	7.84±0.86	2.215/0.029
AUDITORY ATTENTION*	33.70±19.17	46.34±11.65	4.076/0.000	37.20±16.29	48.76±8.47	6.208/0.000
MEMORY DELAY FREE RECALL*	4.00±3.07	6.89±3.00	5.436/0.000	5.27±4.15	8.54±3.47	6.424/0.000
MEMORY DELAY RECOGNIZE*	10.30±4.99	13.09±1.81	3.579/0.001	11.82±3.14	13.79±2.06	5.339/0.000
MULTI-STEP OBJECT USE*	9.67±4.20	11.37±1.90	2.559/0.014	9.46±3.95	11.35±1.62	4.274/0.000

GESTURE PRODUCTION*	**7.72±3.28**	**10.43±1.82**	**5.166/0.000**	**9.81±2.97**	**11.45±1.07**	**4.977/0.000**
GESTURE RECOGNITION *	**5.26±1.35**	**5.84±0.62**	**2.758/0.008**	**4.89±1.27**	**5.42±0.78**	**3.523/0.001**
MEANINGLESS IMITATION*	**8.05±3.84**	**10.16±2.37**	**3.392/0.001**	**9.11±2.92**	**10.33±1.95**	**3.571/0.001**
TASKS RECOGNITION *	**7.58±2.80**	**8.96±1.12**	**3.150/0.003**	**7.92±2.00**	**9.30±1.13**	**5.975/0.000**
NUMBER READING*	**6.05±3.06**	**8.24±1.69**	**4.479/0.000**	**7.00±2.81**	**8.58±1.23**	**5.002/0.000**
NUMBER WRITING*	**1.98±1.96**	**4.43±1.12**	**7.779/0.000**	**2.91±1.92**	**4.64±0.77**	**8.057/0.000**
CALCULATION *	**2.02±1.53**	**3.54±0.79**	**6.191/0.000**	**69.91±13.90**	**3.09±1.08**	**7.624/0.000**
COMPLEX FIGURE COPY*	**20.79±17.49**	**38.20±9.96**	**6.189/0.000**	**1(36/85)**	**38.65±8.16**	**4.279/0.000**
INSTRUCTION COMPREHENSION*	**2.05±0.82**	**2.73±0.56**	**5.128/0.000**	**1(14/84)**	**2.95±0.21**	**2.724/0.008**

Table 5: A1: Chinese patients with writing deficits, A2: Chinese patients without writing deficits; B1 British patients with writing deficits. B2: British patients without writing deficits. *significant different in both dataset between patient with and without writing deficit; #chi-squire was used to compare instead of t-test; ^we only include patients with unilateral lesion here

Figure 13 Correlation matrix of features entering classifier-UK

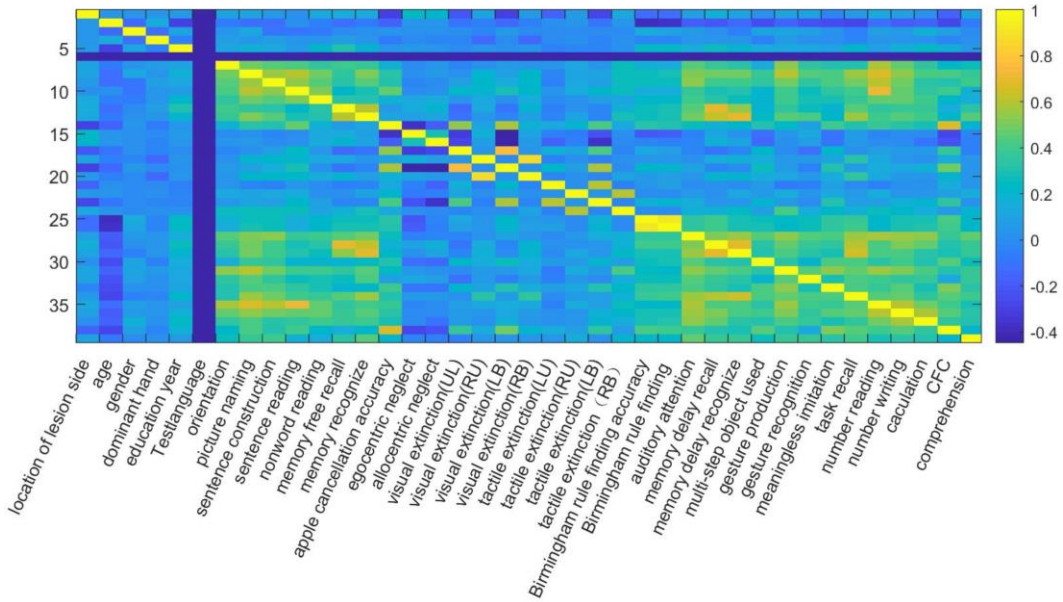
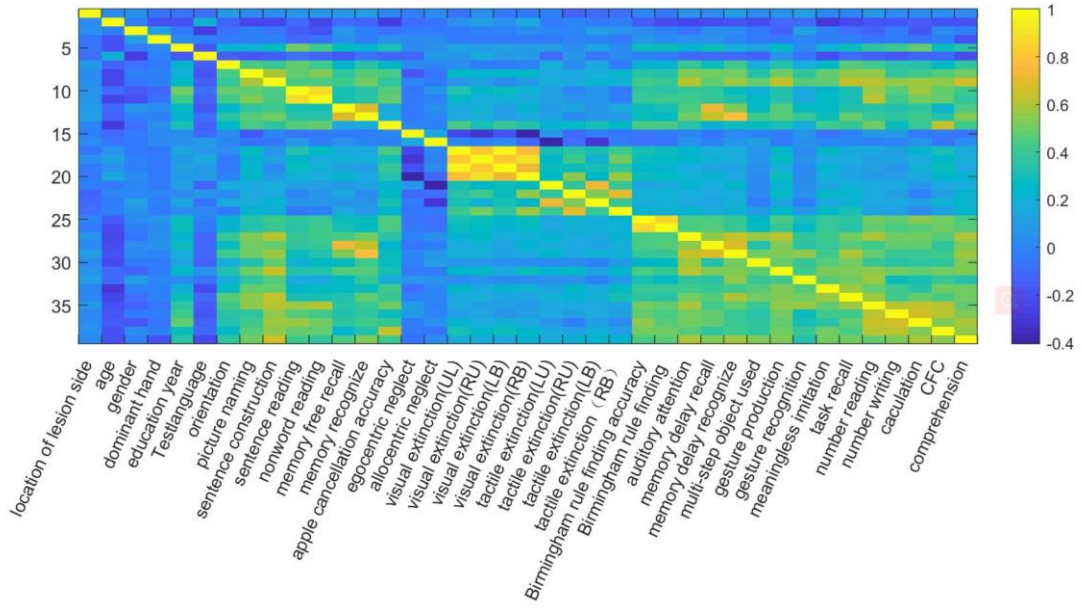


Figure 14 Correlation matrix of features entering classifier-CHN



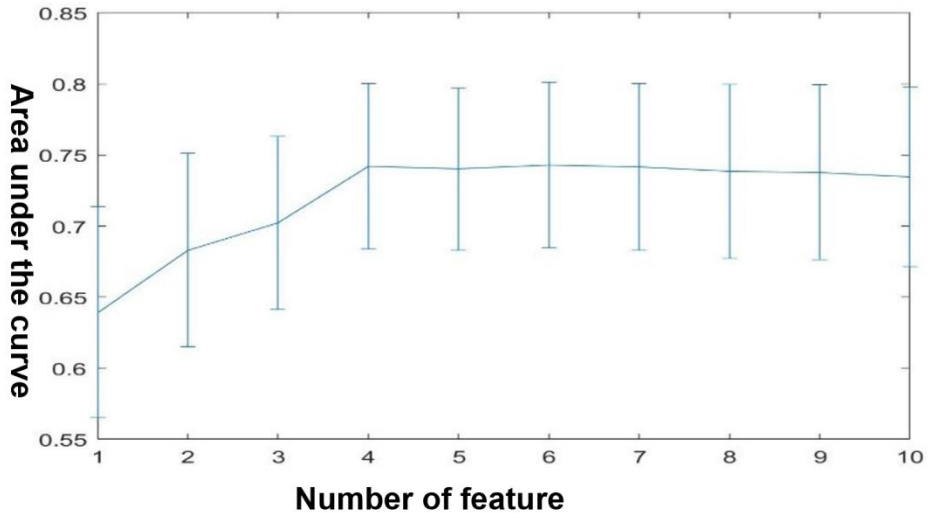
Note: The Chinese dataset used two type of language (Cantonese and Mandarin) assess patients' cognitive function while there is only one in the UK (English).

4.4.2 Classification result and selected features

Database A: Chinese patients

Figure 15 shows the results from database A (CHN). We presented AUC values in the figure that correspond to the top-ranking from 1- 10 features (0.639±0.074 , 0.683±0.068, 0.702±0.061, 0.742±0.058, 0.740±0.057, 0.743±0.058, 0.741±0.059, 0.738±0.061, 0.738±0.062, 0.735±0.063). It is found that recruited from 4-10 features achieved a decent result while 6 features got slightly better than the others (0.743±0.058). And the accuracy, sensitivity, and specificity of the top-ranked 6 features model were 0.814±0.045, 0.65±0.132, and 0.836±0.056 separately. The top six ranking features are apple cancellation test, complex figure copy, auditory attention accuracy, sentence reading, age, Memory delay recognize. (followed by education year, Memory delay recall, memory recognize, and number reading ranking 7-10).

Figure 15 AUC values correspond to top-ranked from 1- 10 features in CHN group

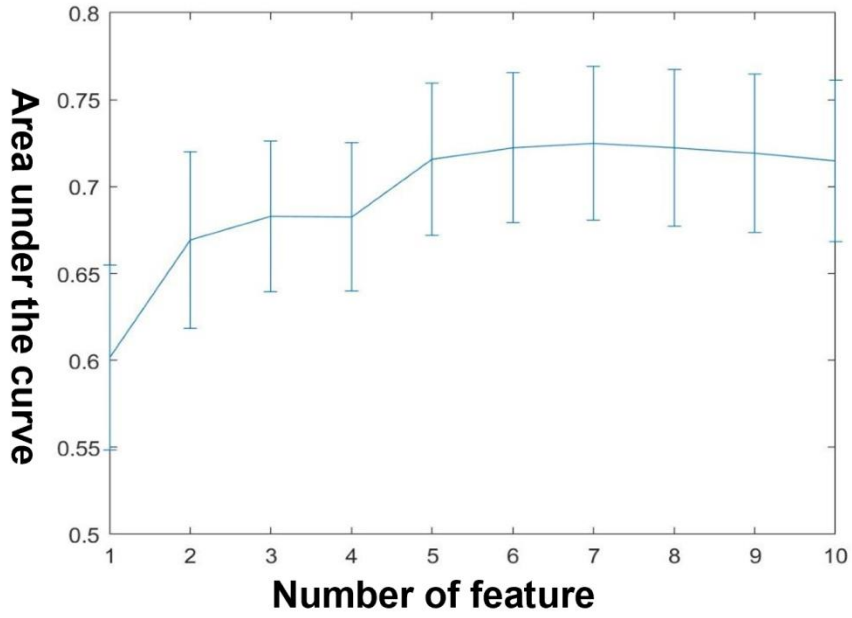


Database B: British patients

The results from database B (UK) are shown in Figure 16. AUC values were presented in the figure that correspond to top-ranking from 1- 10 features(0.598±0.051, 0.666±0.05, 0.680±0.042, 0.678±0.041, 0.712±0.044, 0.719±0.044, 0.721±0.045, 0.721±0.043, 0.717±0.044, 0.713±0.046). Top-ranked 5-10 features achieve a decent result and we reported the 6 features model to consistent with the Chinese model (0.719±0.044). The accuracy, sensitivity, and specificity of the top-ranked 6 features model were 0.786±0.033, 0.624±0.095, and 0.814±0.042 separately. The top six ranking features were apple cancellation test, auditory attention accuracy, age, complex figure copy, sentence reading, Memory delay recall. (followed by picture naming, multi-

objects used, allocentric neglect, and number reading ranking from 7 to 10).

Figure 16: AUC values correspond to top-ranked from 1- 10 features in UK group



In Table 6: the top 10 ranked features in the two models, we presented the top 10 features of the two datasets, China and the UK group.

Table 6: the top 10 ranked features in the two models

	Feature 1	2	3	4	5	6	7	8	9	10
CHN	apple cancellation test	complex figure copy	auditory attention accuracy	sentence reading	age	Memory delay recognize	education year	Memory delay recall	memory recognize	number reading
UK	apple cancellation test	auditory attention accuracy	age	complex figure copy	sentence reading	Memory delay recall	Picture naming	multi-objects used	Allocentric neglect	number reading

In further analysis, after we add all the 38 features into the machine learning model, the best-predicted model remained the same with around 4-10

features taken into account. Adding more features can't improve the prediction effect of the classification models. See results in supplementary figures 2 and 3 in appendix 2.

4.5 Discussion

In the current study, we used machine learning to classify patients with or without writing deficits in the two countries, China and the UK. A total of 38 features were recruited in our studies. We used the Laplacian score to rank features and then put the top-ranking features in the linear support vector machine (SVM) to the classification. Our results showed that models using 6 features effectively classified patients with writing deficits from those without. And although Chinese and English were supposed to compose different cognitive processes, their cognitive models represented similarly in our study.

Our results showed no difference in age, handiness, gender between the two groups. It is easy to understand that patients with higher education performed better than those with lower education. However, to our surprise, there was no difference between the location of the lesion (left of right) between the patient with or without writing deficit in both groups. This might be because of the relative a smaller number of our sample size especially in the two writing deficits subgroups. The other possibility is that we were not able to further analyzed our patients in lesion location due to the limited sample size. We included patients with lesions not only in the hemisphere but also in the brain

stem and cerebellum. And it is also possible that the effect of the lesion side has been absorbed by other covariates that were highly correlated with this factor (e.g. spatial attention, sentence reading). However, the cognitive features that were identified as most relevant have typically associated with opposite lesion laterality. Poor performances on the apple cancelation test assessing visual neglect are typically associated with lesion to right hemisphere; while poor performances on sentence reading are typically associated with left lesion

Writing is a multifaceted cognitive process requiring intact abilities in language, motor, spatial information perception, eye-hand coordination, etc. These cognitive abilities were assessed using different cognitive tasks in BCoS. Not surprisingly, patients in the writing deficit groups showed worse performance in the majority of other cognitive activities. This is in line with our studies in chapter 4 that no patients show pure agraphia and most of the previous cases reporting agraphia showing comorbidities with other functions. This further supported that writing and other cognitive abilities rely on shared cognitive components. It also highlighted the importance of control the effect of other comorbidities when reporting agraphia cases.

As revealed in our results, patients' performance in writing can be predicted by other cognitive tasks. Using 6 features, the accuracy of prediction is ideal at around 80%. We noticed that the two cognitive tasks using pen-paper ranked the top six in both datasets. (top 2 in the Chinese dataset, 1st, and 4th in the UK group) Apple cancellation test was ranked as the first feature in the model.

In the apple cancellation task, an A4 sheet was presented in landscape orientation containing 50 complete apples along with distractors, which were apples with a left or right part missing (the ‘bitten apples’) (Bickerton et al., 2011). Patients were required to delete the complete apples using a pen. Complex figure copy required patients to copy a figure in a paper using a pen (see chapter 3 for details). These two tasks both assess mostly the visual-spatial, eye-hand coordination, and fine motor control with using pen in patients. Not surprisingly they are highly correlated with writing. Patients with a deficit in visual-spatial information perception are usually correlated with spatial agraphia. Eye-hand coordination and fine motor control also play an important role in one’s ability to exercise and everyday tasks like writing. Such as the school-aged children with developmental coordination disorder usually demonstrating agraphia.(Kaiser, Albaret, & Doudin, 2009; Missiuna, Rivard, & Pollock, 2004) According to the neuronal recycling hypothesis, the recent cognitive function should be associated with specific cortical areas coding for an evolutionarily similar function. As VWFA consistently associated with item recognition in reading and closed to other visual tasks, we assumed these three tasks rely on overlapped brain regions correlated with fine motor control in using the pen.

The other three cognitive features in the top six reflect other cognitive processes required in writing. They are sentence reading reflect a linguistic component in writing, delay memory recall or recognize both assessing delay

memory, and auditory attention task reflecting sustained attention and auditory information perception. Sentence reading tasks respond to patients' abilities in grapheme-to-phoneme correspondence "rules", or grapheme onto the orthographic unit and then using the orthographic unit to directly activate a phonological unit corresponding to that word's pronunciation (Rayner & Reichle, 2010). And it also tests patients' abilities in eye movement control. Delay memory may correlate with writing in the retrieve abilities. Auditory attention task ranked prior to others is beyond our expectation. We assumed that it is either because that two tasks both began with precepting auditory information or it is a share brain network for writing and sustained attention. It could also be that sustained attention is a basic resource for maintaining a cognitive set (Sommers, 1989). For example, beyond planning and organization, patients need to be able to maintain their focus and concentration on the task to enable successful task completion.

And we noticed though there is no difference in age between the two groups. Age was ranked as the top six features. This indicated that when predicted patients' performance in writing using a cognitive model should always take age into account.

As the support vector machine (SVM) is a multi-variate method, the classification is not based on single features but a combination of the features. Therefore, in contrast to GLM, the output does not include specification (beta value) on the relationship of each variable to the predicted outcome.

Nevertheless, as can be seen in table 5, apart from age, univariate methods revealed reliable differences between the impaired and not-impaired patients. Though in most tasks impaired patients performed poorer than non-impaired, and the tasks identified by the SVM to form the most informative pattern were not the tasks that showed the most reliable differences in the univariate analyses. For example, number writing, as expected from chapter 5, was the most reliable univariate predictor for word writing impairment. However, it was not included in the first 10 most informative variables following the Laplacian data reduction method in either China or the UK samples. The results suggest that the combined pattern of performances of the other tasks (e.g. spatial and auditory attention; reading) accounted for more (and potentially overlapping) variability in the word writing than number writing task.

The predicted accuracy using 6 features in our models are around 80% in both groups. And this remained true when we include all the cognitive features in the analysis (see results in supplementary figure 2&3 in Appendix 2). This indicated that the majority of the cognitive abilities requiring in writing can be assessed by relatively less cognitive tasks.

By comparing the results between the dataset, A and B, we found patients with writing deficits in different language systems (Chinese and English) shared a similar cognitive pattern. The top-ranking features in the two models indicated that similar cognitive abilities were needed in writing irrespective of the language system. This supports the neuronal recycling hypothesis of cultural

invariant where new cognitive skilled development under the restriction of the previous functional architecture of the brain(Dehaene, 2004; Dehaene & Cohen, 2007). The current study showed that independent of the writing system (logographic or phonological) the same cognitive structure (& potentially the same neural structure) underlies writing abilities.

Limitation

We assessed deficits in the current study using the BCoS, which adopt a shallow but broad approach. The shallow aspect means that a specific ability is assessed using a limited number of items. In the case of word writing, four words and one non-word are dictated in English; in the case of Chinese, writing 4 characters are dictated. BCoS broad aspect means it provides a relative detail profile of cognition, which is not limited to one domain. It provides a powerful research tool to assess the prevalence and comorbidity of deficits in a large and representative patient population. But the limitation is that it cannot replace formal clinical diagnosis of the known syndrome as it does not adhere to formal diagnostic criteria and has a relatively small number of trials per task. Hence our results reflect different components of writing deficits, but we cannot draw a direct conclusion on agraphia symptoms. Secondly, the sample size of the writing deficits group is relatively small which interfered with the power of the statistical results. More patients are to be recruited in future analyses. Finally, as the tasks in BCoS didn't assess patients' primary cognitive abilities, we

should always keep in caution about explaining our results.

4.6 Conclusion

The current study showed that writing abilities can be predicted by the performance in other cognitive abilities. We identified the dissociated features between patients with impaired and intact writing abilities. Our result also supported the neuronal recycling hypothesis showing different language systems share similar cognitive models.

Afterword

In the current chapter, we successfully used machine learning to classify patients with or without writing deficits in both China and the UK. Our results showed that models using 6 features can effectively predict patients' performance in writing. We found that the two classification models shared the same top-ranking features. Taking these together, this chapter supports the neuronal recycling hypothesis in two ways. Firstly, writing is associated with specific cortical areas coding for an evolutionarily similar function. Therefor one's performance in writing maybe predicted by related cognitive tasks. And there is limited cultural invariant between two types of language. These results are also consistent with the high comorbidities and correlation in CFC with other tasks in Chapter 3. We explored the cognitive model in writing with behavior data in this chapter and highlighted the importance of motor output in writing. In the next chapter, we used VBM and PCA to explore the neural substrates associated with writing using both behavior and imaging data for further exploration.

Charter 5

Delineating the cognitive-neural substrates of writing: a large scale Behavioral and voxel based morphometry study

This character has been published in the journal of Scientific Reports (The introduction has been shorted to avoid repetition)

Foreword

In chapter 3 we explored the motor component of copying figures, showing three networks contributing to copying figures. It raised a question that whether writing and copying figure shared similar neural basics, especially in motor output. In chapter 4 our result supported that different languages relied on a similar cognitive frame. In the current chapter, we would focus our study on the motor component of writing using behavior and imaging data. VBM would be used on ischemic stroke patients to explore the neural basis of writing word and number. And we will use exclusive masking *to explore the d*issociated mechanism for Numbers' and Words' Writing. And another objective of this chapter is to delineate the cognitive-neural substrates of writing. We will combine PCA and VBM analysis to explore the delineated processes of writing.

5.1 Abstract

The current study investigated the cognitive and neural substrates that underpin writing ability. We explored similarities and differences in writing numbers and words and compared these to language and manual actions in a large group of sub-acute, stroke patients (n=740). The behavioral data showed association and dissociation in the ability to write words and numbers. Comorbidities of writing deficits with both language and motor impairments were prevalent, with less than a handful showing deficits restricted to the writing tasks. A second analysis with a subset of patients (n=267) explored the neural networks that mediate writing abilities. Lesion to right temporal contributed to writing words, while lesions to left postcentral contributed to writing numbers. Overlapping neural mechanisms included the bilateral prefrontal cortex, right inferior parietal, left middle occipital and the right cerebellum. With the former regions associated with error pattern typical to writing based on prior knowledge (the lexical route), while lesion to left MOG was associated with errors to the phonological (non-lexical) route. Using principle components extracted from the behavioral data, we showed that right prefrontal and right parietal contributed to the ability to use the pen, while lesion to bilateral prefrontal, inferior temporal and cerebellum supported unique use of the pen for writing. The behavioral and imaging data suggested that writing numbers and words primarily relied on overlapping cognitive and neural functions. Incidents of pure writing deficits, in the absence of motor or language deficits, were rare. Nevertheless, the PCA

and neural data suggested that writing abilities were associated with some unique neuro-cognitive functions, specifically dedicated to the use of pen and the ability to transform meaning to motor command.

5.2 Introduction

Recent cognitive processes such as writing were composed of a series of relative abilities. The act of writing involves multifaceted cognitive processes including but not limited, to linguistic related processes, assignment of meaning to visual-symbolic representations, eye-hand coordination, and high-level motor control. Impaired in these cognitive abilities may cause deficits in writing.

For phonological based writing systems (e.g. English), the central component of writing are hypothesized to be utilized by two parallel routes (Castles, Bates, & Coltheart, 2006; Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Rapcsak, Henry, Teague, Carnahan, & Beeson, 2007): a phoneme-grapheme conversion route (non-lexical route, phonological agraphia) which can process words and non-words; and phonic-orthographic route (semantic lexical route, semantic agraphia) which utilizes prior knowledge of words (Purcell et al., 2011; Rapp, Purcell, Hillis, Capasso, & Miceli, 2015). In this context, spelling errors in exceptional words and a large number of phonological errors (writing the words as they sound) reflect impairment of the lexical route and intact non-lexical phonological route. While the error in exceptional and regular words that are not phonological reflect deficits to the semantic lexical

route.

Previous studies supported the above theory showing multi brain regions contributing to writing. (Alfredo Ardila et al., 2000; Exner, 1881; Henschen, 1922; Hillis, 2008; Iwata, 1986; Magrassi et al., 2010; Marcus, 1937; Miyahara, Piek, & Barrett, 2008; Pai, 1999; Planton et al., 2013; Purcell et al., 2011; D P Roeltgen & Heilman, 1984; F.-E. Roux et al., 2010; Hideo Tohgi et al., 1995)

The variety of writing systems developed by different cultures raised the question of whether the different ways of mapping symbols to meaning are associated with different neuro-cognitive mechanisms. The two common writing systems are the phonological conversion of sounds (phonemes)-to-letters (graphemes, e.g. English) and a logographic conversion of ‘units of meaning’-to-symbols (e.g. Arabic numbers, currency symbols, Chinese characters). The neuronal recycling hypothesis (Dehaene & Cohen, 2007), mentioned above, posits that similar brain areas become specialized in reading (/writing) independent of the writing systems. On the other hand, the prevalent assumption dissociates numerical from literacy processing (Dehaene & Cohen, 2007), suggesting the writing numbers may relies on different structures than writing words.

Dissociations and overlaps between different writing systems have been explored extensively in the perception domain, i.e. reading. Fewer studies have examined this question in the motor domain, i.e. writing. Writing models are silent on this question. It can be postulated, that independent of the writing

system, some shared processes are always required. These include mapping visual (or auditory) input or one's own thinking to graphic symbols, eye-hand coordination and higher-level motor control (motor output). In chapter 4, using machine learning, we have found that writing in different language systems might share similar cognitive models. Here, we explore the cognitive-neural substrates of writing in word and another form of language, number.

The inability to process numbers, including writing them correctly, is typically associated with acalculia syndrome (Sinanović, Mrkonjić, Zukić, Vidović, & Imamović, 2011). Deficits in writing numbers are attributed to lesions to the inferior parietal regions (Jefferies, Bateman, & Lambon Ralph, 2005; Mayer et al., 2003), fronto-parietal connections (Klein, Willmes, Jung, Huber, & Braga, 2016) and the left perisylvian area (L. Cohen et al., 2000).

Surprisingly there are only a few studies that attempt to directly compare reading/writing of numbers and reading/writing words. A developmental study with school children reports a high correlation in the ability to write and read Arabic numbers and single words (Lopes-silva et al., 2016). This study suggests that reading/writing words and number uses overlapping cognitive abilities. In line with this, comorbidity of numerical and language deficits is often noted (De Luccia & Ortiz, 2016).

The neuropsychological literature is biased toward cases who demonstrate functional dissociation. Thus, single cases are reported of patients showing deficits in writing numbers and words, despite intact numerical abilities (Luzzi

& Piccirilli, 2003). Single dissociation is reported for patients showing impairment in writing words/letters but not numbers (S. W. Anderson et al., 1990; Starrfelt, 2007). Opposite selective dissociation for writing deficits has not been reported to our knowledge (inability to write numbers with preserve ability to write words). Though cases of acalculia, presumably including an inability to write numbers are reported in the absence of language deficits (Basso, Burgio, & Caporali, 2000).

The current study had two aims: 1) to re-test the linguistic-motor model for writing ability using a data-driven approach and function lesion mapping with formal statistical tests. 2) To explore the overlaps and dissociations of different writing systems: words and numbers. We further assessed evidence for the dual-route hypothesis concerned with the phonological writing systems.

We used function-lesion mapping to answer the above questions. The advantage of this approach over fMRI/PET studies is that neuropsychological studies provide evidence regarding causality (processes in area ‘a’ directly contribute to the measured skill) while fMRI studies only measure correlations.

Previous neuropsychological studies with agraphia patients or patients with number processing deficits reported results based on relatively small sample size, patients were often pre-selected based on symptoms (e.g. showing selective deficits), or lesion location (e.g. unilateral lesion to the left hemisphere). The mapping of the lesion to symptoms rarely applied formal statistical methods to assess the reliability of the results. Comorbidities were

also rarely controlled for. Hence the ability to generalize the results of these studies beyond the single cases is limited.

To increase the generalizability of the results, we did not pre-select patients based on formal neuropsychological diagnosis or specific lesion location. We use an inclusive large sample of stroke survivors recruited at their sub-acute phase (3 months post-stroke). Furthermore, to increase the sensitivity of the analysis, we did not classify the patient based on formal diagnostic criteria, but instead used their performance on relevant tasks and explored patterns in the data with minimal a-priori assumptions.

The cognitive data was collected using the Birmingham Cognitive Screen （BCoS） (G. W. Humphreys, Bickerton, Samson, et al., 2012). Writing is part of the assessments of the language and the number domains. To assess generic language abilities, we used picture naming, sentence construction, and reading. We also used reading numbers to assess the knowledge of autographic numerical representations. We used the imitation of meaningless gestures, the complex figure copy, and the multistep object use tasks to assess the ability to control high-level manual movements.

The rich and large-scale continues nature of the data enabled us to utilize a data-driven approach to test whether the language and motor component could explain variability in writing abilities. In the first analysis (N=740) we report correlations and comorbidities of the writing tasks (number and words) with the tasks assessing other language and high-level motor functions.

In a second analysis, using a sub-set of the data (N=267), we map the function to the lesion, by combining the behavioral data with clinical neuroimaging data (CT) using Voxel-based Morphometry (VBM). We specifically explored neural correlates supporting writing abilities and how these related to generic language and motor capacities. We first assessed the lesion associated with the raw scores of writing performances (model 1). Then we assessed how correlations with writing changed when we controlled for linguistic and motor processes in the model (model 2). We used conjunction analysis and exclusive masking to tap into shared and dissociated words and number writing systems. We then explored whether lesions in these areas were associated with specific error types. In a third analysis (model 3), VBM was used with latent cognitive writing components identified by principal component analysis (PCA). Combining PCA with VBM analysis has been used successfully in the past with this database to answer questions relating to spatial attention, language and drawing (Chechlacz et al., 2014; Chen et al., 2016; Lau et al., 2015).

5.3 Method

5.3.1 Participants

We use a sub-sample of the BUCS trail in our study. (see detail in method chapter 2)

Analysis 1: For the first behavioral analysis we excluded patients who were not assessed on the two writing tasks due to fatigue or other reasons (N=166). This has left us with a sample of 740 patients (see table 7, for demographic details).

Analysis 2: For the function-lesion mapping analysis, we first excluded patients who did not have a CT scan and those with poor quality CT scans or enlarged ventricles (N=281). To reduce heterogeneity in our study, we also excluded patients with hemorrhagic lesions (N=43) and left-handed patients (N=76). Then we excluded 127 patients not assessed on the two writing tasks. Finally, as the evidence for ischemic stroke on a CT scan are unclear within the first 24 hours after stroke, we excluded those who had their scan taken on the same day of the stroke (n=112). The analysis included a total of 267 ischemic stroke patients. (see Table 7 for demographic details of the two samples). Patients that were included in the second VBM analysis did not differ from those excluded in terms of age, gender, education year, Barthel index (all Ps > .05, see Supplementary Table 6 appendix 3 for details).

Table 7a: Demographic data and correlations

Variables			Corr. Word-Writing		Corr. Number-Writing	
	Analysis 1 (N≤740)	**Analysis 2** (N=276)	**Analysis 1** (N≤740)	**Analysis 2** (N=276)	**Analysis 1** (N≤740)	**Analysis 2** (N=276)

Gender (M/F)	322/418	131/136				
Right/left handed	656/68	267/0				
	mean, med (std)	**mean, med (std)**	**r**	**r**	**r**	**r**
Age Years	69.24, 71 [13.94]	70.28, 73 [14.29]	-0.052	-0.137£	-0.170**	-0.188*
Education Years	11.46, 11 [2.74]	11.40, 11 [2.61]	0.172**	0.205£	0.073£	0.152£
Stroke-to-scan Days	6.74, 1 [14.48]	6.75, 2 [11.71]	-0.042	-0.011	-0.019	0.074
Stroke-to-BCoS Days	27.62, 19 [27.24]	23.32, 16 [20.92]	-0.106£	-0.067	-0.146**	-0.151£
Barthel Index	13.32, 14 [5.66]	13.83, 15 [5.33]	0.159**	0.194£	0.251**	0.240**
Cognitive data						
Orientation (max=8)	7.46, 8 [1.41]	7.51 [1.34]	0.420**	0.400**	0.55**	0.519**
Picture naming (max=14)	10.82, 12 [3.36]	10.23, 12 [3.91]	0.527**	0.592**	0.618**	0.640**
Sentence construction (max=8)	6.94, 8 [1.88]	6.50, 8 [2.47]	0.418**	0.506**	0.579**	0.672**
Sentence reading (max=42)	37.44, 41 [9.54]	34.98, 41 [12.72]	0.500**	0.520**	0.554**	0.596**
Number reading (max=9)	7.57, 9 [2.56]	7.16, 9 [2.98]	0.549**	0.574**	0.696**	0.708**
Multi step object use (max=12)	10.26, 12 [3.32]	9.91, 12 [3.58]	0.315**	0.331**	0.46**	0.486**
Meaningless gest imitation (max=12)	9.42, 10 [2.81]	9.31, 10 [2.91]	0.4**	0.465**	0.527**	0.543**
Complex Figure Copy (max=47)	34.48, 38 [11.52]	33.94, 38 [12.56]	0.362**	0.279**	0.492**	0.562**
Writing tasks						
Numb writing (max=5)	3.75, 5 [1.70]	3.54, 5 [1.85]	0.633**	0.700**		
Word writing (max=5)	3.02, 3 [1.75]	2.74, 3 [1.87]			0.633**	0.700**

Table 7a: £p< 0.05 uncorrected; *P<0.05 corrected (uncorrected p<0.05/26), **P<0.005 corrected (uncorrected p < 0.005). Corr, Correlation with number or word writing; Analysis 1 – descriptive and correlation for the sample that contributed to behavioral analyses; Analysis 2 – descriptive and correlation for the sample that contributed to VBM analyses. Abbreviation: Med, median; std, standard deviation; max, maximum score in the task; gest, gesture; Numb, number.

The number of patients contributing to each variable in Analysis 1, age, n=740; Education, n=722; stroke-to-scan, n=477; stroke-to-BCoS n=740; Barthel Index n=733; Orientation, n=733, Picture naming, n=730; Sentence construction, n=730; Sentence reading, n=707; Number reading, n=715; Multistep object use, n=722; meaningless gesture imitation, n=737; complex figure copy, n=721; number and word writing, n=740. In analysis 276 contributed to all analyses.

Table 7b. The skewness quantitatively and the kurtosis of the cognitive data in the two groups

Variables	Analysis 1 (N≤740)		Analysis 2 (N=276)	
	skewness	kurtosis	skewness	kurtosis
Cognitive data				
Orientation (max=8)	-3.415	12.444	-2.033	4.351
Picture naming (max=14)	-1.650	2.439	-1.331	0.897
Sentence construction (max=8)	-2.095	3.957	-1.671	1.546
Sentence reading (max=42)	-2.732	6.630	-1.937	2.228
Number reading (max=9)	-1.891	2.464	-1.561	1.019
Multi step object use (max=12)	-2.109	3.141	-1.881	2.135
Meaningless gest imitation (max=12)	-1.240	1.017	-1.157	0.632
Complex Figure Copy (max=47)	-1.167	0.556	-1.222	0.553
Writing tasks				
Numb writing (max=5)	-1.139	-0.094	-0.924	-0.691
Word writing (max=5)	-0.497	-1.088	-0.264	-1.412

5.3.2 Behavioral measures

5.3.2.1 Cognitive profile

The patients' cognitive profile was assessed using the BCoS(G. W. Humphreys, Bickerton, Samson, et al., 2012). We used the following cognitive

tasks in our study including two writing tasks (Word and number Writing), 4 language correlated covariates (Picture Naming, Sentence Construction, Sentence Reading, Number Reading), three motor related covariates (Multi-Step Object Use Test, Meaningless Gesture Imitation, Complex Figure Copy) and other general cognitive functions (Patient's Orientation, Barthel Index). (see details in method chapter)

In addition, we included the following measures as variables of no interest: age, gender, education, the use of the dominant hand and the time of the cognitive assessment relative to the stroke. See table 7 for description.

Besides, the writing sheets of 199 patients (out of 267) were available in the BUCS database. This enabled further analyses of errors in the writing word tasks. Error type analyses were conducted independently by two native English speakers, disagreements were resolved through discussions. For each patient, performances were coded for exceptional, non-exceptional and non-word. Phonological errors were defined as cases where the pronunciation was correct despite the wrong spelling. The writing quality of the letters was assessed, with a score of 2 indicating good writing quality, 1 recognizable with effort and 0 for those unrecognizable. Of the 199, 16 patients scored zero on the word writing task and their writing sheets were empty. These patients were excluded from the analysis.

Analysis 1: Behavioral Data (N≤740)

Analysis 1: To estimate the relation between the two Writing tasks and demographic data along with all the other covariates, Pearson's correlation (two-tailed) analyses were performed. All together we computed 26 correlations, and the results were corrected for multiple comparisons using Bonferroni correction (p < .0019 (=0.05/26)). Table 7, present the correlation analysis. Patients with missing data were excluded from the relevant analysis. For the comorbidity analyses (Figure 17b), task impairments were defined using the cutoff scores obtained from age and demographic match healthy control reported as part of the BCoS standardized data (Humphreys, Bickerton, Samson, et al., 2012).

Analysis 2: Neuroimaging assessment

The CT scans were acquired as part of the clinical routine when patients were admitted to the hospital. CT scans were acquired using Siemens Sensation 16, GE Medical System Light Speed 16 and Light Speed Plus with an in-plane resolution of 0.5 x 0.5mm and a slice thickness between 4 and 5 mm.

5.3.3 Pre-processing of brain images

We used a same brain images pre-prcessing with the one in chapter 3. (see detail in the method chapter)

5.3.4 Voxel-based morphometry (VBM)

We use VBM analysis to compute the correlation between the behavioral results of the word and number writing in relation to grey matter density (see detail in chapter 2).

Missing data. If data was missing in the covariates it was replaced by the whole group average. The amount of missing data for each task ranged from 0% to5.6% with an average of 1.4%. While the number of missing data points was small, it was not equally distributed across impaired and intact writing groups. Patients who were impaired in the two writing tasks also had more missing data in the language task: 14 missing data points across the four tasks in the impaired group as opposed to 1 missing points in the intact group. Similarly, patients with writing deficits had 12 missing data points in the three motor tasks; while the intact group had only 4 data points missing. The approach we took to replace this missing data was a conservative approach, in which we replaced it by the average of the group. To ensure this did not lead to spurious results, we have re-run the PCA analyses (see below) excluding all patients with the missing data. The pattern of results has not changed; hence we kept the conservative approach for replacing the missing data. Though the approach to replace missing data likely underestimated the prevalence of comorbidities.

In the VBM analyses, we estimated three models. Model 1 included the

Writing (word + number) raw data with no additional language and motor covariates. Model 2 added the language and motor associated tasks as covariates. In both models: we report the shared lesions affecting the writing of numbers and words writing using conjunction with global null. The SPM offers two statistical tests to compute conjunction analysis: Conjunction with global null (Friston, Holmes, Price, Büchel, & Worsley, 1999) and Conjunction with conjunction null(Nichols, Brett, Andersson, Wager, & Poline, 2005).

The conjunction with Global null uses the minimum T statistic which means that joint functions-lesion mapping entails that both contrasts survive a common threshold. It tests the specific case that two (or more) contrasts show consistent relations with a given voxel intensity. As a consequence, conjunction with global null, increase the test sensitivity, as it considers the consistent direction of relationship pattern, similar to the improved sensitivity when using one-tailed as opposed to two-tailed t-test.

Conjunction with conjunction null is a much more conservative test, as it will require that all included contrasts show reliable effects to the same degree. Test sensitivity is not improved when using conjunction with conjunction null. The statistical parametric map resulting from conjunction with conjunction null is identical to map of overlapping same threshold maps of each contrast.

I used Conjunction with global null in the study to increase study power. The dissociated mechanism for Numbers' and Words' Writing was tested using exclusive masking. For example, we look for lesions that correlated with the

ability to write Words using a threshold of (Voxel threshold: *P*uncorr < 0.001 & cluster >150 voxels), but did not correlate with the ability to write Numbers (voxel threshold: *P*uncorr > .05). Function lesion mapping of error types: To explore the relations between lesions and specific cognitive function, we extracted the volumetric of the grey matter from 12mm sphere clusters' peak observed in model 2. These were correlated with the three error types: phonological errors, errors in exceptional and regular words and with the writing quality score (see above for details).

Model 3 was computed to gain further insights into the rule of different regions within the writing network. To this aim, we computed a PCA to identify underlying cognitive components for the two 'Writing' tasks. A KMO and Bartlett's test was performed across the data. The KMO value was 0.910 and its significance level for Bartlett's test was below 0.001 (1647.631 with 36 degrees of freedom). The KMO test results indicated that there were correlations in the data selected and the distributions of data meet the assumptions of multivariate analysis. We also presented a correlation matrix of these tasks in the appendix. (See supplementary table 8 in appendix 3)

The PCA was computed in SPSS, the data was scaled before the PCA was applied. The PCA included the two writing tasks (word and number), four language tasks (Picture Naming, Sentence Reading, Sentence Construction, number reading), and three motor related cognitive tasks (Meaningless Imitation, Multi-object used and Complex Figure Copy). The PCA teased apart

the differential and shared components of writing with the other cognitive tests. Model 3 included all the PCA components. The analysis of the PCA-VBM focused on components that were most clearly and meaningfully linked to latent variables associated with variability in Writing. (see more details of PCA in the method chapter)

We focus on results that survived cluster level family-wise error correction at the cluster level ($p<0.05$, with uncorrected voxel threshold of $p <.001$). The charts represented the effect size (beta) for the covariates of interest, at the sphere of 3mm around the peak. The covariates were scaled to ensure the betas are comparable.

5.3.5 VBM analysis on an expanded PCA

In a further analysis, we run a PCA on the data used in the neuroimaging analysis and included all cognitive tasks from the BCoS excluding number and word writing task. Kaiser's criterion and Varimax rotation was applied. The new PCA would integrate with the VBM data.

In this analysis I excluded the patients for whom we did not have a CT and ended up with 190 participants. Note that this number is lower than 276, as we excluded all patients who had at least one missing data point.

5.4 Result

5.4.1 Analysis 1: Behavioral results (N=740)

Table 7 presents descriptive data for each of the measures and their correlation with the Word and Number Writing tasks. As can be seen, all the behavioral measures were positively skewed (median > mean), with more patients showing intact performances with a tail representing the severely impaired.

Word Writing tasks - the patients analyzed in our study (=740) had an average score of 3.02 (SD: 1.75) in the Word Writing task (see Figure 17A, for the distribution). 34.6% (256/740) of the patients were classified as impaired.

Number Writing tasks - the average score was 3.75 (SD: 1.70) (see Figure 17A, for the distribution). 35.5% (263/740) of the patients were classified as impaired.

Performance on word and number writing correlated (r = 0.63). Of the 740 patients, 352 (47.6%) showed deficits in at least one writing task. Of these 352 patients, 166 (22.4% of the 740) showed impairments in both word and number writing tasks, while 186 (25.1% of the 740) had dissociated abilities with 90 presenting deficits in word writing but intact number writing abilities and 96 presenting an opposite pattern (Figure 17B.i).

Correlation of the two Writing tasks with the demographic data (table 7) – both tasks showed a similar correlation pattern. As expected, the number

of years in education positively correlated with the ability to write words. The Barthel Index had a weak positive correlation with both the writing tasks, indicating that patients with worse performance in activities of daily living were likely to struggle with writing. Age had a weak negative impact on the ability to write numbers, with older individuals performing worse than younger. As reported before with this sample, the number of days from stroke to test negatively correlated with the ability to write numbers. This is because the more severe patients were recruited from the rehabilitation center rather than from acute stroke units.

Correlation of the writing tasks with performances on the other cognitive domains - All the language related tasks positively correlated with both the writing tasks (r ranged from 0.42 to 0.70). Similarly, all the motor related tasks were positively correlated with performances on the writing tasks (r ranged from 0.32 to 0.53). See table 7 for details.

The comorbidity data showed multiple dissociations of impairment patterns. None of the 740 patients showed impairment in the two writing tasks with intact abilities in all the other 7 tasks. Of the entire sample, thirteen patients (1.7%) were impaired only in writing words, and eight patients (1.08%) were impaired only in writing numbers. For the patients who were classified as impaired in both Word and Number Writing (n=166), we counted the numbers showing impairments in the language or high-level motor domains. Of the 166 patients,

only 7 (4%) patients show intact language ability, suggesting a specific writing impairment dissociated from language (Figure 17B.ii), and only 13 (9%) patients had no other high-level manual deficit (Figure 17B.iii). The most prevalent comorbidity was with complex figure copy (81.9%), though some patients (13.3%) showed deficits in writing but intact ability to copy a figure (4.8% of patients didn't complete the copy task due to fatigue or other reasons). (The distribution and comorbidities analysis in the 276 patients recruited in our VBM analysis showing similar results were presented in supplementary figure 4 in appendix 3.)

Figure 17: Behavioral results (N=740)

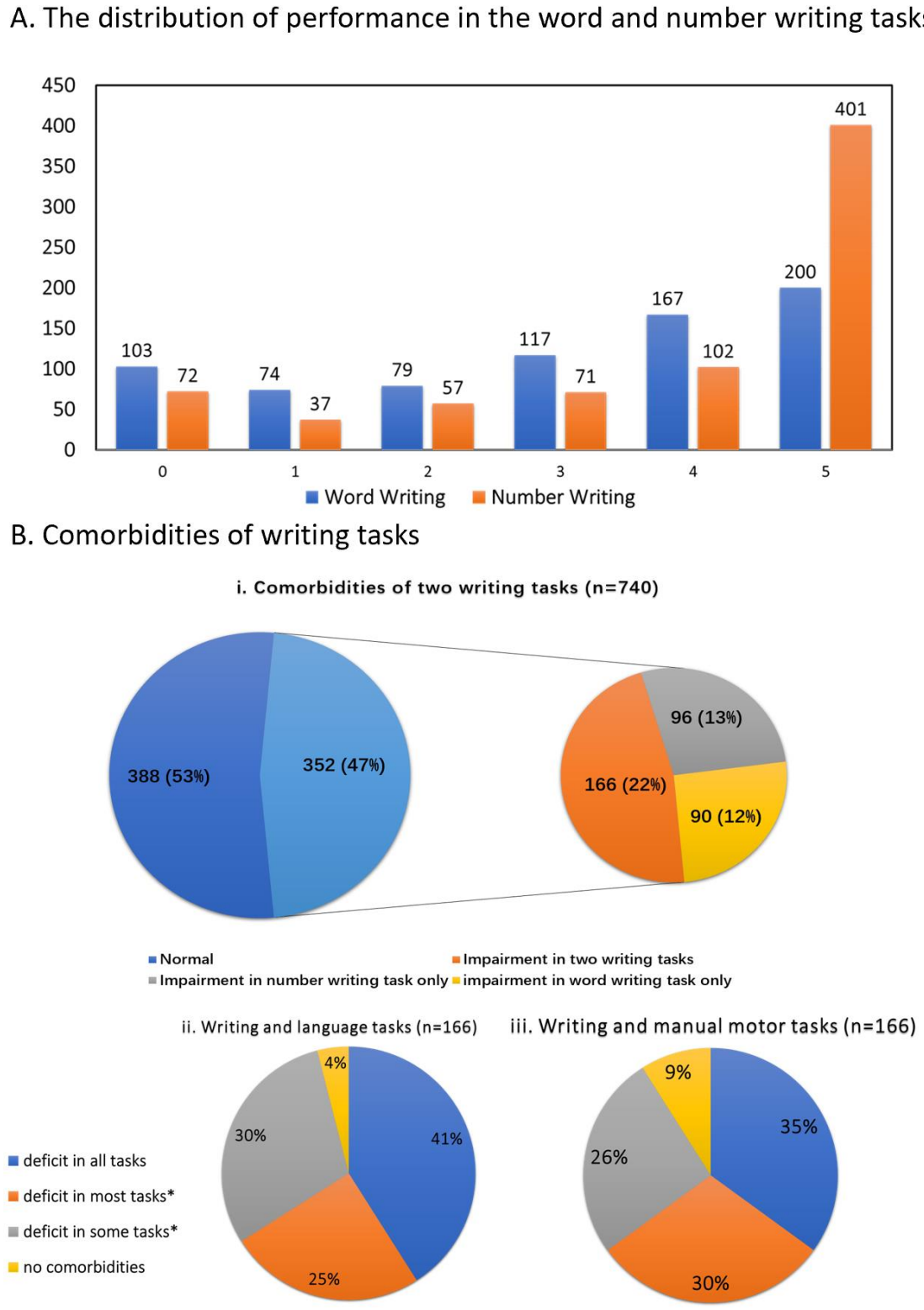


Fig 17: A) The chart represents the distribution of performances for writing words (blue) and numbers (orange).

B) Pie charts representing the prevalence of writing impairments. The pie

chart on the left, green represent patients who show no impairment in writing, blue represents patients who show impairment in at least one of the writing task. The pie chart on the right, break the blue group, to those how show impairment on both writing tasks (orange), or just on one of them (yellow, grey).

C) pie charts that break comorbidities in patients who show deficits in both writing tasks (the orange group) based on the prevalence of comorbidity with the language-based (left) and motor-based (right) tasks. *deficit in most tasks(ii:3 language tasks; iii: 2 motor tasks); deficit in some tasks (ii: 1 or 2 language tasks; iii:1 motor task)

The data above suggest that following stroke, the prevalence of writing deficits with no comorbidity of language and/or motor deficits is very low. As missing data was more prevalent in patients who were impaired in the writing tasks, the actual proportions of pure writing deficits may be even lower. Hence controlling for these comorbidities in the analyses is crucial.

Table 8 presents the error analysis for the sub-sample of patients (n=183) (see supplementary figure 5&6 in appendix 3 for case examples). As expected, patients struggle most with non-words and exceptional words. We also presented a correlation matrix of these error types supplementary table 7 appendix 3.

Table 8: error analysis writing words

Error type	N	Score range	Mean / median / std	Number scoring zero
Writing quality	183	0 - 2	1.39 / 1 / 0.63	15 (8%)
Real words	168	0 - 4	2.09 / 2 / 1.34	30 (17.8%)
Non-word	168	0 - 1	0.35 / 0 / 0.48	109 (64%)
Regular words	168	0 - 2	1.4 / 2 / 0.79	32 (19%)
Exceptional words	168	0 - 2	0.68 / 0.5 / 0.76	84 (50%)
Phonological errors*	168	0 - 4	0.6 / 0 / 0.7	82 (48.8%)

Table 8: *Correct pronunciation but wrong spelling, zero means no phonological errors. Note: Variability in number of patients per error types emerged from the patients who failed to write any word. These patients were given a score of zero by the examiner and there was no indication for lack of response due to misunderstanding. In these cases, errors were coded based on information from the examiner notes. For example, if the examiner noted that the patient did not complete the task because of aphasia, then they were scored with the maximum linguistic errors (non-words, exceptional words, regular words, phonological errors), but we did code the writing quality. Conversely, if they had a motor deficit, their writing quality would be zero, but no coding was provided for linguistic related errors.

We next used the pattern of error data to assess the external validity of the writing measures. First, the quality of writing was positively correlated with the three motor tasks that require fine manual control (Complex figure copy r=.431; Multistep object use, r=.388; meaningless gesture imitation, r=.245; all Ps < .001).

As expected, the number of errors made in words as opposed to non-word, correlated with the number of phonological error (r=.4, p < .001). The number of phonological errors negatively correlated with number writing ability (r=-243, p = .001). Similarly, the number of errors in exceptional (relative to regular) words, positively correlated with number writing ability (r=-.199, p =.011).

The final external validation test utilized relation pattern made by the dual-process model for writing (Coltheart et al., 2001). This model predicts that the number of errors made in writing regular words can be predicted by the number of errors made on exceptional words (lexical route) and non-words (non-lexical

route) (p(REG) = p(IRREG) + [1 − p(IRREG)] × p(NWD) (p=proportion, REG=regular word, IRREG=irregular word, NWD=Nonword). Based on this model, we computed for each patient a predicted number of errors for the regular words using their performances on exceptional words and non-word. The correlation of the predicted and the observed results was reliable r=.71, p <0.001.

Taken together the error analyses demonstrated that despite the low number of items, the data present expected error pattern, supporting its reliability and external validity.

5.4.2 Analysis 2: Neuroimaging Results (N=276)

5.4.2.1 VBM based on raw scores of the Writing Tasks

The shared mechanism for words and numbers writing was assessed using the global null conjunction. Dissociation between writing words vs. numbers was assessed using exclusive masks. Supplementary figure 5&6 (appendix 3) provides case examples of brain lesions and error patterns observed in the data.

Model 1: First we examined the correlation of lesions with the raw scores of the Writing (word + number), without controlling for language and motor (Model 1, Table 9 and Figure 18, red blobs). Lesions that predicted deficits in both the Writing tasks were in the right middle frontal and bilateral inferior occipital gyri. Model 1 showed no above threshold dissociations between

writing numbers and words.

Model 2 controlled for the seven language and motor related tasks (Table 9 and Figure 18, yellow blobs). The previously observed clusters in bi-lateral inferior occipital were below threshold in model 2, suggesting variability in grey matter integrity in these regions could be account for by generic language and motor deficits.

Interestingly, by reducing the overall unexplained variability due to deficits in language and motor abilities, model 2 highlighted a correlation of the Writing tasks with lesions to bilateral superior frontal gyri, (SFG) right middle frontal gyrus, right inferior parietal and inferior temporal (ITG), left middle occipital gyrus (MOG) and right cerebellum.

Dissociation of writing words and numbers were observed, with the lesion to the right middle temporal (MNI: 58 -60 -2, Z_{peak}=3.66, Voxels=192, Cluster P_{FWE} = .023) uniquely associated with Writing words. This region was more posterior to the right ITG lesion observed for the conjunction analysis (Table 9). Conversely, lesion in the left postcentral gyri (MNI: -51 -19 45, Z_{peak}=3.57, Voxels=156, Cluster P_{FWE}= .061) was uniquely associated with Number Writing.

Table 9 VBM results – Analysis 2 (N=276): function-lesion mapping of Writing

Anatomy		*Model 1*	*Model 2*	***Model 3: PC3 pen using***	***Model 3: PC4 meaningful writing***
Frontal lobe					
L SFG	x y z		-15 32 52		-9 70 0
	cluster		537		1771
	Zpeak		4.31		5.00
R SFG	x y z		2 68 9 / 26 44 43		27 44 42 / 16 70 10
	cluster		125 / 201		1791 / 410
	Zpeak		4.07 / 3.88		4.91 / 4.46
L MFG	x y z				-39 48 25
	cluster				394
	Zpeak				4.13
R MFG	x y z	30 8 40	44 18 51	36 6 42	
	cluster	137	868	331	
	Zpeak	3.43	4.02	3.63	
L IFG	x y z				-28 24 -23
	cluster				665
	Zpeak				4.74
Parietal lobe					
R IPC/AG	x y z		54 -46 51	50 -61 46	
	cluster		167	587	
	Zpeak		4.22	4.79	
Temporal lobe					
L MTG	x y z				-58 -64 -5
	cluster				2207
	Zpeak				5.18
L hippocampus	x y z				-22 -19 -12
	cluster				498
	Zpeak				4.07
R ITG Ext MTG	x y z		58 -63 -6		48 -9 -41 / 58 -63 -9
	cluster		391		432 / 279
	Zpeak		4.17		5.18 / 4.18
Occipital lobe					
L MOG	x y z		-18 -94 9		
	cluster		361		
	Zpeak		3.91		
L IOG	x y z	-28 -91 -11			
	cluster	702			
	Zpeak	4.01			
R IOG	x y z	45 -79 -6 / 24 -97 -11			

	cluster	325	325			
	Zpeak	3.99	3.79			
Cerebellum						
L cerebellum	x y z				-44 -72 -45	-18 -90 -30
	cluster				369	394
	Zpeak				4.63	4.13
R cerebellum	x y z		26 -90 -32		20 -88 -30	45 -67 -45
	cluster		119		1114	582
	Zpeak		3.92		5.44	4.42
Vermis	x y z				-3 -57 -23	
	cluster				437	
	Zpeak				4.05	

Table 9: All reported clusters are family wise error corrected at the cluster level, with a voxel threshold of $p < 0.001$, uncorrected. Abbreviation: L: left; R: right; SFG, superior frontal gyrus/cortex; MFG, middle frontal gyrus/cortex; IFG, inferior frontal gyrus; IPC, inferior parietal cortex; AG, angular gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; MOG, middle occipital gyrus; IOG, inferior occipital gyrus. Zpeak, the Z value of the cluster's peak. **Model 1**: cluster that positively correlated with number writing and word writing after controlling for age, education, orientation, days from stroke-to-scans, days from stroke-to-cognitive screen, gender. **Model 2:** Cluster that positively correlated with number writing and word writing after controlling for the covariates in model 1 and in addition for the 4 language and manual motor tasks. **Model 3:** Included the same covariates as in model 1, and the additional PCA scores as covariate. PC3, cluster showing positive correlation with the PCA component that dissociated the use of pen tasks from other fine manual motor tasks; PC4, Clusters showing positive correlation with the PCA component that dissociated the writing tasks from CFC (see Table 9, 11 and text).

Figure 18：VBM results with raw scores (model 1&2) (N=267)

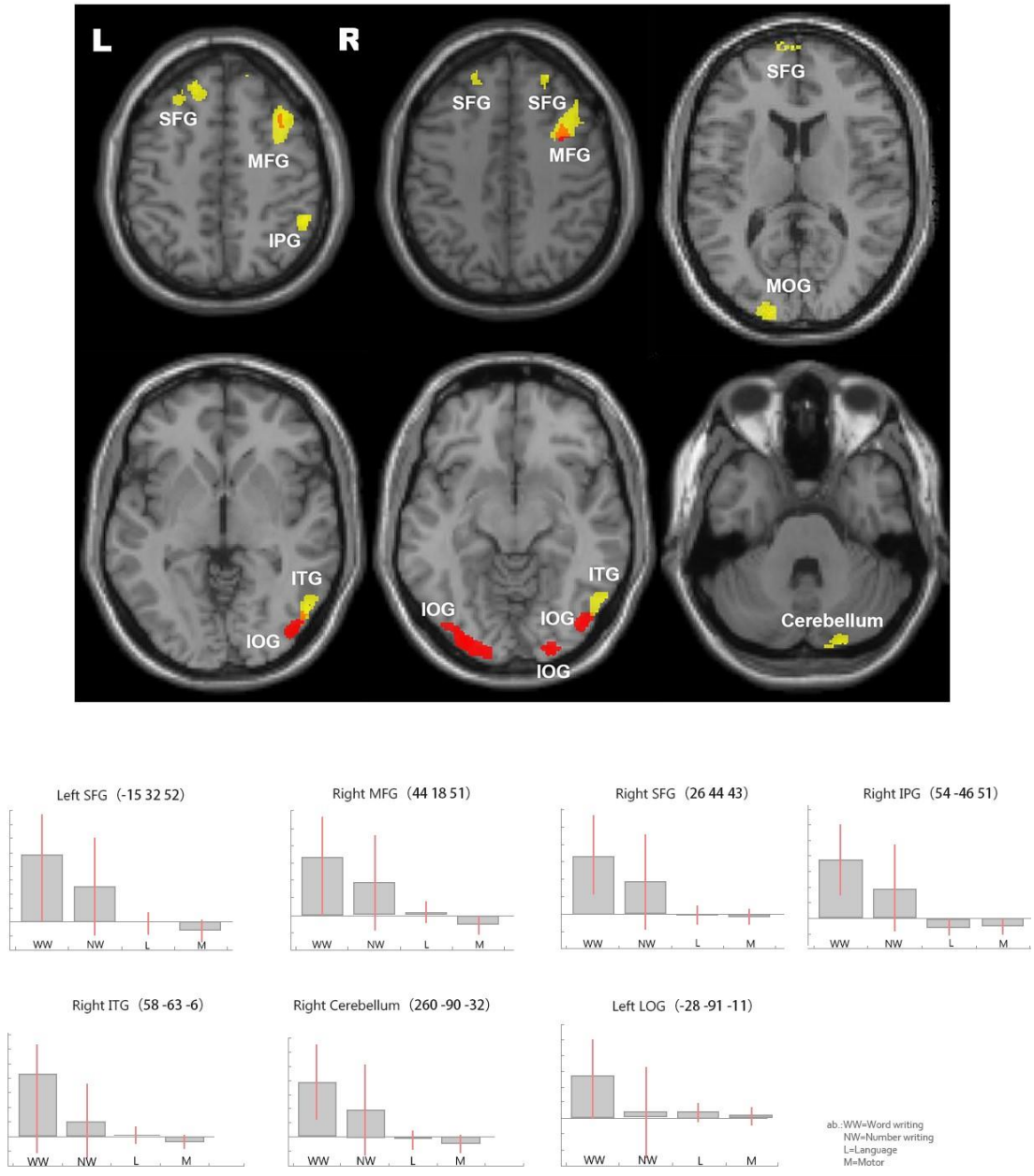


Fig 18: The VBM results overlaid on the canonical T1 images (SPM), showing lesions associated with deficits in both writing tasks (conjunction). Results of model 1 (model not included other language and motor tasks) are presented in red, and for model 2 (model included the 4 language and 3 motor tasks) in yellow. The charts represent effect size for each writing tasks and the average effect size for the language (L) and motor (M) tasks. The error bars are 90% confidence interval of the effect size. Abbreviations: L, left, R: right, SFG,

superior frontal gyrus; MFG, middle frontal gyrus; IPG, inferior parietal gyrus; MOG, middle occipital gyrus; ITG, inferior temporal gyrus, IOG, inferior occipital gyrus; WW, word writing; NW, number writing; L, language, M, motor. See Supplementary Figures 5&6 in appendix 3for case examples of lesion on the CT scans.）

To gain a better understanding of the rule of each of these regions in writing abilities, especially writing words, we further examined the association of grey matter in the above cluster and the error types made by the patients (table 10). The correlations were overall weak and hence should be interpreted with cautious. Lesion to the bilateral PFC and right inferior parietal was positively correlated with the ability to write the exceptional words and negatively correlated with the number of phonological errors, suggesting a rule for these regions in the lexical route. While lesions to left MOG and right MTG positively correlated with the ability to write regular and exceptional words, suggesting a potential contribution to non-lexical processing.

Table 10 Error type & brain regions correlation

Brain region (model 2)	Phonological errors	Regular words	Exceptional words
	r, p	***r, p***	***r, p***
L SFG	-0.20, 0.012		0.197, 0.012
L MOG		0.15, 0.049	0.15, 0.049
R SFG	-0.15, 0.055	0.17, 0.025	0.16, 0.040
R MFG		0.16, 0.036	0.15, 0.049
R IPC	-0.17,0.028		0.15, 0.049
R MTG	-0.176, 0.025		

R ITG	-0.167, 0.034	0.17, 0.034
R Cerebellum		

Abbreviations: L, left, R, right, SFG, superior frontal gyrus; MFG, middle frontal gyrus; IPV, inferior parietal cortex; MTG, middle temporal cortex; ITG, inferior temporal gyrus. Results are not corrected for multiple comparison.

5.4.2.2 VBM based on PCA scores for Writing

Model 3: To provide an alternative way of delineating the underlying cognitive components of Writing, we computed a PCA. The PCA included the nine writing, language, and manual control tasks (see methods) (Table 11). **PC1:** The first component was shared among all the 9 tests and explained 61.97% of the variability. We assumed that this component represented the overall cognitive ability, generic comprehension or stroke severity in general. **PC2:** The second component was mainly loaded on the motor related tasks, differentiated them from the other linguistic tasks. This component explained 9.1% of the variability. It showed nearly no correlation with the two writing tasks. We assumed that this component represented the general motor vs. linguistic processes that contribute minimally to writing. **PC3:** The third component mainly loaded on the two writing tasks and complex figure copy, differentiated them from the other tasks. We speculated that it represented the use of pen

and motor processes associated with writing and drawing. This component explained 7.73% of the variability in the data. It also reliably correlated with the assessed quality of the writing (r=.238). **PC4:** The fourth component dissociated the writing tasks from the complex figure copy. This component explained 5.9% variability of the data. We assumed it primarily reflected processing associated with writing, but not copying. We interpreted it as cognitive processes associated with the translation of knowledge (e.g. meaningful symbols, objects) to motor programs, as this component was also loaded on the multi-step object used task. The last component of interest was **PC6,** it explained around 3.5% of the variability, differentiated Words from Numbers Writing. It specifically contrasted Word Writing and Picture Naming abilities against Number Writing and Sentence Construction. Thus uniquely dissociated writing words from writing numbers, but possibly tapping to an underlying cognitive mechanism that also dissociated these four tasks, e.g. single item trial (word writing and picture naming) as opposed to multiple items trial (number writing and sentence construction). As number writing involved the combination of symbols and multi digits number in a trial.

Table 11 PCA results – Analysis 2 (N=267)

Tasks	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9
WW	0.728	-.087	0.519	0.342	-0.081	0.200	0.064	0.160	-0.029
NW	0.839	0.021	0.274	0.185	0.125	-0.326	0.017	-0.236	0.085

SR	0.832	-0.298	-0.166	-0.178	0.105	0.186	0.277	-0.038	0.187
NR	0.896	-0.224	-0.094	-0.129	0.031	-0.064	0.130	-0.042	-0.314
PN	0.859	-0.184	-0.110	0.017	-0.031	0.239	-0.363	-0.158	0.002
SC	0.847	-0.224	-0.242	0.045	0.064	-0.246	-0.144	0.286	0.067
CFC	0.671	0.377	0.345	-0.517	0.094	0.009	-0.081	0.074	0.015
MSO	0.619	0.601	-0.312	0.255	0.277	0.111	0.048	0.019	-0.032
MI	0.747	0.290	-0.166	-0.006	-0.566	-0.055	0.067	-0.022	0.035
Exp. Var.	61.97 %	9.10%	7.73%	5.93%	4.95%	3.54%	2.94%	2.20%	1.65%

Table 11: Abbreviation: WW: Word Writing; NW: Number Writing; SR: Sentence Reading; NR: Number Reading; PN: Picture Naming; SC: Sentence Construction; CFC: Complex Figure Copy MSO: Multi-step object use; MI: Meaningless Gesture Imitation;

The results of **model 3** are presented in Table 9 and Figure 19. Based on our study objective, we only focus on the components that were loaded on the writing tasks. Low scores in the third component (PC3, representing poor pen use ability) were associated with lesions to the right middle frontal and the right angular gyri. We noted that the right middle frontal gyrus was also observed in model 1 and 2, above. This suggests that in the context of the writing, this region involves in the motor-related component of the tasks (pen-using).

The fourth component mainly loaded on word writing and differentiated it from the complex figure copy. Low scores were associated with bilateral superior frontal, left middle frontal, bi-lateral temporal and bilateral cerebellum. These results were similar to the function-lesions observed in model 2. No

above threshold lesions were found to be associated with component 6, which dissociated numbers from words writing.

Figure 19 VBM results with PCA component (model 3, N=267)

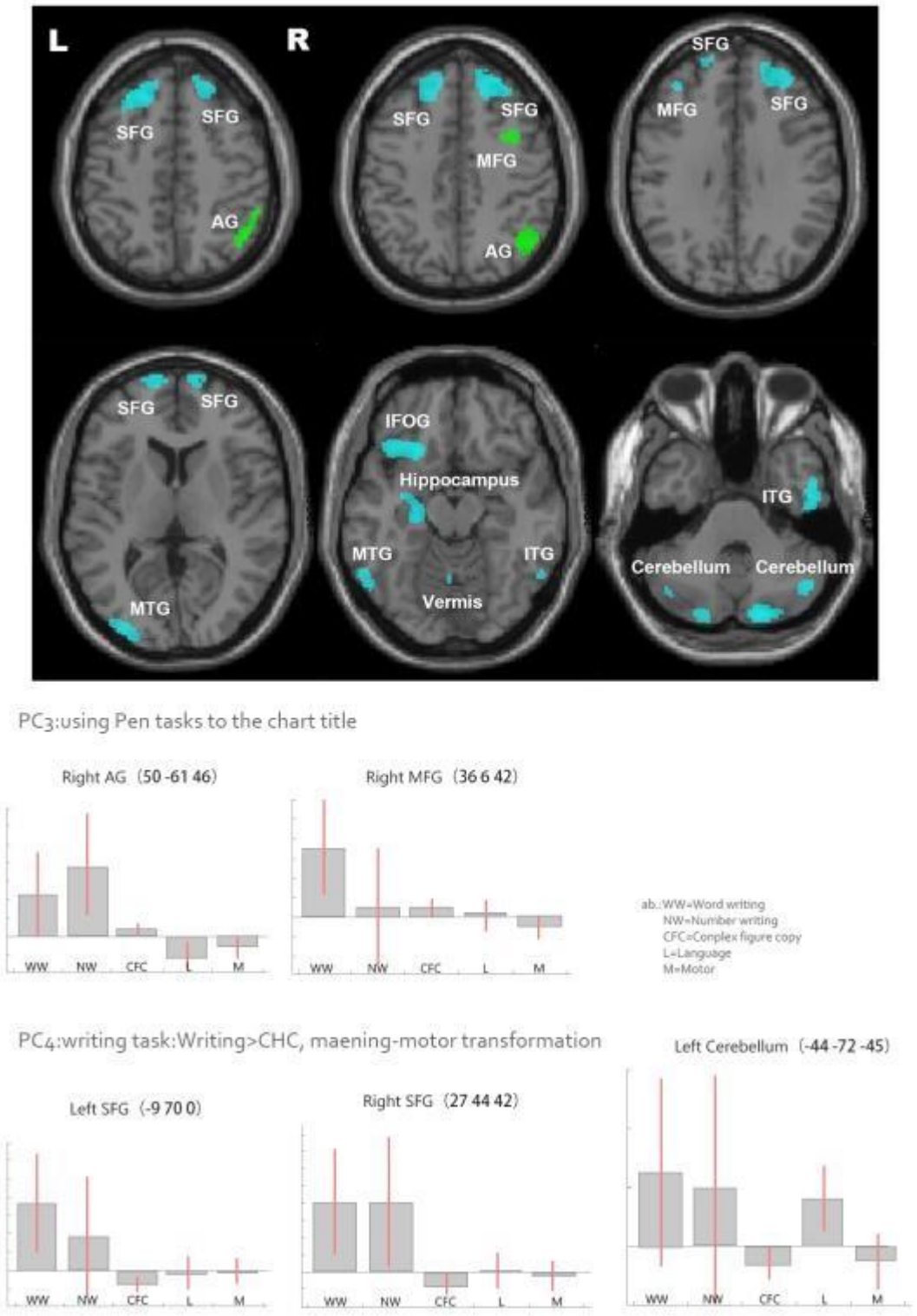


Fig 19: The VBM results overlaid on the canonical T1 images (SPM), showing lesions associated with the PCA writing specific components. Lesion

associated with using pen (PC 3) are presented in green, lesion associated with using pen to produce meaningful symbols (PC 4) are blue. The charts represent effect size for each writing tasks, the complex figure copy and the average effect size for the language (L) and motor (M) tasks. The error bars are 90% confidence interval of the effect size. Abbreviations: L, left, R: right, SFG, superior frontal gyrus; MFG, middle frontal gyrus; IOFG, inferior orbitalis frontal gyrus; AG, angular gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus, IOG, inferior occipital gyrus; WW, word writing; NW, number writing; CFC, complex figure copy; L, language tasks, M, motor tasks. See Supplementary Figures 5&6 in appendix 3 for case examples of lesion on the CT scans.)

5.4.2.3 VBM based on the expanded PCA scores

The expanded PCA revealed 6 components as follow (see table 12): PC1 was mainly loaded on language and number related tasks, PC2 was loaded on the memory tasks, PC3 was loaded on the spatial attention tasks, PC4 was loaded on the praxis and sustain attention tasks, PC5 was loaded on abstract rule finding, potentially reflecting ability to reason and PC6 reflected mainly the orientation tasks. In this PCA, in contrast to the theoretical assumptions, complex figure copy was not loaded on the same component as the praxis tasks, but was loaded on the language and spatial attention components. This matches our observation that using a pen to copy complex figure relies on different praxis ability to processing gestures or the ability to interact with objects to complete an activity of daily living task.

Table 12 PCA results – expaned PCA on all cognitive tasks except the two right tasks

Tasks	PC1	PC2	PC3	PC4	PC5	PC6
Picture naming	0.591	0.401				
Sentence construction	0.574					
Sentence reading	0.803					
Nonword reading	0.734					
Apple cancelation (AC) task	0.446		0.685			
Egocentric asymmetry (AC)*			-0.575*			

Allocentric asymmetry (AC)*			-0.667*		
Visual extinction			0.743		
Tactile extinction			0.618		
Birmingham rule finding accuracy				0.908	
Birmingham rule finding score				0.899	
Auditory sustain attention			0.555		
Memory free recall		0.695			
Memory free recognition		0.805			
Delay memory free recall		0.782			
Delay memory recognition		0.841			
Task recognition		0.560			
Musti-step object use			0.517		
Gesture production			0.377		0.531
Gesture recognition			0.461		
Meaningless imitation			0.415		
Number reading	0.741				
Caculation	0.457				
Complex figure copy	0.509	0.561			
Orientation					0.807
Instruction comprehension			0.721		

Table 12. Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization. a. Rotation converged in 8 iterations. Note: only the loading larger than 0.4 was presented here.

7 models were set up in the VBM analyses. In each of these models I tested the contrast of (writing words > 0) & (writing number > 0) (conjunction with global null-like) and report the results after controlling for various factors. the first one is the writing tasks with brain grey matter (this is similar to what I did in the paper of Model 1. However, I did not include the general cognitive function such as the orientation and comprehension as control covariates as they are already in the PCA). In the other six models, I add the cognitive sub-components identified by the large group PCA one by one to control those aspects:

1e. Writing numbers & writing words control for age, gender, time for screen

to stroke, time for scan to stroke, education.

2e. Model 1e + component 1, language

3e. Model 1e + components 1-2, language & memory.

4e. Model 1e + components 1-3, language, memory & spatial attention

5e. Model 1e + components 1-4, language, memory, spatial attention & praxis

6e. Model 1 + components 1-5, language, memory, spatial attention, praxis & reasoning

7e. Model 1e + components 1-6, language, memory, spatial attention, praxis & orientation (see results in table 13)

Table 13 VBM results – expanded PCA (N=190): function-lesion mapping of Writing

regions	Model 1e	Model 2e	Model 3e	Model 4e	Model 5e	Model 6e	Model 7e
L SFG (x,y,z) cluster size, peak-z					(-14 33 57) 179** 4.23		
R MFG (x,y,z) cluster size, peak-z		(38 12 43) 793** 4.07	(36 11 43) 677** 4.06	(36 15 43) 410** 3.70	(36 9 42) 661**, 4.03	(42 20 52)** 168**, 3.72	(42 20 52)** 474** 4.19
R MTG (x,y,z) cluster size, peak-z		(54 –72 3) 235** 4.90	(54 –72 3) 177** 4.58	(56 -69 9) 125* 4.49	(59 -64 5) ** 313** 4.83	(54 -72 2) ** 249** 4.86	（54 -72 2） ** 390** 4.39
R IPG (x,y,z) cluster size, peak-z			(50 – 54 53) 132* 4.00		(51 -48 51) ** 172** 4.26	(48 -51 54)** 348** 4.51	(48 -48 54） ** 349** 4.40
L ITG (x,y,z) cluster size, peak-z					(-42 -9 -41） * 140* 4.38		
L MOG (x,y,z) cluster size, peak-z						(-14 -97 18) ** 430** 4.02	

L SOG						(-14 -97 18) **
(x,y,z) cluster size, peak-z						264** 3.82
R MOG	(47 –79 21)**					
(x,y,z) cluster size, peak-z	1500** 4.77					
L Cerebellum		(-36 -40 -44) *	(-30 -39 -44) **	(-27 -34 -45)*	(-30 -39 -44) **	(-30 -49 -44)**
(x,y,z) cluster size, peak-z		125* 4.32	167** 4.45	142* 4.63	213** 5.21	366** 5.29
R Cerebellum	(24 –33 –42) *			(26 -90 -32) *	(27 -37 -42) **	(27 -37 -42) **
(x,y,z) cluster	116* 4.00			141* 4.09	180** 4.29	303** 4.49
size, peak-z					(21 -87 -36) **	(53 -64 -36) **
					174** 3.74	274** 3.81
						(12 -66 -47)*
						136* 3.58

5.5 Discussion

The current study aimed to explore the cognitive neural substrates associated with the handwriting of words and numbers. To answer our two questions, the data suggests that handwriting is utilized through the functional adaptation of structures in both hemispheres. This network supports the linguistic and the fine visual-motor control needed for using a pen to reproduce meaningful visual marks. This network was partly dissociated from the generic manual motor and language-based processing. The data supports the classical writing model, which views writing as the intersection between language and motor.

The data also provides some support for the two routes model for phonological writing. The data suggest that bilateral SFG and right IPC

contributed to the lexical route, while left MOG potentially contributing the non-lexical route.

Finally, the second question concerned dissociations in different writing systems (phonological and no-phonological). In line with the neuronal recycling framework, we found that writing numbers and words are largely supported by overlapped neuro-cognitive systems. Though, dissociations do exist at the behavioral as well as the neural level. We first discuss the overlapping cognitive neural mechanisms involved in writing words and numbers, and then the evidence for dissociation.

Within one month post an ischemic stroke, slightly less than half of the patients in our study showed impairments in the Writing tasks (Figure 17a) taken from the BCoS battery (G. W. Humphreys, Bickerton, Samson, et al., 2012). Considering that the analysis excluded patients who were unable to concentrate for at least 30 minutes or had severe limb paralysis, the incidence of writing impairment maybe even higher.

5.5.1 Writing words and numbers

The ability of writing words and numbers correlated. Writing was also associated with other language and motor functions, as revealed by the correlation analyses and the prevalence of comorbid impairments (Table 7, Figure 17b). Significant and positive relationships with the writing tasks were found with all the four language and three motor related tasks. More than half

of the patients who showed deficits in writing had also deficits in other language tasks; while a similar proportion had difficulty in other higher-level manual based motor tasks. None of the tested patients show deficits in both number and word writing tasks with no comorbidity of language and motor. And only a handful showed deficits restricted to the writing content (words/numbers).

The relatively high-level of symptom-associations may not be surprising given that writing required both motor and language cognitive processes (D P Roeltgen & Heilman, 1984; David P Roeltgen & Heilman, 1985). The high prevalence of deficits in the writing tasks and the other cognitive tasks was also evident in the PCA, which suggested that most of the variability in patients' performance could be explained by a single shared component (Table 11).

However, the PCA analysis (table 11) highlighted two unique handwriting components, which explained together around 13.7% of the variability in patients' performances. These components were dissociated from the other language and manual motor-based tasks. One component (PC3) differentiated the three pen-using tasks from all the other tasks. PC3 potentially represented the fine manual visual-motor control processes required for handwriting. A second component (PC4) differentiated the writing tasks from the complex figure copy. PC4 potentially reflecting the underlining transformations of graphemes (from meaning) and orthographic knowledge to manual actions/motor commands associated with writing, but not copying of meaningless figures.

Deficits in the ability to use pen were manifested by poor performances in the Writing tasks as well as in the complex figure copy task. These were associated with the lesion to the right middle frontal gyrus and right angular gyrus. (Table 9, Figure 18&19) We reported an association of lesion to these regions with deficits in the complex figure copy task previously when analyzing data from the same trial (Chen et al., 2016).

A second network for writing (table 13, Figure 19) reflected the observed dissociation of the use of pen for writing (producing graphemes and adhering to prior orthographic rules) as opposed to copying “meaningless” figure (PC4). This network included the more commonly reported writing associated regions. The left superior and middle frontal gyrus, which overlap the classical Exner’s area (Exner, 1881; Henderson, 2008; Hillis, 2008; Marcus, 1937; Planton et al., 2013; F.-E. Roux et al., 2010; F. E. Roux et al., 2009; Vidaković et al., 2015). The right cerebellum is consistently shown to be associated with writing tasks in a meta-analysis of fMRI studies (Planton et al., 2013). However, the meta-analysis showed activation in the right lateral anterior cerebellum (18 -52 -22) and a mid-line posterior structure (6 -72 -18). Both these peaks were in the vicinity to the vermis cluster we report (-3 -57 -23) which had 453 voxels. The other two cerebellum clusters in our studies located in lateral posterior lesions compared to the vermis. We should keep caution about our interpretation, And the left temporal cortices, which overlap the word-form area, typically reported for reading (Dehaene & Cohen, 2007). The error analysis (table 10) showed

that lesions to most of these regions were associated with impairment to the lexical route, as will be expected from areas that support shared processing of writing words and numbers. In contrast, the lesion affecting the left middle occipital gyrus led to increasing errors to both exceptional and regular words, suggesting its potential involvement in non-lexical processes. Though this region did not show an expected increase in the number of phonological errors.

As mentioned in the introduction, the involvement of regions in the right hemisphere in writing has been reported before (Ardila & Rosselli, 1993; Davous & Boller, 1994b; Lee et al., 2015; Ozeki et al., 2008; Roeltgen & Heilman, 1983). We provide now case examples of patients with the lesion to the right hemisphere that also showed impairment in the writing tasks (Supplementary Figure 5 in appendix 3). The involvement of regions of the right hemisphere specifically in the motor related component of writing may link to reports associating the right hemisphere with constructional apraxia (Russell et al., 2010). In support of this, a study by Ardila and Rosselli (Ardila & Rosselli, 1993) report writing errors of spatial and organization nature, following right hemisphere lesions. Further research will be needed to investigate in more detail the relations between constructional apraxia and writing.

Similarly, the involvement of the right inferior occipital cortex, right superior frontal and right inferior temporal in writing was not expected and their involvement in writing is only rarely reported in the literature (Aboo-Baker & Labauge, 1986; Ardila & Rosselli, 1993). Hence, we should exert caution when

interpreting these findings. We can speculate a few reasons why we observed the association between right hemisphere lesions and writing. Regions in the right hemisphere are often recruited as a compensatory mechanism for reading. Studies have suggested the right hemisphere is more active with increased age(Froehlich et al., 2018) and more active in poor readers (Simos et al., 2002) and is involves in the acquisition of the second language (Li, Legault, & Litcofsky, 2014). The right hemisphere has also been associated with wiring systems that are not phonological (Bolger et al., 2005). As the current sample was of relatively older adults, potentially included individuals with pre-stroke poor reading abilities and those that English was their second language; it could be that this is why lesion to their right hemispheres were also seen to impaired their writings. The inferior occipital cortex is strongly associated with visual processing. Its correlation with writing was removed after we controlled for the 7 language and motor tasks. This is owing to both the motor and language tasks rely on processing visual input. Response to pictorial (/drawing) input is required in Picture Naming, Sentence construction and Complex figure copy. Response to visual input (written words/numbers) is required in the words and number reading tasks. The gesture imitation and recognition tasks require responses to a visual input, a gesture made by the examiner. Finally, the multi-step object task relies on the recognition of real objects, as well as half the gesture recognition trials which requires ability to recognized objects from actions (e.g. using a salter). Future researches need to elucidate the exact

contribution of these regions to writing abilities following a stroke and the reproducibility of these observations.

5.5.2 Writing words versus numbers

The data suggested that the two different writing systems: for numbers and words had overlapping cognitive and neural architecture. About half of the patients who could not write words also could not write numbers. But double dissociations of writing words and numbers were also evident, where more than 50% of tested patients showed deficits in one writing system but preserved ability in the other (Figure 17b). This double dissociation accords with the common model that numeracy and literacy are distinct processes (Carreiras, Monahan, Lizarazu, Duñabeitia, & Molinaro, 2015; Dehaene & Cohen, 2007). However, the correlation data and the data-driven approach analysis did not identify any component that dissociates numerosity (number tasks) from literacy (word tasks). Furthermore, we only observed a ‘weak’ component that dissociated numbers writing from words writing (Table 11: PC6). This component did not follow a numerical-literacy division, but grouped number writing with multiple object use task, and contrasted it against words writing and picture naming task.

The deficits analysis supports double dissociation, but the correlation, PCA and VBM analyses highlight overlapping processes. This contradiction may emerge because the deficits analysis is based on cut-offs and is ‘blind’ to the

symptom's severity; while all others analyses use the continues scores and account for the severity of symptoms. This suggests that categorical divisions of data may amplify dissociations, which are potentially marginal.

The VBM analyses revealed reliable clusters representing shared words and number writing processes, see above. But there were also some dissociated structures, with the lesion to the left post-central gyrus affected the ability to write numbers, while lesion to the right inferior temporal interfered with the ability to right words. Previous fMRI study suggests that the left post-central gyrus is involved in processing numerical information(Leibovich, Henik, & Salti, 2015). A case of agraphia has been reported following a lesion to right temporal occipital cortices (Davous & Boller, 1994a). A study with poor reader individuals suggests that right temporal regions maybe recruited as a compensatory mechanism to intact writing/reading abilities (Shaywitz et al., 2002). Though future research needs to assess the replicability of this observation and its specific rule in writing. Taken together, we suggest that the evidence for a dissociation between writing number and words are weak.

5.5.3 effect of control for general cognitive components

The VBM analysis on the expanded PCA showed that controlling for various cognitive components had two effects: 1) reducing the correlations with regions that were presumably affected writing abilities due to non-specific skills, like the right middle occipital gyrus; 2) increasing the reliability of the

correlations between grey matter voxels and writing abilities, as variance in writing due to other factors was reduced. Specifically, in model 2, we observed that controlling for the first component which was loaded on language, number and CFC, and potentially reflected language and sequence processing led to increase reliability of the association between the writing tasks and grey matter volume of the right middle frontal gyrus and right middle temporal gyrus. These function-lesion relations were maintained in all the subsequent models (i.e. after controlling for all other cognitive PCA components). Controlling for verbal memory ability (model 3) made the correlations of writing tasks and the right inferior parietal gyrus and left cerebellum (Lobules IV and VIII) reliable. Not surprisingly, some of the variability that in the right inferior parietal cortex which explained writing abilities was related to spatial attention deficits (model 4). Controlling for praxis, primarily the gesture task and auditory sustain attention (model 5), made the relation between writing abilities and right cerebellum (Lobule VIII) and left inferior temporal gyrus reliable. Left middle and superior occipital gyrus were related to writing only when additionally controlling for reasoning (model 6), and orientation (model 7).

In summary this analysis showed 1) that inability to write may emerge from different pattern of impairment in other cognitive abilities. This conclusion is drawn because model 1, before controlling for any other cognitive abilities showed only two one-to-one clusters who reliably mapped function to lesion, and both clusters became unreliable when controlling for language and

sequence processing (use of pen) in model 2. This suggests that these clusters mostly reflect overlap of processing of writing, with others tasks relying on general language, sequence processing and the use of pen. 2) Once controlling for language tasks and the complex figure tasks (component 1 in model 2-7) we observe that lesions in the right middle frontal and temporal gyri, explained writing abilities. This suggest that there is potentially unique processing required for intact writing which are not captured by any of the other task in the BCoS screen.

In comparison to the results that were obtained when including only a sub-sample of the BCoS tasks. The results highlight similar function-lesion maps and given complementary inference abilities. Specifically I note the following: i) the association between right middle frontal gyrus and the writing tasks was observed when controlling only for the orientation (original model 1) for the language and praxis tasks (original model 2) and appeared to be mostly related to the ability to use pen (correlated with the pen using component 3 in original model 3). ii) The association of writing and right middle temporal gyrus, bilateral cerebellum (lobule VIII) appeared after controlling for language and praxis tasks (original model 2) and seem to be associated with the need to retrieve information for semantic knowledge (writing rather than copying), as these were associated with the fourth PCA - writing vs. complex figure copy, in original model 4).

5.5.4 Limitation and methodological consideration

We used data-driven approaches to delineate the motor and language components of agraphia, applying multiple analyses approaches. VBM-Model 2 controlled for the generic language and motor related tasks. The analysis identified regions that specifically contribute to writing beyond generic language and motor abilities. Second, we used the words' error types of data to investigate a specific rule of each region in writing. Model 3 used PCA data which enabled fine-tune regions' contribution to the fine motor or language component of writing separately.

PCA is a data-driven approach. Therefore, the interpretation of the components is speculative, it was based on the weighting of the tasks on the component. To validate the observed component structure, we reported the number of cases displaying the dissociation identified by the PCA analysis. However, we acknowledge that these interpretations should be taken with caution.

Correlation, VBM, and PCA assess linear parametric relations, whilst our data were not normally distributed. Therefore, the results were likely to be driven by the tail of the distributions. We believe that this is appropriate given the nature of the data and the inclusivity in the way the patients' population was sampled. Hence one would expect that the tail of the distribution representing the abnormal cases would primarily drive the results. Though it hinders the

ability to generalize the component pattern beyond the observed data.

We assessed deficits in the current study using the BCoS, which adopt a shallow but broad approach. The shallow aspect means that a specific ability is assessed using a limited number of items. In the case of word writing, four words and one non-word are dictated; in the case of number writing 5 numbers are dictated. The detailed error analysis confirmed the reliability and external validity of the word writing task. The strength of BCoS is its broad approach, which means it provides a relative detail profile of cognition, which is not limited to one domain. The BUCS dataset provides a powerful research tool to assess the prevalence and comorbidity of deficits in a large and representative patient population. But the limitation is that it cannot replace formal clinical diagnosis of the known syndrome as it does not adhere to formal diagnostic criteria and has a relatively small number of trials per task. Hence our results reflect different components of writing deficits, but we cannot draw a direct conclusion on agraphia symptoms.

Finally, as with all clinical based data, the cognitive, as well as the neural data, are noisy as they are based on sub-optimal parameters (e.g. only five trials for assessing writing; density scans (CT) in different interval time, for assessing neural integrity). We believe that a large number of patients used here compensated for these relatively noisy measures. This is evident by the fact that most of our results replicated previously reported findings. However, we also observed a few unexpected regions. While most previously function-

lesion mapping studies were based on pre-selected patients' samples and single cases, it is difficult to assess the validity of the unexpected results. Future research would need to clarify the reliability of these findings.

5.6 Conclusion

The current study identified two dissociable networks that have been specifically evolved to support writing: a visual-manual motor ability to use pen mediated by right angular and middle frontal gyri; and an ability to transform symbolic representations grapheme) to manual programs for use with the pen. Lesions to the bilateral prefrontal cortex left middle and inferior temporal and right cerebellum (among other regions) contributed specifically to writing. The latter regions are suggested to be primarily involved in lexical based writing. The study also supported a large overlap of number and word writing, though neuro-cognitive dissociations were also observed. The combination of detail description of behavioral performances alongside multiple analyses approaches for functional-lesion mapping enabled us to provide a compressive account of the cognitive-neural networks that support writing abilities.

Afterword

In the current chapter, similar to copying figures, we found high comorbidities and significant correlation of writing numbers and words with related cognitive tasks. This behavior results also consistent with our study in chapter 3 showing writing relies on other relative cognitive functions. Instead of taking the top-ranking features into the VBM model, we only included linguistic and motor related tasks according to our research interests. In line with the neuronal recycling framework, we found that writing numbers and words are largely supported by overlapped neuro-cognitive systems with relatively weak dissociation at the behavioral as well as the neural level. We assumed these dissociations were due to the differences between the numeral and word processing. We then used PCA and detected two components of interest. We found that lesions to the right middle frontal and the right angular gyri contributing to writing in pen using processes. And lesion to bilateral superior frontal, left middle frontal, bi-lateral temporal and bilateral cerebellum associated with the translation of knowledge (e.g. meaningful symbols, objects) to motor.

Chapter 6

Neural substrates associated with writing: a fMRI study on writing and tracing

Foreword

In chapter 3 and chapter 5, we explored the neural basics associated with writing and copying figures using both behavior and imaging data in stroke patients. By combining PCA and VBM analysis, we were able to delineate the neural component associated with copying and writing. In this chapter, using writing and tracing tasks in a block design fMRI analysis we aimed to explore the neural substrates of writing in healthy participants to provide converging evidence. Beyond that, the study presented in chapter 4 suggested that Chinese and English shared a similar cognitive model. We, therefore, compared the neural basics associated with the two types of languages in this chapter.

6.1 Abstract

The current fMRI study investigated the neural substrates associated with writing in two different language systems, alphabetic and logographic language. We recruited 21 healthy undergraduate and postgraduate students. Participants performed writing or tracing (word and nonword) tasks in three different types of languages (Chinese characters, Chinese Pinyin and English words). Especially, the visual cortex involving the left lingual extending to the precuneus and the middle cingulate was more involved when writing words than tracing words and least for tracing non-words, potentially reflecting retrieval of graphemes from semantic knowledge. Bi-lateral middle and inferior occipital cortex were more involved in tracing non-words than words. The left inferior parietal gyrus, middle frontal gyrus responded stronger when writing in Pinyin than English and least in simplified Chinese Characters suggesting their involvement the phonologic to logographic transformation. Our study elucidated the neural substrates of different cognitive processes of writing and further supported the neuronal recycling hypothesis that writing relies on general basic cognitive function and there is limited variation across different language systems.

6.2 Introduction

The diversity of human culture developed different kinds of language

systems by which spoken words are translated to graphic forms. Of most noted are the logographic and the alphabetic system. Both the comorbidities, correlation analysis and machine learning classification study supported that these two languages shared similar cognitive model in behavior level. The objective of this chapter was to investigate the neural substrates associated with different component of writing in different types of language systems. These include a logographic language and two alphabetic language, English word and Chinese Pinyin, an official romanization system for Standard Chinese, using English alphabet to denote the pronunciation of Chinese words

The general writing model (D P Roeltgen & Heilman, 1984; David P Roeltgen & Heilman, 1985) works for most language systems, though there remain some slightly diversity. Alphabetic language and logographic language are different in morphologies and mappings among orthography, phonology, and semantics (D. Zhu et al., 2014). While Most of the alphabetic languages used a grapheme to phonemes transformation based on a serial left to right structure of letter strings (Perfetti, Liu, & Tan, 2005), characters are the basic writing units and encode no clear phonological information at the subsyllabic level in logographic language. (Zhu et al., 2014) And Some neuropsychological case reports support neuro-cognitive differences between writing systems. Aubrey Ku and his colleagues reported a 16-year-old who could not speak, comprehend, repeat, name, read, or write in English, but had relative preservation of most of these facilities in Mandarin. The patient spoke native

Mandarin and after moving to the US at 6 years old received extensive training in English. He suffered from herpes simplex encephalitis involving the left temporal lobe, with resultant selective aphasia (Ku, Lachmann, & Nagler, 1996). Similar case of selective aphasia is reported in bilingual 65 years old patient in Korea. The patient was a Hanja (ideogram, logographic) calligrapher for 40 years and also fluent in the Korean common writing of Hana (phonological) (Kwon et al., 2002). Following lesion to left posterior inferior temporal cortex he lost his fluency in Hanja and performed worth than age-education match controls. Japanese is another language where the writing system relies both on logographic (Kanji) and phonological (Kana) conversion systems. Cases showing impairment to Kanji (logographic) sparing Kana (phonological) have been reported(Jibiki & Yamaguchi, 1993; Kawamura et al., 1987; Mochizuki & Ohtomo, 1988; Soma, Sugishita, Kitamura, Maruyama, & Imanaga, 1989; Sugishita, Otomo, Kabe, & Yunoki, 1992).

On the other hand, despite of these differences, recent meta-analysis studies (Bolger et al., 2005; Tan et al., 2005; L. Zhu et al., 2014) of reading suggested underlying different writing systems neural correlates mediating the cognitive processes in writing are similar; though some specific variations exist as well. However, these previous meta-analyses all based on studies focused on the phonological processing in reading and tested one system at a time. Seldom studies using writing and directly compared the cognitive model in the two language systems.

In current chapter, we use a fMRI studies to explore the neural substrates associated with different components in the two language systems. And we also aimed to compared the difference between the two writing systems.

6.3 Method

6.3.1 participants

Twenty one healthy undergraduate and postgraduate students from the University of Birmingham took part in our study, including 10 male and 11 female, with an average age of 23.52 ± 3.46 years old, and an average Education year of 16.52 ± 2.93 year. They were all native Chinese speakers of Asian origin with a second language of English. All of them were familiar with Pinyin, and commonly used it when typing in Latin-alphabetic keyboard to communicate in Chinese (though typically one types in Pinyin, but the final product is presented as simplified characters). According to the Leap-Q questionnaire (Marian, Blumenfeld, & Kaushanskaya, 2007), they all studied English as a second language for more than 10 years and were able to communicate in English proficiently. All were studying in University of Birmingham various degrees in English. The majority of them started to study English younger than 10 years old. Their overall exposure to English now is 43%±20%, with only 1 less than 10% and 6 larger than 50%. Their preference for English in speaking and reading is around 20%-30%. The average age of start to learn English is 8.55±3.25 (ranged from 3-14, with 2 start to learn after

12 and none of them start to learn before 3). The average level of proficiency in speaking English is 6± 1.61, in understanding English is 6.33+-1.853, and for reading, the average score is 7.33+-1.39. (0. none, 1. Very low, 2. Low, 3. fair, 4. Slightly less than adequate, 5 adequate, 6 slightly more than adequate, 7, good, 8. Very good, 9. excellent, 10. perfect). All participants were in good physical condition, without any history of brain damage, neurological or psychiatric disorders. All of them have intact abilities in watching, and none of them has reading or writing deficits (e.g., dyslexia, dysgraphia). We only recruited right-handed participants in our study, and they gave their written informed consent before participating. The study was approved by the local ethics committee.

6.3.2 study design and tasks

A repeated factorial design was used with the following factors: task: (tracing, writing) and writing system (Simplified Chinese characters, English, Pinyin) and tracing of non-words in all three languages as additional control conditions.

6.3.2.1 Stimuli

24 highly familiar objects were selected such that their name in Chinese are composed of one character and their English name has 3-8 letters. The words were selected to be frequently used in both languages, representing manmade objects, fruits vegetables and animals (see the details of stimuli in table 14). Three people who are familiar with the English and Chinese culture

assess the words for familiarity. Pictures of the objects were obtained from Google website (https://www.google.co.uk/). In addition, for each object we created a scramble version that was used in the non-word tracing task. The pictures of the objects/ scrambled objects were presented in the top half of the screen. For the tracing conditions (see below), the names of the objects were written on the bottom half on the screen, in small letter (size (roughly 72), using font '宋体'for the Chinese, Ebrima for the English and Ebrima for the Pinyin. We chose these font formats because they were clearly showed in the screen to avoid misread. The non-word Chinese condition was created by altering the line configuration of characters, to create meaningless characters. Non-words English and Pinyin were pronounceable, with letter length of 3-4 letters, including consonant and vowels. In the writing condition, the bottom half of the screen was blank (white background).

Table 14 stimuli using in our study

	word frequency (UK)*	word frequency (CHN)*	Length (UK)**	number of phonemes (UK)***
pear	1.33	5.81	4	2
noodle	2.901961	1430.69	6	3
peach	6.35	26.02	5	3
ginger	6.41	9.84	6	5
elephant	11.37	363.08	8	7
lamp	12.88	94.21	4	4
rice	15.08	214.28	4	3
snake	22.35	35.78	5	4
pen	24.73	121.41	3	3
egg	26.04	408.51	3	2
pig	39.14	64.47	3	3
oil	41.08	225.29	3	2

bird	45.45	72.76	4	3
bridge	45.71	40.43	6	4
cup	51.65	223.44	3	3
tea	58.63	44.6	3	2
chicken	61.73	134.95	7	5
cat	66.33	88.19	3	3
fish	83.49	154.22	4	3
window	86.00	76.28	6	5
ship	98.88	213.04	4	3
bed	187.12	185.86	3	3
dog	192.8431	298.41	3	3
watch	330.02	670.24	5	3

Table 14: *Word frequency per million words, which is a standard measure of word frequency independent of the corpus size. (Cai & Brysbaert, 2010; van Heuven, Mandera, Keuleers, & Brysbaert, 2014)

** In the Chinese there is always one character.

*** The Chinese character is always one phoneme.

6.3.2.2 Procedure

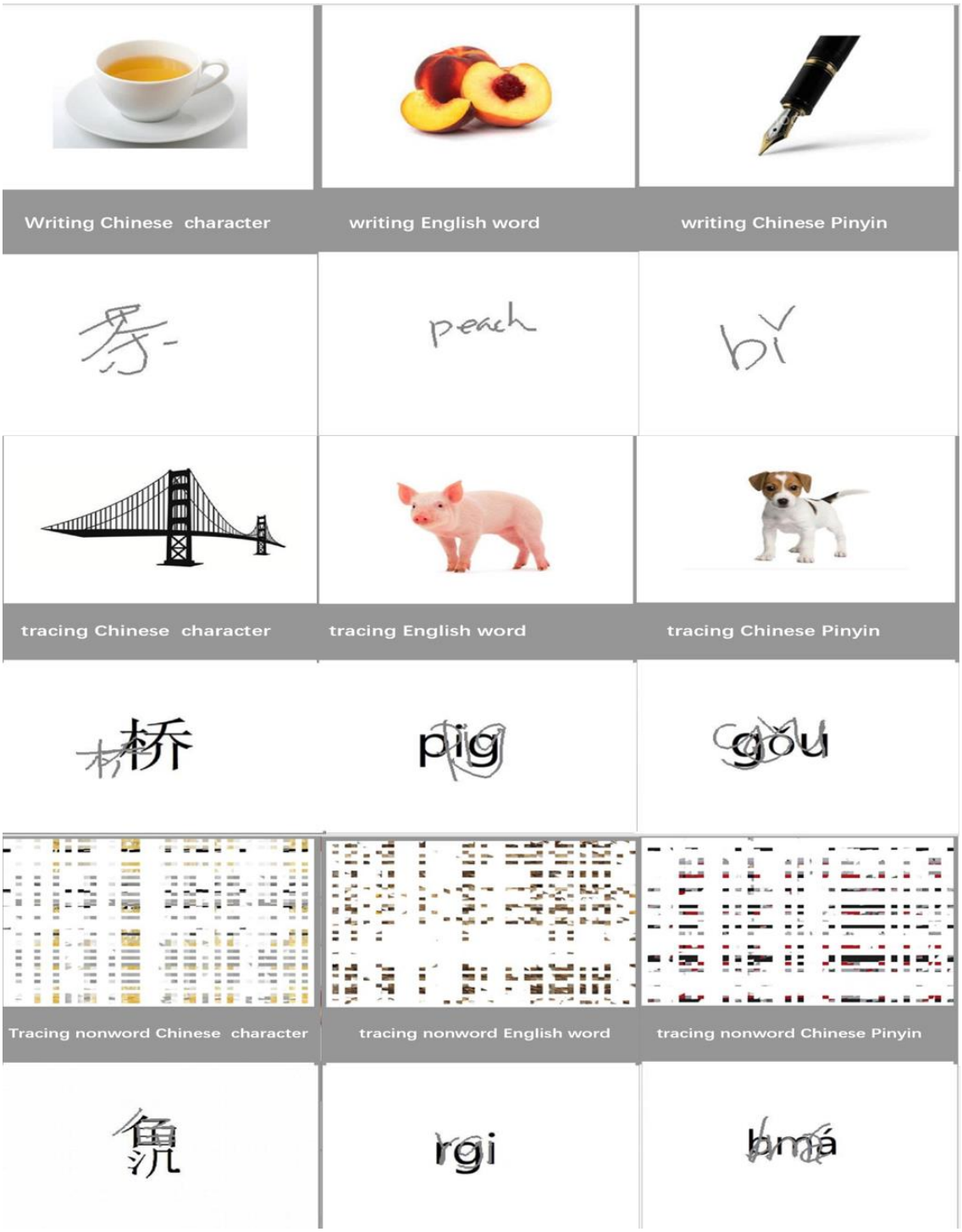
The experiment included a total of 9 conditions (Figure 20): 6 tracing tasks (tracing nonword Chinese character, tracing nonword English word, tracing nonword Chinese Pinyin, tracing Chinese character, tracing English word, tracing Chinese Pinyin), and 3 writing tasks (writing Chinese character, writing English word and writing Chinese Pinyin).

The study was divided to 4 runs, each run presented the 9 conditions, with 6 trials in each, in random order. There were in total 214 trails. Each trial lasted 5000ms and each experimental block lasted 30s (6 trials). Experimental blocks were preceded by a visual instruction (i.e., “writing Chinese”, “tracing Chinese” or “tracing nonword Chinese”). Stimulus presentation was synchronized with the acquisition of functional images. Participants were lying on their back in the MRI scanner. In the writing and tracing tasks, they had to either write or trace using a pen on an MRI-compatible digitizing tablet. The fixating screen showing

the visual stimuli in front of their eyes, in addition the screen display was updated to provide a visual feedback of their writing/tracing. Participants were instructed to avoid eye movement and minimizing the movements of their upper arm and forearm, as much as possible to minimize artefacts. In the three writing tasks, participants were asked to write down the name of the picture showing in the screen in Chinese character, English word and Chinese Pinyin, separately (see Figure 20 for example). In the three tracing real word tasks, participants were asked to trace the real word (Chinese character, English word and Chinese Pinyin) with a relative picture showing in the screen. (see Figure 20) The writing and tracing real words tasks used same pictures as visual stimuli. These stimuli were color pictures showing various easily identifiable everyday objects or animals. Finally, they were asked to trace the three different kinds of nonword (pseudowords) with a meaningless image showing in the screen. (see Figure 20). The order of the conditions was randomized,

All the participants underwent a training session before the scanning session in the mock scanner. The training session aimed to help the participants familiarize with the procedure, namely, the visual stimuli, timings, and, writing or tracing while lying on their back and looking at the screen in front of them. In the training participants were presented with all the stimuli of all conditions, to insure they are familiar with the stimuli and to minimize retrieval duration. The training also enabled participants practice the use of the digital screen for writing when lying on their back.

Figure 20: example of the 9 tasks



6.3.3. Imaging data and Analysis

6.3.3.1 Data Acquisition

MRI data was acquired using Philips 3T Achieve scanner hosted in the Brain Imaging University Centre.

Parameter of the MRI scans: the imaging parameters were TR/TE 3000/35, FA 90 °, slice width 2.0 mm, 1mm gap, FOV 22*22 cm, and 224*224 image matrix resulting in 3*3mm^2 in plane resolution. 38 oblique slices, aligned to ac-pc, covering the whole brain. TR=2250ms. EPI factor=39. Each session included 180 volumes, and the session was run four times.

To assess inhomogeneity in the magnetic field, a field map image was collected using the same geometry parameters as the EPI scan (38 slices, 3x3x3, aligned ac-pc), TR=509ms, short TE=9.2ms, long TE=11.5. The images were pre-subtracted to create a magnitude and a phase image.

For anatomical localization of the functional data and 3D rendering of the cortical surface, high-resolution (1mm^3, matrix 256*256, FOV 25.6 cm) images of the entire brain were acquired for each subject, using a standard 3D inversion recovery prepared FSPGRE T1 weighted sequence (TR/TE 7.3/2.7, FA 20^o, TI 450 ms).

5.3.3.2 Imaging data analysis

The data were pre-processed using SPM12 software (UCL, London, UK, http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB (MathWorks, USA). We first converted the DICOM files to NIFTI format. Consequently, we

coregister the field maps and structure T1 image to the first EPI image. Then we used the magnitude and phase images (the field map parameters) to create voxel displacement map (VDM). The resulting VDM were used realign and unwrap to calculate and correct for the combined effects of static and movement-related susceptibility induced distortions.

The anatomical T1 images were co-registered to the mean EPI image. The T1, was segmented using the unified-segmentation algorithm and realigned to the ac-pc space using affine transformation. The segmented grey and white matter images were used to create a unique dartel template for the group of participants. The final step was normalization of the template to Montreal Neurological Institute (MNI) standard space, and applying these parameters to all the EPI images, finally images were smoothed with an 8 mm^3 full width at half maximum (FWHM) Gaussian kernel.

First and second level statistical analyses were performed using the general linear model (GLM) approach (Friston et al., 1995) and summary statistics. The nine conditions (3 tracing nonword tasks, 3 tracing realword tasks, and 3 writing tasks) were modelled at the first level. The onset of each stimulus was modelled, in addition the time to start using the pen was included as a covariate. This was typically in the range of .7sec. The model includes the movement set of harmonics capturing low frequency (128 seconds) fluctuation in the data, typically associated with physiological and mechanical noise,

Contrasts corresponding to the activation for each of the nine conditions

(beta images) were created for each subject individually and then brought to the second level using a within subjects anova analysis.

We tested he following contrast:

- independent of language:
    - main effect of task: tracing words vs. writing words;
    - main effect of stimuli: tracing words vs, tracing non-words.
- Independent of task (only words): main effect of language Ch vs. En vs. PinYin
- Interaction of task and language
    - Simple effects were also tested only for real words, for each language (writing vs. tracing) and between task as a function of language.
- We used an F contrast to explore which regions participated in the task independent of specific condition.

We reported clusters that survived (or tended to survive) family wise error correction (voxels > 50) with a voxel reliability of $p < .001$ uncorrected. The charts present the activation of the peak's cluster voxel.

6.4 Result

The Table 15 and Figure 21-23 show the results of different contrasts in

our study. In our study, according to our research interests, we compare mainly the four type of contrast.

Table 15: The neural substrates of Writing and Tracing in different langauges

Regions	X Y Z	P(FEW-COR) cluster level	#voxels	T (peak voxel)
Tracing > Writing				
Tracing (words & non-words) > Writing (words)				
L lingual gyrus	-18 -87 -9	0.000	254	6.28
R lingual	21 -84 -6	0.020	75	5.22
Tracing (words) > Writing (words)				
L lingual gyrus	-18 -87 -9	0.000	336	6.31
R lingual	21 -84 -6	0.013	84	4.65
Tracing (Ch-words) > Writing (Ch-words)				
L middle occipital	-27 -90 6	0.005	106	4.64
Tracing (EN, Pi – words) > writing (English and Pinyin)				
L lingual gyrus	-18 -87 -9	0.001	143	4.96
Writing > Tracing				
Writing (words) > Tracing (words, non-words)				
B cuneus	6 -87 15	0.000	1832	8.43
B ant cingulate	0 24 24	0.000	438	4.35
Writing (words) > Tracing (words)				
L calcarine	6 -87 6	0.000	706	5.21
B ant cingulate	-3 21 24	0.019	76	3.70
Writing > Tracing (English-words)				
R cuneus	9 -87 21	0.001	153	4.01
No clusters in writing contrast tracing (Chinese character and Pinyin)				
Realword > Nonword				
Words (tracing) > Non-words (tracing)				
L lingual gyrus	-21 -69 -6	0.000	1031	5.04
Words (writing) > Nonword (tracing)				
B cuneus	6 -87 15	0.000	2242	8.90
L middle cingulate	-3 9 36	0.000	361	4.12
Nonword contrast realword				
Nonword (tracing) > Words (writing)				
L fusiform	-21 -87 -12	0.002	130	4.63

No clusters in Tracing Nonword contrast tracing realword				
Alphabetic language contrast logographic language				
English and Pinyin (words: tracing & writing) > Chinese (words: tracing and writing)				
R calcarine	18 -87 3	0.000	555	5.52
Pinyin contrast Chinese(all tasks)				
L lingual	-6 -75 -3	0.000	1855	6.58
L inf parietal(Angular)	-33 -60 39	0.001	134	4.62
L inf frontal	-48 18 27	0.023	72	4.39
Pinyin contrast Chinese(real word)				
L lingual	-9 -75 0	0.000	553	4.86
L inf frontal	-45 21 27	0.001	138	4.36
L parahippocampal	-18 -36 -12	0.035	64	4.12
English contrast Chinese (all tasks)				
L lingual	-9 -69 0	0.046	59	4.47
English contrast Chinese (realword)				
L lingual	-12 -78 3	0.006	101	4.32
R calcarine	18 -84 0	0.004	107	5.26
English and Pinyin contrast Chinese (tracing tasks)				
L lingual	-6 -72 0	0.000	465	5.33
L cunues	3 -78 36	0.013	84	3.81
No cluster in English and Pinyin contrast Chinese (writing tasks)				
logographic language contrast alphabetic language （No clusters activated in Chinese contrast Pinyin and English neither in writing nor tracing tasks.）				

FWE-correction at cluster level, *p < 0.05; **p < 0.01. % right lingual cluster was part of the R FFG cluster reported in the row above it. Abbreviation: R: right; L: left; IPG: inferior parietal gyrus; aCG: anterior cingulate gyrus; Cluster: Cluster size; Peak: Peak Z; x,y,z: x,y,z(mm)

6.4.1 Tracing compares with Writing

Activations were located in middle-posterior occipital when tracing words contrasted with writing words. Specifically, bilateral lingual gyrus and middle occipital gyrus were more activated when tracing words as opposed to writing words. The effect was observed across all three writing systems (Table 15, Figure 21).

The opposite contrast showed increased response in bilateral cuneus and anterior cingulate when writing contrasting with tracing tasks. This effect was observed across all three writing systems (Table 15, Figure 21).

Figure 21: Tracing VS Writing and Stimulus Effects

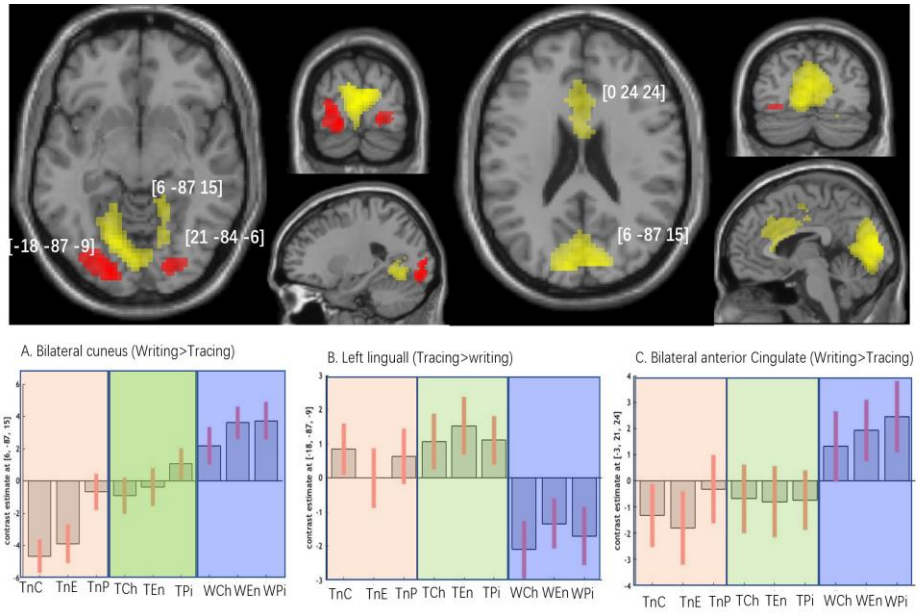


FIG 21：Abbreviation: TnC: tracing nonword Chinese character; TnE: Tracing nonword English word; TnP: tracing nonword Chinese Pinyin; TCH: tracing Chinese character; TEn: Tracing English word; TPi: tracing Chinese Pinyin; WCH: writing Chinese character; WEn: writing English word; WPi: writing Chinese Pinyin;

Figures 21 showing clusters activated corresponding to tracing contrasting writing in red and writing contrasting tracing in yellow. The plot to blobs figures showing the loading of each tasks on the clusters.

6.4.2 Realword compares with Nonword

Activation was observed in bilateral lingual gyrus while tracing realword contrast with tracing nonword (this overlapped the pattern observed for writing words vs. tracing words, above). When contrasting writing realword with tracing nonword, activation located in bilateral cuneus and left middle cingulate (overlap the pattern observed for writing realwords > tracing realwords).

The opposite, when tracing nonword contrast writing realword, the

activation was in left fusiform. However, a plotting tests show left fusiform mainly correlated with tracing contrasting writing rather than nonword subtracting realword (Figure 22, Table 15).

Figure 22: Realword VS. Nonword

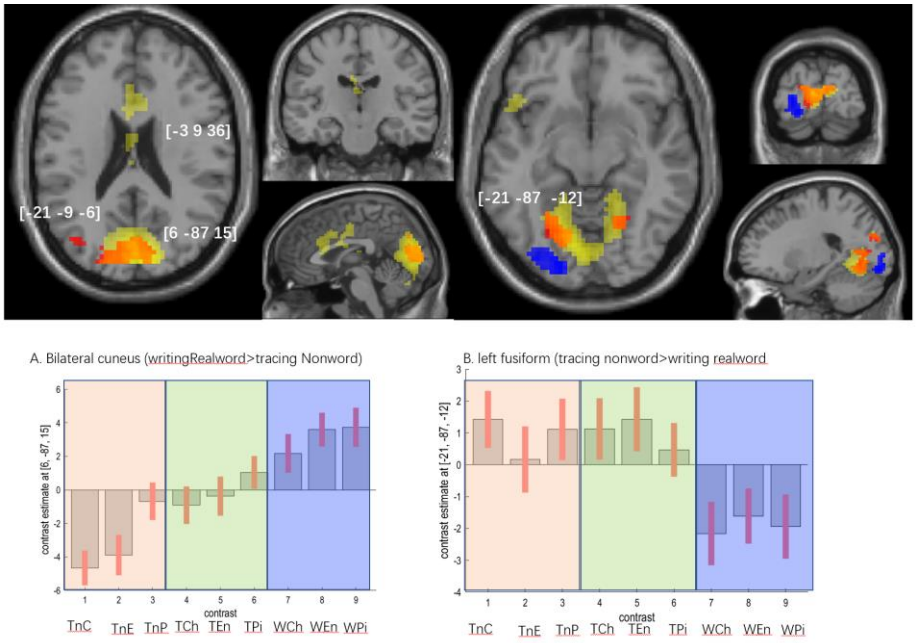


Fig 22: The clusters activated corresponding to Tracing realword > tracing nonword in red, Realword writing > Nonword tracing in yellow and tracing nonword contrasting writing realword in blue. The plot to blobs figures showing the loading of each tasks on the clusters. Abbreviation: TnC: tracing nonword Chinese character; TnE: Tracing nonword English word; TnP: tracing nonword Chinese Pinyin; TCH: tracing Chinese character; TEn: Tracing English word; TPi: tracing Chinese Pinyin; WCH: writing Chinese character; WEn: writing English word; WPi: writing Chinese Pinyin;

6.4.3 Alphabetic language compares with logographic language

When writing and tracing real word English and Pinyin contrast Chinese,

activation was observed in right calcarine. Considering tracing tasks only, left lingual gyrus and left cuneus was activated when alphabetic language contrast logographic language. Separately, we compared pinyin and English with Chinese. We found that left lingual, left inferior and left inferior parietal positively correlated with Pinyin contrasting Chinese, while right lingual activated contrasting English to Chinese. (see table 15 for more details) Interestingly, in the opposite, no cluster was found activated when logographic language contrast to alphabetic language. (table 15, figure 23)

Figure 23: Phonological vs. logographic

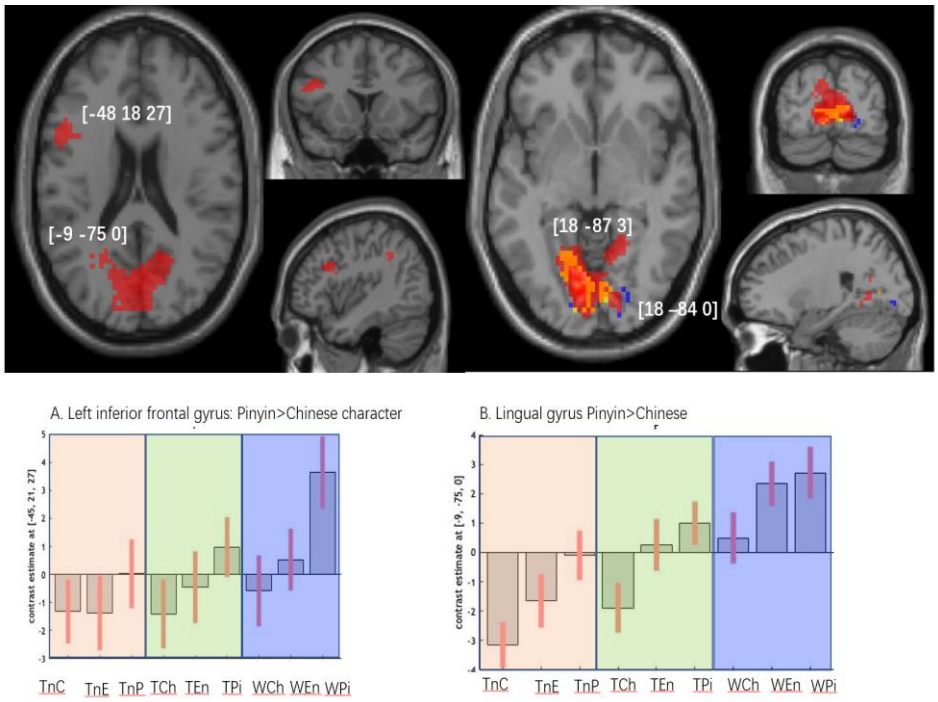


Fig 23: The clusters activated corresponding to pinyin contrast Chinese (all tasks) in red, English+Pinyinn (words: tracing & writing) contrast Chinese (word: writing & tracing)in yellow and English contrasting Chinese (real word: tracing & writing)in blue. The plot to blobs figures showing the loading of each tasks on the clusters. Abbreviation: TnC: tracing nonword Chinese character; TnE: Tracing nonword English word; TnP: tracing nonword Chinese Pinyin; TCH: tracing Chinese character; TEn: Tracing English word; TPi: tracing Chinese Pinyin; WCH: writing Chinese character; WEn: writing English word; WPi: writing Chinese Pinyin;

6.5 Discussion

Current chapter aimed to explore the neural basic associated with writing in logographic and alphabetic language and compare their differences. Our results showed that bilateral occipital regions were associated with tracing contrasting writing reflecting eye-hand coordination in tracing. Bilateral occipital

and limbic were activated in a opposite condition when contrasting writing to tracing which may probably associated with retrieval of writing from phonological and semantic route. Bilateral occipital was correlated with real word contrasting nonword reflecting semantic component of writing, Activation mainly on the left in frontal, parietal and occipital, and right calcarine was observed when contrasting alphabetic language to logographic language while no cluster was detected in the opposite condition.

In our study, to complete the writing tasks, participant required a following series cognitive processes including a visual information perception, a transformation from semantic area (Chinese, Pinyin and English) to visual word images, a transformation from auditory word engrams to a sound letter conversion (mainly on English and Pinyin), and the semantic and phonological route would both work to form the orthographic image of the words. And finally, a fine-motor control with pen using is needed to write. The tracing cognitive model in our study is similar to writing as they both required a visual information perception, fine-motor control coordination. In tracing real word, we believe that the brain region associated with semantic and phonology to word image transformation would activate as well. Though they don’t recall from their long-term memory. And the executive processes of tracing would be continuously monitored by facsimileing the nonwords rely on eye-hand coordination.

6.5.1 Visual symbols perception and visual-motor transformation

Bilateral occipital activated when contrasting tracing to writing tasks, indicating that these regions contributed to visual symbols perception or visual-motor transformation. These regions mainly located at bilateral lingual gyri, left fusiform, and left precuneus. The left fusiform is part of the visual word form area (VWFA). This area in the previous studies is repeatedly identified by contrasting activations induced by strings of letters relative to rest or to low-level stimuli (L. Cohen et al., 2000; Laurent Cohen et al., 2002; Jobard et al., 2003) and also relative to other categories of visual objects such as faces or houses (Ben-Shachar et al., 2007; Ferber et al., 2007; Hasson et al., 2002; Puce et al., 1996). The VWFA is therefore showed to specialized in perceiving and reading visual symbols, independent of the writing systems (Dehaene and Cohen, 2007). The left precuneus was reported to correlated with visual spatial abilities (Wenderoth, Debaere, Sunaert, & Swinnen, 2005) which is required by watching visual stimuli. In our studies, both writing and tracing tasks required participants to watch visual stimuli (picture and words). However, participant remained focus on the visual stimuli (words or nonwords) in tracing tasks while they can rely on other previous knowledge in writing. This may explain why a greater activation was observed in tracing compared with writing.

The observation of bilateral lingual gyri is consistent with our VBM study on complex figure copy task in ischemic stroke patients. In chapter 2, our results showed bilateral lingual gyri correlating with a component differential complex

figure copy from multi step objects use tasks. We assumed this component represented a visual-motor transformation ability in drawing. Previous studies highlighted the important role or bilateral lingual gyri in encoding of complex images (Machielsen et al., 2000), human faces (McCarthy, Puce, Belger, & Allison, 1999) and especially related to letters not words (Mechelli, Humphreys, Mayall, Olson, & Price, 2002). Taking together, our studies indicated that these regions contributed to a general visual perception and visual-motor transformation and not restrained to writing.

Nevertheless, as participants' eyes are not fixated when doing the tracing and writing tasks, the activation of tracing versus writing might differ in the visual input to the two hemispheres.

6.5.2 Writing contrast tracing

Writing contrasting tracing tasks observed activation in bilateral cuneus, anterior cingulate and Left calcarine. The involvement of these regions were not expected in our study. Anterior cingulate is consider to play roles in autonomic functions and some high level cognitive function such as decision making (Bush et al., 2002) and attention allocation (Pardo, Pardo, Janer, & Raichle, 1990). The correlation between anterior cingulate gyrus and writing remain unclear. However, in chapter 2, we found that lesions to the anterior Cingular gyrus (aCG) were associated with CFC performance after we controlled for the four praxis tests. Further SEM analysis showed that aCG

explained variability in CFC that was not accounted by the four praxis tasks. Taking these two together, we suspected that these regions contributed to writing beyond motor components. Similarly, both the bilateral cuneus and left calcarine where occupy or closed to the primary visual cortex. It is most known for their involvement in basic visual processing. As writing without any visual cues (words) rely partly on their retravel of previous knowledge, we assume these regions may play roles in such cognitive processes. However, we should keep caution about this explanation.

6.5.3 Realword contrast Nonword

Compare the writing model of real words and nonword, the activation of contrasting realword tasks with nonword tasks is supposed to associated with the semantic part of writing. And these correlations located in the left lingual gyrus, bilateral cuneus, and the left middle cingulate. Semantic memory refers to knowledge about people, objects, actions, relations, self, and culture acquired through experience. (Binder, Desai, Graves, & Conant, 2009) A meta-analysis using activation likelihood estimate (ALE) technique to analyze 120 functional neuroimaging studies focusing on semantic processing. The studies recruited in the meta-analysis included different typed of semantic contrasts such as words versus pseudowords, semantic tasks versus phonological tasks, and high versus low meaningfulness tasks. Their results showed that left cingulate is one of the 7 reliable regions that associated with the semantic

system (Binder et al., 2009). Another fMRI study investigated the brain activation during semantic access to concepts in different language comprehension (word listening and word reading), production (picture naming) and languages (Dutch-French) in Dutch-French bilinguals. And they found that across modalities and languages, the left lingual gyrus showed semantic overlap across production and word reading (Van de Putte, De Baene, Price, & Duyck, 2018). Similar evident was found in a fMRI study examined the neurological mechanisms underlying short-term (within minutes) and long-term (within days) facilitation of naming from a semantic task that did not include the phonological word form. They found lingual extended to precuneus gyrus were linked to the semantic processing in naming tasks (Heath et al., 2012). Therefor, we concluded that these regions contributed to writing in its semantic processes.

In the opposite, the left fusiform activated when contrasting Nonword tasks to realword tasks. However, the plot to blobs figures showed that this region was mainly associated with tracing contrasting writing. We have discussed it in the previous paragraph.

6.5.4 Alphabetic language contrast logographic language

Multi brain regions mainly on the left activated while contrasting alphabetic language to logographic language. These regions are lingual gyrus, inferior parietal gyrus, inferior frontal gyrus, and cuneus gyrus in the left hemisphere and the right calcarine. Alphabetic language and logographic language are

different in morphologies and mappings among orthography, phonology, and semantics (Zhu, Nie, Chang, Gao, & Niu, 2014). While Most of the alphabetic languages used a grapheme to phonemes transformation based on a serial left to right structure of letter strings (Perfetti, Liu, & Tan, 2005), characters are the basic writing units and encode no clear phonological information at the subsyllabic level in logographic language (Zhu et al., 2014). So we assumed these regions contributed to the grapheme to phonemes transformation process in writing. However, since all of our participants are native Chinese speakers, English is their second language. Besides, Chinese people are more familiar to characters than Pinyin, so these activations may correlate with the familiarity effect of writing as well. The involvement of left inferior parietal gyrus (extended to angular gyrus) and left inferior frontal gyrus in alphabetic language compared with Chinese was consistent with a recent meta-analysis ecruiting fMRI studies from 2005-2012, including 19 experiments for alphabetic languages and 13 for logographic languages (L. Zhu et al., 2014). The left lingual and right calcarine were less mentioned in the previous reports, we assumed that these regions may correlate with either the familiarity issue or the grapheme to phonemes transformation process in writing.

In contrary, no cluster was found when logographic language contrast to alphabetic language. This further support the neuronal recycling hypothesis that new cognitive skilled development under the restriction of the previous functional architecture of the brain (Dehaene, 2004; Dehaene & Cohen, 2007).

Our studied indicated that writing logographic language relies on general cognitive abilities that are required by alphabetic language as well. This explained why no cluster was found in these contrasts.

See a summary result of the above discussion in table 16.

Table 16 activated brain regions in each contrast.

Key contrasts/cognitive processing	Activated brain regions
Tracing>writing / Visual symbols perception and visual-motor transformation	bilateral lingual gyri, left fusiform, and left precuneus
Writing contrasting tracing / retravel of previous knowledge	bilateral cuneus, anterior cingulate and Left calcarine
Realword contrast Nonword / semantic component of writing	left lingual gyrus, bilateral cuneus, and the left middle cingulate
Alphabetic language contrast logographic language / phonological processing of writing	Left lingual gyrus, inferior parietal gyrus, inferior frontal gyrus, and cuneus gyrus and the right calcarine.

6.5.5 The exemption of left middle and superior frontal gyrus

Previous functional imaging and neuropsychological evidence showed that the left SFG (SMA) extending to the MFG (Exner's area) is repeatedly reported in relation to writing tasks. However, no contrasts in our study activated in this region. We observed that all contrast tasks in our study require the motor component of writing (across writing words and tracing word and nonwords), while tracing nonword is absent with semantic component and also phonological processes in writing. We assumed this region may mainly contribute to writing in motor relative processes.

6.5.6 Limitation

In our experiment, eye movements and the distance between screen and participant's eye were not measured. As the font size was fairly large, to enable accurate tracing when lying and not seeing the hand/pen we assume lots of eye movement occur in all conditions. It is likely to be a potential confounds, as Chinese characters occupy less space than English and Pinyin.

6.6 Conclusion

Our study delineated different writing substrates with writing. Specifically, the occipital of the primary visual cortex contributes to general visual information perception and visual motor transformation. The left lingual gyrus, middle cingulate and bilateral cuneus associating with the semantic component of writing while the left inferior parietal gyrus, inferior frontal gyrus contributing to writing in the phonologic to logographic transformation.

Afterword

In this chapter, we performed a block design fMRI study on healthy participants to provide convergent evidence of writing relating neural substrates. Using tracing and writing tasks in different language, we detected different neural basics for writing. Our study showing that different language system

sharing overlap network further support the neuronal recycling hypothesis.

Chapter 7

summary

Neuronal recycling hypothesis indicated that the neural substrates of recent cognitive activities such as writing and figure copying were constrained by the functional architecture of the brain. These activities rely on previous exited relative processes. Both the cognitive model of writing and copying figure require fine motor control with using pen. Similar to VWMF repeatedly showing association with different reading tasks, some brain regions were showed correlated with these pen using tasks in our study. And using different method, we showed that there are largely overlap cognitive substrates in different writing system, indicating that there should be strong cross-cultural invariants between different races and cultures.

7.1 Behavior result of stroke patients

In chapter 2 and chapter 4, the behavior results of both writing and figure copying tasks showed high comorbidities between these tasks and other general cognitive tasks. Especially that none of the 740 patients showed impairment in the two writing tasks with intact abilities in all the other 7 motor or linguistic related tasks. Besides, the correlation tests showed significant positive correlation between the writing and copying figure tasks with others. Further analysis using principle component analysis in both writing and copying tasks showing a shared component explaining most of the variability in patients'

performance of these tasks. Therefore, we suggest that the co-morbidity and high correlation of writing word and copying figure with other relative tasks can be explained by shared cognitive processes. And fine motor control (reflecting by sharing component of writing/copying figures and praxis tasks) especially with pen using is required by writing and copying tasks.

In chapter 3, using machine learning, we classify patients with or without writing deficit in both China and the UK. Cognitive models with 6 features effectively differentiated patient with writing deficits from those without. And despite the differences between alphabetic and logographic language, their classification models represented similar in our study. The top-ranking features in these models consistently support that writing composed of motor and linguistic components plus general cognitive abilities.

Taking these behavioral results together, our study support the neuronal recycling hypothesis that recent cognitive activities such as writing and copying figures rely on basic abilities that existed long before writing was invented. And human's cognitive abilities should represent strong cross-cultural invariants between different races and cultures.

7.2 Lesion-symptom analysis result

In chapter 2 and 4, we used VBM analysis to explore the neural substrates associated with copying figures and writing word and number. After control for relative cognitive tasks as covariates, some brain regions were found specific

contribute to these tasks. Not surprisingly, the writing words and numbers showed largely overlap neural basics. This is consistent with the Machine learning study in chapter 3 indicating that different writing system shared similar cognitive processes. Lesion to the right middle frontal gyrus affected both ability to write and high level of manual control (CFC, Gesture and multi-step object use tasks), as reported in chapter 2 and 4.

Combining VBM and PCA, we delineate the different neuro-cognitive processes associated with copying figure and writing words. We found that in both models, the right middle frontal gyrus showing correlation with the fine-motor control in the three pen-using tasks. We speculated that this brain regions contribute to the basic cognitive process of fine-motor control in using pen. Surprisingly, this region didn't show up in our fMRI study, we assumed that it was because of all our contrasting tasks involved pen using tasks (writing or tracing).

7.3 Primary visual cortex

The primary visual cortex including the bilateral lingual, fusiform were repeatedly showing correlation with copying figures and writing in both the lesion-symptom mapping studies and the fMRI study. These regions were closed or part of the VWFA, which was repeatedly identified visual objects stimuli tasks. (Ben-Shachar et al., 2007; Dehaene & Cohen, 2007; Ferber et al., 2007; Hasson et al., 2002; Puce et al., 1996). Combined with the PCA analysis

in our study, this region correlated to visual-motor transformation not only simple visual perception. We therefore assumed that these regions contributed to a general visual perception and visual-motor transformation in writing and copying figure tasks.

7.4 Motor component of writing and copying figures

Using different method, we detected motor output for the two tasks. Machine learning study showing that copying figure is the top features to the writing classification model, indicating these two sharing large overlap cognitive function and brain networks. In VBM studies we explored the neural substrates associated wth fine-motor control, visual motor transformation and tool using in copying figures. Comparing with VBM study in writing tasks, we found that the overlap between the two in fine motor control mainly located in the right middle frontal gyrus. This is inconsistent with previous studies highlighted the important role of right MFG in fine motor abilities. Filippi and colleagues used tensor-based morphometry (TBM) to map gray matter (GM) volume changes associated with motor learning in young healthy individuals. They found that after a two-week daily training of fine motor skills with the dominant right hand in 31 healthy subjects resulted in significant GM volume increases of multi brain regions including the right middle frontal.(Filippi et al., 2010) Using functional magnetic resonance imaging, Floyer-Lea and colleagues (Floyer-Lea & Matthews, 2004) performed a study in 15 healthy subjects. They were asked to

learn track a moving target by varying the isometric force applied to a pressure plate held in the right hand. Their result showed a significant correlation between BOLD signal changes in middle frontal gyrus and improvements in task performance were observed during short-term motor skill learning (Floyer-Lea & Matthews, 2004). Similar finding was in another short-term motor skill learning tasks highlight the important role of right middle frontal in fine-motor skills(Gryga et al., 2012). We therefore assumed that right middle frontal gyrus contributed to writing and figure copying in fine motor control. However, we didn't detect this area or other motor related substrates in our fMRI study. We believed that it was because that all the contrasting tasks in our experiment required fine motor control in using pen to writing or trace.

7.5 evidence of neural substrates for Neuronal recycling hypothesis

The comorbidities and correlation analysis in stroke patients and machine learning studies back up the neuronal recycling hypothesis in behavioral way.

In neural substrate level, we use exclusive masking to explore the dissociated mechanism for Numbers' and Words' Writing. The results showed mainly overlap with miner diversity in the two writing systems. Similarly, the fMR study supported that writing in either logographic or alphabetic languages rely on similar cognitive processes exempt that a phonologic to orthographic transformation relative more to alphabetic language. These together in favor of

the neuronal recycling hypothesis that neural constraints restrain the acquisition of cognitive processes. And there are strong cross-cultural invariants in recent developed cognitive activities such as writing.

7.6 Methodological Considerations

In this thesis, I combined PCA with VBM to explore the neural substrates with writing and CFC. Instead of using the complete BCoS into PCA, only some tasks were used in our study. This is because of the theoretically reason. Such as for CFC, many studies in the past focused on the impact of spatial attention and executive functions on construal apraxia (measured by the complex figure copy task). Therefore, in the current thesis, the focus was on examining the contribution of eye-hand coordination and high-level motor control processing to the ability to copy complex figure. High level motor control was assessed using the three gesture tasks (production, imitation, recognition) and the multi-step object task which requires interaction with objects. I selected two additional tasks from the BCoS as a control for obvious confounding factors (visual agnosia, spatial bias, and sustained attention).

I agree that for a more complete description of the neuro-cognitive components supporting CFC or Writing, the entire cognitive profile should have been used. However, this was not the main research question of the thesis and of the chapter. Using the entire cognitive profile may have risked occluding the processes that were my interest (namely, fine motor control). Given this

restriction in controlled variable the interpretation of the results should be limited to the context by which the statistical tests were carried out.

Appendix 1 supplementary materials in chapter 3

supp table 1 intercorrelation of the cognitive data

	1	2	3	4	5	6	7	8	9	10
1.CF	-									
2.orientation	.263**	-								
3.picture naming	.412**	.371**	-							
4.ego centric neglect	-.276**	-.122	-.123	-						
5.multistep object use	.309**	.330**	.410**	-.199*	-					
6.gesture production	.382**	.569**	.538**	-.102	.388**	-				
7.gesture recognition	.226**	.418**	.456**	-.139*	.359**	.559**	-			
8.meaningless imitation	.489**	.441**	.471**	-.210**	.444**	.594**	.440**	-		
9.auditory attention	.397**	.434**	.447**	-.106	.417**	.513**	.502**	.440**	-	
10.comprehension	.294**	.308**	.349**	-.007	.213**	.477**	.455**	.388**	.451**	-

*p<.05, **p<.0011 （0.05/45）

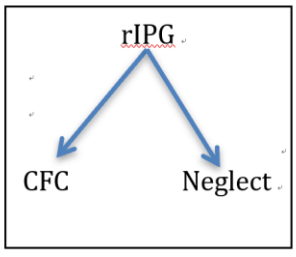
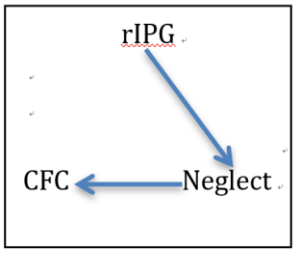
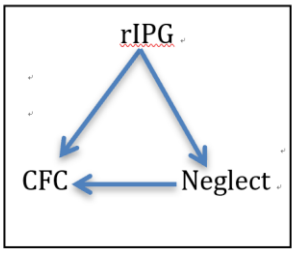
supp table 2 Models comparison (log evidence)

ΔF	Model 1	Model 2	Model 3	Model 4	Model 5
rFFG					
Model 1		-387	-653	-285	-459
Model 2	387		-266	102	-63
Model 3	**653**	**266**		**368**	**203**
Model 4	285	-102	-368		-165
Model 5	459	63	-203	165	
rIPG					
Model 1		172	-155	47	-33
Model 2	-172		-327	-125	-205
Model 3	**155**	**327**		**202**	**122**
Model 4	-47	125	-202		-80
Model 5	33	205	-122	80	
aCG					
Model 1		**292**	**327**	**437**	**302**
Model 2	-292		35	145	10
Model 3	-327	-35		110	-25
Model 4	-437	-145	-110		-135
Model 5	-302	-10	25	135	

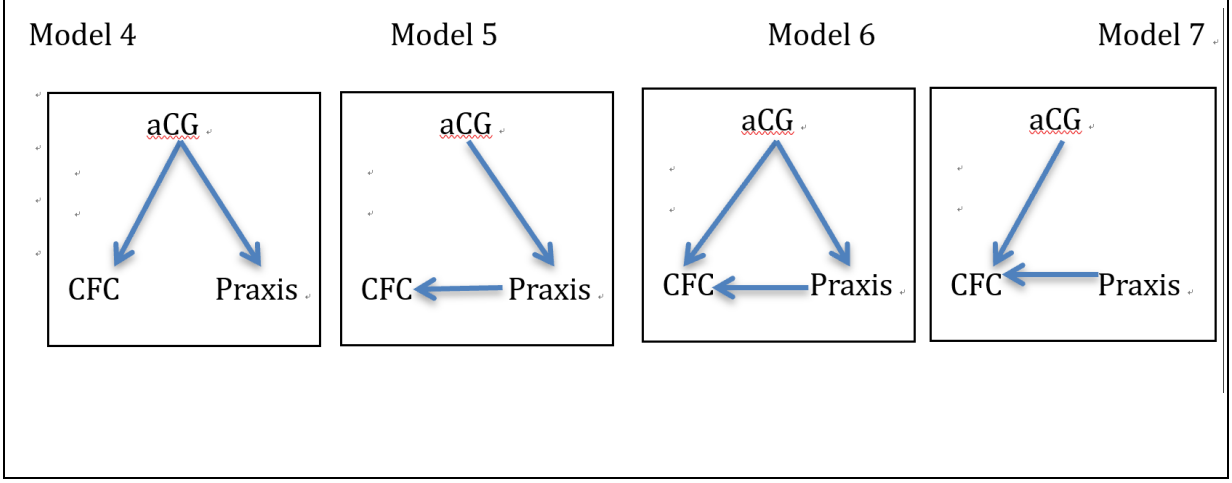
The table represents the log evidence difference between two models: ΔF = model in row – model in column. Model 1: CFC control for orientation; Model 2: CFC control for orientation and the four praxis tasks; Model 3: CFC control for orientation, praxis and neglect tasks; Model 4: CFC control for orientation, praxis, neglect and attention tasks; Model 5: CFC control orientation for praxis, neglect, attention and picture naming tasks. The row representing the model that was most explanatory for each VOI is highlighted in BOLD. We used a model comparison function in SPM (spm_vb_regionF.m) to compute the

log evidence of each model for the specified ROI. The difference between the log evidence was used to infer on the best model. For each ROI we extracted the grey matter probability signal from the peak surrounded by a 6mm sphere and represented it using the first eigen variate. The results demonstrate that the best fitted model varies depending on the region selected and there is no one correct answer that fits all.

supp table 3 SEM model comparison

	AIC	CAIC	CMIN/DF	GFI	CFI	RMSEA
CFC, Neglect and rIPC models comparison						
Model 1	94.404	253.081	1.441	0.977	0.966	0.083
Model 2	82.582	239.258	1.258	0.989	0.995	0.033
Model 3	79.49	240.642	0.832	0.933	1	0
Model 1  Model 2  Model 3 						
aCG, CFC and Praxis tasks model comparison						
Model 4	114.063	248.357	9.011	0.951	0.894	0.183
Model 5	77.658	225.381	3.886	0.988	0.981	0.110

Model 6	71.200	223.400	1.600	0.997	0.997	0.050
Model 7	69.127	203.421	1.521	0.991	0.993	0.047



We used SEM to investigate in more details the relations between CFC, neglect and right IPC (Model 1-3) and the relation between CFC, aCG and the four praxis tasks (Model 4-7). The AIC values, which take into account the fitting accuracy and model complexity (number of parameters) was used to select the best fitting model. A smaller value of AIC represents a better model. Here we found that the correlation between CFC and rIPC are partially mediated via neglect, while the variability in CFC that cannot be accounted by praxis deficits was associated to aCG lesion. In the other hand, variability in CFC that cannot be accounted by praxis deficits was associated to aCG lesion.

The other value (CMIN/DF, CFI, GFI, RMSEA) displayed in the table represent the model fitting degree. Most of the parameters (CMIN/DF<3, GFI≥0.90,CFI>0.90, RMSEA<0.05) of Model 1-3, 6-7 fit well in our study.

supp table 4 PCA result on the re-scaled raw scores of the five praxis tests, picture naming, neglect and sustained attention

Tasks	PC1	PC2	PC3	PC4	PC5
CFC	-0.35	-0.48	-0.60	-0.15	0.32
MOT	-0.435	0.84	-0.26	-0.00	0.15
GP	-0.36	-0.15	0.26	0.20	-0.21
GR	-0.29	-0.06	0.37	0.03	-0.42
GMI	-0.36	-0.12	-0.10	0.17	-0.22
PN	-0.40	-0.14	0.15	0.59	0.31
NEG	-0.11	-0.03	-0.47	-0.08	-0.70
SA	-0.42	-0.09	0.35	-0.74	0.14
Exp. Var.	**48%**	**11%**	**11%**	**8%**	**7%**

Abbreviation: CFC: complex figure copy; MOT: multi-step object use; GP: gesture production; GR: gesture recognition; GMI: meaningless imitation PN: picture naming; NEG: neglect SA: sustained attention

Noted: 1.only the first 5 components were showed.

2. Since the higher score stand for the worse performance in neglect, we showed its opposite number here.

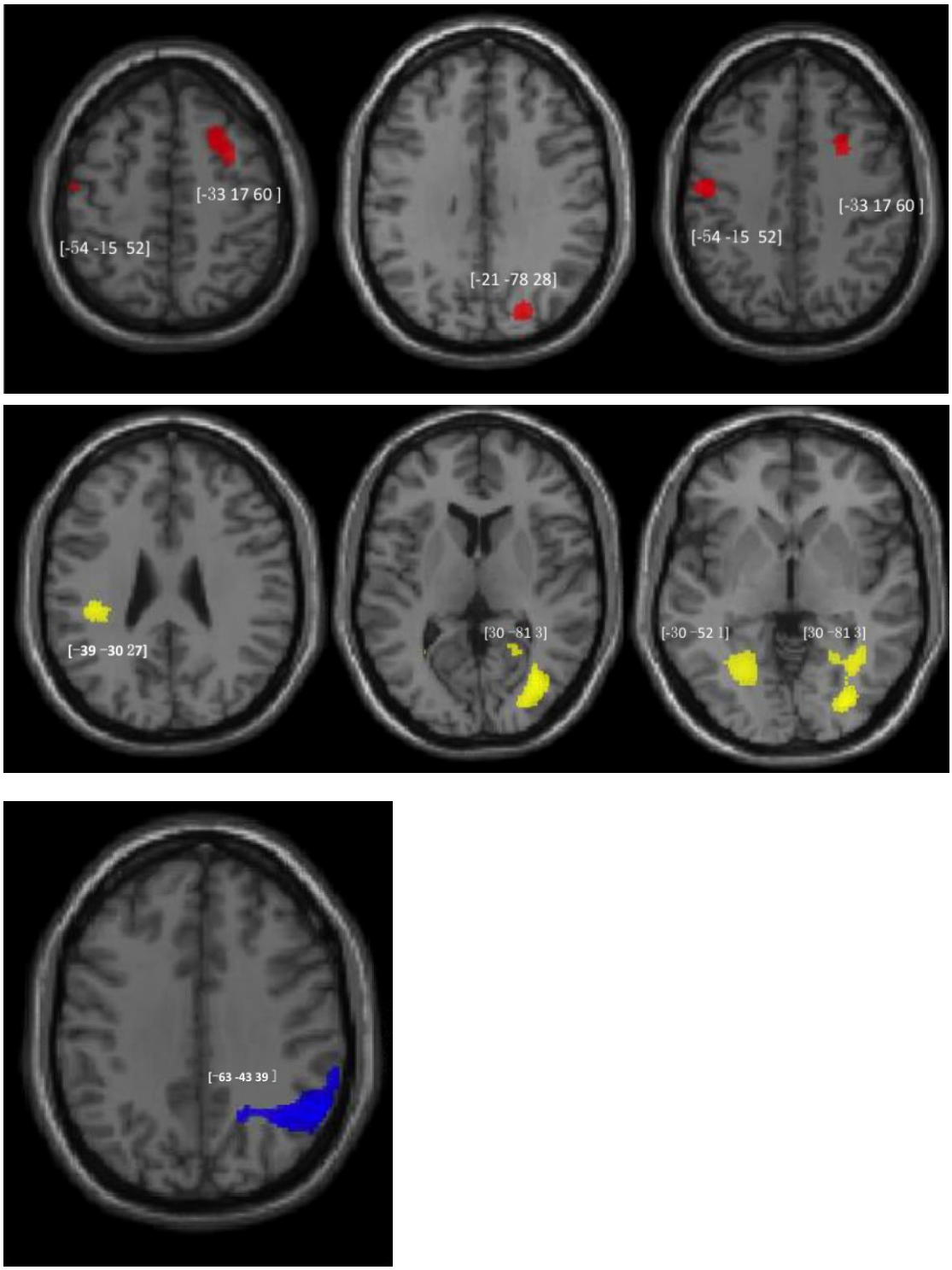
supp table 5 VBM based on the three components teased apart from PCA(including picture naming, neglect and sustained attention).

sTable 2a CP1 shared component (motor schemas, high-level motor control and proprioception processing)				
Anatomy	**BA**	**cluster size**	**peak Z**	**x,y,z {mm}**
R superior Occipital	19	**296****	**3.29**	**21 -78 28**
R MFG	8	**975****	**3.96**	**33 17 60**
L postcentral G	4	**382****	**4.50**	**-54 -15 52**
sTable 2b CP2: CFC > MOT (visual-motor transformation)				
Anatomy	**BA**	**cluster size**	**peak Z**	**x,y,z {mm}**
R MOG extending to R fusiform	19	**1749****	**4.09**	**30 -81 3**
L LG	47	**665****	**3.63**	**-30 -52 1**
L Rolandic Oper	48	**307***	**3.42**	**-39 -30 27**
sTable 2C CP3 CFC + MOT + NEG > Gesture task (interaction with objects, attention and planning)				
Anatomy	BA	**cluster size**	**peak Z**	**x,y,z {mm}**
R Inferior parietal extending to angular and supramarginal gyrus	40	**2267***	**4.41**	**63 -43 39**

FWE-correction at cluster level, *p < 0.05; **p < 0.01.

Abbreviation: R: right; L: left; BA: brodmann area; MFG: middle frontal gyrus; LG: lingual gyrus; Rolandic Oper: rolandic operculum; Cluster: Cluster size; Peak: Peak Z; x,y,z: x,y,z(mm)

supp figure 1 VBM analysis based on the first three components from PCA result

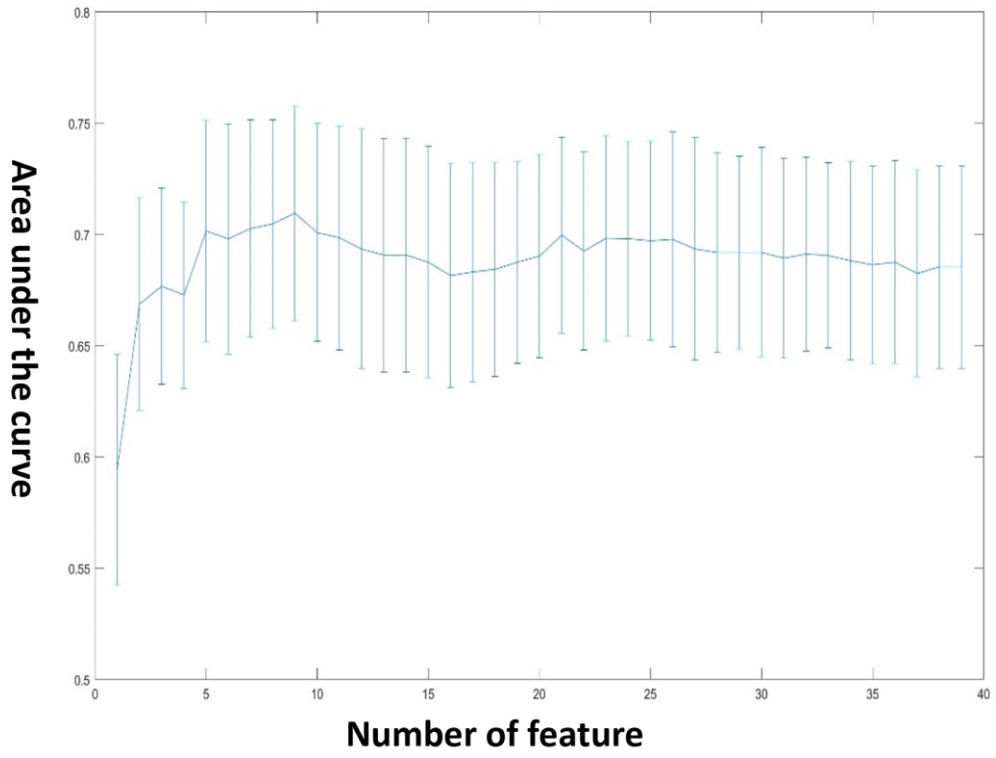


VBM results showing voxels corresponding to grey matter damage in (red) the first shared component, (yellow) the second component and (blue) the third

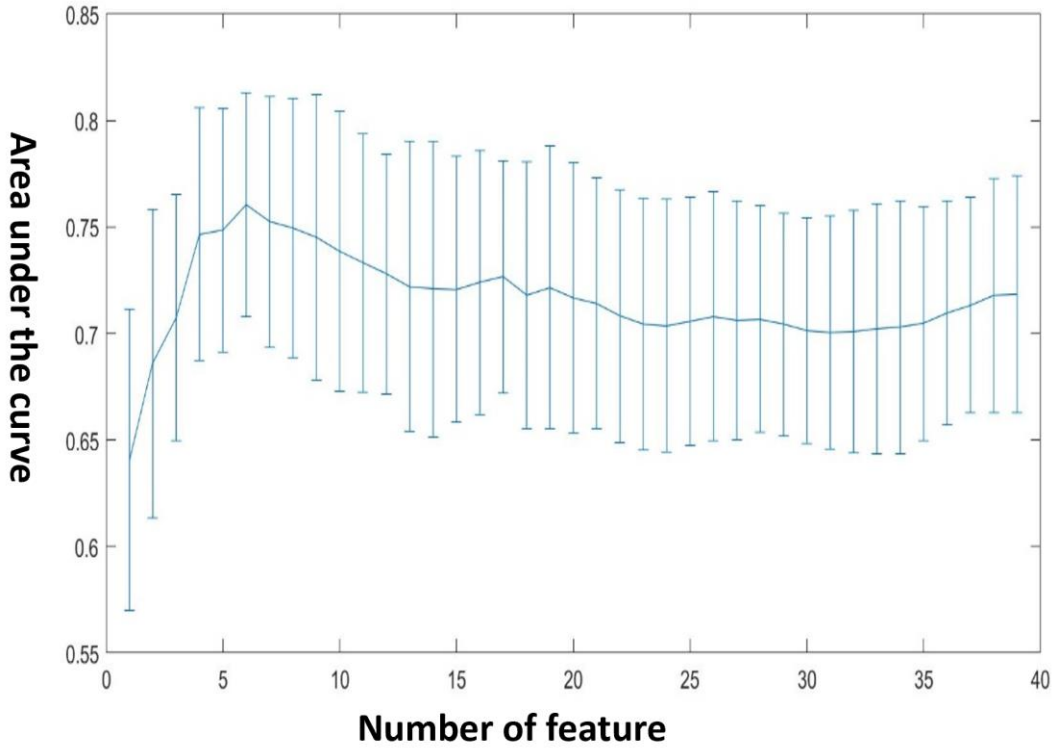
component. The function-lesion maps are overlaid on axial T1-weighted MRI slices of the single subject canonical template provided by SPM. The numbers in brackets represent the peak of the clusters given in MNI coordinates.

Appendix 2 supplementary materials in chapter 4

supp figure 2 AUC values correspond to top-ranked from 1- 38 features in CHN group



supp figure 3 AUC values correspond to top-ranked from 1- 38 features in UK group



Appendix 3 supplementary materials in chapter 5

supp table 6 demographic data of include and exclude patients in writing VBM analysis

	Gender	Age	Education year	Barthel Index
Included patients	131/136	70.28±14.29	11.40±2.61	13.85±5.33
Excluded patients	265/344	69.88±13.57	11.35±2.75	12.65 ±5.82
P	0.129	0.091	0.185	0.275

supp table 7 Correlation matrix of the writing error type analysis

	1	2	3	4	5		7
1. writing scores	1						
2. real words	.964**	1					
3. nonword	.573**	.334**	1				
4. regular words	.802**	.862**	.187*	1			
5. exception words	.891**	.898**	.389**	.555**	1		
6. writing quality	.518**	.494**	.305**	.404**	.461**	1	
7. phonological error	.036	-.086	.384**	-.268**	.099	.133	1

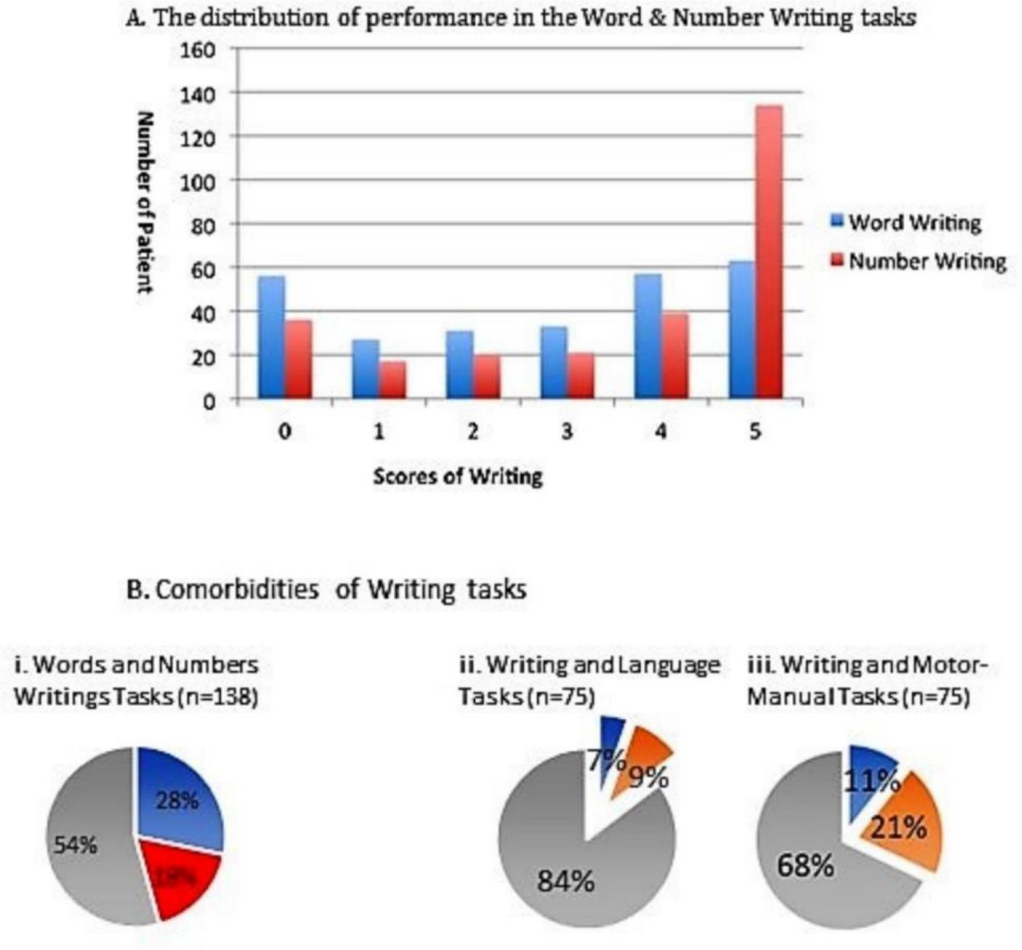
Sup table 7: **p<0.01, *p<0/05

supp table 8 Correlation matrix of the tasks recruited in the PCA

	1	2	3	4	5	6	7	8	9
1.picture naming	1								
2.sentence construction	.742**	1							
3.sentence reading	.732**	.727**	1						
4.Multi-step object use	.457**	.464**	.399**	1					
5.Meaningless imitation	.590**	.572**	.520**	.527**	1				
6.Number reading	.762**	.792**	.821**	.434**	.605**	1			
7.CFC	.478**	.415**	.470**	.427**	.496**	.535**	1		
8.Word Writing	.592**	.506**	.520**	.331**	.465**	.574**	.459**	1	
9.Number writing	.640**	.672**	.596**	.486**	.543**	.708**	.562**	.700**	1

Sup table 8: ***p*<0.01, **p*<0/05

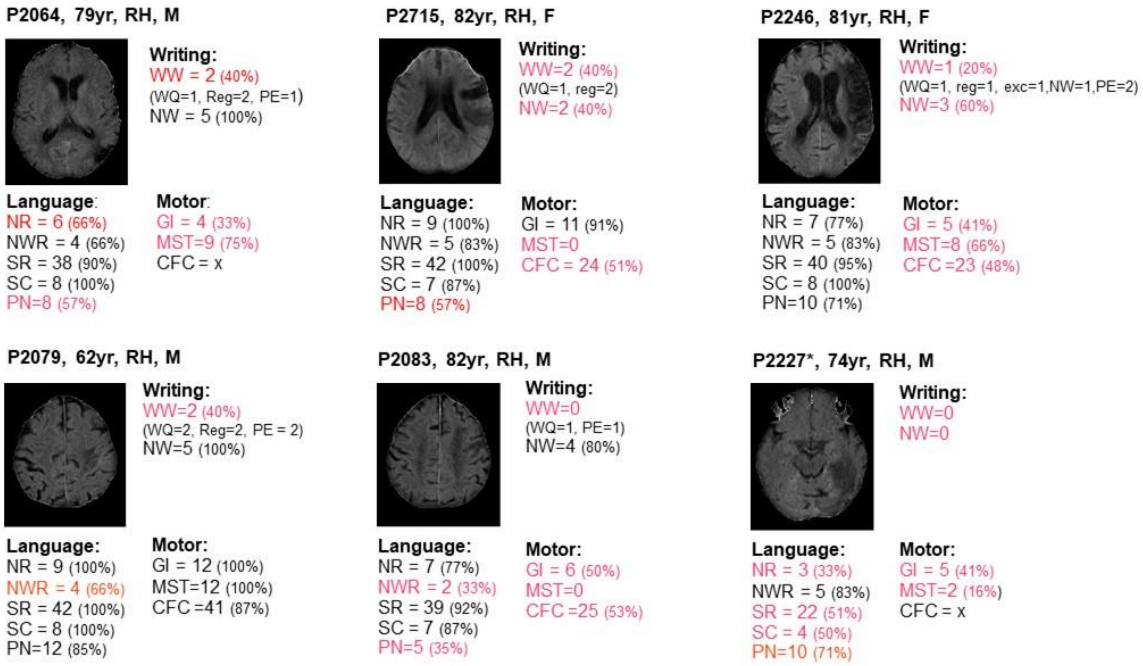
supp figure 4 the distribution of performance in the two writing tasks and their comorbidities analysis in 276 VBM group patients



A) The chart represents the distribution of performances for writing words (blue) and numbers (orange). B) The pie chart on the left present comorbidities of deficits in writing number of words, grey are the proportion of patients who showed impairment in both tasks, red impairment only in writing numbers and blue those how showed impairments only in writing words. The pie chart on the left break comorbidities in patients who show deficits in both writing tasks (the grey

group) based on the prevalence of comorbidity with the language-based (left) and motor-based (right) tasks. On both these pie charts, blue represents the proportion of patients who showed only deficits in writing, orange represents the proportion of patients who had a deficits in only one other task, grey represent the proportion of patients who showed impairment in both writing tasks and at least 2 additional language.

supp figure 5 case examples of brain lesion and error pattern observed in writing VBM study

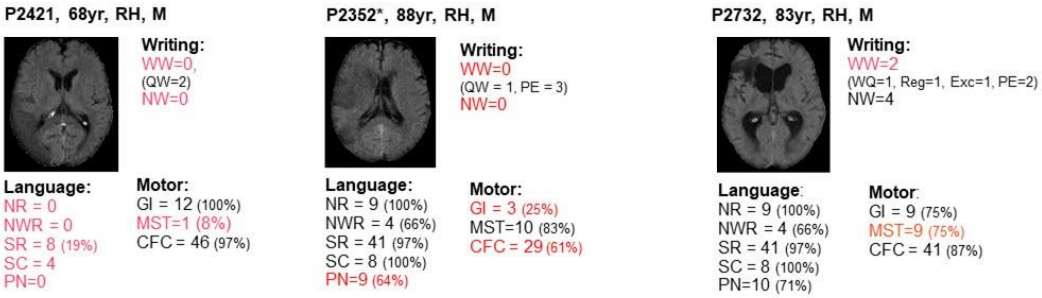


All patients were right-handed and all used their right hand for writing. P2064 had a lesion to right inferior parietal extending to middle occipital and temporal cortices. P2715 had a lesion right frontal and pre-frontal cortices, including middle and superior frontal gyri. P2246 had a lesion to right lateral front-parietal cortices. P2079 had a lesion to right prefrontal cortex. P2083 had a lesion to right lateral prefrontal cortex. P2227 had multiple lesions. Shown are lesion to the right inferior occipital-temporal cortices. But the patient also had a lesion to right frontal and left parietal cortices. red indicate that patients were classified as impaired relative to age match controls.

Abbreviations: yr, years old; RH, right handed; F, female; M, male; WW, word writing; WQ, writing quality; reg, number of correct regular words (max =2); exc, number of correct exceptional words (max=2); pe, phonological errors, number

of errors with correct phonological spellings (max=4); NW, number writing. NR, number reading; NWR, non-word reading (not included in reported analyses); SR, sentence reading; SC, sentence construction; PN, picture naming; GI, meaningless gesture imitation; MTS, Multi-step object task; CFC, complex figure copy.

supp figure 6 case examples of brain lesion and error pattern observed in writing VBM study



All patients were right handed. P2421 had a lesion to left inferior parietal extending to middle occipital and temporal cortices, her used his right hand to write. P2352 had a lesion to the left lateral frontal-parietal cortex and he used his left (non-dominant hand to write). P2732 had a lesion to left prefrontal cortex. red indicate that patients were classified as impaired relative to age match controls. Abbreviations are described in Supp-Figure 5

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