The Posterior Parietal Cortex and its Role in Reading and Writing

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Abstract

Although the posterior parietal cortex in the human brain has been implicated in writing and reading processes for a long time, the role of the different parts of this heterogeneous and complex region of the brain has been difficult to ascertain. Most of what is known about the role of the posterior parietal cortex in reading and writing is general, and is based largely on clinical reports of patients with extensive brain damage to this region. The most famous of these clinical reports are Dejerine's 19th century examinations of patients who after a cerebrovascular accident could no longer read or write. Post-mortem examinations of their brains revealed extensive lesions within the left posterior parieto-occipital area (i.e. including the angular gyrus), which led Dejerine to the conclusion that the angular gyrus is involved in an essential way in reading and writing. However, modern neuroimaging techniques, such as functional magnetic resonance imaging and positron emission tomography, have failed to provide evidence in support of this assertion let alone advance our understanding of the posterior parietal cortex contribution to reading and writing. The present thesis describes a series of experiments involving both functional and structural magnetic resonance imaging (MRI) in healthy subjects. The studies aim to elucidate the contribution of various regions within the posterior parietal cortex to reading and to writing, including the role of the superior parietal lobule (area PE), and the inferior parietal lobule (i.e. the angular gyrus and the supramarginal gyrus).

The first study uses functional magnetic resonance imaging to examine writing related activity under various conditions in various parts of the posterior parietal cortex. The results indicate that, during writing, the anterior aspect of the superior parietal lobule (cytoarchitectonic area PE) primarily is involved, and that there is a correlated increase in activation occurring between area PE and the more anterior region of the inferior parietal lobule (i.e. the anterior part of the supramarginal gyrus) when writing occurs in response to a word that is retrieved when viewing a pictured object. In contrast, when writing occurs in response to a word that has just been read, a correlated increase in activation occurs between

area PE and the more posterior part of the inferior parietal lobule, i.e. within the angular gyrus region. The first study, therefore, dissociates the contributions of the superior parietal lobule from the inferior parietal lobule to reading and writing, as well as the contributions of the supramarginal gyrus versus that of the angular gyrus.

The classical definition of the angular gyrus is the cortical region surrounding the caudal part of the superior temporal sulcus. This is a rather loose definition for a very complex and large expanse of cortex. Characterizing the anatomy of the angular gyrus region in more precise terms was a necessary first requirement in order to examine with greater precision where within the larger angular gyrus region the focal peaks of activation during reading occur. The second study, therefore, provides a detailed description of the gross morphology of the region of the angular gyrus, based on structural magnetic resonance images of a large sample (45) human brains (i.e. 90 hemispheres). The results demonstrate that there are in fact three caudal branches of the superior temporal sulcus that ascend into the inferior parietal lobule and that constitute the angular gyrus (cSTS1, cSTS2, cSTS3), and a fourth branch (the anterior occipital sulcus-ventral component; AOCS-v) located more inferiorly within the temporal-occipital junction. Probability maps of the location of these sulcal branches in Montreal Neurological Institute (MNI) standard stereotaxic space are also provided, in order to facilitate the localization of functional activation peaks in relation to these branches, which are most commonly reported in the same standard stereotaxic MNI space.

The third study draws heavily on the findings from the second study, and aims to relate functional activation peaks during reading to specific sulcal landmarks (i.e. caudal branches of the superior temporal sulcus) within the larger angular gyrus region. The results from the third study suggest that reading-related activation falls within the central part of the angular gyrus region, namely in the region between the second and third branches of the caudal superior temporal sulcus (i.e. between cSTS2 and cSTS3) which is occupied by cytoarchitectonic area PG. Furthermore, there is a correlated increase in activation occurring between area PG and the left posterior temporo-occipital area in an area of the temporal lobe previously identified as a visual word form area. It is suggested that while the visual word form area may support reading in identifying words as visual objects as part of the ventral visual processing stream, area PG supports reading because it is part of the dorsal processing stream that supports spatial cognition and that reading involves visuo-spatial processing.

Taken together, the data from all three studies presented in the present thesis not only confirm the involvement of the posterior parietal cortex in reading and in writing, but also dissociate the contributions of various regions within this large and heterogeneous part of the human brain to reading and writing processes, thereby advancing our understanding of the contribution of the posterior parietal cortex to reading and writing.

Résumé

Chez l’homme, bien que le cortex pariétal postérieur soit connu pour être impliqué dans les processus d’écriture et de lecture, le rôle des différentes subdivisions de cette vaste région complexe et hétérogène reste à être déterminé. Les connaissances concernant le rôle du cortex pariétal postérieur dans l’écriture et la lecture proviennent largement des études cliniques menées chez des patients atteints de larges lésions dans cette région. L’étude la plus fameuse a été effectuée par Dejerine au 19ième siècle et a montré une incapacité à lire et écrire chez des patients ayant subit un accident cerebrovasculaire provoquant une lésion spécifique de l’aire pariéto-occipitale postérieure dans l’hémisphère gauche, et plus particulièrement du gyrus angulaire. Cependant, les techniques de neuroimagerie modernes, telle que l’imagerie par résonance magnétique fonctionnelle et la tomographie par émission de positons, n’ont pas permis une meilleure compréhension du rôle du cortex pariétal postérieur dans l’écriture et la lecture. La présente thèse décrit une série d’expériences d’imagerie par résonance magnétique fonctionnelle et structurelle menées chez des sujets humains sains. Le but de ces études était de déterminer la contribution des différentes subdivisions du cortex pariétal postérieur dans l’écriture et la lecture, incluant le lobule pariétal supérieur (aire PE) et le lobule pariétal inférieur (i.e. le gyrus angulaire et le gyrus supramarginal).

La première étude examine, grâce à l’imagerie par résonance magnétique fonctionnelle, les activités observées pendant l’écriture dans des conditions variées et dans les différentes subdivisions du cortex pariétal postérieur. Les résultats montrent que la région antérieure du lobule pariétal postérieur (l’aire cytoarchitectonique PE) est fortement impliquée dans l’écriture et qu’il existe une corrélation entre l’augmentation d’activité observée dans l’aire PE et dans celle observée dans la région la plus antérieure du lobule pariétal inférieur (i.e. la partie antérieure du gyrus supramarginal) dans le cas où l’écriture est produite à la présentation de la photo d’un objet (le nom de l’objet doit être rappelé en mémoire et écrit). Par contre, quand l’écriture est produite en réponse à un mot qui vient d’être lu, il existe une corrélation entre l’augmentation d’activité

observée dans l'aire PE et celle observée dans la région postérieure du lobule pariétal inférieur, i.e. dans la région du gyrus angulaire. Cette première étude montre ainsi une dissociation entre les contributions respectives 1) du lobule pariétal supérieur versus du lobule pariétal inférieur et 2) du gyrus supramarginal versus du gyrus angulaire dans l'écriture et la lecture.

Classiquement, le gyrus angulaire est décrit comme étant la région corticale localisée autour de la partie caudale du sillon temporal supérieur. Cette définition reste largement imprécise pour une région corticale complexe et vaste. La caractérisation de l'anatomie de la région du gyrus angulaire dans des termes plus précis est fondamentale pour examiner avec précision la localisation des activités observées lors de la lecture. La seconde étude vise à décrire en détail la morphologie de la région du gyrus angulaire sur la base d'images structurelles obtenues chez 45 sujets humains sains (i.e. 90 hémisphères) grâce à l'imagerie par résonance magnétique. Les résultats démontrent que, caudalement, trois branches émergent du sillon temporal supérieur et remontent dans le lobule pariétal inférieur, constituant le gyrus angulaire (cSTS1, cSTS2, cSTS3). Une quatrième branche (la composante ventrale du sillon occipital antérieur; AOCS-v) est observée dans la jonction temporo-occipitale. Les cartes de probabilité de ces branches dans l'espace stéréotaxique standard de l'Institut Neurologique de Montréal (MNI) sont présentées dans le but d'analyser la localisation des activités fonctionnelles en relation avec ces branches, une analyse qui n'est pas réalisée communément dans le même espace stéréotaxique standard (MNI).

La troisième étude est basée sur les résultats obtenus dans la seconde étude et vise à déterminer les relations entre la morphologie locale (les branches caudales du sillon temporal supérieur) et les activités observées pendant l'écriture et la lecture dans la région du gyrus angulaire. Les résultats suggèrent que l'activité observée pendant la lecture est localisée dans la partie centrale de la région du gyrus angulaire, i.e. dans la région localisée entre la seconde et la troisième branche du sillon temporal supérieur caudal (i.e. entre cSTS2 et cSTS3). Cette région est occupée par l'aire cytoarchitectonique PG. De plus, il existe un lien corrélationnel entre l'activité observée dans l'aire PG et celle observée dans l’aire temporo-occipitale postérieure dans l’hémisphère gauche. Alors que l’aire temporo-occipitale postérieure fait partie de la voie ventrale de traitement visuel et a été suggérée comme impliquée dans l’identification des mots en tant qu’objets visuels, l’aire PG fait partie de la voie dorsale de traitement visuel et a été suggérée comme impliquée dans la cognition visuo-spatiale. De façon très importante, l’identification des mots en tant qu’objets visuels et l’analyse visuo-spatiale sont des aspects fondamentaux de la lecture, montrant les contributions respectives de ces deux aires dans la lecture.

L’ensemble des données présentées dans cette thèse confirment l’implication cruciale du cortex pariétal postérieur dans l’écriture et la lecture et démontrent une dissociation entre les contributions des différentes subdivisions de cette région dans ces processus. Cette thèse permet des avancées significatives dans notre compréhension de la contribution du cortex pariétal postérieur dans l’écriture et la lecture.

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Statement of originality

The studies presented in chapters two, three, and four, represent novel findings about the structure of the posterior parietal cortex in the human brain, and about the involvement of the posterior parietal cortex in reading and writing. These studies have all been prepared in manuscript format and submitted for publication in peer-reviewed journals. The studies in chapters two and three have been published in the European Journal of Neuroscience. The study in chapter four has been submitted for publication also to the European Journal of Neuroscience and is currently under consideration (at the "revise and resubmit" stage).

These studies were also presented at various international conferences. Conferences include the Society for Neuroscience annual meeting in 2007 (San Diego), in 2009 (Washington), and in 2011 (Washington), and at the Federation of European Neurosciences Society 2012 (Barcelona). Presentations about the research findings were also given in Montreal at McGill University and the Montreal Neurological Institute, including the Neurosurgical Residents' Day and Cognitive Neuroscience Unit's weekly seminar series.

Contribution of authors

The manuscripts have been co-authored with Dr. Michael Petrides. I performed the experiments and data analysis, while the experimental design was decided with the guidance of Dr. Petrides. The manuscripts were all written by myself with guidance from Dr. Petrides.

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Chapter One

1. General Introduction

This thesis is concerned with the neural basis of reading and writing. In order to examine the functional localization of reading and writing in the human brain, experiments were conducted using functional magnetic resonance imaging (fMRI). In addition, a detailed anatomical study of the sulci of the inferior parietal lobule (i.e. the inferior part of the posterior parietal cortex) was performed by examining the anatomical magnetic resonance images (MRIs) of the brains of 45 human subjects (i.e. 90 hemispheres). The aim was to characterize the anatomical variability of this region because the inferior parietal lobule is believed to support reading and writing functions in humans. However, the morphology of the inferior parietal lobule has not been characterized consistently by the major anatomical atlases of the human brain, making it difficult to investigate with precision the relationship between reading and writing functions and the specific anatomical structures within the inferior parietal lobule that may support these processes.

Most of what is currently known about the localization of reading and writing in the human brain comes from both experimental neuroimaging studies and clinical case reports in the fields of neurology, neurosurgery, neuropsychology, and neurolinguistics. The most famous clinical cases relating reading impairments (alexia) and writing impairments (agraphia) to a particular brain region are Dejerine's 19th century post-mortem examinations of the brains of patients who, after a cerebrovascular accident affecting the angular gyrus in the language dominant hemisphere, could no longer read or write (Dejerine, 1891; 1892; 1914). However, while the post-mortem examinations of the brains of alexic and agraphic patients enabled Dejerine to establish that lesions centered in the region of the angular gyrus result in reading and writing problems, the damage that was caused by the cerebrovascular accidents could not enable him to rule out the possibility that the alexia and agraphia may have been caused by damage to the multiple white matter fiber tracts that run beneath the angular gyrus. There are numerous white matter fiber tracts, for example, that originate in the occipital lobe and pass under the angular gyrus to continue towards the intraparietal sulcus, the prefrontal cortex, and other temporal language areas (Martino *et al.*, 2012). It may very well have been the case that these fiber pathways were damaged to cause the alexia and agraphia, rather than damage to the angular gyrus proper. Thus, while Dejerine's case reports are seminal in that they indicate that damage to the angular gyrus region of the language dominant hemisphere leads to reading and writing impairments, they cannot provide further detail about whether the reading and writing is supported by the angular gyrus in and of itself, or if reading and writing is supported by other areas of the brain that are connected to each other via white matter fiber tracts that run beneath the angular gyrus, or both.

The possibility that multiple brain regions support reading and writing is likely, considering that reading and writing are complex behavioral capacities in humans and a single brain area is unlikely to support any highly complex cognitive process. The notion that reading and writing are widely distributed in the human brain is supported by the results of functional neuroimaging studies that demonstrate collectively that peaks of activation occur in multiple regions of the brains of healthy individuals while these individuals perform varied reading and writing tasks (Cohen *et al.*, 2000; Katanoda *et al.*, 2001; Menon & Desmond, 2001; Beeson *et al.*, 2003; Jobard *et al.*, 2003; Price *et al.*, 2003; Culham & Valyear, 2006; Rektor *et al.*, 2006; Sugihara *et al.*, 2006; Cattinelli *et al.*, 2013). Interestingly, however, most functional neuroimaging studies do not report reading-related or writing-related activation in the angular gyrus region proper, and a main goal of the present thesis was to investigate why the data from neuroimaging studies do not confirm in an overwhelming way the classic neurological model as originally put forth by Dejerine and expanded upon by Geschwind (Dejerine, 1914; Geschwind, 1965), whereby the angular gyrus is the critical structure for reading and writing.

The aim of the present thesis was to develop functional magnetic resonance imaging paradigms of reading and writing that would elicit activation in the angular gyrus region in order to understand better the circumstances of reading and writing that require involvement of the angular gyrus region. Additionally, we wished to explore the extent to which the angular gyrus region may be interacting functionally with other brain areas to support reading and writing abilities.

The introduction provides a description of the anatomy of the posterior parietal cortex, with an emphasis on the region of the angular gyrus, its gross morphology and its various cytoarchitectonic areas. This will be followed by an overview of what is currently known about the functional localization of reading and writing in the posterior regions of the human brain. The introduction will conclude with a summary of the studies that were conducted as part of this thesis in an attempt to understand better the functional localization of reading and writing in the human brain, and to examine the contributions to reading and writing of the angular gyrus region in particular.

1.1 Anatomy of the parietal lobe

1.1.1 Gross morphology

The parietal lobe is a large and heterogeneous region of the brain, occupying the upper posterior quadrant of each cerebral hemisphere. At the anterior boundary of the parietal lobe we find the central sulcus, which marks the border between the parietal lobe and the frontal lobe. From the central sulcus, the parietal lobe continues back towards the occipital lobe until it reaches the parieto-occipital fissure. The parieto-occipital fissure is more prominent on the medial surface of the brain, where it forms the anterior limit of the cuneus, and also serves as the posterior boundary of the medial parietal lobe. On the lateral surface of the brain, the very short continuation of the parieto-occipital fissure again serves to mark the border between the parietal lobe and the occipital lobe. The Sylvian fissure is used on the lateral surface to indicate the ventral border of the parietal lobe, marking the boundary between the parietal lobe and its ventral neighbor, the temporal lobe; however, as the Sylvian fissure continues posterior and into the inferior aspect of the parietal lobe, it terminates and there is no clear boundary between the parietal lobe and temporal lobe anymore. At this point, an imaginary line is drawn from the posterior aspect of the Sylvian fissure to the transverse occipital sulcus, and it is taken as the approximate border between the temporal and parietal lobes (see Figure 1.1).

1.1.2 The posterior parietal cortex

A distinction can be made between the cortex in the anterior portion of the parietal lobe that lies immediately behind the central sulcus, and the cortex of the parietal lobe within the region of the posterior parietal cortex. The cortex in the anterior portion of the parietal lobe is considered to be the primary somatosensory cortex (Penfield & Boldrey, 1937; Jasper *et al.*, 1960; Fox *et al.*, 1987; Kurth *et al.*, 1998), and in gross morphological terms the primary somatosensory cortex corresponds to the posterior bank of the central sulcus and the post-central gyrus. The primary somatosensory cortex, however, consists of four distinct cytoarchitectonic areas (from anterior to posterior: Brodmann areas 3a, 3b, 1 and 2) that differ from each other in terms of their somatotopic organization, their representations of different specific skin surfaces, their neuronal characteristics, and their connectivity profiles with different nuclei of the posterior thalamus (Merzenich *et al.*, 1978; Kaas *et al.*, 1979; Jones & Porter, 1980; Nelson *et al.*, 1980; Pons *et al.*, 1985; Geyer *et al.*, 1999; Moore *et al.*, 2000). Although the four cytoarchitectonic areas within the anterior parietal cortex are all involved in the processing of basic somatosensory information, it has been proposed that the true primary somatosensory cortex corresponds to area 3b only (Merzenich *et al.*, 1978; Kaas *et al.*, 1979; Nelson *et al.*, 1980), which is found within the caudal bank of the central sulcus. This has been proposed because only area 3b has the defining characteristics of primary somatosensory cortex as has been described in cats, rats, and other mammals, which includes a distinctive laminar appearance with a densely granular layer IV that receives input from the ventroposterior nucleus of the thalamus, receptive fields that are activated almost exclusively by light touch on the skin, and a systematically organized somatotopic representation of the contralateral body surface (Nelson *et al.*, 1980).

By contrast to the anterior parietal cortex, the cortex posterior to the postcentral gyrus, i.e. the cortex of the posterior parietal cortex, is involved in the processing of higher order information, concerning the integration of somato-motor, somatosensory, auditory, and visual information. One example of such higher-order processing that has been shown to be supported by the superior aspect of the posterior parietal cortex is visually guided reaching, whereby information from visual cortex about the shape and position of an object is integrated with the somatosensory areas that provide feedback to the motor cortex about the correct orientation of the arm and hand in space in order to successfully reach for the object (Deiber *et al.*, 1991; Georgopoulos, 1991; Clower *et al.*, 1996; Kalaska *et al.*, 1997; Andersen & Buneo, 2002). Chapter two considers whether this same posterior parietal area that supports visually guided reaching may have been adapted in the human brain to support writing, as a function of its interactions with the language processing areas that are located inferiorly within the inferior parietal lobule of the posterior parietal cortex.

A distinction therefore can be made on the brain's lateral surface between the anterior parietal cortex that is involved more in basic somatosensory processing, and the posterior parietal cortex that is involved in higher-order processing. It is relevant to note that when Dejerine performed his post-mortem examinations of the brains of the alexic and agraphic patients, he found that the damage due to the cerebrovascular accident had affected the posterior parietal cortex, as opposed to the anterior parietal cortex. That the posterior parietal cortex would be involved in reading and writing makes sense, given that reading and writing are complex processes and therefore are likely to depend on the integration of somato-motor, somatosensory, auditory, and visual information.

1.1.3 The angular gyrus

A horizontal sulcus, called the intraparietal sulcus, divides the lateral posterior parietal cortex into a superior parietal lobule and an inferior parietal lobule (see Figure 1.1). In the human brain, two sulci occupy the inferior parietal lobule, around which two gyri are defined: the caudal aspect of the Sylvian fissure around which the supramarginal gyrus is found; and the caudal aspect of the superior temporal sulcus (cSTS), around which the angular gyrus is found (see Figure 1.1). Dejerine's position is that the cerebrovascular accidents occurring within the posterior parietal cortex that produce alexia and agraphia preferentially involve the angular gyrus (Dejerine, 1892; 1914).

The morphology of the inferior parietal lobule, and especially of the angular gyrus, has been difficult to understand in the human brain. Relative to the brains of lower primates, the morphology of the inferior parietal lobule in the brains of humans is considerably more complex. In the brain of the macaque monkey, for example, there can be found two sulci within the inferior portion of the posterior parietal lobe: the caudal aspect of the Sylvian fissure, and the caudal aspect of the superior temporal sulcus. Importantly, in the brain of the macaque monkey, the caudal superior temporal sulcus remains as a single sulcus as it continues into the inferior parietal lobule. In the brains of the great apes (e.g. gorillas, orangutans, and chimpanzees), however, the caudal aspect of the superior temporal sulcus starts to become more convoluted, and as it extends into the inferior parietal lobule it contains several sulcal branches, rather than extending into the inferior parietal lobule as a single sulcus (Shellshear, 1927; Hosokawa *et al.*, 1965). In the human brain, the sulcal morphology of the inferior parietal lobule appears to undergo a degree of evolutionary expansion that rivals that of the prefrontal lobe. The caudal aspect of the superior temporal sulcus divides into several branches that diverge away, making it difficult to trace with ease the caudal aspect of the superior temporal sulcus as it extends into the inferior parietal lobule (Critchley, 1966). Since the angular gyrus is defined classically as the gyrus surrounding the caudal extent of the superior temporal sulcus, it is a necessary prerequisite for any study wishing to examine the relationship between reading and writing functions and the anatomical region of the angular gyrus (which the neurological model suggests is the critical structure for reading and writing) to be able to identify, morphologically, the caudal branches of the superior temporal sulcus that constitute the angular gyrus region. The purpose of the research reported in Chapter three was to investigate the caudal branches of the superior temporal sulcus in a large sample of human brains in order to characterize their morphological variability across individuals.

In part, Chapter three was motivated by the observation that the majority of today's leading atlases of the human brain rarely provide a detailed description of the sulcal morphology of the superior temporal sulcus as it continues caudally into the inferior parietal lobule (Ono *et al.*, 1990; Watson, 1995; Duvernoy, 1999; Mai *et al.*, 2007; Haines, 2008; Woolsey *et al.*, 2008; Kiernan & Barr, 2009; Felten & Shetty, 2010). As pointed out in the introduction to Chapter three, two of the leading atlases that have attempted to address the anatomical morphology of the inferior parietal lobule in greater detail (Ono *et al.*, 1990; Duvernoy, 1999) are both internally inconsistent and inconsistent with each other. Both the atlases by Duvernoy (1999) and Ono et al. (1990) depict two sulcal branches related to the caudal superior temporal sulcus within the inferior parietal lobule. However, a careful examination reveals that these atlases actually have identified unknowingly two different pairs of branches related to the caudal superior temporal sulcus. This is problematic because researchers referring to these atlases are left with an inconsistent picture of the caudal branches of the superior temporal sulcus, and as a consequence, an inconsistent definition of the gross morphology of the angular gyrus region. As a further aim, the study in Chapter three was designed to investigate the branches of the superior temporal sulcus in 45 magnetic resonance images (MRIs) of human brains that were transformed to standard stereotaxic space (that of the Montreal Neurological Institute, which is the most widely used standard stereotaxic space) so as to provide an accurate anatomical map of these caudal branches and to record the variability in their locations across individual brains, in an effort to understand with greater precision the variability in morphology and location of the angular gyrus region.

1.2 Cytoarchitecture of the posterior parietal cortex

While it is of obvious importance to understand the anatomy of the posterior parietal cortex in gross anatomical terms, i.e. in terms of the morphology of its sulci and gyri, it is also of great relevance to investigators wishing to study relationships between areas of the brain and specific cognitive functions to understand the anatomy of the posterior parietal cortex on a microscopic scale, i.e. its cytoarchitecture. Cytoarchitectonic investigation of the cortex defines distinct cortical areas based on variations in neuronal characteristics (such as differences in cell shape, cell density, and cell size, and degree of development of various layers) (Brodmann, 1909; Economo & Koskinas, 1925). Often, these discrete areas are found to have distinct functional properties (Eickhoff *et al.*, 2005; Eickhoff *et al.*, 2007), suggesting a tight correlation between structure and function. For example, the cytoarchitectonic characteristics that differentiate the primary motor cortex on the anterior bank of the central sulcus from the primary somatosensory cortex on the posterior bank of the central sulcus are in accordance with the functional differences between these two areas (as their names imply). The primary motor area, characterized by very large pyramidal neurons, known as the Betz cells, in layer V and an absence of a granular layer IV, is involved in the motor control of the body (Penfield & Boldrey, 1937), while the adjacent primary somatosensory area (3a), characterized by a granular layer IV and the absence of the Betz cells in layer V, is involved in receiving sensory information about the body (Merzenich *et al.*, 1978; Kaas *et al.*, 1979; Nelson *et al.*, 1980). Cytoarchitectonic areas will also often have distinct white-matter fiber pathways that connect them to other areas in other parts of the brain (Pandya *et al.*, 1996; Petrides & Pandya, 1999), a feature which further serves to differentiate one cytoarchitectonic area from another.

The posterior parietal cortex of the human brain has been partitioned into several cytoarchitectonic areas on the basis of cytoarchitectonic criteria. All of the cytoarchitectonic maps that have been published to date suggest that the expanse of cortex more generally referred to as posterior parietal cortex is quite heterogeneous and contains several cytoarchitectonic areas. Over time there have been several cytoarchitectonic maps produced that detail the cytoarchitectonic attributes of the posterior parietal cortex (Brodmann, 1909; Economo & Koskinas, 1925; Caspers *et al.*, 2006). Differences exist in the number of proposed cytoarchitectonic areas detailed in each map, as well as in the nomenclature that is used to label what appear to be shared cytoarchitectonic areas across maps. Despite these differences, however, cytoarchitectonic investigations all make the same fundamental point, which is that multiple cytoarchitectonic areas exist within the posterior parietal cortex, implying that it is an anatomically heterogeneous region of the brain. Accordingly, there is reason to expect that there is functional heterogeneity within the posterior parietal cortex as well. This raises the important question as to whether discrete aspects of the reading and writing processes can be related to discrete cytoarchitectonic areas within the posterior parietal cortex. Cerebrovascular accidents cannot provide us with a way to establish such refined associations between structure and function because the damage encompasses multiple cytoarchitectonic areas. However, carefully designed magnetic resonance imaging studies do permit more discrete associative investigation (albeit with fMRI's own methodological limitations).

1.2.1 Brodmann

German neurologist Korbinian Brodmann (1909) proposed a cytoarchitectonic parcellation scheme of the human cerebral cortex that subdivides the lateral cortex into 44 cytoarchitectonic areas (see Figure 1.2). Within the posterior parietal cortex, the superior parietal lobule and inferior parietal lobule are differentiated into four cytoarchitectonic areas. In the superior parietal lobule, we find cytoarchitectonic areas 5 and 7. While area 5 occupies the most anterior part of the superior parietal lobule, area 7 is found more posterior. In the inferior parietal lobule, we find cytoarchitectonic areas 39 and 40. The more anterior area 40 surrounds the posterior aspect of the Sylvian fissure as it courses into the inferior parietal lobule and constitutes the cortex of the supramarginal gyrus. By contrast, area 39 is found more posterior, and surrounds the caudal aspect of the superior temporal sulcus as it courses up into the inferior parietal lobule, and therefore area 39 would appear to constitute the cortex of the angular gyrus. Note, however, that in Brodmann's schematic map of the cytoarchitectonic areas, the caudal superior temporal sulcus is represented as a single sulcus as it courses up into the inferior parietal lobule, with area 39 neatly surrounding it. However, as pointed out previously, the caudal aspect of the superior temporal sulcus does not course into the inferior parietal lobule as a single sulcus around which exists an angular gyrus (and an area 39), but instead divides into several caudal branches, making the precise borders of the angular gyrus unclear.

1.2.2 Economo and Koskinas

In 1925, Economo and Koskinas produced another cytoarchitectonic map of the human cerebral cortex, this time with 107 cytoarchitectonic areas, compared to the 44 of Brodmann. Within the superior parietal lobule in the Economo and Koskinas map, we find area PE as a major cytoarchitectonic area, which appears to cover the same expanse as areas 5 and 7 of Brodmann. There are several subdivisions to area PE, with the introduction of areas PEm, PE(D), PEp, and PEj. In the inferior parietal lobule of the Economo and Koskinas cytoarchitectonic map we find two major subdivisions (area PF and area PG). These appear to be comparable to the two areas that are found in the inferior parietal lobule in the cytoarchitectonic map of Brodmann (areas 40 and 39, respectively). Area PF is the more anterior area, occupying the cortex that surrounds the Sylvian fissure as it ascends into the inferior parietal lobule and forms the supramarginal gyrus. However, area PF has been subdivided further into areas PFD, PFop, PFt, PFcm, and PFm. Area PG occupies the more posterior part of the inferior parietal lobule region, presumably corresponding to the cortex of the angular gyrus. Interestingly, however, in the schematic map by Economo and Koskinas, the caudal aspect of the superior temporal sulcus is no longer presented as a single sulcus rising up into the inferior parietal lobule. Instead, there are two sulci found within the inferior parietal lobule that have a relationship with the main body of the superior temporal sulcus, based on their nomenclature (see Figure 1.3, panel A). The most anterior of these branches depicted in the inferior parietal lobule on the Economo and Koskinas map appears to fall within the region of cytoarchitectonic area PF, while the more caudal superior temporal sulcus-related sulcal branch falls within the region of cytoarchitectonic area PG (see Figure 1.3, panel B).

Therefore, while some major cytoarchitectonic subdivisions of the posterior parietal cortex, according to the map of Economo and Koskinas, are comparable to those provided by the map of Brodmann, it was already apparent in the Economo era that the larger cytoarchitectonic areas that had been identified by Brodmann could be subdivided even further.

1.2.3 Present day

Cytoarchitectonic investigation of the posterior parietal cortex continues to build upon the seminal work of Brodmann, and of Economo and Koskinas. With respect to the inferior parietal lobule, cytoarchitectonic investigation of the macaque monkey (Pandya & Seltzer, 1982) suggests that there are four areas: PF, PFG, PG, and Opt. Although similar names (e.g. PF, PG) to those used by the Economo and Koskinas were used to label the cytoarchitectonic areas in the inferior parietal lobule of the macaque monkey, a systematic comparative investigation of the cytoarchitectonic areas within the inferior parietal lobule across the two primate species (Petrides & Pandya, in preparation) suggests that there is not a direct correspondence between similarly named areas. Area PF in the macaque monkey most likely corresponds to the anterior part of PF of human inferior parietal lobule (i.e. area PF of Economo and Koskinas), and area PFG in the macaque monkey most likely corresponds to the posterior part of human area PF. Similarly, human area PG may include both macaque areas PG and Opt. Thus, what appear to be "new" areas in the macaque monkey (PFG, Opt) most likely refer to subdivisions within classic human areas. For example, area PFG in the macaque monkey is not an area that is unique to macaques but most probably corresponds to the posterior part of the human area PF, while macaque area PF corresponds to the anterior part of human PF. The precise cytoarchitectonic homologies across the two species is an important area of research because it will assist in the direct translation of the known functional properties of these areas in the monkey brain, as studied elegantly by electrophysiology, to the human brain, in order to draw inferences about what functions the same cytoarchitectonic area supports in the human brain.

A problem of nomenclature exists in the cytoarchitectonic maps of the human brain, making it difficult to know the extent to which commonly used cytoarchitectonic labels actually refer to the same physical cytoarchitectonic areas. For example, in a recent cytoarchitectonic investigation of the human brain, the inferior parietal lobule was proposed to consist of areas PFm, PFcm, PFG, PGa, and PGp (Caspers *et al.*, 2006). Areas PGa and PGp of Caspers et al. are defined as the anterior and posterior parts of area PG, but there are no cytoarchitectonic criteria provided that define cellularly areas PGa (the anterior part of area PG) and PGp (the posterior part of area PG), and so it is not clear to what extent the labels used by Caspers et al. to define the similarly named areas to those of Economo and Koskinas actually concur physically. For example, it may be possible that area PGa in Caspers et al. actually corresponds to area PFG, rather than to an anterior part of PGa. The provision of the criteria of cytoarchitectonic areas is important in order to avoid such potential confusion.

The relationship between cytoarchitectonic areas and the sulci of the inferior parietal lobule also remains to be established. If a cytoarchitectonic area can be predicted by a sulcal landmark, this information would be very valuable in interpreting the activation from functional neuroimaging studies. For example, the central sulcus can be used as a landmark for the primary motor and somatosensory areas, with correlated activation that is located in the anterior bank of the central sulcus and immediately anterior to it indicating primary motor cortex (i.e. Brodmann area 4) involvement, and correlated activation that is located in the caudal bank of the central sulcus indicating primary somatosensory cortical area 3b involvement. Within the inferior parietal lobule, it is relevant to understand the relationship between sulci and cytoarchitectonic areas so that neuroimaging results that demonstrate activation within the inferior parietal lobule correlated with the performance of reading and writing tasks may be interpreted properly, and reported with specificity, for example as occurring in relation to one particular branch of the caudal superior temporal sulcus. Part of the problem has been the lack of consistent identification of the sulci in the inferior parietal lobule. One aim of the research reported in Chapter three, therefore, was to provide a greater degree of clarity about the morphology of the sulci within inferior parietal lobule so that relationships between sulci, cytoarchitectonic areas, and functions could be reported with precision.

1.3 Evolution of the superior temporal sulcus and of the angular gyrus

The morphology of the superior temporal sulcus has been studied from an evolutionary developmental perspective (Shellshear, 1927). A great degree of expansion in the human brain has occurred in relation to the caudal aspect of the superior temporal sulcus (i.e. the region of the angular gyrus). An implication of the finding that a massive structural expansion took place in the human brain in the cortex surrounding the caudal superior temporal sulcus is that the classic definition of the angular gyrus as surrounding the caudal aspect of the superior temporal sulcus is too vague. Functional neuroimaging studies looking to relate reading and writing activation peaks to the angular gyrus region need to consider the considerable extent of the angular gyrus and the difficulty in defining it.

According to Joseph Shellshear (1927) the superior temporal sulcus in the human brain is comprised of three sulci in a rostral (anterior temporal pole) to caudal (inferior parietal lobule) direction: an *anterior temporal sulcus* in the most anterior part of the temporal lobe, an *inferior parallel sulcus* running parallel to the Sylvian fissure in the main part of the temporal lobe, and a *superior parallel sulcus* taking a more or less vertical direction into the parietal lobe caudal to the ascending ramus of the Sylvian fissure. At the time of Shellshear's work, the caudal parts of the superior temporal sulcus were called the superior parallel sulcus (inferior and superior), owing to the fact that the superior temporal sulcus runs parallel to the Sylvian fissure. Shellshear maintains that an impressive evolutionary expansion takes place in the human brain in relation to the most posterior of these segments, the superior parallel sulcus (see Figure 1.4). In the macaque monkey, the caudal aspect of the superior temporal sulcus courses into the inferior parietal lobule as a single sulcus. However, in the brains of the great apes (orangutans, gorillas, chimpanzees), an additional sulcus can be found, called the anterior occipital sulcus (AOCS; called AOS by Shellshear). Shellshear argues that the anterior occipital sulcus in the brains of great apes and humans is a sulcus that has been extruded from the posterior bank of the superior parallel sulcus. Between this newly extruded anterior occipital sulcus and the caudal superior temporal sulcus from which it is extruded, Shellshear argues, an additional fold is formed, called the angular sulcus. Shellshear's work therefore predicts that we should observe three sulcal branches of the caudal superior temporal sulcus in the inferior parietal lobule, with a fourth caudal branch found ventral to the inferior parietal lobule, within the region of the posterior inferior temporal cortex.

Shellshear's work has important relevance to the localization of reading and writing, as functionally correlated activation that is observed in relation to each of these three branches during reading and writing tasks could be considered as activity in the angular gyrus region (which is defined as the cortex surrounding the caudal aspect of the superior temporal sulcus). As mentioned in the introduction to Chapter three, leading atlases of the human brain tend to refer to only two caudal branches of the superior temporal sulcus within the inferior parietal lobule. This tended to lead neuroimaging researchers to discount peaks of activation within the posterior part of the angular gyrus region, i.e. activation occurring between the second and third caudal branches of the superior temporal sulcus, as occurring within the angular gyrus region.

1.4 Neurolinguistic models of reading

Although the classic neurological model of reading emphasizes the importance of the angular gyrus in reading and in writing (Dejerine, 1914; Geschwind, 1965; Damasio & Geschwind, 1984), a discrepancy exists between the classic neurological model of reading and the more recently developed models of reading in the field of neurolinguistics. In contrast to the neurological model, these models do not emphasize the angular gyrus as having a particularly important role in reading and writing. These models of reading have been developed to reflect more recent findings of dissociable reading syndromes that seem to be produced by lesions to different parts of the brain.

Neurolinguistic models of reading have proposed that reading consists of semantic processing, orthographic processing, and phonological processing, and that each process is supported by different regions of the brain. Orthography involves the identification of whole words based on their overt visual features. In other words, in orthographic reading there is the direct association between a word's visual form and its semantic meaning. Damage to the brain structures that support orthographic reading is believed to produce surface dyslexia. Surface dyslexia is characterized by a difficulty in reading familiar words that have irregular or inconsistent spelling-to-sound conversions (e.g. words such as yacht, pint, sew) and that depend on an orthographic lexicon for their successful recognition during reading (Coltheart *et al.*, 1983; Hanley *et al.*, 1992). Orthographic processing has been associated with the posterior portion of the mid-fusiform gyrus, within the posterior inferior temporal cortex (Cohen *et al.*, 2000; Coltheart, 2000; Price *et al.*, 2003).

By contrast, phonological reading involves the identification of words based on their sound, requiring first the transformation of words into their auditory counterparts, and subsequently an association between a word's sound and its semantic meaning. Damage to brain structures that support phonological processing is believed to produce phonological dyslexia. Phonological dyslexia is characterized by a difficulty in reading non-words, e.g. kleb, and in reading unfamiliar real words, as patients cannot use letter-by-letter reading strategies to sound out new words and rely instead on recognizing familiar words using a whole-word recognition strategy (Beauvois & Dérouesné, 1979). It has been suggested that the inferior aspect of the prefrontal cortex in the left hemisphere supports phonological processing (Coltheart, 2000; Price *et al.*, 2003).

Damage to the brain structures that support semantic understanding is believed to produce deep dyslexia. Symptoms of deep dyslexia are similar to phonological dyslexia but deep dyslexia is distinguished by the presence of semantic errors (e.g. reading CORRECT as "right"). Semantics is believed to be supported by a wide range of brain regions, including the cortex near the border between superior and middle temporal gyrus (Brodmann areas 22/21), the left anterior temporal pole, the angular gyrus, and the anterior portion of the left fusiform gyrus (Nobre *et al.*, 1994; Coltheart, 2000; Price *et al.*, 2003).

Some neurolinguistic models of reading suggest that orthography, phonology, and semantic processes depend on left (i.e. language dominant) hemisphere structures, and that different dyslexic syndromes arise from disconnections between particular brain regions within the left hemisphere that support the three processing systems. For example, it has been suggested that deep dyslexia arises from a disconnection between neural areas supporting phonological (left frontal operculum) and semantic (left posterior superior temporal cortex) processing (Price *et al.*, 2003). However, it also has been argued that deep dyslexia is not due to a disruption to any particular part of the reading related areas in the left-hemisphere, but rather that it is due to the disconnection of the left hemisphere language processing areas from the orthographic processing that is supported by right hemisphere structures (Coltheart *et al.*, 1980; Coltheart, 2000).

There is also controversy regarding the extent to which orthographic, phonological, and semantic processing systems are independent from one another. For example, the dual-route cascade theory of reading (Coltheart *et al.*, 2001) proposes that the orthographical system and the phonological system are not entirely independent from one another, based on evidence from studies involving the reading of non-words in healthy individuals, showing that the phonological system and orthographic system do influence each other. For example, the pronunciation of non-words that have ambiguous pronunciation properties, such as "houch", can be influenced by previously presented words such as "touch" or "couch". The implication is that the brain regions supporting phonology and orthography may be shared to some extent or that they interact closely.

In summary, neurolinguistic models of reading posit that reading depends on three sub-process: orthography, semantics, and phonology. The precise neural correlates of these processes remain to be fully understood. Aside from a recent meta-analysis of functional neuroimaging studies of reading (Cattinelli *et al.*, 2013), most neurolinguistic models of reading do not present the angular gyrus region as having a particularly essential role in reading, beyond its involvement, along with the involvement of several other brain regions, especially the posterior superior temporal cortex (BA 21/22), in some form of semantic processing. That the left angular gyrus is not highlighted as a center for word recognition in most neurolinguistic models of reading (Coltheart *et al.*, 1980; Bookheimer *et al.*, 1995;

Pugh *et al.*, 2001; Jobard *et al.*, 2003; Price *et al.*, 2003) is in contradiction to the classic neurological model of reading. The study in Chapter four was designed to clarify the discrepancy between the classic neurological model of reading that places the angular gyrus as the critical structure, and the neurolinguistic models of reading that emphasize the role of the posterior inferior temporal cortex in word recognition during reading.

1.4.1 Pure word blindness

The idea that the posterior part of the inferior temporal cortex of the left hemisphere is critical for reading, i.e. it is a visual word form area, is supported by the clinical finding that cerebrovascular damage involving the region of the posterior inferior temporal cortex produces an impairment in reading known as pure word blindness (also referred to as pure alexia).

According to the clinical findings summarized by Dejerine in 1914, pure word blindness is a form of alexia that results from damage to the white matter fiber pathways of the language dominant hemisphere that carry information from the primary visual cortex to the angular gyrus (pli courbe). The patient diagnosed with pure word blindness is able to see the written word, as he is capable of copying it, albeit in a slavish manner, but he cannot recognize the meaning of the word that he sees. It is as though the patient sees words like he sees designs, without the ability to relate the corresponding idea to the visual pattern. Spontaneous writing and writing to dictation are preserved, and there is no trace of jargon aphasia or paraphasia, features of pure word blindness that distinguish it from the damage to the angular gyrus region that produces alexia with agraphia, and what Dejerine refers to as "altered interior language." According to Dejerine's viewpoint, the neuroanatomy underlying pure word blindness consists of bilaterally intact visual cortex and an intact angular gyrus of the language-dominant (left) hemisphere, but where the connection between the visual cortex and the angular gyrus has been damaged.

While pure word blindness has been associated with damage to the left occipito-temporal region (in the posterior part of the inferior temporal cortex), the association between pure word blindness and damage to the posterior inferior temporal cortex may potentially be explained as resulting from damage to the fiber pathways that course within the posterior regions of the brain, including the white matter tracts that run beneath the posterior inferior temporal cortex (Dejerine, 1914; Geschwind, 1965). In fact, pure word blindness is often accompanied by right lateral homonymous hemianopsia, a visual field defect involving the two right halves of the visual fields of both eyes, as a result of damage to the left half of the optic radiations (fiber pathways that carry visual information from the lateral geniculate nucleus of the thalamus to the primary visual cortex of the left hemisphere) that lie medial to the posterior inferior temporal cortex in the left hemisphere. The presence of hemianopsia indicates that the white matter fiber tracts medial to the posterior inferior temporal cortex have been damaged in the case of pure word blindness, and leaves open the possibility for the white matter damage to include also the fiber tracts that carry information from the primary visual cortex to the language-dominant angular gyrus region.

It is important to stress that in describing pure word blindness, Dejerine does not claim that the left occipito-temporal region is a store of word forms per se. If anything, it is the angular gyrus that Dejerine considers as the "center of the visual images of words" (Dejerine, 1914). Rather, pure word blindness is conceptualized as being due to a disconnection of visual cortex from the region within the posterior language zone that processes words, i.e. the angular gyrus. Nevertheless, the syndrome of pure word blindness (pure alexia) was extended to interpret data from neuroimaging studies showing correlated reading-activation in the posterior inferior temporal cortex of the left hemisphere (Cohen *et al.*, 2000; Cohen *et al.*, 2002; Dehaene & Cohen, 2011).

1.4.2 Neuropsychological evidence for the VWFA

It is important to mention at the outset that the boundary between the posterior inferior temporal cortex and the angular gyrus region is not clear. Therefore, damage to what is identified as the posterior inferior temporal cortex in clinical case studies involving cerebrovascular accidents may actually be extensive enough to include damage to the inferior aspect of the angular gyrus region or disconnect input to the angular gyrus. With this caveat in mind, patients with damage reported to affect the posterior inferior temporal cortex show impairments in the spelling of irregular words to dictation but preserved ability to write words that obey the phonological rules of English, in other words they demonstrate surface dysgraphia (Rapcsak & Beeson, 2004). For example, words such as tomb are written incorrectly as toom. It has also been reported that when patients lose the skilled ability to read whole words rapidly, a laborious letter-by-letter phonological strategy is adopted, namely surface dyslexia (Warrington & Shallice, 1980; Binder & Mohr, 1992; Cohen *et al.*, 2004). These results have been interpreted in light of the dual route model of reading (Coltheart *et al.*, 1993) whereby the rapid visual recognition of whole words as orthographic forms occurs distinctly from phonological processing (symbol-sound conversion/grapheme-to-phoneme conversion). However, the neuro-anatomical correlates of the dual-route systems are not clear. It has been suggested that the orthographic word forms are stored in the posterior inferior temporal cortex, and that when this region of the brain is damaged, patients are forced to adopt a phonological letter-by-letter reading strategy with remaining areas elsewhere in the brain, perhaps the angular gyrus of the inferior parietal lobule (Pugh *et al.*, 2001). However, the patients in the study by Binder & Mohr (1992) had damage to what appears to be the temporal-occipital cortex, whereas those in the study by Warrington & Shallice (1980) had damage to the peri-Sylvian language regions, including what appears to be the anterior aspect of the angular gyrus region. Thus, the existence of an orthographic word form area within the posterior aspect of the inferior temporal cortex is not established necessarily by these case reports. As well, a careful inspection of the extent of the damage does not rule out the possibility that the posterior-inferior aspect of the angular gyrus region was damaged in the study of Binder & Mohr (1992).

One of the most frequently cited clinical studies to support the posterior inferior temporal cortex as a visual word form area involves electrophysiological recordings from the fusiform gyrus in the brains of 27 patients with epilepsy during the presentation of several classes of stimuli: words or letter-strings, faces or cars or butterflies (scrambled and unscrambled), and checkerboard patterns (Nobre *et al.*, 1994). The posterior part of the fusiform gyrus in both hemispheres was found to exhibit a response that was preferential to alphabetic strings, whether words or pseudo-words, but not to faces, cars, butterflies, or checkerboard patterns. Thus, while the results from the Nobre et al. (1994) study suggest that the posterior aspect of the mid-fusiform gyrus, bilaterally, is involved in reading, they also suggest that it is involved in reading insofar as this region supports the perception of alphabetic forms in a purely visual sense. There is therefore no evidence from this study that the mid-to-posterior part of the fusiform gyrus in the language-dominant hemisphere has any semantic capacity during word reading, as it is equally engaged in words and pseudo-words. This is in contrast to the portrayal of the region as semantically engaged during the reading of words (Cohen *et al.*, 2002; Price *et al.*, 2003). Therefore, there is evidence to support the idea that the visual word form area is involved in the orthographic process, but there is controversy regarding the capacity of the visual word form area to translate the perception of an orthographic visual word form into a lexical unit that has semantic meaning.

1.4.3 Neuroimaging evidence for the Visual Word Form Area

The evidence for the claim that the posterior aspect of the inferior temporal cortex (i.e. the region of the mid-fusiform gyrus) in the language dominant hemisphere is a visual word form area comes from the results of neuroimaging studies that consistently find reading-related activation in the posterior inferior temporal cortex of the left hemisphere, along the mid-fusiform gyrus and more specifically localized to the occipital temporal sulcus (Cohen *et al.*, 2000; Cohen *et al.*, 2002; McCandliss *et al.*, 2003; Henry *et al.*, 2005; Dehaene & Cohen, 2011).

Upon further examination of the neuroimaging results, it becomes apparent that the precise anatomical location of the so-called visual word form area is rather ambiguous, calling into question the validity of the visual word form area as a precisely defined entity, both functionally and anatomically. Early neuroimaging studies associating reading-related activation with the posterior inferior temporal cortex in the left hemisphere reported clearly that the activation occurs along the middle part of the fusiform gyrus (Cohen *et al.*, 2000; Cohen *et al.*, 2002). However, the proposal that the mid-fusiform gyrus is a word form area was criticized because the mid-fusiform has been shown to be involved in the visual perception of many classes of objects, such as faces, tools, animals, and fruit (Kanwisher *et al.*, 1997; Tong *et al.*, 2000; Grill-Spector, 2003; Kanwisher & Yovel, 2006; Liu *et al.*, 2008). A review of the neuroimaging results of several studies demonstrated that activation in response to viewing many classes of visual objects overlaps with the "visual word form" area, suggesting the visual word form area is a more general visual area that is not specific to processing words per se (Price & Devlin, 2003). Subsequently, studies were designed to examine functional segregation within the mid-fusiform gyrus of the human brain, in order to demonstrate that the site where words are processed within the mid-fusiform gyrus is distinct from, but adjacent to, regions of the mid-fusiform where other classes of visual objects are processed (Hasson *et al.*, 2002; Gaillard *et al.*, 2006; Baker *et al.*, 2007). However, a recently published study demonstrates that the classically defined visual word form area is not partial to processing words, and that it is the level of visual complexity of a given stimulus that drives activation in this brain region, regardless of whether it is a word or not (Vogel *et al.*, 2012). While the controversy continues surrounding the claim that a region within the mid-fusiform gyrus can be considered as a visual word form area, the localization of the so-called visual word form area has started to shift, with a more lateral position along the occipital temporal sulcus, a sulcus which forms the lateral boundary of the fusiform gyrus, being emphasized (McCandliss *et al.*, 2003; Dehaene & Cohen, 2011).

The coordinate of the activation peak that is maximally associated with the visual word form area is reported on average at around x = -43 in the sagittal plane in Montreal Neurological standard stereotaxic space (McCandliss *et al.*, 2003), which corresponds to the lateral part of the mid-fusiform gyrus that is closest to the occipital temporal sulcus. However, inspection of the figures from the visual word form area neuroimaging studies (Cohen *et al.*, 2000; Cohen *et al.*, 2002; McCandliss *et al.*, 2003; Cohen *et al.*, 2004; Cohen *et al.*, 2008; Dehaene & Cohen, 2011; Szwed *et al.*, 2011), shows clearly that the reading-related activation spreads medially within the middle part of the fusiform gyrus region and is well-situated between the occipital temporal sulcus and the more medial collateral sulcus. As well, studies attempting to localize the visual-word-form-area report activation as far medial in Montreal Neurological standard stereotaxic space as x = -33 (Cohen *et al.*, 2002; Szwed *et al.*, 2011). And, in more recent papers, the visual-word-form-area is referred to as a visual word form "region" or "system" (Szwed *et al.*, 2011). Therefore, the neuro-anatomical correlates of the cortical region that has been referred to as the visual word form area does appear to span the middle part of the fusiform gyrus of the left hemisphere, rather than being lateralized particularly to the occipital temporal sulcus.

It has been proposed that the region encompassing the so-called visual word form area within the mid fusiform gyrus is involved in reading because it is in a position to receive top-down connections from other regions of the brain, such as the region of the angular gyrus of the language-dominant hemisphere (Price & Devlin, 2011). One aim of the study described in Chapter four was to explore the relationship between the angular gyrus region and the region of the posterior inferior temporal cortex during word reading, and to examine a potential functional interaction between them during word reading in healthy individuals.

1.5 Aims and Overview

The primary aims of this thesis were: (1) to design functional magnetic resonance imaging task paradigms that would elicit activation in the angular gyrus during specific circumstances of reading and writing so as to clarify the extent to which the angular may be involved in both of these processes; (2) to understand the morphology of the angular gyrus region with more precision than is currently available when referring to currently available anatomical atlases; (3) to reconcile the difference between the neurological model of reading, which emphasizes the angular gyrus as the critical neural structure, and the more modern neuroanatomical models of reading, which highlight instead the region of the mid-fusiform gyrus (i.e. the region of the so called visual word form area).

In this thesis, the neural substrates of reading and writing were investigated in healthy subjects using structural and functional magnetic resonance imaging. In Chapter two, we examined the role of the angular gyrus region under various conditions of writing and its relationship to the superior parietal lobule. We were able to examine the role of the angular gyrus in writing and its relationship with the superior parietal lobule because of the anatomical study described in Chapter three, which is a detailed anatomical study of the angular gyrus region within the inferior parietal lobule, including the provision of probability maps of the sulci of the inferior parietal lobule in the Montreal Neurological standard stereotaxic space, which is the coordinate space most commonly used to report the location of functional neuroimaging peaks of activation. In Chapter four, we performed a functional neuroimaging study of reading in order to localize reading-related activation in the region of the angular gyrus with greater precision, again drawing on the anatomical knowledge gained from the study reported in Chapter three. We explored the functional relationship between the reading-related activations within the angular gyrus and the region of the mid-fusiform gyrus, which is an area of the brain that has recently been described as a visual word form area.

1.6 Figures

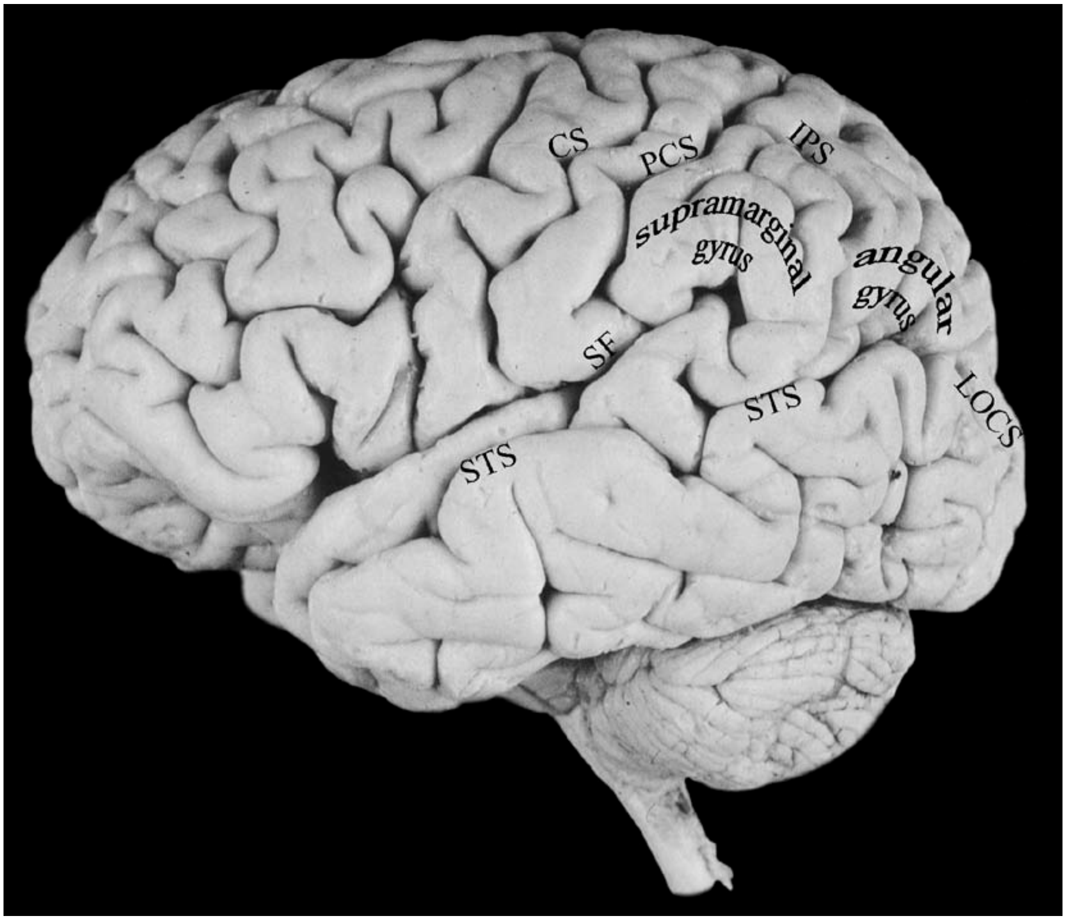


Figure 1.1 The left cerebral hemisphere of the human brain, photographed from its lateral aspect. Labels that can be found identifying the sulci and gyri are those that are relevant to the parietal lobe. CS central sulcus; IPS intraparietal sulcus; LOCS lateral occipital sulcus; PCS postcentral sulcus; SF Sylvian fissure; STS superior temporal sulcus.

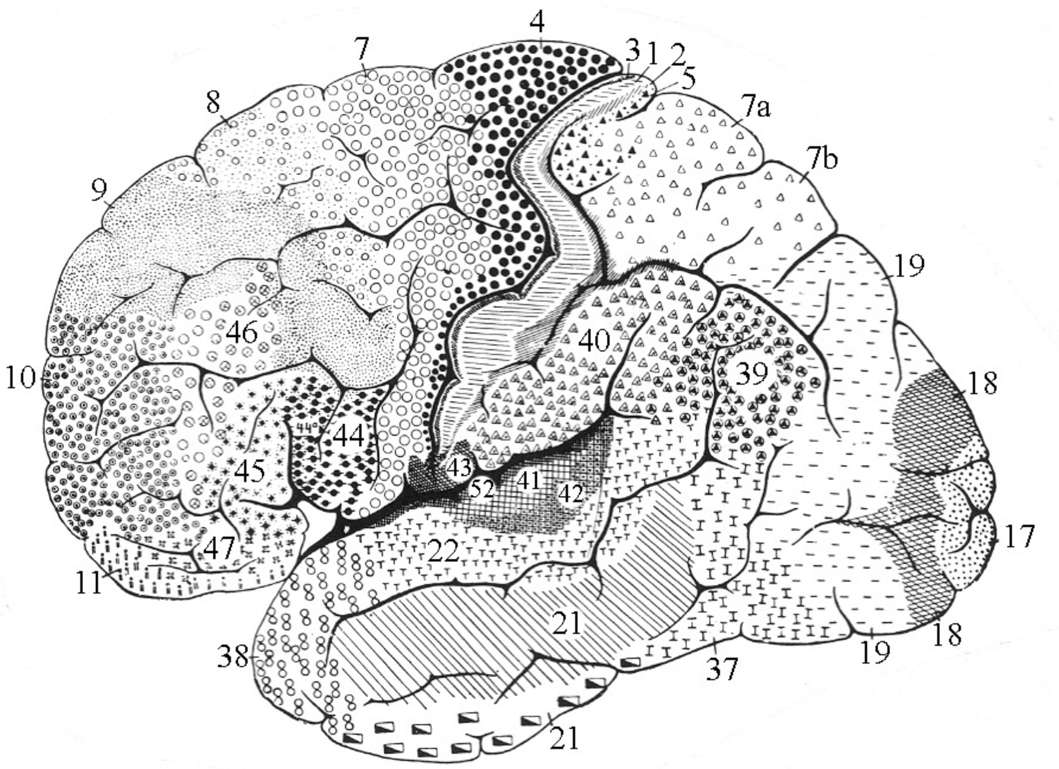
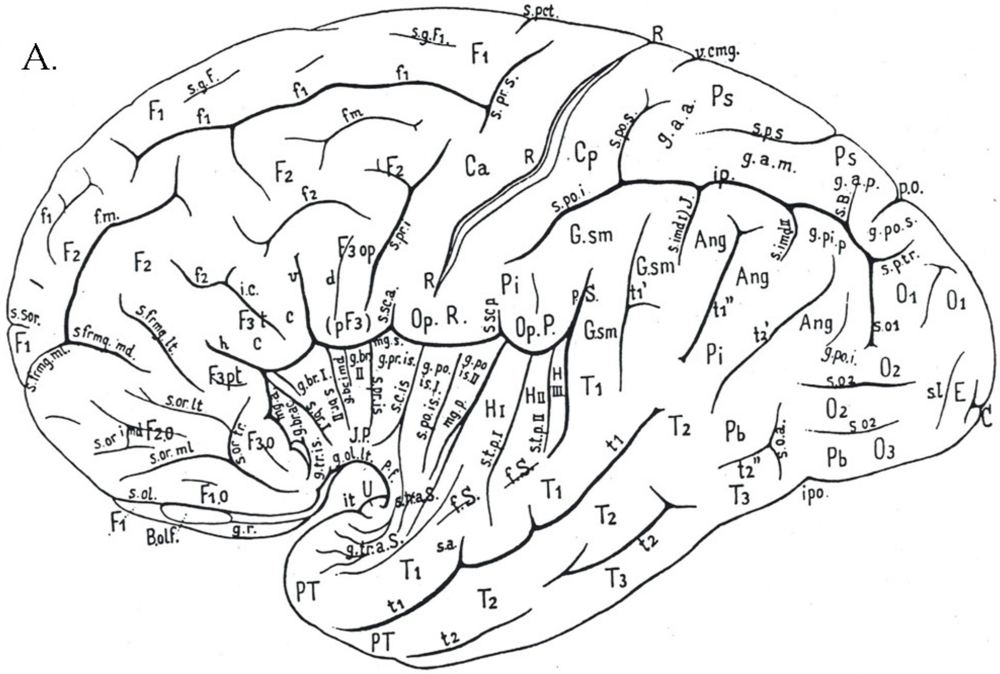


Figure 1.2. Cytoarchitectonic map of the left cerebral hemisphere by Brodmann (1909). Areas 3, 1, and 2 comprise the anterior parietal cortex. Areas 5 and 7 (a and b) comprise the superior aspect of the posterior parietal cortex and areas 40 and 39 comprise the inferior aspect of the posterior parietal cortex. Note how the superior temporal sulcus ascends into the inferior parietal lobule as a single sulcus, around which can be found cytoarchitectonic area 39.

A.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Ps
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g.a.p.
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g.po.s.
f1
f.m.
F2
F2
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i.c.
F3 op
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T1
g.po.i.
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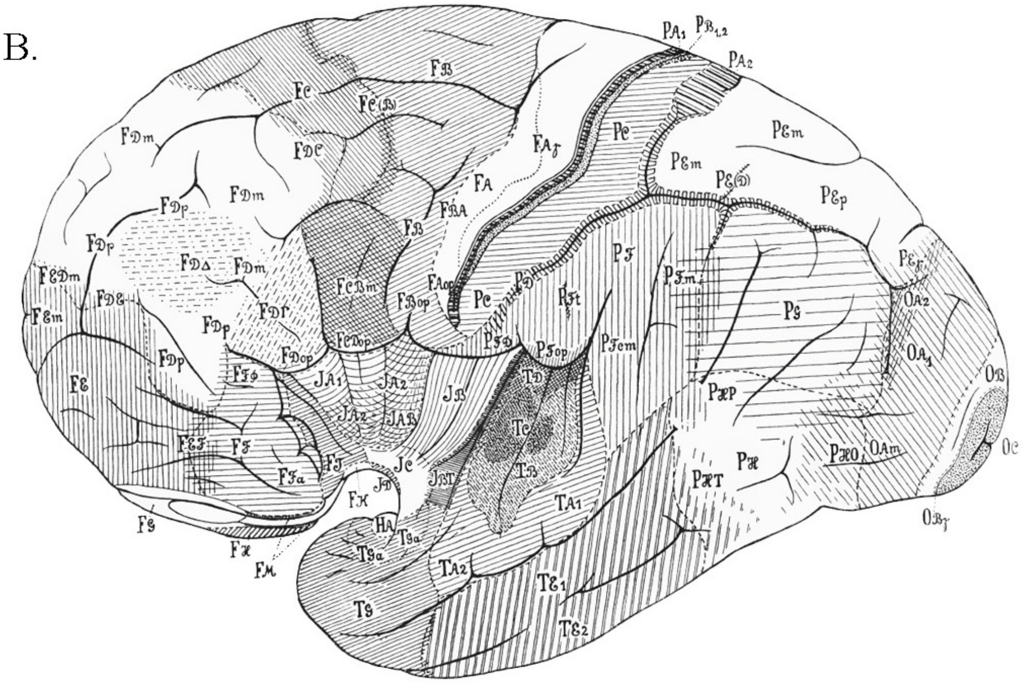
B.


PA1
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FB
PF
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FCBm
FAop
Pc
PFt
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PEF
FEDm
FDE
FDΓ
FBop
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OA1
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JA1
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JB
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Figure 1.3. Sulcal and gyral, and cytoarchitectonic maps of the left cerebral hemisphere by Economo & Koskinas (1925). Panel A. The sulci and gyri of the lateral cerebral cortex. Note that the superior temporal sulcus (t1) appears to have a relationship with two sulci in the inferior parietal lobule (t1', t1''), but the definitive relationship between these sulci and the superior temporal sulcus is not provided. Panel B. The cytoarchitectonic areas of the posterior parietal cortex and their relationship to surrounding sulci can be appreciated. Area PE occupies the superior parietal lobule, while areas PF and PG occupy the inferior parietal lobule. The posterior parts of area PF surround the most anterior sulcus found within the inferior parietal lobule (t1'), while area PG is bound by the middle and posterior sulci (t1'' and t2'). PF cytoarchitectonic area PF; PFm cytoarchitectonic area PFm; PFcm cytoarchitectonic area PFcm; PG cytoarchitectonic area PG.

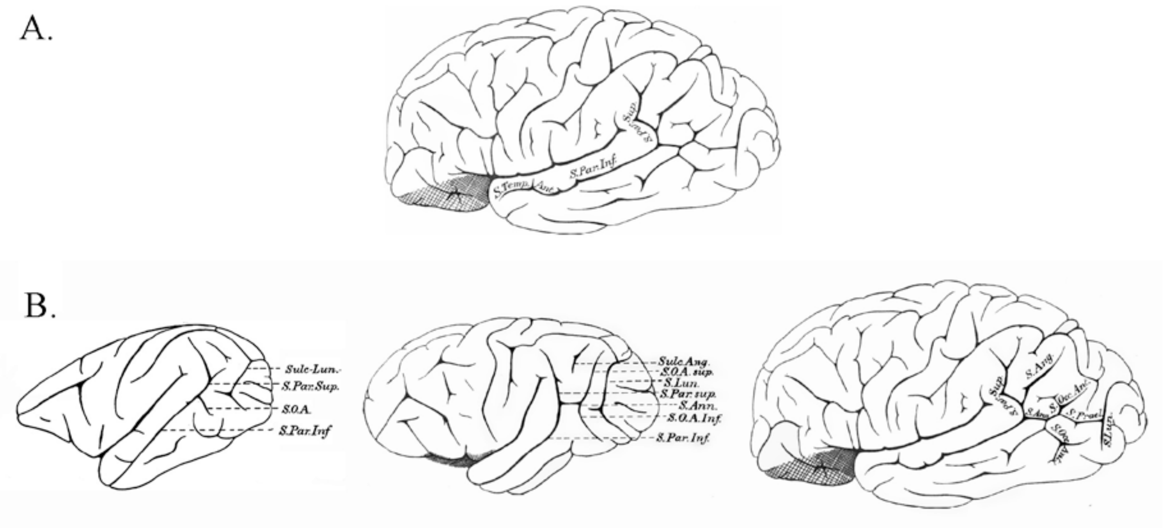

Figure 1.4. The evolutionary development of superior temporal sulcus (historically also called the parallel sulcus) according to Joseph Shellshear (1927). Panel A. The superior temporal sulcus can be divided into three segments in an anterior-to-posterior direction. S. Temp. Ant. anterior temporal sulcus; S. Par. Inf. *inferior parallel sulcus*; S. Par. Sup. *superior parallel sulcus*. Panel B. There is a great deal of expansion in relation to the superior parallel sulcus that takes place in human brain, which is illustrated by comparing the brains of the gibbon, orangutan and the human (from left to right). From the posterior wall of the superior parallel sulcus in lower primates (such as the gibbon), the anterior occipital sulcus (AOCS), here labeled as SOA, is extruded in the brains of higher primates (such as the orangutan and human), and is divided into an inferior and a superior branch. The dorsal AOCS stays within the inferior parietal lobule, while the ventral AOCS is located in the posterior temporo-occipital cortex. In the orangutan, the angular sulcus has made its appearance between the superior parallel sulcus and the dorsal AOCS, and in the human brain the angular sulcus is even more prominent. S. Ang. sulcus angularis; S. Ann, annectant sulcus; S. Lun. lunate sulcus; SOA and S.Occ. Ant., anterior occipital sulcus; S.O.A. sup superior part of the anterior occipital sulcus; S.O.A. inf inferior or ventral part of the anterior occipital sulcus; S. Par. Inf. inferior parallel sulcus; S. Par. Sup. superior parallel sulcus; S. Prael. prelunate sulcus; Sulc. Ang. angular sulcus.

Chapter Two

2. The anterior superior parietal lobule and its interactions with language and motor areas during writing

Segal E., and Petrides M. (2012) The anterior superior parietal lobule and its interactions with language and motor areas during writing. *The European Journal of Neuroscience, 35 (2)*, 309-322.

2.1 Abstract

Past neuroimaging studies of writing demonstrate activation foci in several regions of the posterior parietal cortex (PPC). The present study aimed to dissociate the role of the superior parietal lobule (SPL) from the other PPC regions using functional magnetic resonance imaging (fMRI) and functional connectivity. First, parametric event-related fMRI permitted the categorical comparison of experimental writing conditions with control conditions that were carefully chosen to match the experimental conditions in terms of variables extraneous to the motor act of writing, such as visual stimulus characteristics, and generating and retrieving verbal information. A selective focus of increased activation in the PPC restricted to the rostral part of the SPL (area PE) in the left hemisphere was demonstrated. Subsequently, functional connectivity analysis showed that area PE flexibly interacts with different language areas depending on the linguistic demands of the writing task. Activity in area PE correlates with the left angular gyrus, a region implicated in reading, when the writing is in response to words that are read; in sharp contrast, when the writing is in response to pictured objects, then area PE correlates with the supramarginal gyrus, a region involved in the articulatory and phonological loop, as well as with prefrontal regions that are involved in the retrieval and selection of semantic information. The results suggest that area PE serves as a critical interface between posterior cortical regions in the left hemisphere involved in language processing and the central motor and sensory regions that are directly involved in the control of movement.

2.2 Introduction

The ability to write has been associated, traditionally, with the functional and structural integrity of the lateral posterior parietal cortex (PPC) in the language-dominant hemisphere (Critchley, 1953; Geschwind, 1970). However, the primate PPC is a large expanse of cortex, extending from the postcentral sulcus (i.e. posterior to the primary somatosensory cortex) to the parieto-occipital fissure, and consists of several subareas that can be differentiated architectonically (Brodmann, 1909; Economo & Koskinas, 1925; Pandya & Seltzer, 1982; Petrides & Pandya, 1984; Matelli et al., 1998; Caspers et al., 2006) and functionally (Critchley, 1953; Sakata et al., 1973; Mountcastle et al., 1975; Taira et al., 1990; Rizzolatti et al., 1997; Culham et al., 2006). Evidence that the PPC is important for writing has come largely from classic studies of patients who suffered cerebrovascular accidents (Dejerine, 1914; Critchley, 1953; Geschwind, 1970; Auerbach & Alexander, 1981; Otsuki et al., 1999). Sometimes a dissociation within the PPC is made between those lesions involving the angular gyrus that produce a writing impairment with impaired reading (agraphia with alexia; Dejerine, 1914; Critchley, 1953; Geschwind, 1970) and those involving the superior parietal lobule (SPL) that produce impaired writing (apraxic agraphia; Auerbach & Alexander, 1981; Otsuki et al., 1999). Clinical case studies, however, cannot specify the areas of the architectonically and functionally differentiated PPC that are critically involved in writing because the damage is extensive and encompasses several (if not all) subdivisions of PPC, many adjacent cortical areas, and white matter below the cortex that inevitably will disconnect various areas from each other.

Functional neuroimaging permits the investigation of changes in activity within specific parts of the brain that are involved in particular cognitive and behavioral processes, including writing, in normal subjects. Past neuroimaging studies report many writing-related foci of activation within the PPC, including foci in the SPL, in the supramarginal gyrus of the inferior parietal lobule, as well as in the intraparietal sulcus (Katanoda et al., 2001; Matsuo et al., 2001; Menon & Desmond, 2001; Beeson et al., 2003; Rektor et al., 2006; Sugihara et al., 2006). This is not surprising given the fact that much of the parietal lobe plays a role in the control of action in space (Mountcastle et al., 1975; Georgopoulos et al., 2005; Goodale & Milner, 2005). What is now necessary is to design studies that attempt to define the role of specific parts of the PPC in particular aspects of the writing process. The present study addresses the role in writing of the rostral SPL, a specific subdivision of the PPC, as an interface between the somato-motor system that is involved in action in space and a separate system involved in linguistic processes, such as reading and naming. The rostral SPL should support writing insofar as it has privileged direct cortico-cortical connections with the sensorimotor system, on one hand, and the various areas of the superior and inferior parietal cortex on the other (e.g. Pandya & Seltzer, 1982; Petrides & Pandya, 1984; Matelli et al., 1998).

2.3 Materials and methods

Ethics statement

This study was approved by the Montreal Neurological Institute’s Research Ethics Board. Informed, written consent was obtained from all participants according to the guidelines set forth by the Ethics Committee of the Montreal Neurological Institute.

Subjects

Nine healthy right-handed volunteers (six males), average age 26 ± 3.72 years, participated in the study. All subjects were bilingual – four of the subjects learned English as their second language (either with German, French or Chinese as mother tongues), but all worked and/or studied exclusively in English. For the purpose of performing this task there were no differences between English learned as a first or second language.

Experimental design

The experimental conditions of interest involved writing. In order to isolate regions of the brain crucially involved in the central act of writing, we included control conditions that would engage brain regions related to peripheral aspects of writing, such as basic visual processing, attentional requirements, naming, reading and word retrieval, as well as basic movements of the hand and eyes. Subjects performed the writing tasks and the control tasks during successive blocks of five trials. A written instruction appeared on the screen to inform the subjects about the task they would be performing. The subjects knew that after five trials a new set of instructions would appear. Each trial lasted 4.5 s. A variable intertrial interval (ITI) of 2.5–7.5 s allowed us to treat individual trials for each task as separate events during the statistical analysis. Stimulus presentation was programmed and controlled with E-Prime Software 1.1.

Writing the names of pictures of objects task minus writing control task (Wr - NmL)

These tasks were designed to isolate the regions of the brain that are related to the act of writing the name of a pictured object, i.e. a word retrieved mentally in response to a visual stimulus. Both of these conditions involved written output in response to a pictured object. During the Writing task (Wr), the subjects were presented with the pictures of objects (different object on each trial), and they had to generate silently the name of the object and to write it. By contrast, in the writing control task (NmL), the subjects were also presented with the picture of an object (different object on each trial), and they also had to generate silently the name of the object, but instead of writing the name they would have to draw a loop for each syllable of the item’s name (Figure 2.1). For example, if a picture of an apple was presented, the subject would draw two loops (ap ⁄ ple); if by contrast a spoon was pictured, the subject would draw one loop (see Table 1 for a list of stimuli). The pictures of the objects were presented in a random order in the center of the screen on a gray background. Each stimulus picture appeared on the screen for a fixed duration of 4.5 s. The subjects had the entire 4.5-s duration to perform the required task. A fixation cross appeared during the ITI, which separated the trials for a variable duration of 2.5–7.5 s.

Copying English words task and copying control tasks (CpE - RdL and CpE - CpNs)

These tasks were designed to isolate the regions of the brain that are related to the act of copying an English word. All of these conditions involved writing in response to words. During the copying English words task (CpE), the subjects were presented with an English word (different word on each trial), and they had to read it silently and then copy it. For the reading plus loops (RdL) control task, the first of the two control tasks, the subjects were also presented with an English word (different word on each trial), and they also had to read it silently but, instead of writing it, they had to draw a loop for each syllable of the word (Figure 2.1). For example, if the word ‘angel’ was presented, the subject would draw two loops; if the word ‘salt’ was presented, the subject would draw one loop. For the copying nonsense control task (CpNS), the second of the two control tasks, the subjects were presented with a pseudo-English word (different word on each trial) that they had to read silently as best they could and then write it. These pseudo-words resembled English words in that they were composed of English letters and obeyed the rules of English for word formation and thus could be ‘pronounced’, but they had no meaning (e.g. danga). The pseudo-words used in this condition were in fact real African words (e.g. Afrikaans words and Wolof words), but their meaning was inaccessible to our English-speaking subjects who did not know those African languages. Thus, for the purpose of this study, these words are nonsense English words (see Table 1 for a list of stimuli). Each word stimulus was presented for a fixed duration of 4.5 s. The subjects had the entire 4.5-s duration to perform the required task. A fixation cross signaled the end of the trial.

In all five conditions, the subjects wrote their responses for all five conditions using a pencil and a pad of paper. On the day of scanning, the subjects received a short training session of about 15 min during which they practiced, in a random counterbalanced order, all five conditions that they would have to perform in the scanner. The subjects were instructed to write their responses on the same spot on the page (i.e. one word was written on top of the other) in order to limit hand and wrist movement, and to limit the need to recruit additional cognitive functions such as monitoring the spatial layout of the page. Because the subjects were not seeing the written responses as they were lying in the scanner and writing, there was no possibility of visual interference of one word being written on top of the other. During the practice session, the subjects practiced writing words and drawing loops while looking away from what they were writing because, they were told, during the scan they would not be able to see their written responses as they would be lying supine in the scanner with the writing pad out of view at their side. Subject performance was monitored closely during the training session. All subjects performed at 100% accuracy, and it was assumed that the same performance would be executed during the scan.

During the scanning session the subjects were given a pencil with which to write their responses and a pad of paper that rested at their right side near their thigh. They therefore could not see what they were writing. They were instructed to write words in their normal writing style, either printing in lower-case or capital letters or in cursive, more or less at the same spot on the page, just as they had practiced. The experimenter went into the scanner to give the subjects a new sheet of paper before each scanning run, and to collect the sheet of paper used during the previous run to verify as much as possible that subjects were in fact performing the tasks.

The picture stimuli were chosen at random to be representative of common everyday objects (e.g. heart). The English word stimuli were basic nouns that represented common objects (e.g. house). The nonsense word stimuli (African words) were words that were pronounceable but had no meaning for our English-speaking subjects (e.g. haemb). All of the subjects reported that they could easily recognize the pictured objects and generate their names, and all of the subjects stated that they were familiar with all of the English words but did not recognize as familiar any of the nonsense words presented to them. No condition was reported as being more difficult or easier than any other. The conditions had a mean number of approximately 60 words or 60 pictures presented (63 pictures to write; 62 pictures to name silently and draw loops; 60 English words to copy; 58 English words to read silently and draw loops; 63 nonsense words to copy). Stimulus names were not repeated across conditions; i.e. picture names were never also printed words. The stimuli for a given task were chosen by the computer program in a random counterbalanced way throughout the runs. The English and nonsense words and the pictured object names were matched in terms of number of letters (F = 1.838, df = 4, 363, ns) and number of syllables (F = 1.338, df = 4, 363, ns). The matching of the words and names in terms of number of letters and syllables was necessary to equalize the motor act across the various conditions.

Magnetic resonance imaging (MRI) acquisition

All imaging was acquired on a 1.5-T Sonata MRI Scanner (Siemens, Erlangen, Germany). After a high-resolution T1 anatomical scan (whole head, 1-mm3 isotropic resolution), six runs of 145 images each (38 oblique T2* gradient echo planar EPI images covering the whole head; 3.4 x 3.4 x 3.4 mm; time to repeat 3.5 s; time to echo 45 ms) sensitive to the blood oxygen level-dependent (BOLD) signal were acquired. Each run comprised a total of 50 trials – the conditions were presented in blocks of five trials, which repeated twice in a random counterbalanced order for a total of 10 trials per condition per run. For example, one condition began with an instruction that was followed by five trials, followed by new instructions for the next condition that was followed by five trials, etc., until the subjects performed the five different tasks, twice. One run lasted approximately 9 min. Subjects performed seven runs (except for one subject who performed six runs).

Data analysis

Categorical subtractions

To establish which brain regions are involved in the act of writing the names of objects, we compared the BOLD signal of the writing task with that of the naming plus loops task (Wr - NmL). To establish which brain regions are involved in the act of writing English words, we compared the BOLD signal of the copying English words task with that of the reading English words plus loops task (CpE - RdL). In the same category, we also compared the BOLD signal of the copying English words task with that of copying nonsense (actually African) words task (CpE - CpNs), to see if any differences could be observed for writing familiar and meaningful words in comparison to novel unfamiliar words.

Statistical analysis

Medical Images NetCDF (MINC) images were acquired of the structural T1 scan and of the functional runs. The first three volumes of each functional run were excluded due to T1 saturation effects. Functional images were first realigned with an AFNI image registration software (Cox & Jesmanowicz, 1999), and then smoothed using MINC blur software that applied a 6-mm full-width halfmaximum (FWHM) isotropic Gaussian kernel. With respect to the moving hand inside the magnetic field, while it would be possible that the hand movement may have contributed to micro head movement, the voxel sizes that were acquired during the functional scans are several orders of magnitude larger. Factor in blurring and spatial averaging and small displacements < 1 mm or 1 degree will likely not have a significant impact. It would also be possible for there to be some field distortions due to motion (e.g. for the field distortion to be different between the experimental writing conditions and their control conditions). To correct for distortion due to motion, the functional images as well as the T1 anatomical image were linearly registered to the Montreal Neurological Institute (MNI) standardized stereotaxic space using in-house software, which is based on multiscale, 3D cross-correlation with an average MR image volume aligned with the MNI stereotaxic space (Collins et al., 1994). Functional data for each subject were then superimposed onto the subject’s structural scan to visualize the anatomical regions that had a correlated increase in BOLD activity during the various tasks as measured by the functional scans.

Statistical analysis of the functional data was performed with fmristat (Worsley et al., 2002). The analysis model was built for an event-related design with six conditions (five tasks plus the ITI). We excluded from the model the temporal period during which the instructions were presented. For all tasks, trial durations were 4.5 s, and ITI durations varied between 2.5 and 7.5 s. The scanner acquired whole-brain images at a fixed repetition time (TR) of 3.5 s. This produced desynchrony between TR and trial onset time, which allowed for there to be sufficient sampling across the hemodynamic response function. The statistical analysis of functional (f)MRI data was based on a general linear model (GLM) with correlated errors. The design matrix of the GLM was convolved with a hemodynamic response function modeled as the difference of two gamma functions timed to coincide with the acquisition of each slice. Temporal drift was removed by adding a cubic spline in the frame times to the design matrix (one covariate per 2 min of scan time), and spatial drift was removed by adding a covariate in the whole volume average.

The correlation structure was modeled as an autoregressive process of degree 1 (Bullmore et al., 1996). At each voxel, the autocorrelation parameter was estimated from the least squares residuals using the Yule–Walker equations, after a bias correction for correlations induced by the linear model. The autocorrelation parameter was first regularized by spatial smoothing with a 15-mm FWHM Gaussian filter, and then used to ‘whiten’ the data and the design matrix. The linear model was then re-estimated using least squares on the whitened data to produce estimates of effects and their standard errors, as well as t-statistics for each comparison of interest.

In a second step, runs, sessions and subjects were combined using a mixed-effects linear model for the effects (as data) with fixed-effects standard deviations taken from the previous analysis. This was fitted using residual error maximum likelihood implemented by the estimation maximization algorithm. A random-effects analysis was performed by first estimating the ratio of the random-effects variance to fixed effects variance, and then regularizing this ratio by spatial smoothing with a 15-mm FWHM Gaussian filter for runs and a 10-mm FWHM Gaussian filter for subjects. The variance of the effect was then estimated by the smoothed ratio multiplied by the fixed-effects variance to achieve higher degrees of freedom. More information on the fMRI analysis is available at http://www.math.mcgill.ca/keith/fmristat/.

The resulting t-statistic images were thresholded using the minimum given by a Bonferroni correction, random field theory and the discrete local maximum, taking into account the non-isotropic spatial correlation of the errors. Significance was determined on the basis of exploratory and directed search as well as on the basis of the spatial extent of consecutive voxels. A cluster volume extent > 697 mm3 with a t-value of > 3 was significant ($P < 0.05$), corrected for multiple comparisons for directed search using the method of Friston et al. (1995). For a single voxel in an exploratory search involving all peaks within an estimated gray matter of 600 cm3 covered by the slices, the threshold for reporting a peak as significant ($P < 0.05$) was $t = 4.75$ (Worsley et al., 1996).

We also used fmristat to assess whether the functional connectivity between the rostral SPL and other brain regions would be modulated by our tasks. The interaction method in fmristat is based on the method described by Friston et al. (1997). Functional connectivity is computed as the correlation across time of the BOLD signal between a reference voxel (e.g. a voxel that is chosen based on the previous categorical comparisons) and all voxels in the rest of the brain. The correlation per se is not of primary interest; the larger investigation is about how this correlation is modulated by the task (how brain regions strengthen or weaken their connectivity with each other as a function of a given task that the subject is being asked to perform). We identified a reference voxel in the left hemisphere in the rostral SPL where we reported differences in activity in the writing words minus control comparisons (i.e. cytoarchitectonic area PE). The voxel values were extracted for each subject from native space after having applied slice time correction. We used the GLM where we added regressors for the task events and drift, and then added a regressor for the time course at the reference voxel. We then added an interaction (product) between the task events and the reference voxel time course as a regressor. Finally, we estimated the effect, standard error and t-statistic for the interaction in the same manner as described above. Increased functional connectivity between the reference voxels and other voxels in the brain during the experimental writing trial compared with the control trial is represented by positive t-values.

2.4 Results

The five task conditions are abbreviated as follows: writing the names of pictured objects (Wr); naming pictured objects silently plus making loops (NmL); copying English words (CpE); reading English words silently plus making loops (RdL); and copying nonsense words (CpNs).

Categorical Comparisons

Writing the names of pictured objects (Wr - NmL)

In both of these conditions, the subjects saw pictures of common objects, had to retrieve the name of the item shown in the picture, and had to use pencil and paper to produce a written response. The only difference was that in the writing condition (Wr) the subjects had to write a word (retrieved name of the object shown in the picture), while in the control condition (NmL) the subjects had to write loops (one loop per syllable of the item's name). The subjects were instructed to draw the loops from left to right so as to simulate the motor act of writing the names of the items. Thus, the tasks were well matched in terms of visual perceptual input, retrieving object names (i.e. verbal retrieval), and in terms of basic motor and somatosensory processes, and differed in the fundamental variable of interest, namely the act of writing a word. The categorical comparison of activity in the two conditions should therefore identify areas centrally involved in the act of writing.

Comparison of the BOLD signal between the Wr and NmL conditions demonstrated increased activity during writing, unilaterally in the left hemisphere, in the rostral part of the SPL (-30, -46, 70, t = 4.79) and in the premotor cortex, as well as in the primary motor and sensory hand region. In addition, there was increased activity in the cingulate motor areas, the secondary somatosensory cortex (SII) in the upper bank of the Sylvian fissure and the insula, again unilaterally in the left hemisphere. In the right hemisphere, activity was restricted to the cerebellum (Figure 2.2; Table 2.2a).

Writing English words

In this writing task, subjects had to write (i.e. copy) an English word that they read (CpE). In order to identify brain regions critical for the act of copying words, and to differentiate these regions from those that are more generally involved in hand–arm movements and in reading, we first compared activity in the writing task (CpE) with that in the control condition involving reading English words silently and making loops (RdL). This control condition (RdL) differed from the copying task only in terms of its writing requirements. In both the experimental condition and in this control condition the subjects were presented with written English words, had to read the words silently, and had to use pencil and paper to produce a written response, but only in the experimental condition (CpE) did the subjects have to write down an English word; in the control condition (RdL) the subjects wrote a series of loops – one loop per syllable of the English word. The subjects were instructed to draw the loops from left to right so as to simulate the motor act of writing the words. The tasks were thus well matched in terms of visual input, linguistic processing related to reading words, and in terms of basic motor and somatosensory processes, and differed in the fundamental variable of interest, namely copying (i.e. writing) English words.

Just as in the task requiring writing the names of pictured objects (Wr - NmL), the comparison of CpE - RdL revealed increased activity, unilaterally in the left hemisphere, in the rostral part of the SPL (-22, -44, 62, t = 3.97) and in the premotor cortex, as well as in the primary motor and sensory hand region, the cingulate motor areas, the SII in the upper bank of the Sylvian fissure, and the insula. In the right hemisphere, activity was restricted to the cerebellum (Figure 2.3; Table 2.2b).

In summary, the comparison of the BOLD signal obtained during the act of copying English words that were read (CpE - RdL) produced essentially the same results as the comparison of BOLD signal obtained in the writing names of objects (Wr - NmL). Thus, regardless of whether the word to be written is generated by the subjects (i.e. retrieved names of objects) or read by the subjects, a common set of brain regions, in the left hemisphere, show increased activity during the act of writing words – the rostral part of the SPL (area PE) together with the premotor cortex and the primary and secondary motor and sensorimotor areas related to hand–arm control, as well as the cingulate motor areas. Direct comparisons between the experimental conditions confirms the involvement of rostral SPL in both writing tasks because when we compare the two writing conditions with one another directly (i.e. Wr - CpE and CpE - Wr), activity is no longer observed in the left hemisphere in the anterior region of the SPL (Tables 2.2c,d).

One could argue that differences exist between the experimental writing tasks and their control tasks of drawing loops in terms of the motor activity movements, and that these differences may account for some of the differences in BOLD activation. To investigate this possibility, eight of the nine subjects were asked to produce two loops per syllable, rather than one loop, during a second Naming control task (NmLL), thereby increasing the planning requirements and motor demands of this naming control task. The results of the Wr - NmLL comparison demonstrate the same peak in SPL observed previously, but a more limited extent of activity in sensorimotor cortical regions(Fig. 4; Table 2e). Thus, increasing the motor complexity of the control task reduces activation differences in the sensorimotor regions, but reveals the same peak in rostral SPL together with the reduced motor involvement.

In the second comparison involving copying English words, subjects were presented with a nonsense word that they had to read silently and then copy, i.e. write down (CpNs). This control condition was chosen specifically to differ from the copying English words task only in terms of its language requirements. In both the experimental condition of copying English words and in this control condition of copying nonsense words, the subjects were presented with written words, had to read the words silently, and had to use pencil and paper to write down the presented word. However, in the CpE condition, the subjects had to write down an English word, which they could read and understand, whereas in the CpNs control condition, the subjects had to write down a nonsense word, which they could read superficially (i.e. sound out) but could not understand. In addition, the English words differed from the nonsense words because the English words represent a series of letters, the sequence of which the subjects have experience writing, compared with the nonsense words that contain the same elements (i.e. alphabetic letters) but whose arrangement or sequence for writing is novel for our subjects as they had no previous experience writing these nonsense words.

The comparison of CpE - CpNs demonstrated increased activity in the inferior parietal lobule that was situated in the angular gyrus and in the posterior supramarginal gyrus, lateralized to the left hemisphere (Table 2.2f). Thus, when the comparison equalizes the act of writing in terms of a sequence of letters, but the experimental condition involves the writing of real comprehended words, inferior parietal activity (angular and supramarginal gyri) in the left hemisphere is observed.

Functional connectivity

The comparison of the experimental conditions requiring writing (writing the retrieved names of objects or copying words) with the appropriate control conditions demonstrated consistently greater activity in one specific part of the PPC in the left hemisphere – the rostral part of the SPL, which is occupied by a distinct architectonic area, namely area PE (Economo & Koskinas, 1925). The results from these categorical comparisons therefore indicate that area PE in the left hemisphere is involved in the writing of words, regardless of whether the words are presented visually (as in copying English words that were read) or generated internally (as in writing the names of objects that were shown as pictures). We therefore proceeded to examine whether activity in area PE in the rostral SPL is interacting with different brain regions in these two different contexts of writing. For example, during the act of copying English words, would area PE show increases in functional connectivity with the angular gyrus, a brain region implicated in reading, as a function of the requirement of reading and then writing down the word? We performed an interaction analysis of functional connectivity to try to answer these questions.

The reference voxel was selected from the peak in the anterior SPL (area PE) that showed increased activity in the writing object names minus naming objects (Wr - NmL) comparison. During the writing (Wr) condition, relative to the control (NmL) condition, the interaction analysis showed that the reference voxel increased its functional connectivity with the superior temporal gyrus (part of Wernicke's region) and the posterior part of the SPL, the depth of the intraparietal sulcus, the anterior supramarginal gyrus and the hand-knob region of the central sulcus where the somato-motor representation of the hand lies (Amiez et al., 2006) (Figure 2.5; Table 2.3a). Thus, during writing driven by the internal retrieval of a word, the rostral SPL peak increased its coupling with a part of Wernicke's region and various somato-motor parietal and central sulcus areas. By contrast, during the copying English words (CpE) condition relative to the control task (RdL), the rostral SPL reference voxel increased its functional connectivity with the angular gyrus, and the ventral frontal opercular cortical region (Broca's region) and a part of the middle temporal gyrus (part of Wernicke's area; Figure 2.6; Table 2.3b). Thus, writing words that one is reading requires interaction of the rostral SPL with the angular gyrus (reading region), while writing in response to internal generation of words does not require such interaction.

Direct comparison between the two writing tasks (Wr and CpE) using functional connectivity was also investigated, using the same reference voxel in anterior SPL (area PE). During the writing (Wr) condition, relative to the copying English words (CpE) condition, the interaction analysis showed that the reference voxel increased its functional connectivity (functional coupling) with dorsal motor and premotor areas, and with somatosensory areas, all in the left hemisphere. Within the parietal lobe, increased coupling was observed in the supramarginal gyrus, bilaterally (Figure 2.7; Table 2.3c). By contrast, during the reverse comparison of copying English minus writing (CpE - Wr), area PE increased its coupling with the angular gyrus in the inferior parietal lobe (Figure 2.8; Table

2.3d). Therefore, the results from the direct comparisons of writing minus copying English (Wr - CpE) and vice versa (CpE - Wr) show the same results.

2.5 Discussion

The key question posed in the present investigation was the following: which one of the many areas of the PPC is centrally involved in the act of writing? To isolate parietal activity related to writing independently of activity related to the processing of verbal information (as in reading) and retrieval of such information (as in naming) on which writing is necessarily based, we compared activity in two writing tasks with appropriate control tasks. These comparisons demonstrated that the rostral part of the SPL in the language-dominant left hemisphere is the key area involved in writing when word retrieval and reading are controlled for. The cortex of the rostral SPL comprises a distinct architectonic area, area PE (Economo & Koskinas, 1925), and the activity peak in this anterior region of the left SPL was shown to be a consistent focus during both experimental writing tasks. Experimental anatomical studies in the macaque monkey (Pandya & Seltzer, 1982; Petrides & Pandya, 1984; Morecraft et al., 2004) and diffusion tensor imaging studies in the human brain (Rushworth et al., 2006) show that the rostral part of the SPL, where area PE is located, is massively interconnected with the premotor hand–arm region, the supplementary motor cortex and the cingulate motor areas, via the first branch of the superior longitudinal fasciculus (Petrides & Pandya, 1984). Furthermore, single neuron recording studies in the monkey (Sakata et al., 1973; Mountcastle et al., 1975; Taira et al., 1990; Lacquaniti et al., 1995) and functional neuroimaging in human subjects (Sakata et al., 1973; Katanoda et al., 2001; Matsuo et al., 2001; Menon & Desmond, 2001; Beeson et al., 2003; Sugihara et al., 2006) as well as the clinical study of human patients (Critchley, 1953; Sakata et al., 1973; Mountcastle et al., 1975; Taira et al., 1990; Rizzolatti et al., 1997; Culham et al., 2006) have shown that this is an area important for reaching out and manipulating objects in space and knowledge of the body. These anatomical and functional facts suggest that area PE of the SPL is a critical part of the somato-motor system involved in coordinating action in space. The present results show that, in the language-dominant left hemisphere of the human brain, this high-level motor control area is a critical node in the somato-motor circuitry involved in writing.

It is important to point out here that we should not think of area PE in the rostral SPL in the left hemisphere as a writing center, but rather as an area of high-level motor control which, in the language dominant left hemisphere, is in an ideal position to interact with different language and motor areas during the act of writing. The first writing systems developed approximately 5000 years ago, far too short a period for the brain to have evolved a dedicated ‘writing area’. In other words, with the development of writing, a high-level somatomotor control area of the primate parietal cortex, area PE in the language-dominant hemisphere, may have been recruited to serve the act of writing. Earlier functional neuroimaging investigations of the neural substrates of writing also reported increased activity in the SPL of the language-dominant hemisphere, but this activation focus occurred together with increased activity within other parts of the PPC, such as the supramarginal gyrus and the intraparietal sulcus, leaving open the question of which part of the large and heterogeneous parietal cortical region is the critical one for writing. In the present study, no activity was observed in the inferior parietal lobule either in the supramarginal gyrus or in the angular gyrus when comparisons were made of each writing task with its carefully selected control task that controls for aspects of linguistic processing. This is not to deny that the inferior parietal cortex is involved in writing, but rather to dissociate the role of area PE in the SPL from those of areas PF (supramarginal) and PG (angular) in the inferior parietal lobule.

In addition to the rostral SPL, writing resulted in increased activation foci in the premotor cortex, as well as in the central sulcus region involving the primary motor and sensory hand–arm region. There was also increased activity in the cingulate motor areas, the SII in the upper bank of the Sylvian fissure and in the insula, again unilaterally in the left hemisphere. In the right hemisphere, activity was restricted to the cerebellum. These increases in the somato-motor circuitry of the brain are consistent with many earlier functional neuroimaging studies that examined activity related to writing (Sakata et al., 1973; Katanoda et al., 2001; Matsuo et al., 2001; Menon & Desmond, 2001; Beeson et al., 2003; Sugihara et al., 2006). Of particular interest here is the increased activity we observed in the premotor cortex because of the classic claim by Exner (1881) that there is a graphic frontal motor center. Roux et al. (2009) have recently reported that direct electrical stimulation of cortex just anterior to the primary motor hand area, namely in the premotor cortex (area 6), impaired writing without disturbing hand movements or other oral language tasks. The authors suggested that the premotor hand region is an important region in forming a link between orthography and the motor programs required for handwriting. This premotor region of the cortex is bidirectionally connected with area PE in the SPL (Petrides & Pandya, 1984), and reinforces the notion that area PE in the language-dominant hemisphere may be a central node coordinating the act of writing by interacting with language areas, on one hand, and premotor ⁄ motor areas on the other.

The specific contribution of area PE in writing was tested and confirmed with interaction analysis of functional connectivity. Having isolated the superior posterior parietal node in the left language dominant hemisphere that is critical during the act of writing (when verbal retrieval, reading and other semantic variables that could contribute to activation were strictly controlled), we proceeded to examine whether this region increased its functional interaction with various other left hemisphere parieto-temporal cortical areas known from the lesion and functional neuroimaging literature to be involved in verbal retrieval, reading and other linguistic ⁄ semantic processes.

We write in response to what we have just read (i.e. when we copy), or to what we have just heard, or in response to information that we have just retrieved from memory and are keeping in our verbal working memory. Therefore, we might expect area PE in the SPL to interact with different parietal, temporal and prefrontal areas depending on the context of the writing. Area PE in the left hemisphere, which controls motor activity in relation to writing should have the flexibility to interact with a number of brain areas involved in reading, verbal retrieval or subvocal articulation of speech, depending on the linguistic and cognitive demands of the writing task at hand. The interaction analysis (functional connectivity) demonstrated that area PE interacts with a subset of these brain areas under different conditions (Tables 2.2b and 2.3a). Interestingly, when the writing is in response to words that are read, area PE increases its functional interaction with the left angular gyrus in the posterior IPL, an area for which there is evidence from lesion studies (Dejerine, 1914; Benson, 1979; Hillis et al., 2001) that it is critically involved in the reading process. In sharp contrast, when the writing is in response to pictured objects, then the increased functional interaction is with the supramarginal gyrus in the anterior IPL, an area involved in the articulatory and phonological loop (Baddeley, 2003), as well as with prefrontal regions that are involved in the retrieval and selection of semantic information (Thompson-Schill et al., 1997; Petrides, 2002; Cadoret & Petrides, 2007). The functional connectivity results therefore confirm that area PE, situated in the anterior aspect of the SPL and identified as a region of high-order motor control, can modify its interactions with other cognitive areas in response to the linguistic and cognitive demands of a given writing condition.

The results of this study are based on a group of right-handed subjects and, naturally, the question arises as to whether the same pattern of results, i.e. lateralized to the left hemisphere, might also be found with left-handed subjects. We expect that, with left-handed subjects, we would find a focus of activation in rostral area PE in the right hemisphere, reflecting the fact that these subjects would be using their left hand to perform the tasks. However, we also predict a focus of significant activation in rostral area PE of the left hemisphere in left-handed subjects, at least in those with left hemisphere dominance for language. The reason for this prediction is that, anatomically speaking, area PE of the left hemisphere would be in a privileged location to interact with the language areas also in the left hemisphere. We suspect that because area PE of the left hemisphere directly communicates with area PE of the right hemisphere via the corpus callosum, then the activation focus of area PE in the left hemisphere would strongly co-vary with the focus of activation in area PE of the right hemisphere.

In conclusion, the present study has permitted the selective demonstration of area PE in the SPL of the language-dominant hemisphere as the critical high-level motor control area in the context of a left hemisphere somato-motor circuit involved in the act of writing. The functional connectivity results suggest that this region may serve as an interface between the cortical motor regions and the language regions in the brain. That the parietal lobe contributes to the motor aspects of writing is not surprising in light of electrophysiological recordings of the macaque demonstrating its role in the manipulation of objects in space (Sakata et al., 1973; Mountcastle et al., 1975; Taira et al., 1990; Lacquaniti et al., 1995; Georgopoulos et al., 2005). The non-linguistic role of PE in macaque monkeys in reaching and manipulating objects in space appears to have been adapted in the language-dominant hemisphere of the human brain to serve writing, which involves the use of hand action to produce a complex sequence of hand strokes that produce letters to convey linguistic meaning. Identifying these areas and studying how they work can affect how we attempt to rehabilitate patients who have developmental agraphia or acquired agraphia due to traumatic brain injury or other organic changes to the brain. It can also offer important insight into the fundamental nature of how and why we as humans can write. That monkeys and humans share this region is consistent with the fact that writing is a human skill recently acquired, which must imply that it recruits a general motor control area in the service of writing. A more basic capacity of the monkey appears to have been harnessed in the human brain to support writing, and this provides a glimpse into the evolutionary origins of the human capacity to write.

2.6 References

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2.8 Abbreviations

BOLD, blood-oxygen level-dependent; CpE, copying English words; CpNs, copying nonsense words; fMRI, functional magnetic resonance imaging; FWHM, full-width half-maximum; GLM, general linear model; ITI, intertrial interval; NmL, naming pictured objects silently plus making loops (one loop per syllable of the object’s name); NmLL, naming pictured objects silently plus making loops (two loops per syllable of the object’s name); PPC, posterior parietal cortex; RdL, reading English words silently plus making loops; SII, secondary somatosensory cortex; SPL, superior parietal lobule; TR, repetition time; Wr, writing the names of pictured objects.

2.9 Tables

Table 2.1. List of stimuli used for each condition

Writing the names of Pictured Objects (*Wr*)	**Naming plus Loops (*NmL*)**	**Naming plus Double Loops (*NmLL*)**	**Copy the English Words (*CpE*)**	**Copy the African Words (*CpNs*)**	**Reading plus Loops (*RdL*)**
anchor	apple	arrow	alley	akipe	archway
bananas	bagel	axe	banjo	alemb	angel
bat	basketball	backpack	belly	baesee	beans
belt	bed	balloon	blouse	bettai	bread
books	boat	baseball	building	baridi	buoy
boxes	bottle	bee	candle	biboi	candy
broom	briefcase	bell	canteen	chann	cape
cactus	butterfly	bag	carpet	chesch	cereal
cane	cake	broccoli	cheetah	chumvint	chicken
cap	canoe	bus	clock	chupoh	coffee
carrots	car	buttons	cow	dibe	crow
cat	cat	camel	curtain	dairds	depot
chair	chocolate	camera	doll	danga	eagle
cigar	comb	cards	easel	dukhar	edge
cookies	corn	cd	elbow	enend	emu
croissant	crown	cheese	ferry	elimu	fibre
cup	dice	cherry	fox	furndath	frame
dog	doorknob	cow	glass	garr	gnome
ear	earphones	donuts	graph	hapana	handle
egg	elephant	fan	hook	heko	house
envelope	eye	feather	insect	hata	islet
fence	fish	flag	jeans	rhonce	juice
flowers	flute	foot	kangaroo	haemb	kennel
folder	frog	fork	kite	kidog	knee

giraffe	glasses	fox	koala	kwa	ladle
gloves	goggles	golfball	leaf	kalite	leopard
grapes	guitar	gorilla	map	krupwaz	marble
hammer	hanger	grass	mill	kwahb	mosquito
harp	heart	hair	mountain	kabiss	nachos
horse	igloo	hand	nails	kesh	napkin
kettle	key	hourglass	needle	klaemb	noodles
kleenex	ladder	house	nymph	lenck	ocean
ladybug	lamp	iron	orchid	lesd	owl
lemon	lettuce	kiwi	paintbrush	lillmo	pebble
lion	lipstick	lighter	phoenix	mogh	pig
luggage	mirror	lobster	pool	masg	pudding
monkey	mouse	medal	quay	nozure	quiche
mushrooms	panda	moon	quill	nenn	quilt
pants	parrot	necklace	receipt	nax	relic
peanuts	pencils	oranges	rhubarb	nayes	river
penguin	piano	owl	saddle	nambiar	salmon
pie	pizza	pear	sand	nyams	sandal
plant	pumpkin	pen	satyr	paktaine	saucer
pylon	pyramid	pig	school	pwance	shepherd
rabbit	razor	pipe	skiis	paes	soap
ring	rooster	popsicle	spatula	ratibe	statue
scissors	shark	pretzels	stove	raiste	straw
shell	shoe	rainbow	sugar	shtoome	suit
shorts	shovel	saw	symbol	scoannth	ticket
slide	snail	scarf	tattoo	subrai	tongue
snake	soccerball	sheep	toes	simu	ukulele
socks	speakers	shell	town	takk	vacuum
spider	spoon	skeleton	urn	twambie	wagon
squirrel	stamp	snowflake	vault	tahfdhal	whale

stapler	table	snowman	walker	tungo	whistle
telephone	tent	star	whale	ugine	wok
throne	tire	tie	window	upesi	wrapper
toilet	tomato	tiger	worm	vaif	yogurt
tooth	trampoline	toaster	wrench	wallahi	
tree	turtle	nose	zoo	wasio	
umbrella	violin	whale		yani	
wallet	watch	whistle		yake	
	zebra	zipper		zoezi	

Table 2.2a Writing task minus naming plus loops task (picture stimuli)

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Dorsal premotor cortex (Area 6)	-56	-6	40	4.38
Dorsal premotor	-54	-2	42	4.28
Cingulate motor cortex	-4	-24	56	4.48
Cingulate motor cortex	-8	-28	44	4.12
Cingulate cortex	-4	-12	52	3.71
Cingulate sulcus	-8	-28	44	4.48
Thalamus (VPL)	-12	-22	6	6.55
Anterior putamen	-24	-8	2	4.28
Posterior putamen	-28	-22	8	4.85
Motor insula (caudal short insular gyrus)	-38	-2	12	4.17
Primary motor cortex (M1)	-38	-16	62	5.36
Primary somatosensory cortex	-32	-30	55	7.64
Primary somatosensory cortex	-50	-30	56	5.88
Rostral Superior Parietal Lobule (area PE)	-30	-46	70	4.79
Insula SII	-48	-26	20	4.69
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Cerebellum V follium	18	-52	-24	8.31
Cerebellum VI follium	26	-50	-26	7.84
Cerebellum	2	-66	-18	5.96
Cerebellum	10	-66	-46	5.41

All *t* statistics are significant at *p* <0.05 corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.2b Copying English task minus reading plus loops task (word stimuli)

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Dorsal premotor cortex (Area 6)	-24	-12	56	4.15
Ventral premotor	-60	-4	40	5.79
Cingulate motor cortex	-2	-12	52	4.31
Cingulate motor cortex	-8	-18	74	4.14
Cingulate motor cortex	-2	-24	54	4.94
Posterior putamen	-14	-24	4	3.24
Primary motor cortex (M1)	-56	-18	48	5.56
Primary Somatosensory cortex	-36	-28	62	7.77
Posterior insula/parietal operculum	-44	-34	20	5.28
Rostral Superior Parietal Lobule (area PE)	-22	-44	62	3.97
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Cerebellum	18	-52	-24	7.37

All *t* statistics are significant at *p* <0.05 corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.2c Writing the names of pictured objects minus copying English Words

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Anterior Insula/Broca’s area	-44	16	2	4.62
Area 46v	-46	36	8	4.56
Thalamus (VPL)	-12	-18	-6	4.14
Parahippocampal gyrus	-12	-34	-6	4.38
Fusiform gyrus	-28	-67	-12	7.03
“Visual Word Form Area”	-50	-48	-14	4.8
Visual association area	-24	-98	12	5.52
Visual association area	-14	-98	-2	5.77
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Anterior Insula/Broca's	34	18	0	4.86
Area 46v	50	36	9.8	5.40
Parahippocampal gyrus	16	-32	2	3.96
Fusiform	28	-72	-14	7.81
Visual association area	28	-96	18	6.25
Visual association area	12	-92	-8	8.17

All *t* statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.2d Copying English words minus writing the names of pictured objects

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Anterior temporal area, inferior	-50	-2	-34	4.99
Anterior temporal area, superior	-60	2	-10	5.53
Middle temporal area	-48	-38	0	4.45
Angular gyrus	-58	-64	26	5.29
Angular/Caudal IPL	-50	-72	44	4.99
Midline	*x*	*y*	*z*	*t statistic*
Medial PG	0	-60	42	6.74
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Anterior temporal area, inferior	66	-4	-20	5.78
Anterior temporal area	66	-22	-26	5.66
Anterior temporal area	58	8	-28	5.23
Area 9	20	44	40	6.8
Angular gyrus	58	-56	26	4.9
Angular/Caudal IPL	48	-72	42	6.56

All t statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.2e Writing the names of pictured objects minus naming plus double loops task (pictures)

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Cingulate motor cortex	-4	-24	68	4.08
Cingulate sulcus	-4	-30	44	4.08
Thalamus (VPL)	-12	-22	4	3.40
Primary motor cortex (M1)	-26	-16	64	5.47
Primary somatosensory cortex	-26	-28	72	5.94
Primary somatosensory cortex	-34	-30	56	6.11
Primary somatosensory cortex	-50	-26	56	4.33
Rostral Superior Parietal Lobule (area PE)	-34	-50	64	4.29
Insula SII	-46	-26	20	4.04
Visual area 19	-44	-78	32	3.66
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Cerebellum, VI follium	26	-50	-24	5.47

All t statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.2f Copying English words minus copying nonsense words

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Broca's Area	-50	22	-8	3.07
Angular gyrus	-58	-66	26	3.78
Supramarginal gyrus	-66	-52	24	3.52

All *t* statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.3a Functional Connectivity: copying English words minus reading plus making loops

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Area 10	-26	60	14	3.05
Area 47/12	-48	34	-4	3.14
Area 46	-36	38	10	3.27
Broca’s area	-42	16	-4	3.41
Premotor area	-46	4	6	3.55
SII	-40	-16	20	3.37
Caudal STS	-66	-16	-6	3.41
Pulvinar/Posterior lateral thalamus	-24	-30	12	2.73
Area 8	-10	-32	76	3.09
Cingulate	-6	-38	48	2.86
Caudal STS	-62	-50	10	3.37
Angular	-46	-68	38	2.95
Angular	-36	-68	42	3.00
Cuneus/Calcarine	-16	-70	14	3.14
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Area 10	22	64	6	2.91
Anterior Cingulate	4	44	42	3.46
Cingulate	10	44	10	3.41
Area 6DR	24	14	44	3.50
Pulvinar/Posterior lateral thalamus	28	-22	12	3.23
Caudal sylvian fissure	56	-30	20	3.96
IPL	60	-42	54	3.05
SPL	20	-44	74	3.23
IPS	46	-48	62	2.95

Posterior area PGp	40	-70	40	3.82
Posterior Superior Parietal Lobule	28	-72	52	3.41
Posterior inferior temporal-occipital	42	-76	8	3.37
Posterior calcarine	8	-86	2	2.91

All t statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.3b Functional Connectivity: writing the names of pictured objects minus naming plus loops

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Anterior circular sulcus/insula	-24	24	12	2.99
Cingulate motor area	-8	-14	74	4.19
Primary motor area	-32	-14	68	3.61
Primary motor area	-36	-20	65	3.19
Anterior Inferior Parietal Lobule	-44	-26	36	2.92
Superior Parietal Lobule	-36	-36	68	3.80
Superior Parietal Lobule	-30	-50	74	5.46
Superior Parietal Lobule	-28	-52	56	5.73
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Primary Motor	52	-16	36	2.76
Primary Motor	20	-24	66	3.65
Superior Parietal Lobule	16	-46	62	2.84
Superior Parietal Lobule	8	-54	62	2.95
Posterior Superior Parietal Lobule	34	-66	60	2.84

All *t* statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.3c Functional Connectivity: writing the names of pictured objects minus copying English words

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Area 45	-42	26	10	2.8
Area 8	-36	16	50	2.98
Cingulate motor area	-2	-2	50	3.21
Cingulate motor area	-2	-14	62	3.88
Dorsal premotor hand area	-34	-12	66	3.71
Dorsal premotor hand area	-44	-12	46	3.83
Superior Parietal Lobule	-30	-50	74	5.12
Superior Parietal Lobule	-28	-52	56	6.36
Supramarginal gyrus	-60	-32	44	3.09
Visual area 19	-26	-76	38	2.64
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Dorsal premotor hand area	58	-16	44	3.27
Supramarginal gyrus	60	-34	30	2.98
Inferior parietal lobule area 40	38	-36	48	3.26

All t statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

Table 2.3d List of peaks: Functional Connectivity: Copying English words minus writing the names of pictured objects

	MNI Coordinates			
Left Hemisphere	*x*	*y*	*z*	*t statistic*
Area 10	-18	60	2	3.31
Anterior Cingulate Cortex	0	28	36	2.77
Angular gyrus	-44	-64	34	3.01
Medial area PG	-8	-48	34	3.01
Posterior Inferior Temporal area	-46	-74	6	2.72
Retrosplenial	0	-56	4	2.77
Right Hemisphere	*x*	*y*	*z*	*t statistic*
Prefrontal area 8	48	26	36	2.96

All *t* statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system that is based on the Talairach and Tournoux (1988) stereotaxic space.

2.10 Figures

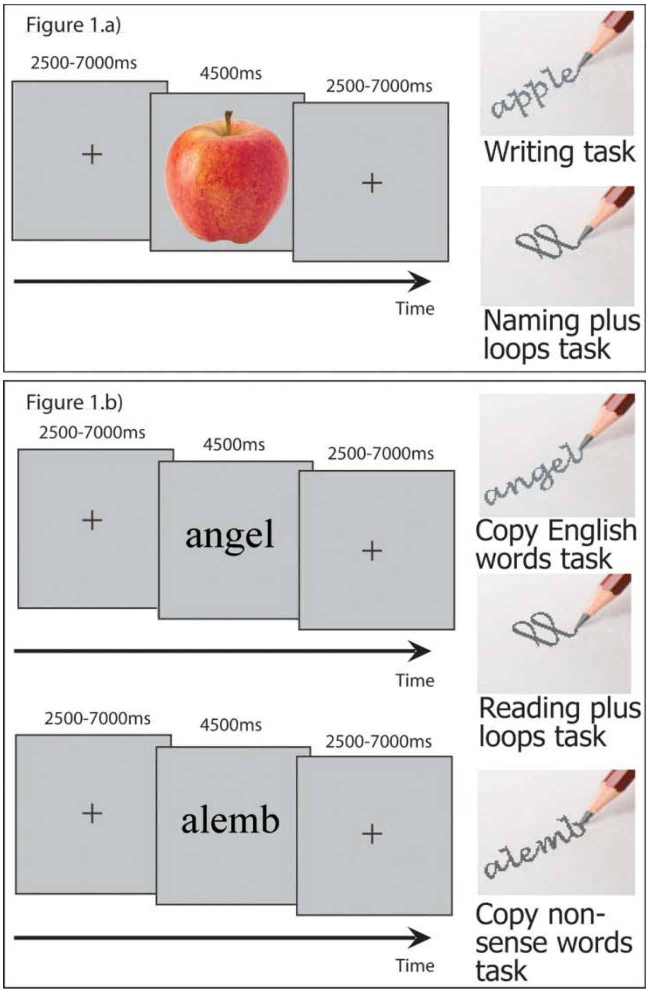

Figure 2.1. Task paradigm. Subjects performed five task conditions. (A) Two of the task conditions used pictures as stimuli: writing down the name of a pictured object (Wr); and its control task, naming a pictured object and making one loop per syllable of the object's name (NmL). (B) Three conditions used words as stimuli: copying the English word (CpE); and its two control tasks, reading the English word and making one loop per syllable of the word (RdL), and copying the nonsense words task (CpNs).

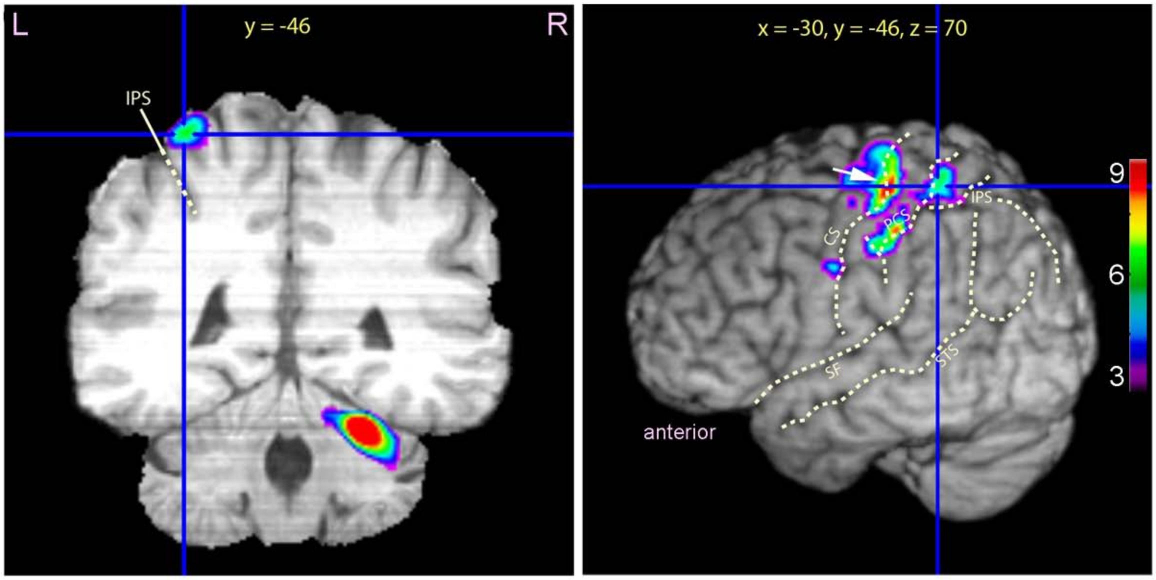

Figure 2.2. Writing minus naming plus loops (Wr - NmL). BOLD activity resulting from the subtraction of the writing task minus the naming plus loops task. The average BOLD activity from all subjects is presented in a selected coronal section (left), and on the 3D surface reconstruction (right) of a single subject’s anatomical scan. Activity is observed in the motor and somatosensory cortex around the hand region of the central sulcus of the left hemisphere (see activity around the dotted line labeled CS, central sulcus, and indicated by an arrowhead on the 3D lateral view), and in the rostral portion of the SPL (area PE) also of the left hemisphere (activity at the intersection of the two blue lines on the coronal section taken at y = -46 and the 3D lateral view of the brain). The coordinates of the activation related to area PE in MNI standard stereotaxic space are x = -30, y = -46, z = 70. Activity in the right hemisphere is limited to the cerebellum (Table 2.2a). Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

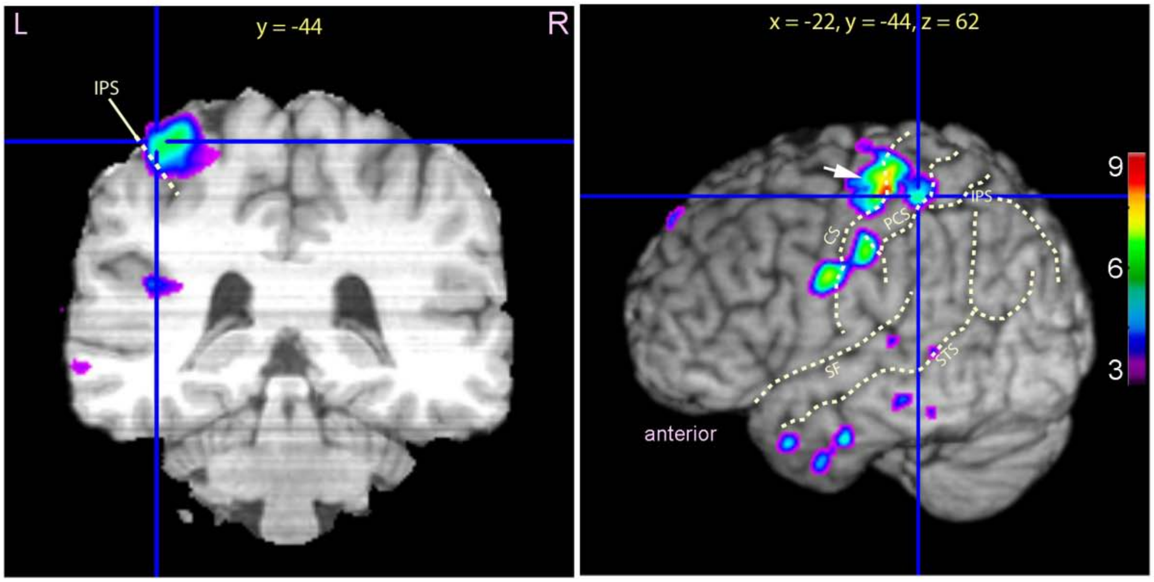

Figure 2.3. Copying minus reading plus loops (CpE - RdL). BOLD activity resulting from the subtraction of the copying English words task minus the reading plus loops task. Average BOLD activity from all subjects is presented on a selected coronal section (left) and on the 3D surface reconstruction (right) of a single subject's anatomical scan. Activity is observed in the primary motor and primary somatosensory cortex of the left hemisphere (see the activity around the dotted line labeled CS, central sulcus, and indicated by an arrowhead on the lateral 3D view), and in the rostral portion of the SPL (area PE) in the left hemisphere at MNI standard stereotaxic space coordinates x = -22, y = -44, z = 62 (activity around the intersection of the two blue lines on the coronal section and the 3D view of the brain). Activity in the right hemisphere is limited to the cerebellum (Table 2.2b). Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

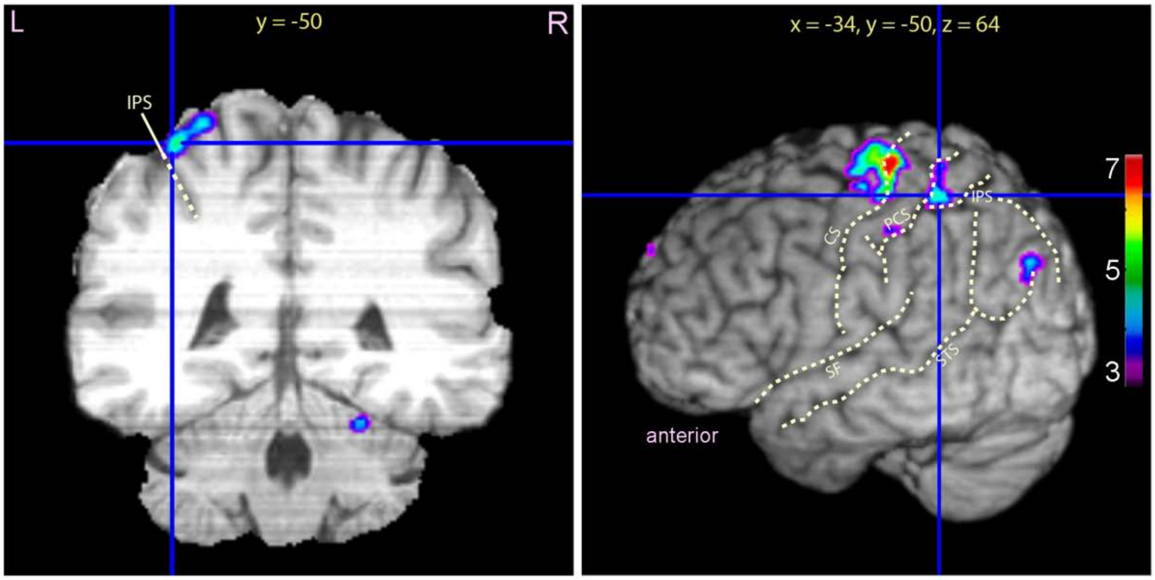

Figure 2.4. Writing minus naming plus double loops (Wr - NmLL). BOLD activity resulting from the subtraction of the writing task minus the naming plus double loops task, which was another control task (NmLL) that served to increase the motor and cognitive demands of the original control task (NmL). Subjects had to draw twice as many loops per syllable as before, thereby requiring from the subjects more monitoring and a greater number of hand movements. Average BOLD activity from all subjects is presented on a selected coronal section (left) and on the 3D surface reconstruction (right) of a single subject's anatomical scan. Activity continues to be observed in the primary motor and primary somatosensory cortex of the left hemisphere (see the activity around the dotted line labeled CS, central sulcus, on the 3D lateral view), and in the rostral portion of the SPL at coordinates x = -34, y = -50, z = 64 (area PE) also of the left hemisphere (activity at the intersection of the two blue lines on the coronal section and the 3D view of the brain). Activity in the right hemisphere is again limited to the cerebellum (Table 2.2e). Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

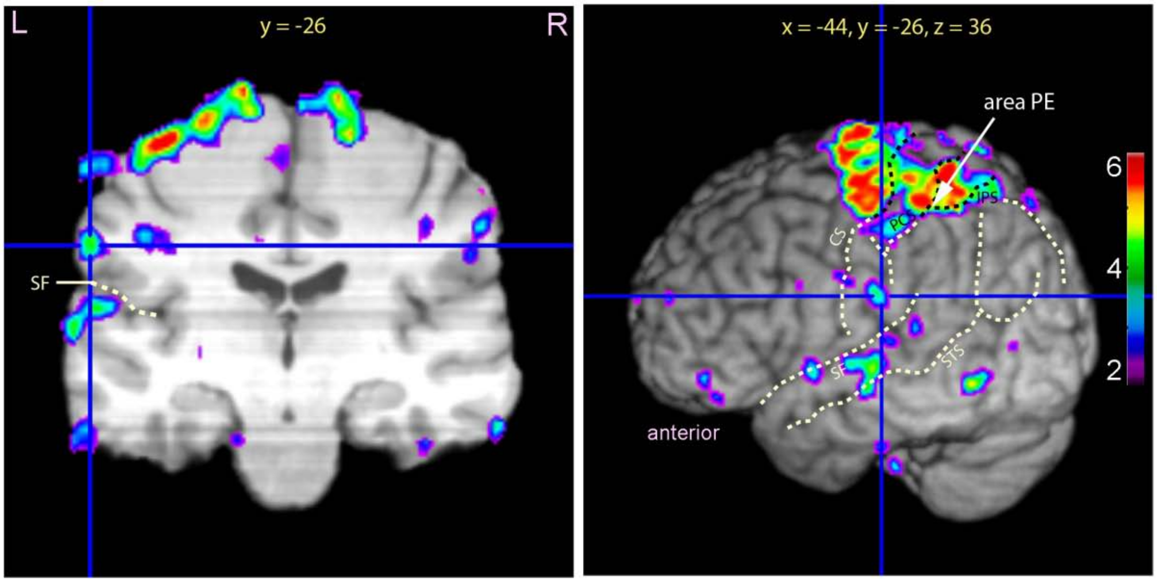

Figure 2.5. Functional connectivity: writing minus naming plus loops (Wr - NmL). A peak in rostral SPL (area PE) of the language-dominant hemisphere (i.e. left hemisphere) was identified by the categorical subtractions for both writing conditions minus their control conditions (i.e. Wr - NmL; and CpE - RdL). The rostral SPL peak (see arrow for the location) was the reference voxel for the functional connectivity analysis. The results show that, when subjects write down the name of the pictured object, this reference voxel increases its functional connectivity with the anterior part of the supramarginal gyrus (see the activity around the intersection of the two blue lines on the coronal and 3D view of the brain). The supramarginal gyrus is an area of the brain involved in the subvocal rehearsal of verbal information (the phonological loop) (Table 2.3a). The coordinates of the activation related to the anterior supramarginal gyrus in MNI standard stereotaxic space are x = -44, y = -26, z = 36. Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

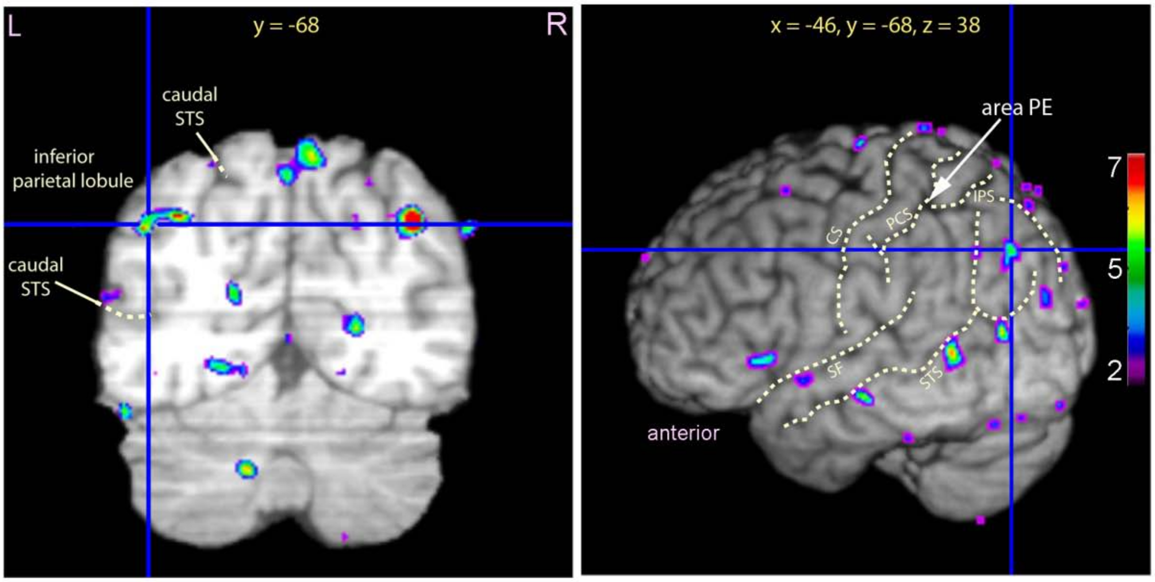

Figure 2.6. Functional connectivity: copying English words minus reading plus loops (CpE - RdL). A peak in rostral SPL (area PE) of the language-dominant hemisphere (i.e. left hemisphere) was shown to have increased activity in response to both writing conditions minus their control conditions (i.e. Wr - NmL; and CpE - RdL). The rostral SPL peak (see arrow for the location) was entered as the reference voxel for the functional connectivity analysis. The results show that, when the subjects write down (i.e. copy) an English word that they read, this reference voxel increases its functional connectivity with posterior language areas in the brain that are related to reading, such as the angular gyrus region (MNI coordinates x = -46, y = -68, z = 38) at the caudal aspect of the STS (see the activity around the intersection of the two blue lines) and with the anterior areas of the brain related to language production, such as the pars triangularis and opercularis of the ventrolateral frontal cortex (Table 2.3b). Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

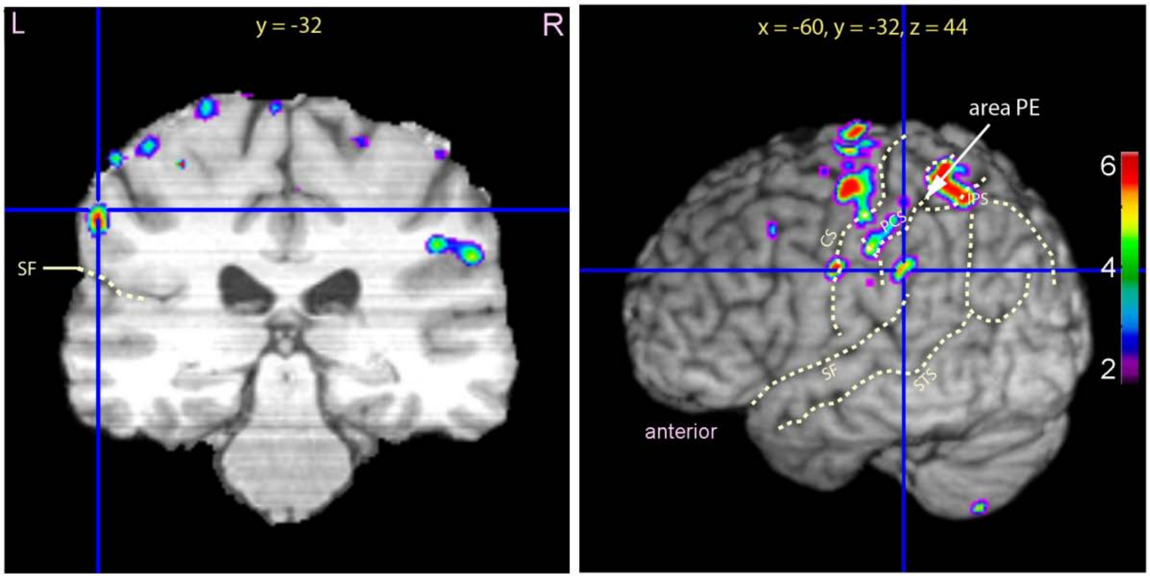

Figure 2.7. Functional connectivity: writing the names of pictured objects minus copying English words (Wr - CpE). A peak in rostral SPL (area PE) of the language-dominant hemisphere (i.e. left hemisphere) was shown to have increased activity in response to both writing conditions minus their control conditions (i.e. Wr - NmL; and CpE - RdL). The rostral SPL peak (see arrow for the location) was entered as the reference voxel for the functional connectivity analysis. The results show that, when subjects write down (i.e. copy) an English word that they read, this reference voxel increases its functional connectivity with areas in the brain that are implicated in the subvocal rehearsal of verbal information (the phonological loop), such as the anterior supramarginal gyrus (see the activity around the intersection of the two blue lines at MNI standard stereotaxic coordinates x = -60, y = -32, z = 44) (Table 2.3c). Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

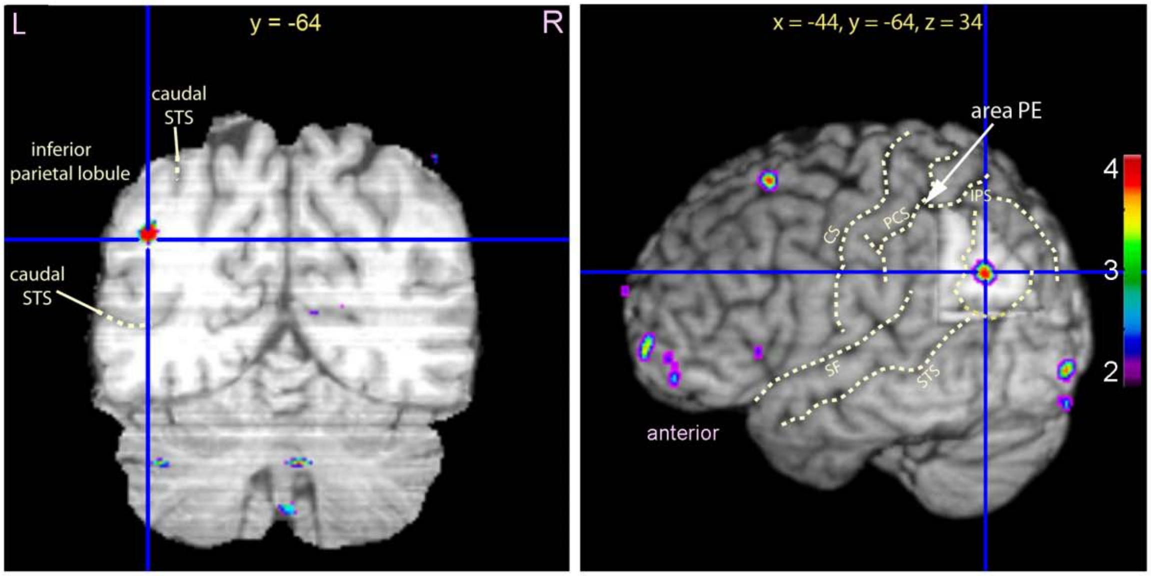

Figure 2.8. Functional connectivity: copying English words minus writing the names of pictured objects (CpE - Wr). A peak in rostral SPL of the language-dominant hemisphere (i.e. left hemisphere) was shown to have increased activity in response to both writing conditions minus their control conditions (i.e. Wr - NmL; and CpE - RdL). The rostral SPL peak (see arrow for the location) was entered as the reference voxel for the functional connectivity analysis. The results show that, when subjects write down the name of a pictured object, compared with when they write down (i.e. copy) an English word that they read, this reference voxel increases its functional connectivity with areas in the brain that are important for reading, such as the angular gyrus region (see the activity around the intersection of the two blue lines at MNI standard stereotaxic coordinates x = -44, y = -64, z = 34) (Table 2.3d). Abbreviations: CS, central sulcus; IPS, intraparietal sulcus; L, left hemisphere; PCS, postcentral sulcus; R, right hemisphere; SF, Sylvian fissure; STS, superior temporal sulcus.

Chapter Three

3. The morphology and variability of the caudal rami of the superior temporal sulcus

Segal E., and Petrides M. (2012). The morphology and variability of the caudal rami of the superior temporal sulcus. *The European Journal of Neuroscience, 36 (1),* 2035–2053

3.1 Prelude

Our first functional study (Chapter two) demonstrated a functional interaction between area PE and the region of the angular gyrus during word writing. We were interested in determining where precisely within the angular gyrus region reading-related activation could be localized. The angular gyrus is traditionally defined as the gyrus surrounding the caudal superior temporal sulcus (cSTS) as the cSTS ascends into the inferior parietal lobule. However, the anatomy of the parietal extent of the cSTS is complex, and is inconsistently characterized by most of the leading atlases of the human brain, making it difficult to relate functional activity to local sulcal landmarks within the angular gyrus region. We were therefore limited in our ability to comment with any relative precision on the structure-function relationship between the region of the angular gyrus and the processes of reading and writing. It became apparent that in order to explore further the functional contribution of the angular gyrus to reading and writing, it would be necessary first to characterize the anatomy of the angular gyrus region. Therefore, we performed a detailed investigation of the anatomy of the angular gyrus region in a large sample of MRIs of human brains.

3.2 Abstract

The caudal branches of the superior temporal sulcus (cSTS) have been difficult to characterize because of the considerable degree of morphological variability across individuals. Leading atlases of the human brain are inconsistent with each other in terms of the number of branches identified and the nomenclature used to refer to them. Examination of the magnetic resonance images (MRIs) of 45 human brains (90 hemispheres) demonstrates three branches of the cSTS that ascend into the inferior parietal lobule: an anterior branch (cSTS1), a central branch (cSTS2) and a posterior branch (cSTS3). The cSTS1 is found immediately posterior to the ascending limb of the Sylvian fissure, followed by the cSTS2, and then the last branch, cSTS3, at the parieto-occipital junction. The temporal part of the STS joins most frequently with the cSTS2 (approximately 60% of cases), the cSTS1 (approximately 30% of cases) and least frequently with the cSTS3 (approximately 10% of cases). At the temporo-occipital junction, there is another sulcus that is related to the STS, the ventral anterior occipital sulcus (AOCS-v), a sulcus that has been functionally linked to area MT/v5 in the human brain. While the STS may appear to join AOCS-v from the surface of the brain, it can be established from examination of the depth of the sulci that they are not continuous. The variability in location of each one of the cSTS branches is expressed quantitatively in the MNI standard proportional stereotaxic space.

3.3 Introduction

The morphology of the caudal part of the superior temporal sulcus (cSTS), which extends into the inferior parietal lobule (IPL), is complex in human brains. Comparative investigation (Shellshear, 1927) suggests that, from the single cSTS of lower primates (also called the superior parallel sulcus), two sulci are extruded in the human brain, the dorsal and ventral anterior occipital sulci (AOCS-d and AOCS-v). The AOCS-d remains within the IPL near the parietooccipital region, while the AOCS-v lies more ventrally at the temporooccipital junction. Between the newly extruded AOCS-d and the parallel sulcus from which it is extruded, a new fold is formed – the angular sulcus (see Figure 3.1). Thus, based on the evolutionary research of Shellshear (1927), we should expect three branches of the cSTS within the human IPL: an anterior branch behind the ascending limb of the Sylvian fissure, a posterior branch near the occipital region and a central branch running between them.

Most modern texts and atlases (e.g. Watson, 1995; Parent & Carpenter, 1996; Mai et al., 2007; Haines, 2008; Woolsey et al., 2008; Kiernan & Barr, 2009; Felten & Shetty, 2010) do not discuss the sulci of the IPL in any detail, and there are discrepancies between the few that do deal with them (Ono et al., 1990; Duvernoy, 1999). For example, schematic illustrations of the brain's lateral surface in both Duvernoy (1999) and Ono et al. (1990) represent two cSTS branches within the IPL. The schematic diagram in Duvernoy (1999, p. 7) labels two branches of the cSTS as the ascending and the horizontal posterior segments, while Ono et al. (1990, Ch. 2, p. 16) identify two cSTS branches as the angular sulcus and the anterior occipital sulcus. At first, it may seem that the same two branches are represented in these two atlases but under different names; closer examination indicates otherwise. The cSTS branch labeled as ascending by Duvernoy (1999) lies immediately behind the posterior ascending ramus of the Sylvian fissure (ascSF; see Duvernoy, 1999; sagittal sections, pp. 258–259). However, in Ono et al. (1990) a similar sulcus found just behind the ascSF is treated as an infrequent configuration of the STS and called the double parallel-type termination (Ch. 10, p. 77). The angular sulcus of Ono et al. (1990) now appears to refer to the horizontal posterior segment of Duvernoy. Thus, the above two atlases refer to two cSTS branches but they do not seem to identify the same two sulci (see Table 3.1 for summary). Clearly, the morphology of the cSTS requires re-evaluation. The aim of the present study was to investigate the morphology of the cSTS branches. We provide anatomical descriptions of the cSTS branches and their variability in relation to surrounding sulci, as well as probability maps of their stereotaxic coordinates in the standard space of the Montreal Neurological Institute (MNI), which is the commonly used space for modern functional and structural neuroimaging studies.

3.4 Materials and methods

MRI scans of 45 brains (90 hemispheres) from the MNI International Consortium for Brain Mapping (ICBM) database were randomly selected for the present investigation. The mean age of the subjects (27 male, 18 female) was 25.2 (±5.3) years (range: 18–40 years). Three of the subjects (one male, two female) were left-handed and the other 42 subjects were right-handed. The MRI scanning was performed with a 1.5-Tesla Philips Gyro scanner. First, stereotaxic registration of the MRI volumes was achieved using the average 305 linear symmetric target (Mazziotta et al., 2001). Cortical surfaces were extracted using the MNI CIVET pipeline (MacDonald et al., 2000; Kim et al., 2005; Ad-Dab'bagh et al., 2006). Registered MRI volumes were then visually examined and labelled using display, a freely available software program (MacDonald, 1996) which permits the simultaneous viewing of a brain in three 2-D sections (axial, coronal and sagittal planes) as well as the brain's 3-D surface. The software marks the location of a sulcus as the cursor is moved from voxel to voxel. When a chosen voxel is labelled in the coronal plane, for example, the voxel is also automatically labelled on the sagittal and axial planes. The voxel's labels are also updated on the 3-D surface. In this manner, when labelling sulci a thorough examination can be achieved because the sulci can be inspected both on the cortical surface and, importantly, within in the sulcal depth. This examination allows for an accurate examination of any submerged discontinuities in sulci that may appear as one continuous sulcus on the surface.

Probability maps

Probability maps were registered to and represented on a surface template in MNI ICBM 152 nonlinear space (Lyttelton et al., 2007). These probability maps provide a quantitative description of the location and variability of a sulcus at each x, y, z coordinate in MNI standard stereotaxic space. The sulcal labels that were created in the volume space for each brain were first transposed on to the individual cortical surfaces that had been registered to the MNI ICBM 152 nonlinear surface template (Lyttelton et al., 2007). As voxels were labelled within the cerebrospinal fluid that lies between the banks of a particular sulcus, the labelled region was first dilated to 1 mm to ensure enough coverage of the sulcus and its sulcal walls when it was transposed onto the registered cortical surface. The labels on the registered cortical surface vertices were then averaged together, for each hemisphere separately, and probability maps were computed by dividing the number of times that a labelled surface vertex was identified as a certain sulcus by the number of subjects examined. For example, a vertex at x, y, z MNI location with 100% probability value would mean that in every subject it was identified as part of the same sulcus. Thus, the probability values, displayed as color-coded maps, represent the likelihood that a given voxel is identified as a particular sulcus at a particular x, y, z location in MNI 152 nonlinear space (see Figure 3. 10).

To visualize the probability maps on an average cortical surface, we created an average mid-surface from the 45 subjects in this study (midpoint between the gray and white matter). An average of the registered mid-surfaces was created separately for the left hemisphere and for the right hemisphere. The probability maps of the sulci for the left hemisphere were then superimposed on the left hemisphere mid-surface average (45 hemispheres), and likewise the probability maps of the sulci of the right hemisphere were superimposed on the right hemisphere mid-surface average (45 hemispheres). In addition, we also regenerated surface averages by gender (an average asymmetric brain was comprised of 18 female left hemispheres and 18 female right hemispheres and an average asymmetric brain comprised of 27 male left hemispheres and 27 male right hemispheres (see Figures 3.11 and 3.12). Probability maps were then generated for the sulci that were identified in the brains of the female subjects and were superimposed on the average registered mid-surface female brain (see Figures 3.11A and C, and 3.12A and C); likewise, probability maps were generated for the sulci that were identified in the brains of male subjects and were superimposed on the average registered mid-surface male brain (see Figures 3.11B and D, and 3.12B and D).

Sulcal identification

In order to identify the branches of the cSTS, it is necessary to identify several nearby sulci that provide the boundaries of the region within which the four branches lie. These nearby sulci include the ascSF, the IPS, the anterior intermediate parietal sulcus (sometimes referred to as the anterior intermediate parietal sulcus of Jensen; aipsJ), the posterior intermediate parietal sulcus (pips), the parietal–occipital fissure (POF), the transverse occipical sulcus (TOCS), the lateral occipital sulcus (LOCS or prelunate sulcus) and the ascending limb of the inferior temporal sulcus (ALITS) ⁄ AOCS-v (see Figure 3.2). These are defined below (Iaria & Petrides, 2007).

The ascSF refers to a short sulcus that ascends more-or-less vertically from the most caudal aspect of the Sylvian fissure and is the axis around which the supramarginal gyrus is formed (see Figure 3.2).

The intraparietal sulcus (IPS) is the horizontally oriented sulcus that divides the parietal lobe into the superior parietal lobule and the IPL (see Figure 3.2).

The TOCS is found at the caudal extremity of the paroccipital part of the IPS (see Figure 3.2).

The LOCS or prelunate sulcus is a horizontal sulcus that extends anteriorly from the lunate sulcus (also called the sulcus prelunatus by Elliot Smith, 1907 and by Shellshear, 1927). The LOCS is found ventral to the TOCS (see Figure 3.2).

The aipsJ and the pips are relatively short, downwardly oriented sulci that branch off from the ventral aspect of the IPS (see Figure 3.2). The POF demarcates, mostly on the medial surface of the hemisphere, the parietal from the occipital lobe. It extends onto the lateral surface for a short distance (see Figure 3.2).

The AOCS-v is a sulcus in the posterior temporal region (at its border with the occipital lobe) that runs more-or-less vertically (see Figure 3.2). This sulcus, which is the ventral part of the AOCS (Shellshear,1927), has recently become the focus of considerable interest in functional neuroimaging studies because it is found to be related to the motion area MT (V5). It was called the ALITS in the first neuroimaging study that identified the motion region at the temporooccipital junction (Watson et al., 1993).

3.5 Results

Three sulci in the IPL were identified as related to the cSTS: an anterior branch, cSTS1, a central branch, cSTS2 and a posterior branch, cSTS3.

cSTS1

The anterior branch, cSTS1, is a long sulcus that originated in the caudal temporal lobe and coursing within the IPL just behind the ascSF. It could be visualized in sagittal sections that demonstrated clearly that it was emerging from the temporal lobe and the temporal part of the STS. The anterior branch extended dorsally to approach the IPS in 16.7% of hemispheres (13.3% left, 20.0% right) but it never continued into the IPS, as could be clearly established in horizontal sections that permitted examination of the relation of the intraparietal sulcal complex and the sulci of the inferior parietal region. In these few cases, the cSTS1 maintained a superficial relationship with the IPS and clearly did not originate from it (see Figure 3.3A–F). The cSTS1 could, in some cases, be confused with another totally separate sulcus that appears in the same region close to the IPL, namely the aipsJ. In cases of ambiguity, an examination of horizontal sections established which of the two sulci originated close to the IPS. Such an examination revealed that the aipsJ was clearly related to the IPS while the anterior branch of the cSTS originated from the temporal region and, only superficially, approached the IPS in a few cases.

The anterior branch (i.e. cSTS1) approached the termination of the Sylvian fissure and made superficial contact with it when viewed on the brain's lateral surface in approximately 15.5% of hemispheres (17.8% left, 13.3% right; see Figure 3.3G–L). The anterior branch was usually found anterior to the aipsJ; in only approximately 5.6% of hemispheres (2.2% left, 8.9% right) did the cSTS1 appear posterior to the aipsJ. When viewed on the brain's lateral surface, in approximately 30% of hemispheres (28.9% left, 31.1% right) the anterior branch could appear to join the aipsJ, but they were established to be separate entities because in horizontal sections it was clear that there was a submerged gyrus that separated the cSTS1 from the aipsJ (see Figure 3.4A–G). The anterior branch usually ran as a continuous sulcus but in approximately 8.9% of hemispheres (6.7% left, 11.1% right) it appeared to be in short broken segments. In approximately 32.2% of hemispheres (22.2% left, 42.2% right) the anterior temporal segment of the STS continued with the cSTS1. When viewed on the lateral surface of the brain, it could appear that the STS continued with the cSTS1 at a more frequent rate and in a more ambiguous way than what actually happened in the sulcal depths. For example, according to the lateral surface the STS could ambiguously appear to be joining with the cSTS1 along with the cSTS2, and in some cases along with the cSTS3, in an additional 13.3% of hemispheres (8.9% left, 17.8% right). It was therefore important to look into the sulcal depths to resolve the ambiguity about which of the cSTS branches the STS actually joined with (see Figure 3.4H–M). The MNI coordinates with the highest probability of being identified as the anterior branch were: for the left hemisphere, x = -55, y = -50, z = 35; and for the right hemisphere, x = 55, y = -41, z = 37 (see Figure 3.10A and Table 3.2).

cSTS2

The central branch, cSTS2, was found between the anterior and the posterior branches. Its dorsal extent approached the aipsJ in approximately 5.6% of hemispheres (4.4% left, 6.7% right; see Figure 3.5A–F) and the pips in approximately 11.1% of hemispheres (11.1% left, 11.1% right; see Figure 3.5G–L). In approximately 12.2% of the cases (15.6% of left hemispheres, 8.9% of right hemispheres), the central branch extended dorsally and touched the IPS. Again, this was a superficial relation and it was clear from examining the horizontal sections that the central branch did not originate from the IPS (see Figure 3.6A–F). In approximately 58.9% of hemispheres (62.2% left, 55.6% right) the temporal lobe segment of the STS joined with the central branch. When viewed on the lateral surface of the brain, it could appear that the STS continued with the cSTS2 at a more frequent rate and in a more ambiguous way than what actually happened in the sulcal depths. For example, according to the lateral surface the STS could ambiguously appear to be joining with the cSTS2 along with the cSTS1, and in some cases along with the cSTS3, in an additional 13.3% of hemispheres (4.4% left, 22.2% right) and it was therefore important to examine the sulcal depths to resolve the ambiguity about which of the cSTS branches actually joined the temporal segments of the STS (see Figure 3.6G–L). The MNI coordinates with the highest probability of being identified as the central branch were x = -44, y = -58, z = 37 and, for the right hemisphere, x = 47, y = -53, z = 35 (see Figure 3.10B and Table 3.2).

cSTS3

The posterior branch, cSTS3, was found behind the central branch of the cSTS. There could also be a short connecting (i.e. annectant) sulcus, running horizontally between this branch and cSTS2 (see Figure 3.7A–F). This annectant sulcus was often located at the point where the cSTS3 separated from the AOCS-v, a ventrally located sulcus in the temporooccipital junction. The terminal end of the posterior branch pointed towards the caudal part of the IPS and above the TOCS. In approximately 12.2% of hemispheres (11.1% left, 13.3% right), the cSTS3 approached the TOCS or the IPS, but examination of horizontal sections clearly demonstrated that the cSTS3 did not originate from either the TOCS or the IPS and that it was a separate sulcus (see Figure 3.7G–L). A reliable way to identify the posterior branch is to examine its terminal end, which usually points towards the POF (see Figure 3.8A–F).

In approximately 10.0% of cases (15.6% of left hemispheres, 4.4% of right hemispheres) the temporal lobe segment of the STS continued with the posterior branch. When viewed on the lateral surface of the brain, it could appear that the STS continued with the cSTS3 at a more frequent rate and in a more ambiguous way than what actually happened in the sulcal depths. For example, according to the lateral surface, the STS could ambiguously appear to join with the cSTS3 along with the cSTS2, and in some cases along with the cSTS1, in an additional 17.8% of hemispheres (15.6% left, 20.0% right). It was therefore important to examine the sulcal depths to resolve the ambiguity about which of the cSTS branches actually joined with the temporal lobe segment of the STS (see Figure 3.8G–M). The MNI coordinates with the highest probability of being the posterior branch were for the left hemisphere, x = -38, y = -72, z = 23 and, for the right hemisphere, x = 41, y = -64, z = 24 (see Figure 3.10C and Table 3.2).

Ventral to the posterior branch of the cSTS were two sulci: the AOCS-v and the LOCS. The AOCS-v approached the posterior branch of the cSTS in approximately 40.0% of cases (37.8% of left hemispheres, 42.2% of right hemispheres; see Figure 3.9A–F), and the LOCS approached the cSTS3 in approximately 33.3% of cases (33.3% of left hemispheres, 33.3% of right hemispheres; see Figure 3.9G–L). When the lateral surface of the brain was examined, the AOCS-v could appear to extend to the temporal segment of the STS and to join it superficially in approximately 3.3% of cases (6.7% of left hemispheres, 0.0% of right hemispheres). However, according to our study of the sulcal depths, the AOCS-v did not continue as a posterior continuation of the temporal segment of the STS. The AOCS-v and LOCS approached each other in approximately 24.4% of hemispheres (15.6% left, 33.3% right). The MNI coordinates with the highest probability of being identified as the AOCS-v were for the left hemisphere, x = -41, y = -70, z = 2 and, for the right hemisphere, x = 43, y = -63, z = 1 (see Figure 3.10D and Table 3.2).

Hemispheric asymmetry

The average probability maps of the cSTS1, cSTS2, cSTS3 and AOCS-v for all subjects were computed separately for the left and for the right hemispheres (see Figure 3.10A–D). The probability maps in the left hemisphere compared to the probability maps in right hemisphere show that, for all four of the cSTS branches, there is a posterior displacement of each cSTS branch in the left hemisphere compared to its counterpart in the right hemisphere (see the y co-ordinates in the left hemisphere vs. the right hemisphere in Figure 3.10A–D).

Gender differences

The average probability maps of the cSTS1, cSTS2, cSTS3 and AOCS-v were computed for female and male subjects separately. The probability map for the sulci in the female subjects was presented on the average female registered mid-surface and the probability map for the male subjects on the average male registered mid-surface (see Figure 3.11 and 3.12). There were no significant differences observed in the left hemisphere between males and females in terms of the x, y, z location of each one of the cSTS branches. In addition, in the right hemisphere, males and females did not appear to differ in terms of the x, y, z location of each one of the cSTS branches. However, both males and females showed a posterior displacement of the cSTS branches in the left hemisphere relative to the right hemisphere (see Figures 3.11 and 3.12), consistent with the overall finding of hemispheric asymmetry from the total-subject average noted above.

3.6 Discussion

The present study demonstrates that three branches of the cSTS can be identified in the IPL of the human brain: an anterior branch, cSTS1, a middle branch, cSTS2, and a posterior branch, cSTS3. When the lateral surface of the brain is examined, these branches may appear as the posterior continuations of the temporal segment of the STS that is running ventral and parallel to the Sylvian fissure. However, when the temporal segment of the STS is examined in the sulcal depth, it appears to continue into the inferior parietal region by joining with a single cSTS branch, with the other two cSTS branches emerging in close proximity. It most frequently joins with the cSTS2 (approximately 60% of cases), then with the cSTS1 (approximately 30% of cases) and, least frequently, with the cSTS3 (approximately 10% of cases). In addition to the three cSTS branches that ascend into the IPL, there is another cSTS branch that is more ventrally located in the temporo-occipital junction region, called the AOCS-v. When the lateral surface of the brain is viewed, the dorsal point of the AOCS-v may at times extend to reach the temporal segment of the STS and to join it superficially.

The most variable in location in MNI standard space is the cSTS1 (i.e. it has the lowest percentage of overlap in voxels belonging to this sulcus), followed by the cSTS2 and the cSTS3. This suggests that of the three cSTS branches that ascend into the IPL, the cSTS1 may be the most difficult to identify. In our study, the cSTS1 could be identified in every single hemisphere that was examined, based on the strict criteria that the cSTS1 is 1) a significant sulcus found immediately posterior to the ascSF and 2) it originates from the posterior temporal lobe region. The cSTS1 can sometimes be confused with the aipsJ, another sulcus that is sometimes present on the surface of the IPL in a location similar to that of the cSTS1. In such cases, the distinction can be made based on the fact that the aipsJ originates in the IPS, in contrast to the cSTS1 which originates close to the temporal lobe segment of the STS. In some cases the cSTS1 may appear to blend with the aipsJ on the surface of the hemisphere, and it is necessary to examine the sulcal depths using the 2-D volumes (e.g. in the horizontal plane) to establish the separation of the cSTS1 from the aipsJ.

The cSTS1 is probably one of the sulci most frequently misidentified in the IPL. Ono et al. (1990, Ch. 2, p. 77) refer to a double parallel type termination of the STS occurring infrequently (12% in right hemispheres and 4% in left hemispheres). Inspection of their figures shows that this double parallel STS termination may represent rare cases in which the cSTS1 is clearly separate from aipsJ and also some distance in its origin from the temporal component of the STS. We observe that the cSTS2 serves as the most frequent posterior continuation of the STS (in approximately 60% of cases). The cSTS2 may be identified by qualitative descriptive criteria, such as its relationship to surrounding sulci, and also quantitatively by its highest probable location in MNI standard stereotaxic space (see the Results section). Ono et al. (1990) identify this sulcus and refer to it, inconsistently, as the anterior occipital sulcus (Ono et al., 1990, Ch. 2, p. 10) or as the angular sulcus (Ono et al., 1990, Ch. 10, p. 78). Duvernoy (1999, p. 7) refers to it as the ascending part of the STS but, in the sagittal sections of the atlas, as the horizontal posterior part of the STS.

Relation to MT / v5

The sulcus that we have identified as the posterior cSTS branch (cSTS3) has been referred to historically by different names. This has created some confusion in the literature and fails to highlight its relation to the STS. For example, the cSTS3 has also been called the superior (dorsal) anterior occipital sulcus (AOCS-d; Smith, 1907; Shellshear, 1927; Cunningham & Romanes, 1981). This choice in nomenclature is most likely a reflection of the fact that the cSTS3 is a sulcus close to the border of the occipital lobe and the posterior parietal region, and the fact that the AOCS-v is a sulcus close to the border of the occipital lobe and posterior temporal region (Smith, 1907; Cunningham & Robinson, 1931). As pointed out in the introduction, evidence from the evolutionary study of Shellshear (1927) directly suggests that the anterior occipital sulcus (both the superior and ventral divisions) is a component of the STS. The cortex that was in the cSTS in the macaque monkey has expanded and has come onto the lateral surface of the brains of higher primates, including humans.

The cSTS in lower primates is a relatively deep and complex fossa of buried sulcal elements, rather than a simple and shallow cortical fold (Saleem & Logothetis, 2007; Paxinos et al., 2008). Electrophysiological recordings of the cortex buried within the cSTS in the macaque have revealed several functional areas that are involved in higher-order aspects of visual spatial processing and, in particular, the processing of motion. One of these motion areas was first studied in owl monkeys by Allman & Kaas (1971) and named MT, and in macaques by Zeki (1974) and named as area V5. In both species, the motion area was found in the posterior middle temporal region that is related to the STS. In owl monkeys, the STS is a simple dimple but, in the macaque, a deep sulcus. Because MT ⁄ v5 is consistently related to the region of the STS in both owl monkeys and macaques, it would be reasonable to assume that a comparable area in the human brain would also be anatomically linked to the STS, and would be similarly found at the junction of the occipital lobe with the parietal and temporal lobes. Various studies attempting to localize MT ⁄ v5 in the human brain using functional neuroimaging have demonstrated a peak of activation related to motion processing within this region (Zeki et al., 1991; Watson et al., 1993; Dupont et al., 1994; Tootell & Taylor, 1995; Tootell et al., 1995; DeYoe et al., 1996; Beauchamp et al., 1997; O'Craven et al., 1997; Culham et al., 1999; Dumoulin et al., 2000).

The activation related to MT ⁄ v5 in the human brain according to the neuroimaging studies is found consistently near a sulcus at the temporo-occipital junction, which has been called the 'ascending limb of the inferior temporal sulcus' (ALITS; Watson et al., 1993; Dumoulin et al., 2000). The sulcus labelled as ALITS, however, may refer to the posterior branch of the cSTS (cSTS3) or to the AOCS-v as we have defined them in the present study. For example, in Figure 6 in Watson et al. (1993), the activation related to MT ⁄ v5 is shown at the intersection of the base of cSTS3 and LOCS but in their Figure 7 the activity is shown at the intersection of AOCS-v and LOCS, leaving ALITS, ambiguously, to refer at once to both the cSTS3 and to the AOCS-v. The stereotaxic coordinates of MT ⁄ v5 as reported by Watson et al. (1993) (left hemisphere, x = -41, y = -69, z = 2; right hemisphere, x = 41, y = -67, z = 2) refer to the junction of the cSTS3, AOCS-v and LOCS. When the same coordinates are entered into the probability maps of the current study (Figure 3.10), they have an approximately 62% probability of being identified as the AOCS-v, and refer to a location just ventral to the probability map of the cSTS3 (see Figure 3.13A). If we now consider the location of MT ⁄ v5 within the buried cortex of the macaque STS, we should not expect to find MT ⁄ v5 in the human brain at the most dorsal part of cSTS3 (near the IPS) nor at the most ventral part of the AOCS-v, but rather at the intersection of these two related sulci that often blend with each other. This is exactly the location of MT ⁄ v5 according to the standard coordinates from functional neuroimaging studies.

Interestingly, a recent cytoarchitectonic examination of MT ⁄ v5 using histological sections from postmortem brains (Malikovic et al., 2007) has similarly determined that the MT ⁄ v5 region in the human brain is located at the junction of cSTS3, LOCS and the AOCS-v, which is the same area that is identified by the neuroimaging studies. If the stereotaxic coordinates from the cytoarchitectonic study (x = -43, y = -73, z = 10) are entered into the probability maps of the cSTS branches of the present study (Figure 3.10), again we arrive at the junction of the ventral part of the cSTS3 and the dorsal part of the AOCS-v (see Figure 3.13B). As previously pointed out, it is at the junction of these two cSTS branches that we would expect to find MT ⁄ v5 in the human brain. The fact that MT ⁄ v5, an area involved in motion processing is related to a cSTS branch agrees with what we know from classic lesion studies about the dorsal processing stream for spatial and motion information (Mishkin & Ungerleider, 1982).

Hemispheric asymmetry and gender differences

Asymmetry of certain temporal lobe structures, such as the length of the Sylvian fissure and the shape of the planum temporale, has been repeatedly reported (e.g. Geschwind & Levitsky, 1968; Wada et al., 1975; Galaburda et al., 1978; Ono et al., 1990; Steinmetz et al., 1990; Witelson & Kigar, 1992; Loftus et al., 1993; Habib et al., 1995; Duvernoy, 1999; Westbury et al., 1999; Toga & Thompson, 2003; Lyttelton et al., 2009). The present results also suggest asymmetry of the cSTS branches. Probability maps based on data from all subjects were generated for each cSTS branch separately for each hemisphere. In Figure 3.10, we present the co-ordinates in MNI standard stereotaxic space that have the highest probability of being identified as the cSTS1, cSTS2, cSTS3 and AOCSv, within each hemisphere (Figure 3.10A–D). All of the cSTS branches appear to have a more posterior location in the left hemisphere than in the right hemisphere. We subsequently performed a separate analysis that enabled us to examine hemispheric differences according to gender. Figures 3.11 and 3.12 present the co-ordinates in MNI standard stereotaxic space that have the highest probability of being identified as the cSTS1, cSTS2, cSTS3 and AOCSv, within each hemisphere, for females and for males separately. We observe a posterior displacement of the sulci in the left hemisphere relative to the right hemisphere in both females and males, similar to what is observed in the total-subject average probability map. These findings are consistent with earlier reports of asymmetry in the caudal part of the STS that does not appear to be related to gender (Ono et al., 1990; Ochiai et al., 2004), although these earlier studies had examined only two of the branches of the cSTS identified in the present study.

Relation of the cSTS branches to IPL cytoarchitecture

An interesting question is the possible relationship between the cSTS branches within the IPL and various cytoarchitectonic areas. The central branch, i.e. cSTS2, clearly lies in the middle of the angular gyrus and would therefore correspond to area 39 of Brodmann (1909) or area PG of Economo and Koskinas (1925). A recent cytoarchitectonic study of the IPL in 10 post-mortem brains (Caspers et al., 2008) reported several subdivisions of the above two classical areas. As the latter study provides the co-ordinates of these cytoarchitectonic areas in MNI standard stereotaxic space, we compared these co-ordinates with those of the sulci provided by the present study. Cytoarchitectonic area PFm (x, y, z: -53, -54, 44; 55, -49, 45) appears to correspond well to the cortex immediately adjacent to cSTS1, area PGa (x, y, z: -46, -65, 43; 52, -59, 39) to cSTS2 and area PGp (x, y, z: -43, -76, 37; 47, -73, 38) to cSTS3. Thus, the cSTS branches may relate to the different cytoarchitectonic areas within the IPL.

Conclusion

In conclusion, the present study has examined the morphology of the cSTS in a large sample of human brains using MRIs. The location of these branches has been quantified in the form of probability maps which provide information about the location of each cSTS branch in the MNI standard stereotaxic space. The results from the present study indicate that there are three cSTS branches that ascend into the IPL, and another cSTS branch that is found lower in the region of the temporo-occipital junction. Studies of the functional significance of the region that lies at the junction of the parietal, temporal and occipital lobes have tended to report the locus of their findings in rather general terms, such as the parieto-occipitotemporal junction or the parieto-occipital or the parietotemporal junction. The provision of a detailed description of the morphology of the sulci that are found in this region and a quantitative presentation of their variability in MNI space, i.e. the standard stereotaxic space most often utilized by the neuroimaging research community, should allow functional and anatomical findings to be related to specific sulci rather than merely stated in terms of a general region.

3.7 References

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3.8 Acknowledgements

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3.9 Abbreviations

aipsJ, anterior intermediate parietal sulcus of Jensen; ALITS, ascending limb of the inferior temporal sulcus; AOCS-v, anterior occipital sulcus, ventral division; ascSF, ascending limb of the Sylvian fissure; CS, central sulcus; cSTS, caudal aspect of the STS; cSTS1, anterior branch of the cSTS; cSTS2, central branch of the cSTS; cSTS3, posterior branch of the cSTS; ICBM, International Consortium for Brain Mapping; IPL, inferior parietal lobule; IPS, intraparietal sulcus; LOCS, lateral occipital sulcus; MNI, Montreal Neurological Institute; PCS, postcentral sulcus; PFm, supramarginal cytoarchitectonic area PF, magnocellular part; PGa, angular gyrus cytoarchitectonic area PG, anterior part; PGp, angular gyrus cytoarchitectonic area PG, posterior part; pips, posterior intermediate parietal sulcus; POF, parietal–occipital fissure; STS, superior temporal sulcus; TOCS, transverse occipital sulcus.

3.10 Tables

Table 3.1. List of cSTS branches according to different authors and atlases

Segal & Petrides (2012)	Economo (1925)	Shellshear (1927)	Cunningham's Textbook of Anatomy, 6th edition (1931), pg 670	G.E. Smith (1907), Figure 2	Ono et al. (1990)	Duvernoy (1999)
Anterior Branch (cSTS1)	t1'	Sulcus parallelis superior	Not present	Not present	Angular Sulcus in Ch. 2 (p. 10); referred to as "double parallel" type in Ch. 10 (p. 77).	Not present on p. 7; Superior Temporal Sulcus ascending part in Continuous Sagittal Sections
Central Branch (cSTS2)	t1"	Sulcus Angularis	Sulcus Angularis	Sulcus Angularis	Anterior Occipital Sulcus in Ch. 2 (p. 10); referred to as Angular Sulcus in Ch. 10 (p. 78).	Superior Temporal Sulcus ascending part on p. 7; Superior Temporal Sulcus horizontal posterior segment in Continuous Sagittal Sections
Posterior Branch (cSTS3)	t2'	Sulcus Occipitalis Anterior, superior	Sulcus Occipitalis Anterior	Sulcus Occipitalis Anterior	Inferior Temporal Sulcus in Ch. 2 (p. 10); referred to as Anterior Occipital Sulcus in Ch. 10 (p. 78)	Superior Temporal Sulcus horizontal posterior segment on p. 7; LOCS in Continuous Sagittal Sections
AOCS-v	t2"/Sulcus Occipitals Anterior	Sulcus Occipitalis Anterior, inferior	Not present	Sulcus Occipitalis Inferior	Inferior temporal sulcus in Ch 10 (p. 79)	

Table 3.2. Coordinates of each cSTS branch in MNI standard stereotaxic space with the highest probability value.

Left Hemisphere	***X***	***Y***	***Z***	***Probability***
Anterior branch (cSTS1)	-55	-50	35	53%
Central branch (cSTS2)	-44	-58	37	60%
Posterior branch (cSTS3)	-38	-72	23	67%
AOCS-v	-41	-70	2	71%
Right Hemisphere	***X***	***Y***	***Z***	***Probability***
Anterior branch (cSTS1)	55	-41	37	51%
Central branch (cSTS2)	47	-53	35	56%
Posterior branch (cSTS3)	41	-64	24	69%
AOCS-v	43	-63	1	76%

All peaks are reported in MNI standard stereotaxic space. Probability refers to the likelihood that the voxel (x, y, z coordinates) is labelled as a particular sulcus. For example, in the left hemisphere the voxel with the highest likelihood (at a 53% probable chance) of being identified as cSTS1 is at MNI coordinates -55, -50, 35 whereas in the right hemisphere the voxel with the highest likelihood (at a 51% probable chance) of being identified as cSTS1 is at MNI coordinates 55, -41, 37, suggesting there is slightly less variability in the location of cSTS1 in the left hemisphere than in the right hemisphere.

3.11 Figures

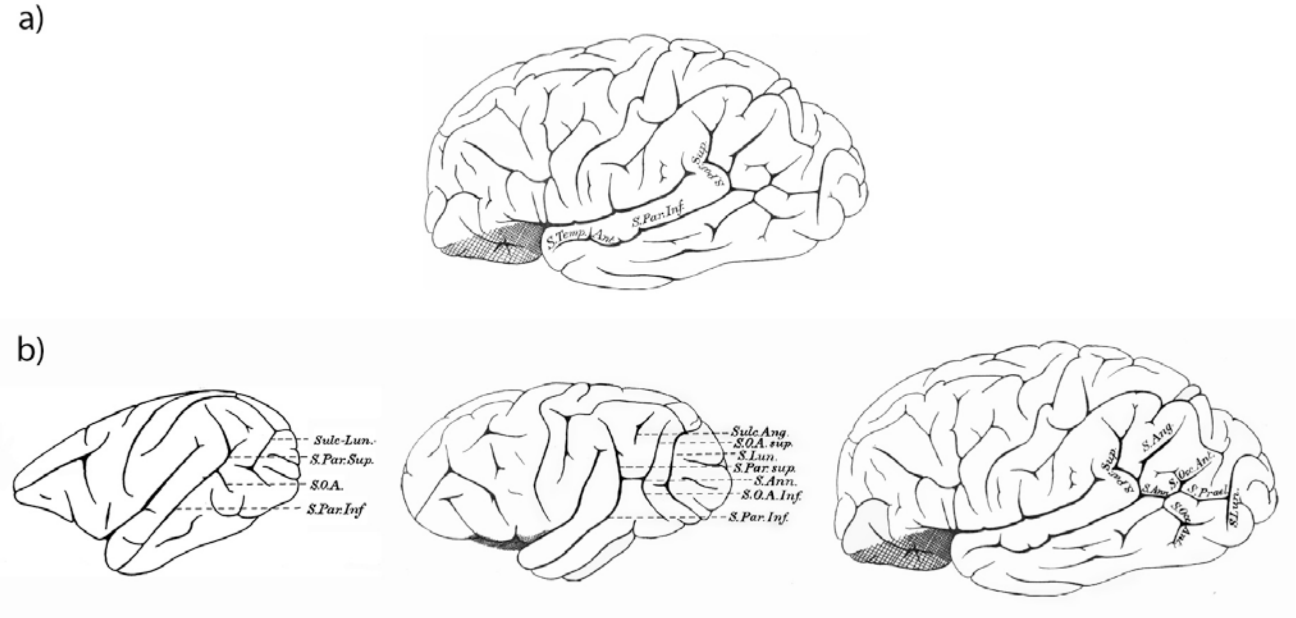


Figure 3.1. (A) The three segments of the STS in the antero-posterior direction, adapted from Figure 10 in Shellshear (1927). The STS can be divided into an anterior temporal segment (anterior temporal sulcus) and a posterior temporal segment (the inferior parallel sulcus). One of its posterior parietal segments is here labelled the superior parallel sulcus. S. Temp. Ant., anterior temporal sulcus; S. Par. Inf., inferior parallel sulcus; S. Par. Sup., superior parallel sulcus. (B) The evolutionary expansion of the cSTS branches illustrated by a comparison of the brains of the gibbon, orangutan and the human (from left to right), adapted from Figures 5, 7 and 10 in Shellshear (1927). From the posterior wall of the superior parallel sulcus in lower primates (such as the gibbon), the anterior occipital sulcus (AOCS), here labelled as SOA, is extruded in the brains of higher primates (such as the orangutan and human) where it is divided into a dorsal and a ventral branch. The dorsal AOCS stays within the inferior parietal lobule while the ventral AOCS is located in the posterior temporo-occipital cortex. In the orangutan, the angular sulcus has made its appearance between the superior

parallel sulcus and the dorsal AOCS, and in the human brain the angular sulcus is even more prominent. S. Ang., sulcus angularis; S. Ann., annectant sulcus; S. Lun., lunate sulcus; SOA and S.Occ. Ant., anterior occipital sulcus; S.O.A. sup, superior or dorsal part of the anterior occipital sulcus; S.O.A. inf, inferior or ventral part of the anterior occipital sulcus; S. Par. Inf., inferior parallel sulcus; S. Par. Sup., superior parallel sulcus; S. Prael., prelunate sulcus; Sulc. Ang., angular sulcus.

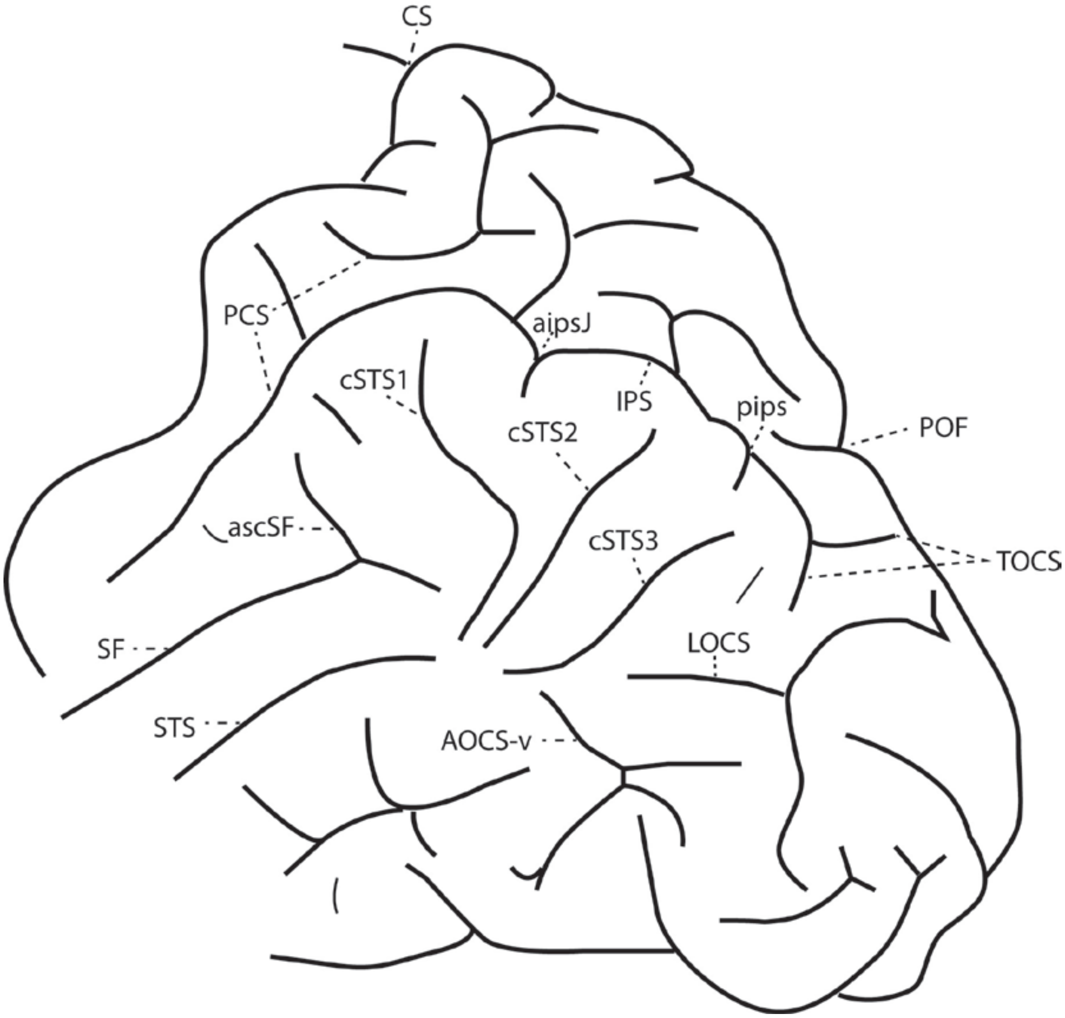
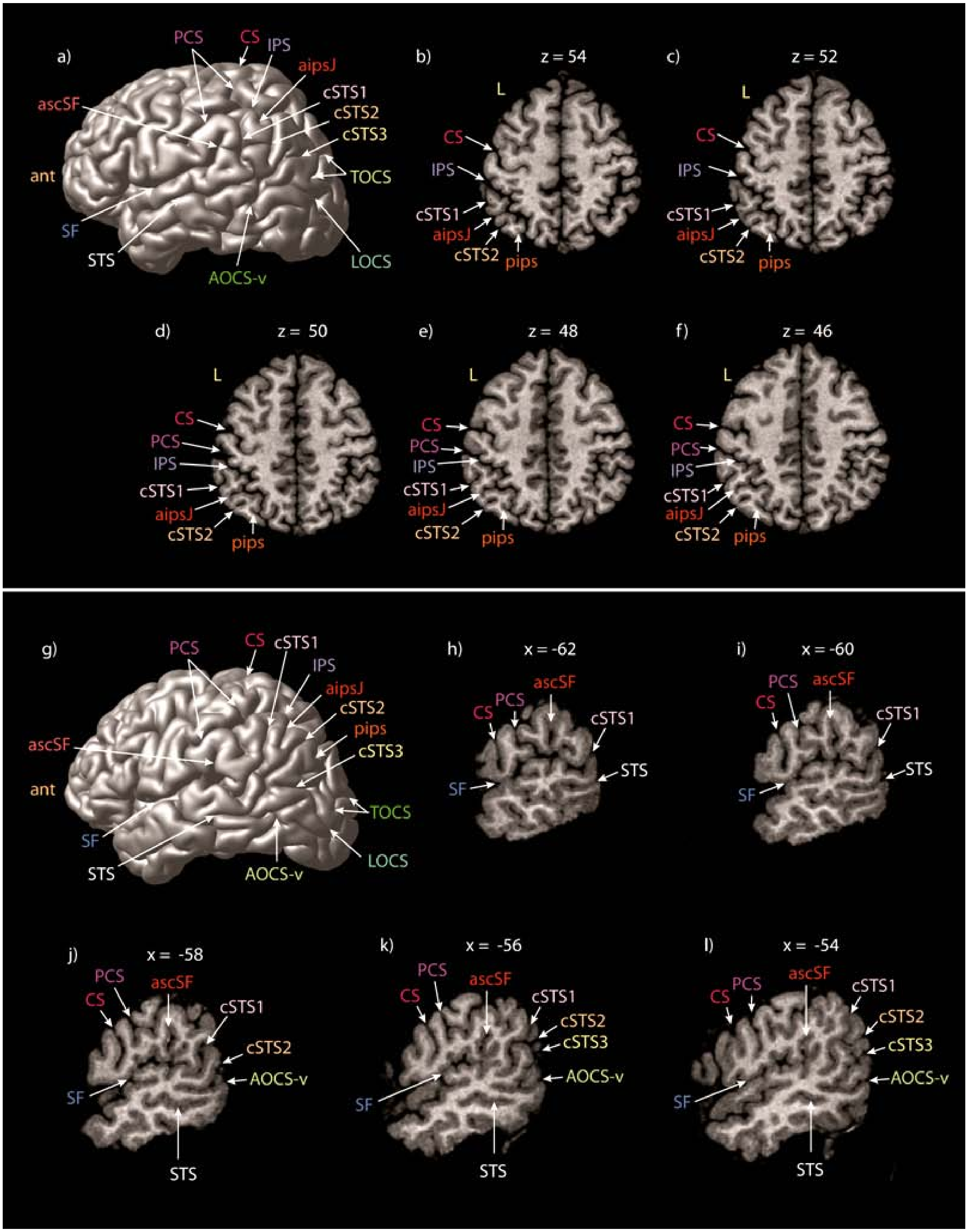


Figure 3.2. A schematic illustration of the posterior part of the lateral surface of the brain depicting the sulci relevant as landmarks for identifying the cSTS branches. aipsJ, anterior intermediate parietal sulcus of Jensen; AOCS-v, ventral division of the anterior occipital sulcus; ascSF, ascending limb of the Sylvian fissure; CS, central sulcus; cSTS1, anterior branch of the caudal STS; cSTS2, central branch of the caudal STS; cSTS3, posterior branch of the caudal STS; IPS, intraparietal sulcus; LOCS, lateral occipital sulcus; PCS, post-central sulcus; pips, posterior intermediate parietal sulcus; POF, parieto-occipital fissure; SF, Sylvian fissure; STS, superior temporal sulcus; TOCS, transverse occipital sulcus.


a)
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IPS
aipsJ
ascSF
cSTS1
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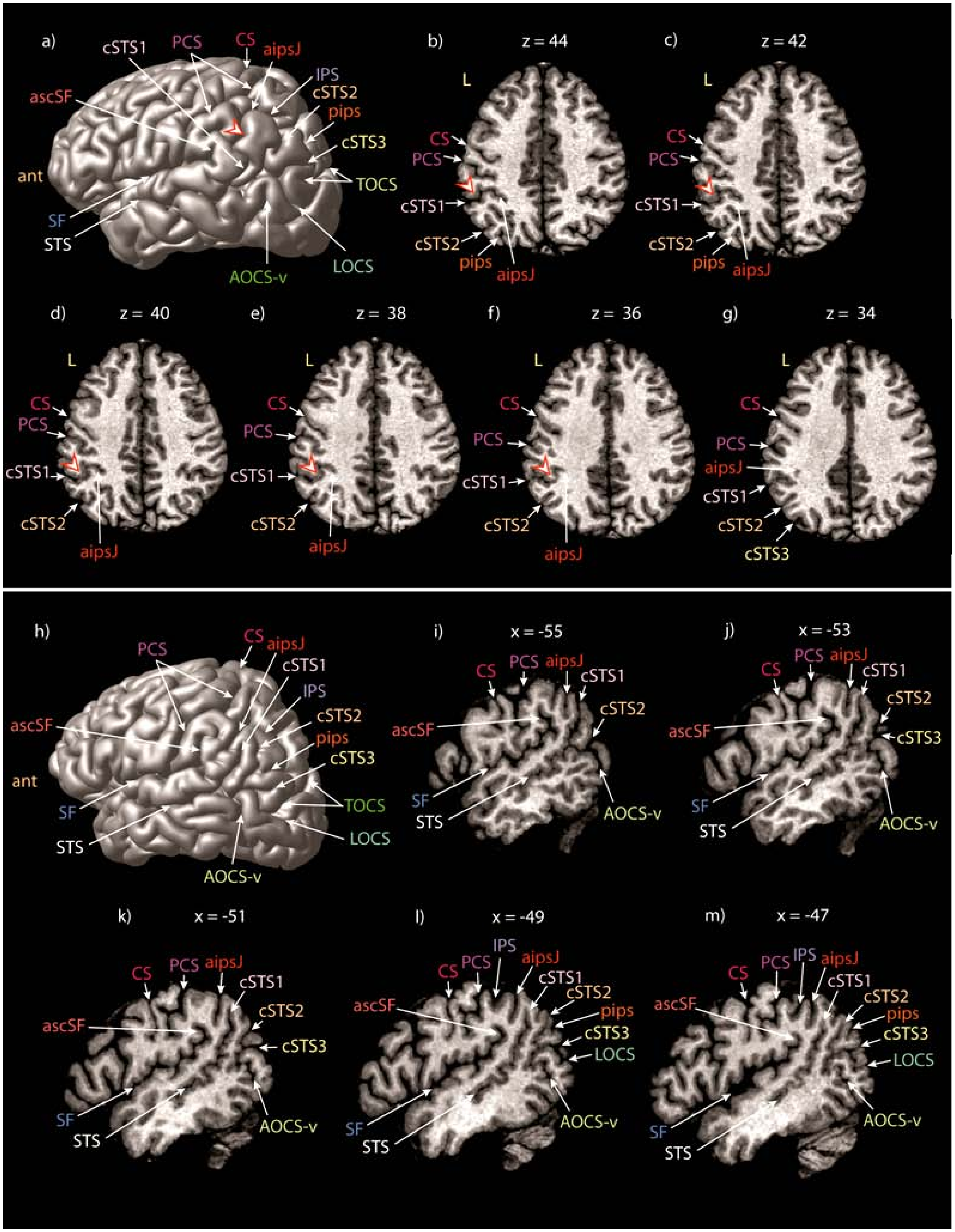
TOCS
ant
SF
STS
AOCS-v
LOCS
b) z = 54
c) z = 52
L
CS
IPS
cSTS1
aipsJ
cSTS2
pips
d) z = 50
e) z = 48
f) z = 46
L
CS
PCS
IPS
cSTS1
aipsJ
cSTS2
pips
g)
PCS
CS
cSTS1
IPS
aipsJ
cSTS2
pips
cSTS3
ascSF
ant
TOCS
SF
STS
AOCS-v
LOCS
h) x = -62
i) x = -60
CS
PCS
ascSF
cSTS1
STS
SF
j) x = -58
k) x = -56
l) x = -54
CS
PCS
ascSF
cSTS1
cSTS2
cSTS3
AOCS-v
SF
STS

Figure 3.3. (A–F) The cSTS1 may approach the IPS as observed on (A) the 3-D lateral surface view, but (B–F) horizontal sections show that the cSTS1 is in fact a sulcus that is separate from the IPS and that does not originate within the IPS. (G–L) The cSTS1 approaches the posterior aspect of the Sylvian fissure on (G) the 3-D lateral surface view, but (H–L) sagittal sections show that the cSTS1 is an independent sulcus, separate from the Sylvian fissure. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.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b)
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PCS
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cSTS2
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aipsJ
c)
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AOCS-v
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x = -55
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AOCS-v
j)
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cSTS1
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ascSF
cSTS3
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AOCS-v
l)
x = -49
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PCS
aipsJ
cSTS1
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ascSF
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AOCS-v
m)
x = -47
CS
PCS
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aipsJ
cSTS1
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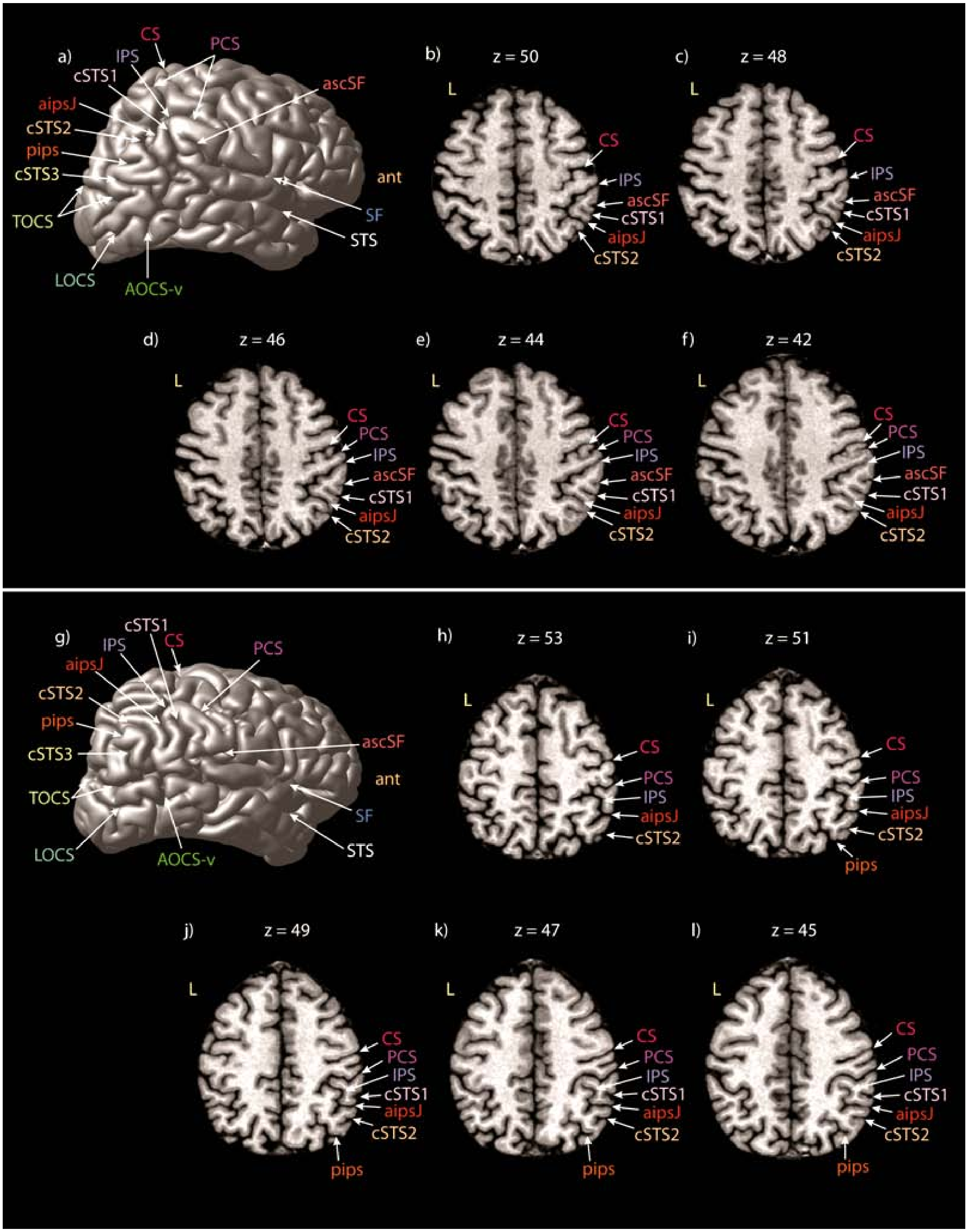
ascSF
pips
cSTS3
LOCS
SF
STS
AOCS-v

Figure 3.4. (A–G) The cSTS1 may join the aipsJ on (A) the 3-D lateral surface view but the two sulci are distinct, as can be observed in horizontal sections (B–G). The arrowhead indicates the location of the submerged gyrus that separates cSTS1 from aipsJ. (H–M) The temporal lobe segment of the STS may appear to join posteriorly with the cSTS2 and the cSTS1, according to (h) the 3-D lateral surface view, but (I–M) the sagittal sections show that, in this case in the sulcal depth, the temporal lobe segment of the STS does not join the cSTS2 but instead joins with the cSTS1, thus highlighting the importance of examining the sulcal depths and going beyond the lateral surface view. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.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b)
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cSTS2
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l)
z = 45
L
CS
PCS
IPS
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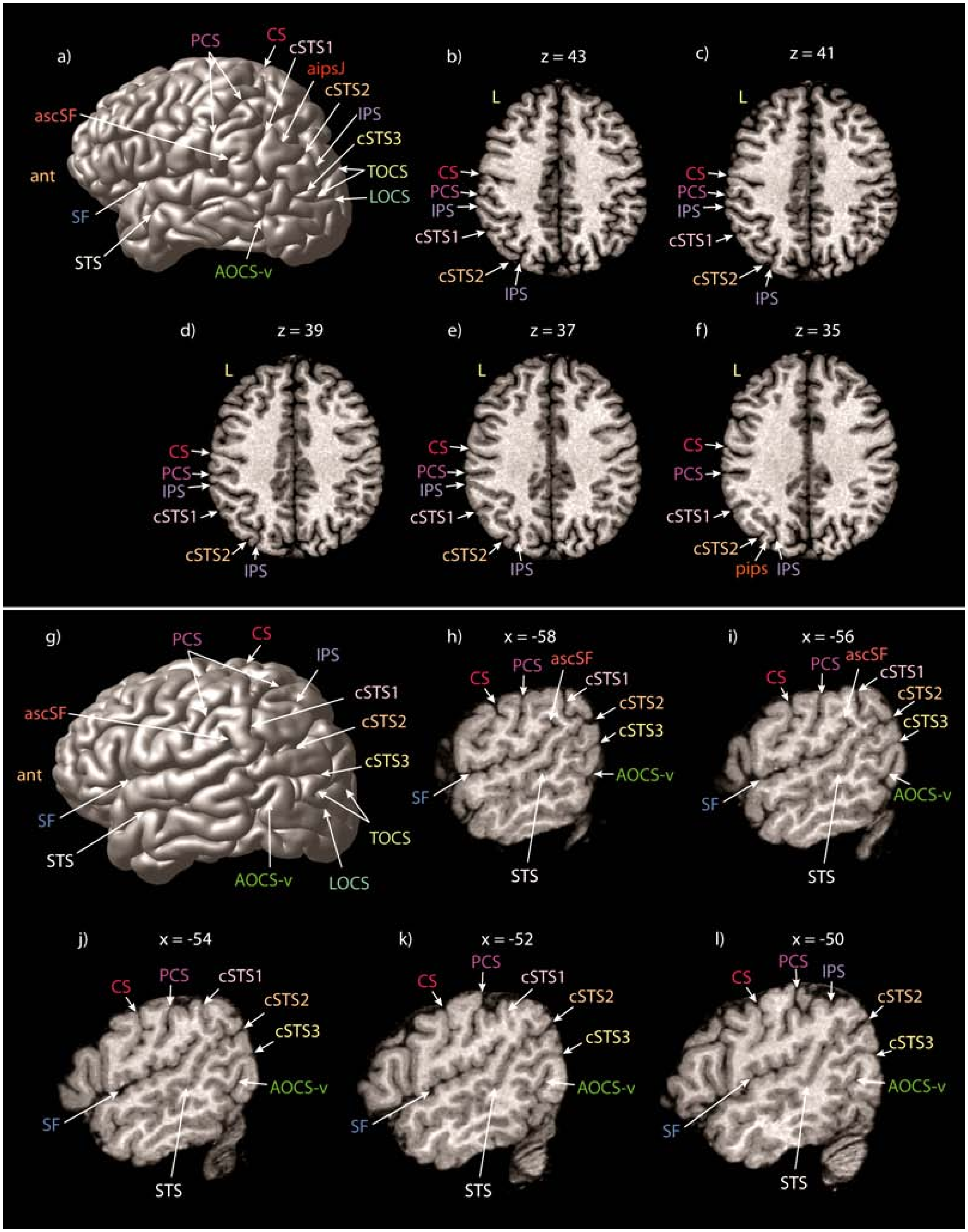
aipsJ
cSTS2
pips

Figure 3.5. (A–F) The cSTS2 may extend dorsally to reach the aipsJ as observed in (A) the 3-D lateral surface view, but (B–F) examination of the horizontal sections demonstrate that the cSTS2 is separate from the aipsJ which originates in the IPS. (G–L) cSTS2 may extend dorsally to reach the pips (G) but (H–L) the horizontal sections show that it is a separate sulcus and any contact with the pips is superficial. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.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c)
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x = -50
CS
PCS
IPS
cSTS2
cSTS3
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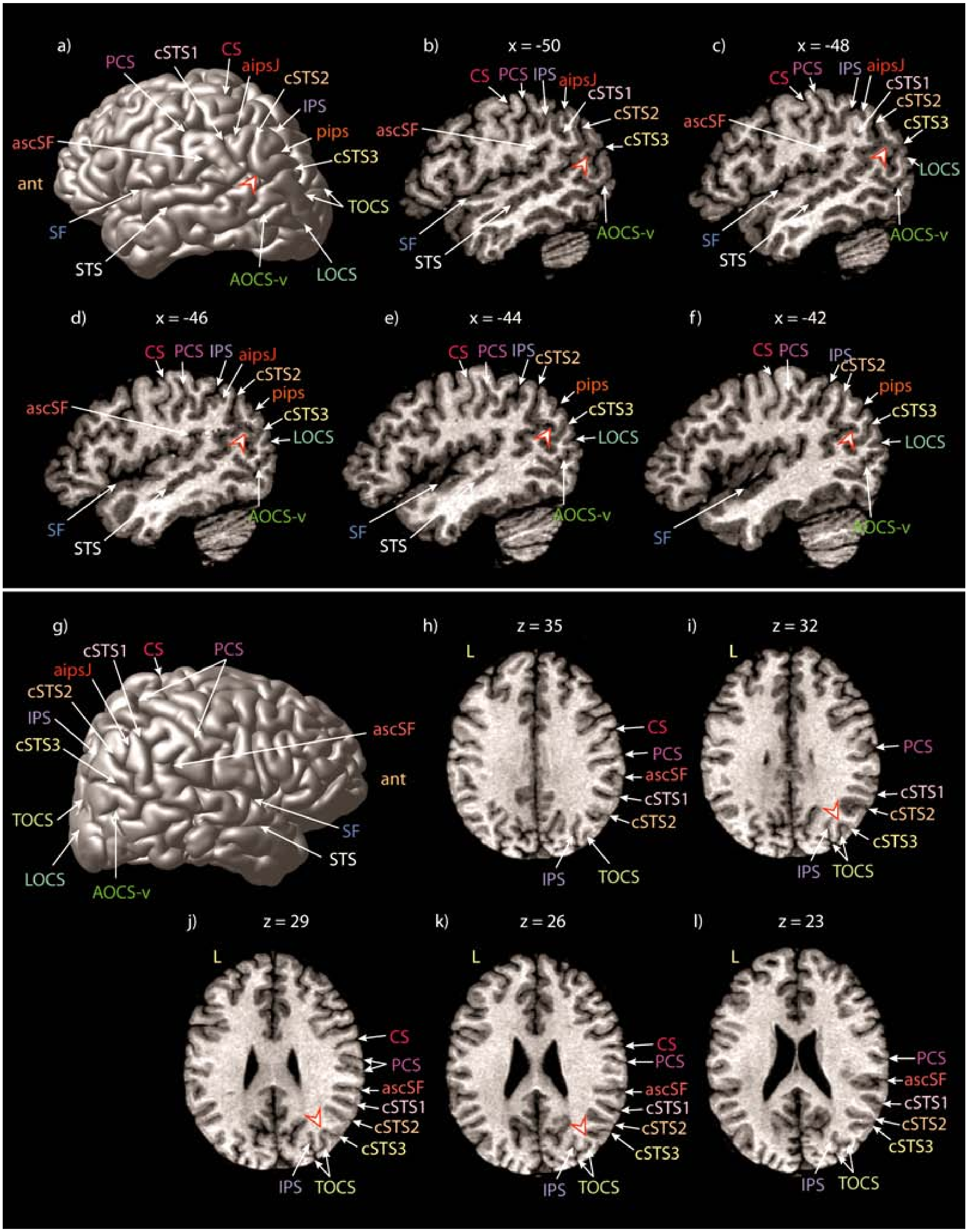
SF
STS

Figure 3.6. (A–F) The cSTS2 may reach dorsally and make contact with the IPS as observed from (A) the lateral surface of the brain, but (B–F) horizontal sections clearly show the separation between the cSTS2 and the IPS. (G–L) The temporal lobe segment of the STS appears continuous with cSTS1 along with the cSTS2 when viewed in (G) the 3-D lateral surface view of the brain, but (H–L) examination of the sagittal sections shows that in this case, when the sulcal depths are examined, the temporal lobe segment of the STS in fact does not join with the cSTS1 but instead joins with cSTS2, thus highlighting the importance of examining the sulcal depths and going beyond the lateral surface view. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.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PCS
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cSTS2
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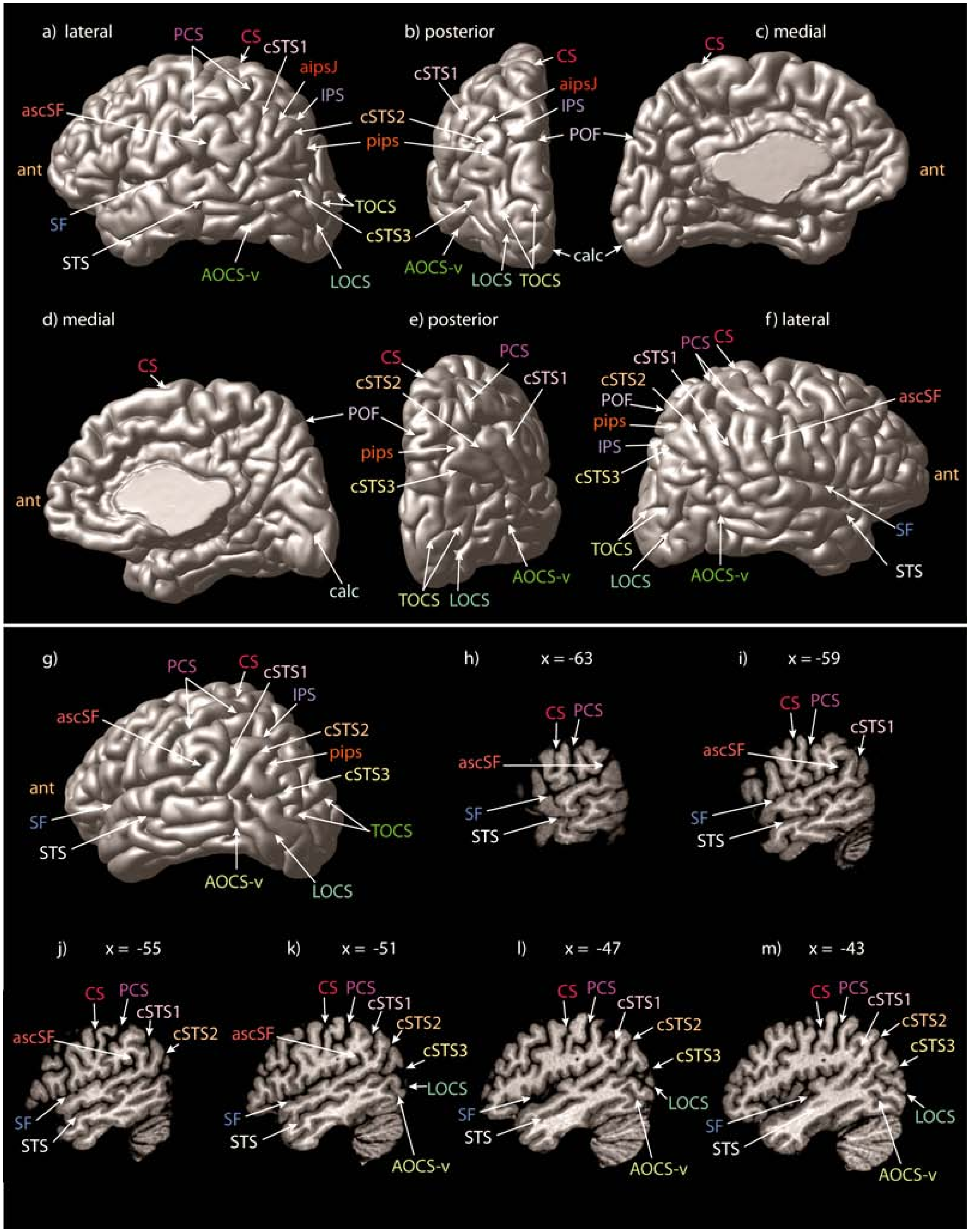
TOCS

Figure 3.7. (A–F) An annectant sulcus may run between the cSTS2 and cSTS3. In some cases, the annectant sulcus can be observed from (A) the 3-D lateral surface view of the brain, but (B–F) most often it is buried in the sulcal depth and can be seen in sagittal sections. An arrowhead indicates the location of the annectant sulcus.(G– L) The dorsal extent of the cSTS3 may reach adjacent sulci, such as the TOCS at the ventral extent of the IPS, and appear to make contact with it, according to (G) the 3-D lateral surface view. (H–L) The horizontal sections clearly show that the cSTS3 does not originate from either the TOCS or the IPS and any contact with the TOCS or IPS is superficial. An arrowhead indicates the location of a submerged gyrus that separates the cSTS3 from the IPS/TOCS junction. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.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cSTS3
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LOCS
TOCS
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c) medial
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d) medial
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POF
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TOCS
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LOCS
h) x = -63
CS
PCS
ascSF
SF
STS
i) x = -59
CS
PCS
cSTS1
ascSF
SF
STS
j) x = -55
CS
PCS
cSTS1
ascSF
cSTS2
SF
STS
k) x = -51
CS
PCS
cSTS1
ascSF
cSTS2
cSTS3
LOCS
SF
STS
AOCS-v
l) x = -47
CS
PCS
cSTS1
cSTS2
cSTS3
LOCS
SF
STS
AOCS-v
m) x = -43
CS
PCS
cSTS1
cSTS2
cSTS3
LOCS
SF
STS
AOCS-v

Figure 3.8. (A–F) Lateral, posterior and medial views of (A–C) the left and (D–F) the right hemispheres show that the terminal end of the cSTS3 points towards the POF. Note that, in (A, B) the left hemisphere, the cSTS3 is more ventrally located than (D, E) the right hemisphere. Note also that, following the displacements of CSTS3, the POF in (B, C) the left hemisphere is more ventrally situated than the POF in (E, F) the right hemisphere. (G–M) The temporal lobe segment of the STS appears to join with both the cSTS3 and the cSTS2, according to (G) the 3-D lateral surface view, but (h–m) the sagittal sections show that in this case, in the sulcal depth, the temporal lobe segment of the STS does not join with the cSTS3 but instead joins with the cSTS2, thus highlighting the importance of examining the sulcal depths and going beyond the lateral surface view. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.

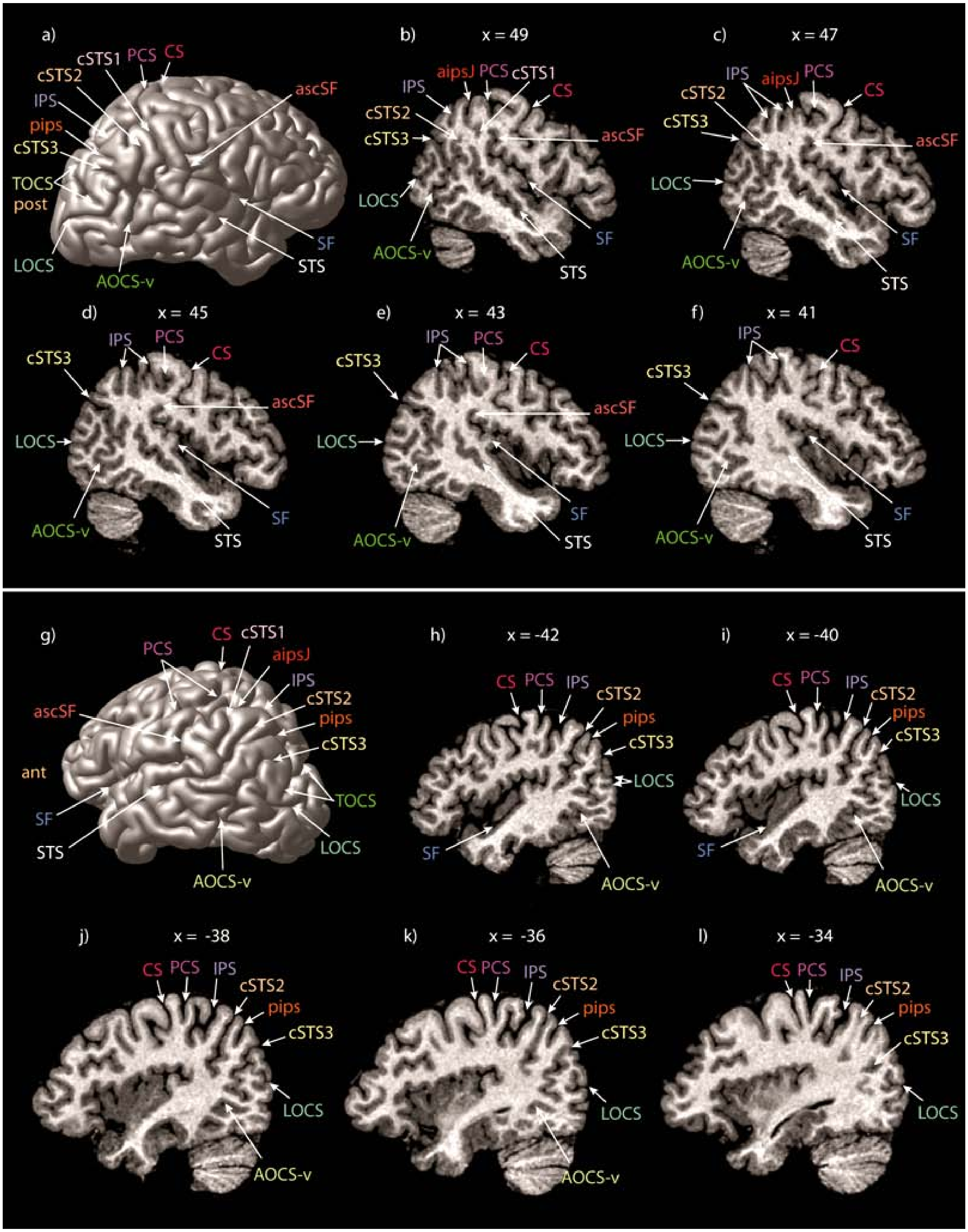
a)
cSTS1
PCS
CS
cSTS2
IPS
pips
cSTS3
TOCS
post
LOCS
AOCS-v
ascSF
SF
STS
b)
x = 49
aipsJ
PCS
cSTS1
IPS
CS
cSTS2
cSTS3
ascSF
LOCS
AOCS-v
SF
STS
c)
x = 47
IPS
aipsJ
PCS
CS
cSTS2
cSTS3
ascSF
LOCS
AOCS-v
SF
STS
d)
x = 45
IPS
PCS
CS
cSTS3
ascSF
LOCS
AOCS-v
SF
STS
e)
x = 43
IPS
PCS
CS
cSTS3
ascSF
LOCS
AOCS-v
SF
STS
f)
x = 41
IPS
CS
cSTS3
LOCS
AOCS-v
SF
STS
g)
PCS
CS
cSTS1
aipsJ
IPS
cSTS2
pips
cSTS3
ascSF
ant
TOCS
SF
STS
LOCS
AOCS-v
h)
x = -42
CS
PCS
IPS
cSTS2
pips
cSTS3
LOCS
SF
AOCS-v
i)
x = -40
CS
PCS
IPS
cSTS2
pips
cSTS3
LOCS
SF
AOCS-v
j)
x = -38
CS
PCS
IPS
cSTS2
pips
cSTS3
LOCS
AOCS-v
k)
x = -36
CS
PCS
IPS
cSTS2
pips
cSTS3
LOCS
AOCS-v
l)
x = -34
CS
PCS
IPS
cSTS2
pips
cSTS3
LOCS

Figure 3.9. (A–F) The dorsal extent of the AOCS-v may reach dorsally to make contact superficially with the cSTS3, according (A) to the 3-D lateral surface view. (B–F) Sagittal sections demonstrate that the two sulci are separated from one another in the sulcal depths. (G–L) The LOCS may appear to join the cSTS3, according to (G) the 3-D lateral surface view, but (H–L) the sagittal sections show that, in the sulcal depths, the LOCS is separate from the cSTS3. ant, anterior; L, left hemisphere; SF, Sylvian fissure; other abbreviations in Figure 3.2 and main list.

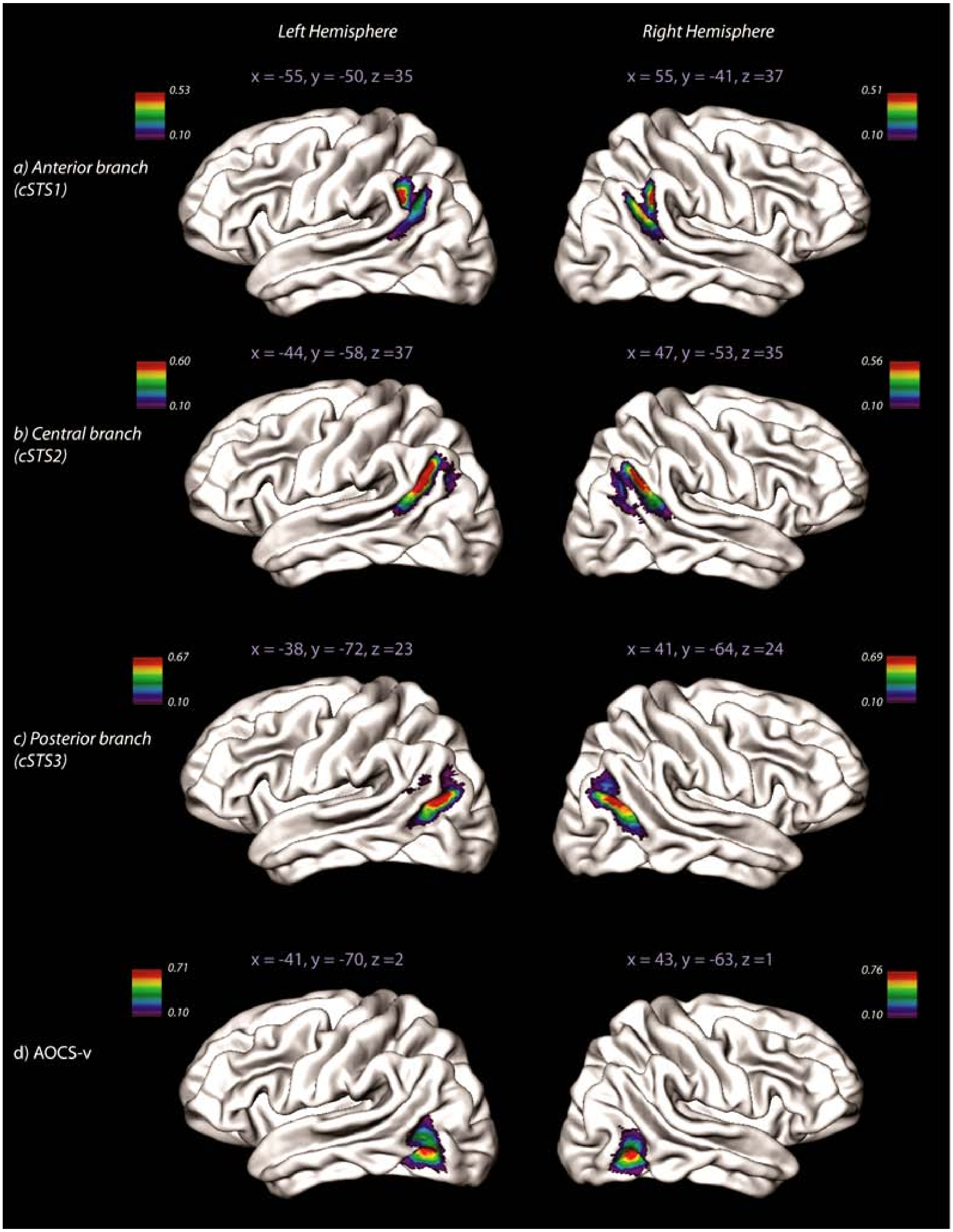
Left Hemisphere
Right Hemisphere
x = -55, y = -50, z =35
x = 55, y = -41, z =37
0.53
0.10
0.51
0.10
a) Anterior branch
(cSTS1)
x = -44, y = -58, z =37
x = 47, y = -53, z =35
0.60
0.10
0.56
0.10
b) Central branch
(cSTS2)
x = -38, y = -72, z =23
x = 41, y = -64, z =24
0.67
0.10
0.69
0.10
c) Posterior branch
(cSTS3)
x = -41, y = -70, z =2
x = 43, y = -63, z =1
0.71
0.10
0.76
0.10
d) AOCS-v

Figure 3.10. The probability maps for each cSTS branch are shown on an average mid-surface of the 45 left hemispheres (left column) and 45 right hemispheres (right column). (A) cSTS1, (B) cSTS2, (C) cSTS3 and (D) AOCS-v. The minimum value for each scale is 0.1 (10% of the subjects included in this study). The highest probability value varies for the different branches, indicated by the maximum value on each color bar. The x, y, z coordinates reported above each of the brains in (A– D) express the location in MNI standard stereotaxic space with the highest probability of being identified as each of the branches.

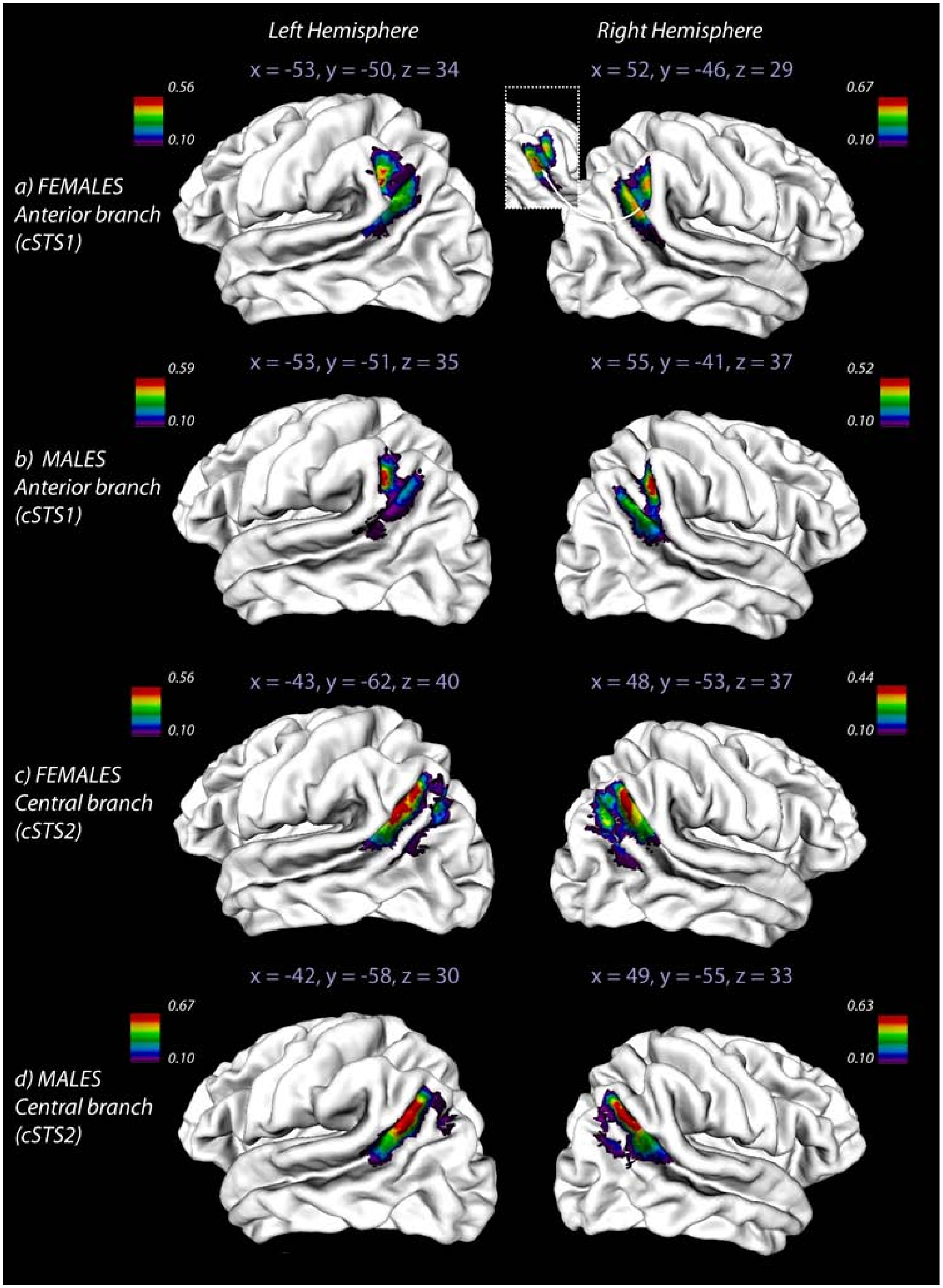
Left Hemisphere
Right Hemisphere
x = -53, y = -50, z = 34
x = 52, y = -46, z = 29
0.56
0.10
0.67
0.10
a) FEMALES
Anterior branch
(cSTS1)
x = -53, y = -51, z = 35
x = 55, y = -41, z = 37
0.59
0.10
0.52
0.10
b) MALES
Anterior branch
(cSTS1)
x = -43, y = -62, z = 40
x = 48, y = -53, z = 37
0.56
0.10
0.44
0.10
c) FEMALES
Central branch
(cSTS2)
x = -42, y = -58, z = 30
x = 49, y = -55, z = 33
0.67
0.10
0.63
0.10
d) MALES
Central branch
(cSTS2)

Figure 3.11. Probability maps of cSTS1 and cSTS2 for the left and right hemispheres, presented separately for (A and C) female subjects and for (B and D) male subjects. (A) The probability map of the cSTS1 for female subjects is superimposed on an average registered female mid-surface brain and(B) the probability map of the cSTS1 for male subjects is superimposed on an average registered male mid-surface brain. Similarly, (C) the probability map of cSTS2 for female subjects is superimposed on an average registered female mid-surface brain and (D) the probability map of cSTS2 for male subjects is superimposed on an average registered male mid-surface brain. The minimum value for each scale is 0.1 (10% of the subjects included in this study). The highest probability value varies for the different branches, indicated by the maximum value on each color bar. The x, y, z coordinates reported above each of the brains in (A–D) express the location in MNI standard stereotaxic space with the highest probability of being identified as each of the branches.

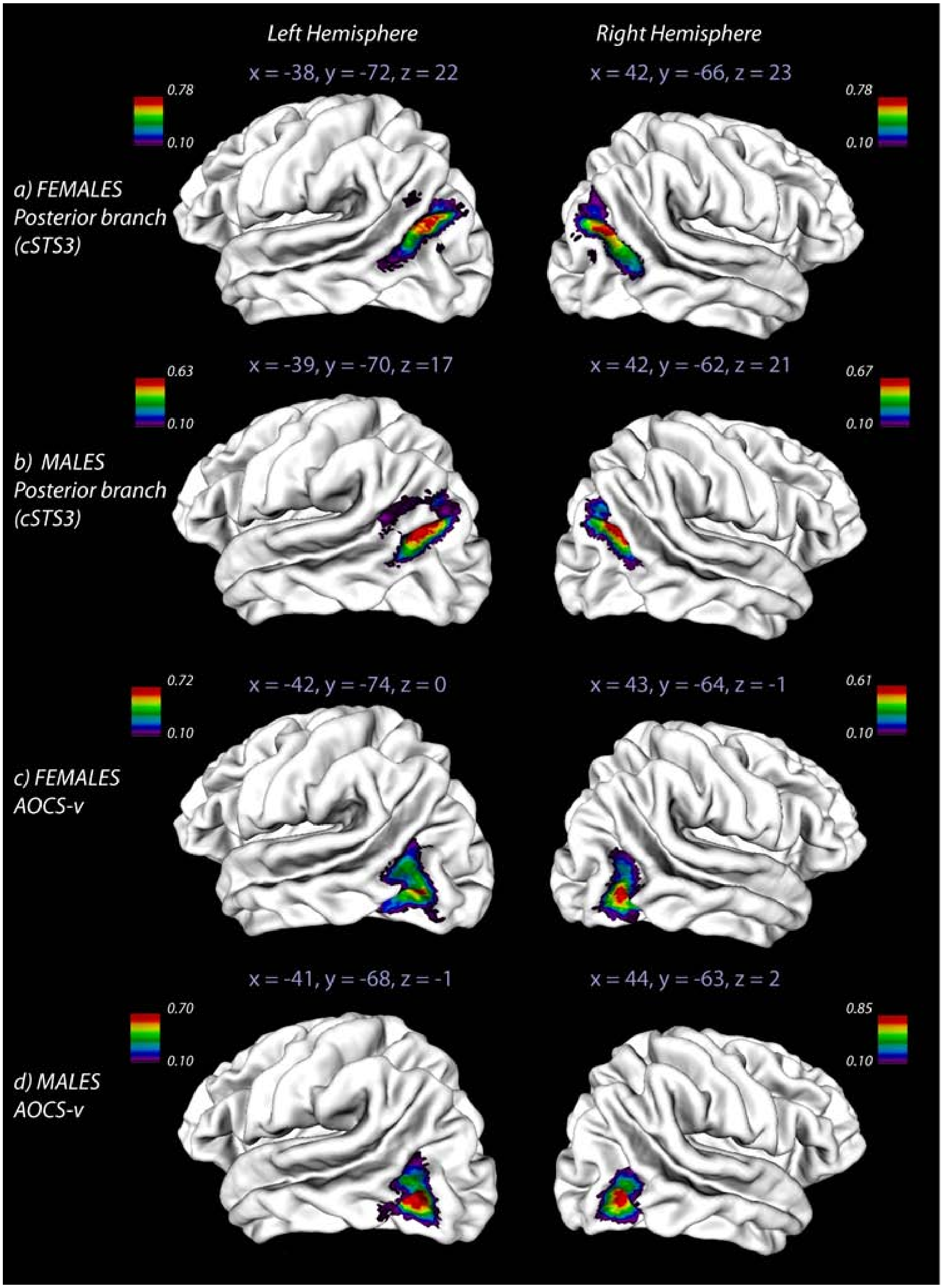
Left Hemisphere
Right Hemisphere
x = -38, y = -72, z = 22
x = 42, y = -66, z = 23
0.78
0.10
0.78
0.10
a) FEMALES
Posterior branch
(cSTS3)
x = -39, y = -70, z =17
x = 42, y = -62, z = 21
0.63
0.10
0.67
0.10
b) MALES
Posterior branch
(cSTS3)
0.72
0.10
x = -42, y = -74, z = 0
x = 43, y = -64, z = -1
0.61
0.10
c) FEMALES
AOCS-v
x = -41, y = -68, z = -1
x = 44, y = -63, z = 2
0.70
0.10
0.85
0.10
d) MALES
AOCS-v

Figure 3.12. Probability maps of cSTS3 and AOCS-v for the left and right hemispheres, presented separately for female subjects and for male subjects. (A) The probability map of the cSTS3 for female subjects is superimposed on an average registered female mid-surface brain and (B) the probability map of the cSTS3 for male subjects is superimposed on an average registered male mid-surface brain. Similarly, (C) the probability maps of AOCS-v for female subjects is superimposed on an average registered female mid-surface brain and (D) the probability maps of AOCS-v for male subjects is superimposed on an average registered male mid-surface brain. The minimum value for each scale is 0.1 (10% of the subjects included in this study). The highest probability value varies for the different sulci, indicated by the maximum value on each color bar. The x, y, z coordinates reported above each of the brains in (A–D) express the location in MNI standard stereotaxic space (ICBM 152 nonlinear) with the highest probability of being identified as each of the branches.

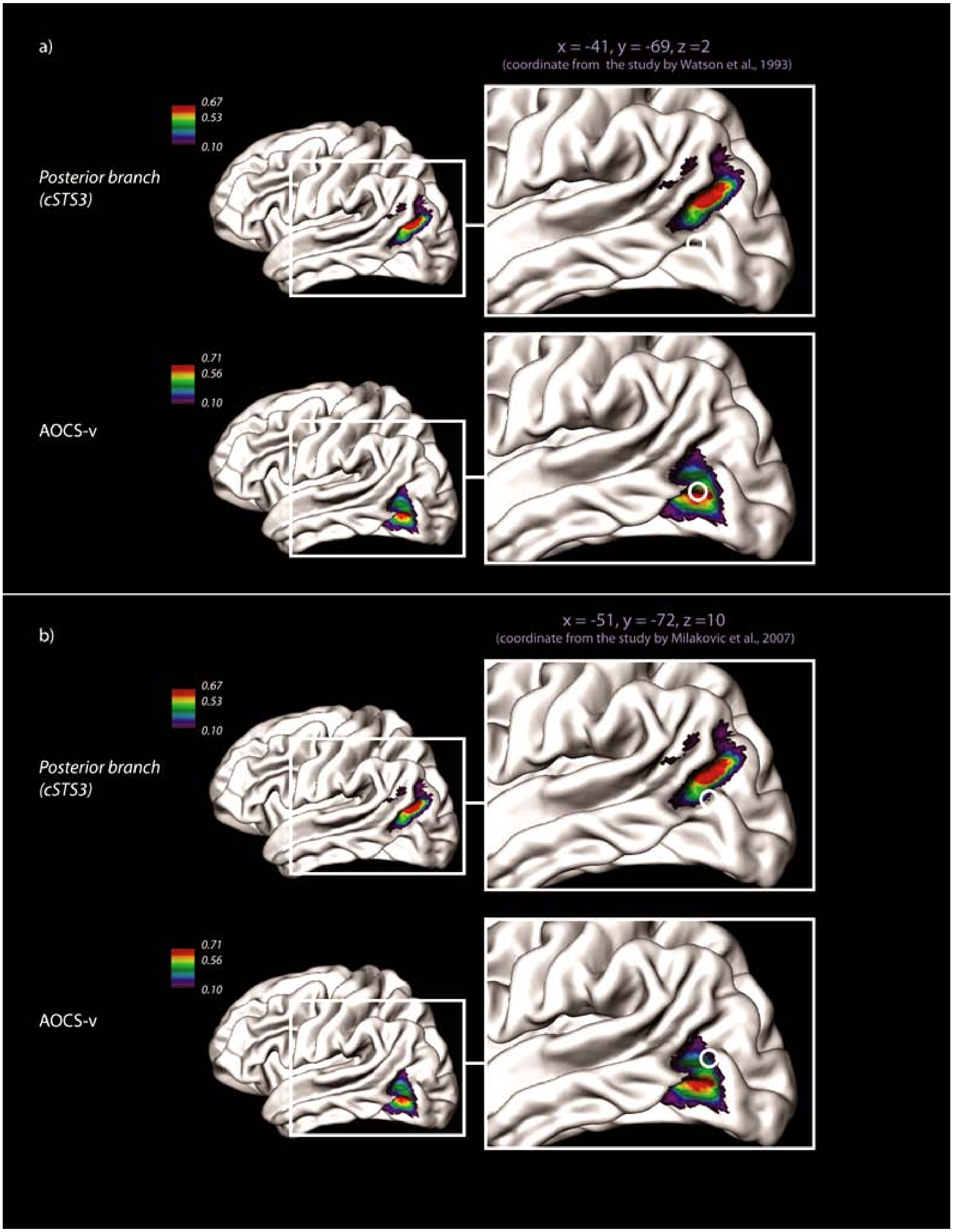
a)
x = -41, y = -69, z =2
(coordinate from the study by Watson et al., 1993)
0.67
0.53
0.10
Posterior branch
(cSTS3)
0.71
0.56
0.10
AOCS-v
b)
x = -51, y = -72, z =10
(coordinate from the study by Milakovic et al., 2007)
0.67
0.53
0.10
Posterior branch
(cSTS3)
0.71
0.56
0.10
AOCS-v

Figure 3.13. The stereotaxic coordinates of motion area MT⁄ v5 as determined by past neuroimaging studies in humans is presented in relation to the probability maps of the cSTS3 and of the AOCS-v from the present study. (A) The standard stereotaxic MNI coordinates (reported above the magnified brain area) from the neuroimaging study of area MT⁄ v5 in the human brain by Watson et al. (1993) entered into the probability maps from the present study (from Figure 3.10) show its location in relation to the location of cSTS3 and AOCS-v (enlarged area). The white circle on the lateral surface surrounds the vertex of the average mid-surface brain that corresponds to the MNI coordinates from the functional neuroimaging study. (B) The standard stereotaxic MNI coordinates (reported above the magnified brain area) from the cytoarchitectonic study by Malikovic et al. (2007) entered into the probability maps from the present study (from Figure 3.10) to show the location of the putative cytoarchitectonic MT⁄ v5 area in relation to the location of cSTS3 and AOCS-v (enlarged area). The white circle on the lateral surface surrounds the vertex of the average mid-surface brain that corresponds to the MNI coordinates from the cytoarchitectonic study. The color bar in (A) and (B) indicates the range in probability that a given set of coordinates is identified as a particular sulcus. The minimum value for each scale is 0.1 (10% of the subjects included in this study). The highest probability value varies for the different branches, indicated by the maximum value on each color bar.

Chapter Four

4. Functional activation during reading in relation to the sulci of the angular gyrus region

Segal E., and Petrides M. (2013). Functional activation during reading in relation to the sulci of the angular gyrus region. *The European Journal of Neuroscience*, doi:10.1111/ejn.12277

4.1 Prelude

The anatomical investigation of the angular gyrus region in the preceding chapter reveals that there are three caudal branches of the caudal superior temporal sulcus (cSTS) that ascend into the inferior parietal lobule and that serve to define the angular gyrus region: cSTS1, cSTS2, cSTS3. We were interested in testing whether reading-related activation occurring within the angular gyrus region could be related in a reliable way to either one of these sulcal branches. In other words, we wanted to test whether the local morphology of the angular gyrus region could predict the location of functional activation related to reading. A second goal of this study was to examine the relationship between the region of the angular gyrus, an area of the brain that has been established as important for reading according to classic neurological case studies of patients, and other areas of the brain including language areas, and including especially the region of the visual word form area, an area of the brain that has been shown to have an increase in functional MRI activity during word reading tasks that are performed by healthy subjects. With this final study, we hoped to understand better the neural correlates of reading in the human brain, and to reconcile the seeming inconsistency between the classic neurological model of reading based on clinical case studies, and the more modern models of reading that have emerged based on data from neuroimaging studies.

4.2 Abstract

Neurological studies suggest that the angular gyrus region of the inferior parietal lobule may be critical for reading. However, unambiguous demonstration of angular gyrus involvement from lesion and functional neuroimaging studies is lacking, partly because of the absence of detailed morphological descriptions of this region. On the basis of our recent anatomical examination of this region and a tightly controlled functional magnetic resonance imaging paradigm, the present investigation demonstrated reading-related activity in the region of the angular gyrus that lies between the central and posterior branches of the caudal superior temporal sulcus, namely cytoarchitectonic area PG. Analysis of functional connectivity showed increased functional coupling during reading of area PG with the language areas of Broca and Wernicke, and a region previously identified as the visual word form area. Thus, the parietal reading area has been precisely localized, and its interactions with other cortical areas during reading have been demonstrated.

4.3 Introduction

The classic neural model of reading considers the angular gyrus in the inferior parietal lobule (IPL) of the language-dominant hemisphere to be critical (Damasio & Geschwind, 1984). The model is based on case studies of patients showing reading and writing difficulties after brain injury (e.g. cerebrovascular accidents and brain tumours) involving the inferior parietal region, especially the angular gyrus (Dejerine, 1914; Geschwind, 1965a; Greenblatt, 1976; Warrington & Shallice, 1980; Damasio & Geschwind, 1984; Henderson, 1986). The angular gyrus is traditionally defined, loosely, as the cortex surrounding the caudal extension of the superior temporal sulcus (cSTS). We examined the morphological variations of this region in the human brain, and demonstrated that the cSTS is divided into three branches as it extends into the IPL: an anterior branch, a central branch (cSTS2), and a posterior branch (cSTS3) (Segal & Petrides, 2012b). It is unclear which one of these branches might relate to reading. The present study used functional magnetic resonance imaging (fMRI) to define precisely the critical locus for reading-related activity with reference to the three caudal branches of the superior temporal sulcus (STS) that define the angular gyrus region.

Many neuroimaging studies of reading in healthy subjects do not report activation within the IPL (Fiez & Petersen, 1998). Instead, activation in the middle part of the fusiform gyrus, near the lateral occipital temporal sulcus is often reported (Petersen et al., 1990; Cohen et al., 2000, 2002; Dehaene et al., 2002; McCandliss et al., 2003; Dehaene & Cohen, 2011). This mid-fusiform gyrus region in the language-dominant hemisphere [average xyz coordinates in Montreal Neurological Institute (MNI) standard space: -43, -54, -12] (Cohen et al., 2000) has been named the ‘visual word form area’ (VWFA), in order to emphasize its importance in word reading. However, the claim that the mid-fusiform region is dedicated to the processing of visual word forms has been called into question by several investigators (Price & Devlin, 2003, 2011; Hillis et al., 2005), who cite both neuroimaging and clinical evidence of the involvement of the midfusiform region in colour naming and visual object recognition, in addition to reading. These investigators propose that the VWFA may be involved in reading as a function of its interactions with other brain regions, including the angular gyrus in the IPL (Price & Devlin, 2011). The relative contributions to reading made by the mid-fusiform gyrus and the angular gyrus remain unclear.

The aims of the present study were: first, to provide a precise localization of reading-related functional activity within the angular gyrus based on our recent anatomical study of the morphology of the three cSTS branches that define this region; and second, to investigate the relative involvement of the angular gyrus and the mid-fusiform region (VWFA) in reading, and to examine their potential functional interaction during single word reading in healthy control subjects. Specifically, our hypothesis is that the visuo-spatial nature of words requires the contribution of the IPL, of which the angular gyrus is the critical part.

4.4 Materials and methods

Ethics statement

The present study conformed with the Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (18 July 1964). This study was also approved by the Montreal Neurological Institute's (MNI) Research Ethics Board. Informed, written consent was obtained from all participants according to the guidelines set forth by the Ethics Committee of the MNI.

Subjects

Nine healthy volunteer right-handed subjects fluent in English (six males), with an average age of 26 ± 3.72 years, participated. Although four of our subjects had learned English as a second language, including one subject who had learned a dialect of Chinese as a mother tongue, their competency in the English language was very high. At the time of testing, all subjects were functioning at university level in the English language, as demonstrated by the fact that they were studying at the anglophone McGill University.

Experimental Design

Reading minus Pictures of Objects: Copying English words minus writing the names of pictured objects

To isolate brain activation related to reading, we compared an experimental condition requiring reading of single words with a control condition that did not involve reading. In both conditions, subjects wrote a word after seeing a visual stimulus on the screen. In the experimental condition, a written word was presented on the screen, the subject read it, and then wrote that word. By contrast, in the control condition, a picture of an object was presented on the screen, the subject saw it, and then wrote down the name of that object. Both conditions therefore required the writing of words, but the subjects read and copied the words in the experimental condition, whereas, in the control condition, the subject saw pictures of objects and wrote the names of those objects. Although, in the experimental condition, it was possible for the subjects to have viewed the words and copied them passively, i.e. like viewing the words as though they were linguistically meaningless designs, subjects were instructed to read silently the words on the screen and then write them. The university-educated subjects reported having performed all tasks as instructed. Note that the cognitive process of word retrieval was identical in both conditions, except that, in the experimental condition, it was happening through reading. Because, in both conditions, the subject was required to write down words, the motor processes for the common written output were strictly controlled. In addition, as both conditions involved the presentation of stimuli in the visual modality, basic visual processing in the occipital lobe (i.e. primary visual cortex, V1, and peristriate visual areas V2 and V3) should be subtracted out in the categorical comparison between the experimental and the control conditions. Thus, as both tasks required the writing of words, but differed in that, in the experimental condition, the words were accessed via reading, the categorical comparison should show activity related to the reading process as such.

Stimulus presentation

The present study was part of a larger investigation exploring reading and writing, which involved five task conditions. The isolation of writing-related activity, independent of reading, i.e. pure writing, has been described previously (Segal & Petrides, 2012a).

All task conditions involved approximately 60 items (i.e. approximately 60 words or 60 pictures) (Table 4.1). Stimuli were counterbalanced across the runs. Stimulus items did not differ in terms of number of letters [F = 1.838, degrees of freedom (d.f.) = 4, 363, not significant (NS)] or number of syllables (F = 1.338, d.f. = 4, 363, NS). Items were selected to be high-frequency words, and the subjects reported that both tasks were equally easy to perform. For a detailed list of the stimuli used, see Table 1 in Segal & Petrides (2012a).

An instruction on the screen informed the subjects what task condition to perform for the next set of trials. The subjects knew that, after five trials, a new set of instructions would appear. Each trial lasted for 4.5 s. A variable intertrial interval (ITI) of 2.5–7.5 s allowed us to analyse individual trials for each condition as separate events during the event-related statistical analysis. Stimulus presentation was programmed and controlled with E-PRIME 1.1.

Subject training and task performance

On the day of scanning, the subjects received a short training session of 15 min, during which they practised all tasks that they would have to perform in the scanner. During the practice session, subjects were instructed to practise writing words while looking only at the computer screen and away from what they were writing, because, during the scan, they would not be able to view their responses, as they would be lying supine in the scanner with the writing pad at their right side and out of view. The subjects were instructed to write their responses on the same spot on the page (i.e. one word was written on top of the other) in order to limit hand and wrist movement, as well as to limit the recruitment of additional cognitive resources, such as monitoring the spatial layout of the page. Subject performance was monitored closely during the training session. All subjects performed at 100% accuracy.

During the scans, subjects were given a pencil with which to write, and a pad of paper that rested at their right side near their thigh. They could not see what they were writing, removing the possibility of visual interference. The subjects were instructed to write words in their normal writing style, more or less at the same spot on the page, just as they had practised. Before each scanning run, the experimenter gave the subjects a new sheet of paper, and collected the sheet of paper used during the previous run in order to verify that subjects were, in fact, performing the required task. All of the subjects reported that they easily could recognize the pictures of objects and retrieve their names, and that they were familiar with all of the English words that were presented to them. No condition was reported as being easier than any other.

MRI Acquisition

All images were acquired on a 1.5-T Sonata MRI Scanner (Siemens, Erlangen, Germany). After a high-resolution T1 anatomical scan (whole head, 1-mm3 isotropic resolution), seven runs of 145 images each [38 oblique T2* gradient echo planar images covering the whole head; 3.4 x 3.4 x 3.4 mm; time to repeat (TR), 3.5 s; time to echo, 45 ms], sensitive to the blood oxygen level-dependent (BOLD) signal, were acquired. Each run comprised a total of 50 trials: the conditions were presented in blocks of five trials, which were repeated twice in a random counterbalanced order, giving a total of 10 trials per condition per run. For example, one condition began with an instruction that was followed by five trials, followed by new instructions for the next condition, which was followed by five trials, and so on, until the subjects performed the five different tasks twice. One run lasted for approximately 9 min. All of the subjects performed seven runs, except for one subject who performed six runs.

Statistical analysis

Medical Images NetCDF images were acquired from the structural T1 scan and the functional runs. The first three volumes of each functional run were excluded, owing to T1 saturation effects. Functional images were realigned with AFNI image registration software (Cox & Jesmanowicz, 1999), and smoothed with Medical Images NETCDF blur software, which applied a 6-mm full-width half maximum (FWHM) isotropic Gaussian kernel. To correct for possible distortion resulting from motion, the functional images and the T1 anatomical image were linearly registered to the MNI standardized stereotaxic space with in-house software, which is based on multiscale, three-dimensional cross-correlation with an average magnetic resonance image volume aligned with the MNI stereotaxic space (Collins et al., 1994). Functional data for each subject were then superimposed onto the subject's structural scan to visualize the anatomical regions that had a correlated increase in BOLD activity during the various tasks as measured by the functional scans.

Statistical analysis of functional data was performed with FMRISTAT (Worsley et al., 2002). The analysis model was a parametric event related design with six conditions (five tasks plus the ITI). We excluded from the model the temporal period during which the instructions were presented. For all tasks, trial durations were 4.5 s, and ITI durations varied between 2.5 and 7.5 s. The scanner acquired whole brain images at a fixed TR of 3.5 s, producing desynchrony between TR and trial onset time, which allowed for there to be sufficient sampling across the haemodynamic response function. The statistical analysis of fMRI data was based on a general linear model (GLM) with correlated errors. The design matrix of the GLM was convolved with a haemodynamic response function modelled as the difference between two gamma functions timed to coincide with the acquisition of each slice. Temporal drift was removed by adding a cubic spline in the frame times to the design matrix (one covariate per 2 min of scan time), and spatial drift was removed by adding a covariate in the whole volume average.

The correlation structure was modelled as an autoregressive process of 1° (Bullmore et al., 1996). At each voxel, the autocorrelation parameter was estimated from the least squares residuals with Yule–Walker equations, after a bias correction for correlations induced by the linear model. The autocorrelation parameter was regularized by spatial smoothing with a 15-mm FWHM Gaussian filter, and then used to ‘whiten’ the data and the design matrix. The linear model was then re-estimated by the use of least squares on the whitened data, to produce estimates of effects and their standard errors, as well as t-statistics for each comparison of interest. Runs, sessions and subjects were combined by use of a mixed-effects linear model for the effects (as data) with fixed-effects standard deviations taken from the previous analysis. This was fitted by use of residual error maximum likelihood implemented with the estimation maximization algorithm. A random-effects analysis was performed by first estimating the ratio of the random-effects variance to fixed effects variance, and then regularizing this ratio by spatial smoothing with a 15-mm FWHM Gaussian filter for runs and a 10-mm FWHM Gaussian filter for subjects. The variance of the effect was then estimated by multiplying the smoothed ratio by the fixed effects variance to achieve higher d.f. More information on fMRI data analysis with FMRISTAT is available at http://www.math.mcgill.ca/keith/fmristat/.

The resulting t-statistic images were thresholded with the minimum given by a Bonferroni correction, random field theory, and the discrete local maximum, taking into account the non-isotropic spatial correlation of the errors. Significance was determined on the basis of exploratory and directed searches, and on the basis of the spatial extent of consecutive voxels. For a directed search, a cluster volume extent of > 697 mm3 with a t-value of > 3 was significant ($P < 0.05$), corrected for multiple comparisons with the method of Friston et al. (1995). For a single voxel in an exploratory search involving all peaks within an estimated grey matter of 600 cm3 covered by the slices, the threshold for reporting a peak as significant ($P < 0.05$) was $t = 4.75$ (Worsley et al., 1996).

We performed an analysis of functional connectivity to examine increases, as a function of the task, in the correlation between a specified reference voxel and other voxels across the brain. The FMRISTAT method is based on the method described by Friston et al. (1997). Functional connectivity is computed as the correlation across time of the BOLD signal between a reference voxel and all voxels in the rest of the brain. The correlation as such is not of primary interest; the relevant investigation is about how this correlation is modulated by the task (how brain regions increase or decrease their correlation with each other as a function of a given task that the subject is being asked to perform). For example, we identified a reference voxel of interest in the left hemisphere of the IPL at the region between the cSTS2 and cSTS3. Its activity profile during the reading process was found to correlate with the activity profiles of other brain regions, which were then considered to be functionally connected with this reference voxel. The reference voxel values were extracted for each subject from native space after the application of slice time correction. We used the GLM, in which we added regressors for the task events and drift, and then added a regressor for the time course at the reference voxel. We then added an interaction (product) between the task events and the reference voxel time course as a regressor. Finally, we estimated the effect, standard error and t-statistic for the interaction in the same way as described above. Increased functional connectivity between the reference voxels and other voxels in the brain during the word copying task relative to during the picture name writing task is represented by positive t-values.

4.5 Results

Categorical Comparison

Reading (Copying English words) minus Pictures of Objects (Writing the Names of Pictures of Objects)

The aim of this comparison was to isolate regions of the brain that support single word reading (see Experimental design). Activity was observed in the posterior part of the IPL within the angular gyrus region. The activity surrounded the cSTS2, but the greatest intensity was in its posterior bank, and spread onto the cortex that lies between the cSTS2 and cSTS3 (Figure 4.1A; Table 4.2). The multi-subject average xyz coordinates in MNI standard stereotaxic space were as follows: for the left hemisphere, -58, -64, 26, t = 5.29; and for the right hemisphere, 58, -56, 26, t = 4.90. Activation within the angular gyrus region was then investigated on a subject-by-subject basis. The reading-related activity was clearly located between the cSTS2 and cSTS3 in every subject (Figure 4.1B; Table 4.3). Our subjects, all of whom are fluent in English and studying at the anglophone McGill University, were divided into: (i) native English speakers; (ii) speakers with English as a second language; and (iii) one native Chinese speaker (i.e. a native language that is non-alphabetic). For group (i), native English speakers, the average xyz coordinates in MNI standard stereotaxic space were: -56, -64, 32, t = 3.63. For group (ii), English as a second language, the average xyz coordinates in MNI standard stereotaxic space were: -62, -66, 28, t = 4.27. For the native Chinese speaker, the xyz coordinates in MNI standard stereotaxic space were: -56, -62, 20, t = 4.54. In all subjects, the location of the functional peak was between the cSTS2 and the cSTS3 in the angular gyrus region (Figure 4.1B; Table 4.3).

No other activity was observed in the multi-subject average anywhere else in the posterior parietal region. In other words, there was no activity in the postcentral gyrus, the superior parietal lobule, the intraparietal sulcus (IPS), or the anterior part of the IPL (i.e. the supramarginal gyrus). This observation is important, because it emphasizes the specificity of the reading-related activation in the parietal lobe. There was also no activation in Broca’s region (cytoarchitectonic areas 44 and 45) in the ventrolateral frontal lobe. By contrast, activation could be observed in the STS within the lateral temporal cortex (xyz coordinates in MNI standard stereotaxic space: -48, -38, 0, t = 4.45), in what is traditionally thought of as the receptive language zone (Rasmussen & Milner, 1975; Ojemann, 1979).

Functional Connectivity

In order to examine interactions (changes in connectivity) during reading between the region in the angular gyrus in the left hemisphere and the rest of the brain, the voxel with the highest t-value in the peak that was isolated by the categorical comparison was entered as a reference for the functional connectivity analysis. This analysis showed that, during word reading (copying English words minus writing the names of pictured objects), the activity peak within area PG increased significantly in functional connectivity with the inferior frontal region that is involved in orofacial control and expressive language, including ventral premotor area 6 on the precentral gyrus (xyz coordinates in MNI standard stereotaxic space: -56, 2, 30, t = 2.17), area 44 on the pars opercularis (xyz coordinates in MNI standard stereotaxic space: -56, 12, 22, t = 2.46) (Tomaiuolo et al., 1999), and area 45 on the pars triangularis (xyz coordinates in MNI standard stereotaxic space: -38, 36, 4, t = 2.95). There was also an increase in the functional connectivity of this reading-related region of the angular gyrus with brain regions that comprise the ventral visual object processing stream, including the posterior occipito-temporal region (xyz coordinates in MNI standardstereotaxic space: -24, -92, -18, t = 3.64), the mid-fusiform gyrus (xyz coordinates in MNI standard stereotaxic space: -32, -38, -18, t = 2.85), and the posterior part of the superior temporal gyrus, bordering the posterior aspect of the Sylvian fissure (xyz coordinates in MNI standard stereotaxic space: -48, -38, 16, t = 2.56), in what is traditionally thought of as the receptive language zone (Rasmussen & Milner, 1975; Ojemann, 1979) (Figure 4.2; Table 4.4).

4.5 Discussion

Precise localization of reading-related activity within the angular gyrus region

The first aim of the present study was to determine whether reading related activity identified in the IPL in the left hemisphere could be located specifically within the angular gyrus region and to establish its relationship with the details of the morphology of this region, namely the sulcal patterns that recently have been examined (Segal & Petrides, 2012b). Three branches of the cSTS define the angular gyrus region (Segal & Petrides, 2012b), and any activity within the posterior IPL could, in principle, be related to any one of these precise landmarks. The present results demonstrated, first, that reading related activity in the parietal region can be shown to be specifically related to the angular gyrus, with no other significant activity peak occurring in the parietal lobe, and second, that this reading-related activity is centred around the cSTS2.

This precise function–morphology relationship was based on each individual subject’s anatomy (Figure 4.1; Table 4.3). Further confirmation that reading activation is related to the cortex between the cSTS2 and cSTS3 came from entering the stereotaxic coordinates of the average parietal reading peak (xyz: -58, -64, 26) into our cSTS probability maps (Segal & Petrides, 2012b): the reading peak falls clearly posterior to the probability map of the cSTS2. This finding is important, because the cortex lying between the cSTS2 and cSTS3 is cytoarchitectonic parietal area PG (Economo & Koskinas, 1925; Caspers et al., 2008). Therefore, it can be concluded that area PG is the critical region for reading in the IPL. Note that the reading-related activation in the angular gyrus region starts where a short annectant sulcus separates the STS within the temporal lobe from the branches of the cSTS that rise into the parietal lobe. Reading related activity therefore is located clearly in the angular gyrus region of the IPL between the cSTS2 and cSTS3, and not in the posterior temporal region. Also, note that reading-related activity involves the inferior region of the IPL occupied by area PG, and not the more dorsal region that is near the IPS.

Although the classic neurological model of reading based on clinical studies of neurological patients suggests that the angular gyrus region might be critical for reading (Dejerine, 1914; Geschwind, 1965b; Damasio & Geschwind, 1984), the extent of lesions in those studies prevented reading from being related to any precise part of the angular gyrus region. Furthermore, earlier neuroimaging studies either failed to report activity in the angular gyrus or reported activity more generally within the IPL (Bookheimer et al., 1995; Price et al., 1996; Horwitz et al., 1998; Turkeltaub et al., 2002; Joubert et al., 2004; Callan et al., 2005; Church et al., 2008), with the anterior–posterior coordinate, ranging from y -38 to y -72, covering most of the parieto-occipital region. This lack of precision relates both to the paradigms used to study such activity and the absence of detailed anatomical examination of this region of the brain (Segal & Petrides, 2012b). For example, most leading anatomical atlases of the human brain (Talairach & Tournoux, 1988; Ono et al., 1990; Duvernoy, 1999; Mai et al., 2007) have identified only two branches of the cSTS as it continues into the IPL whereas there are three branches. With the use of detailed morphological analysis in individual subjects and a reading paradigm, it could be shown in the present study that reading-related activity was restricted to a specific part within the angular gyrus region (area PG) (Figure 4.1).

Reading-relating activity within the VWFA

The experimental and control task conditions used in the present study both involve stimuli that are presented visually, require subvocal rehearsal of the presented words or of the names of the pictured objects, and require written output. The main difference is that the experimental condition involved reading, whereas the control condition involved pictures of objects. Although reading-related activity in this study was observed in the angular gyrus after comparisons of the experimental and control task conditions (a finding that is consistent with the classic neural model of reading), no activity was observed in the middle part of the fusiform gyrus, i.e. the region previously identified as the VWFA (Dehaene et al., 2002; Dehaene & Cohen, 2011). Interestingly, however, results from the functional connectivity analysis showed that, during the reading of words, activation in area PG of the angular gyrus of the left hemisphere increases its functional interaction with the mid-fusiform gyrus in the inferior temporal region (along with other brain regions), namely the region previously identified as the VWFA (Figure 4.2).

The medio-lateral coordinate that is maximally associated with the VWFA has been reported, on average, at approximately x -43 in MNI standard space (McCandliss et al., 2003), corresponding to the anatomical location of the occipito-temporal sulcus, which forms the lateral boundary of the fusiform gyrus. The activation often spreads into the central part of the fusiform gyrus at various anterior–posterior coordinates (Cohen et al., 2000, 2002, 2008; McCandliss et al., 2003; Cohen & Dehaene, 2004; Dehaene & Cohen, 2011; Szwed et al., 2011) (Figure 4.2B). The functional connectivity results from the present study showing increased functional coupling between a region within the angular gyrus and the middle part of the fusiform gyrus during the reading of words are consistent with the interactive account of reading (Price & Devlin, 2011), which argues that the mid-fusiform gyrus may be involved in reading words through interactions with other brain regions, including the angular gyrus.

The VWFA in the middle part of the fusiform gyrus is likely to be involved in reading because it is part of the occipito-temporal stream that is specialized for processing many classes of visual forms (Vogel et al., 2012). Activation is found in the same region during the viewing of objects and of complex scenes (Malach et al., 1995; Grill-Spector, 2003; Grill-Spector et al., 2006; Kim & Biederman, 2011; Harel et al., 2012). There is a known anatomical connection that directly links posterior IPL with the middle part of the ventromedial temporal region in the macaque monkey (Seltzer & Pandya, 1994; Schmahmann et al., 2007). Therefore, it is possible that, in the human brain, a scene-analysis region of the mid-fusiform gyrus and the parietal reading-related angular gyrus region interact functionally to support the reading process (Turkeltaub et al., 2003; Hashimoto & Sakai, 2004). This notion is supported by studies showing that dyslexia is associated with reduced functional connectivity between the angular gyrus and other brain regions, including the fusiform and lingual gyri of the inferior temporal cortex, as well as Broca’s area (Horwitz et al., 1998). According to our functional connectivity results, the mid-fusiform pattern perception region is not the only part of the cortex interacting with area PG during reading. There are significant interactions with Broca’s region in the left ventrolateral frontal cortex, possibly via the superior longitudinal fasciculus (Petrides & Pandya, 2009), as well as interactions with the posterior superior temporal region (Wernicke’s receptive language region) (Figure 4.2A).

Reading-relating activity within the angular gyrus region

Studies of the effects of lesions on reading have suggested that posterior parietal lesions that involve the angular gyrus impair various aspects of the reading process, including phonological (Warrington & Shallice, 1980; Binder & Mohr, 1992) and semantic processing (Coltheart, 2000; Price et al., 2003). It is important to point out, however, that studies based on lesions resulting from brain disease cannot be localized to specific parts of the posterior parietal region, and even less to specific parts of the angular gyrus region (Brodmann, 1909; Economo & Koskinas, 1925; Critchley, 1966; Caspers et al., 2006; Seghier, 2013). Functional neuroimaging activity in combination with subject-by-subject analysis can provide precise information on whether reading-related activity is located in the angular gyrus and which specific parts (if any) of this large region contribute to the reading process. Our task paradigm isolated a focal peak of activation within the angular gyrus region that lies between the cSTS2 and cSTS3, i.e. the part of the angular gyrus that is related to area PG (Caspers et al., 2006, 2008).

What might be the reason for the involvement of area PG in reading, given that it is the endpoint of the dorsal visuo-parietal processing stream? Word reading is an exquisite example of retrieving semantic meaning from the analysis of visuo-spatial patterns (compare ba with da) in the context of directional movement through space (for example, we read words from left to right, and read paragraphs from top to bottom). Words and letters can be differentiated from one another according to the spatial arrangements of their elements (Vernon, 1957). For example, the words ‘eat’, ‘ate’ and ‘tea’ are all composed of the same basic visual elements (i.e. the same letters), and what distinguishes these words from one another is the spatial order of the elements. Likewise, in words such as ‘pen’ and ‘den’ and in the syllables ‘ba’ and ‘da’, the fundamental distinction is the spatial orientation of certain letter elements (that is, p and d and b and d are rotations of the same visual objects). By contrast, unlike words and letters, objects may be differentiated from one another (e.g. an apple vs. a butterfly) on the basis of size, colour, texture, and form, features which may be apprehended sufficiently by the inferior temporal cortex. The subtraction of picture stimuli from word stimuli demonstrates the engagement of area PG, the endpoint of the visuo-spatial stream, during reading. In other words, aspects of orthographic processing that rely more on visuo-spatial analysis appear to be processed in this specialized part of the dorsal visual processing stream in the left hemisphere, whereas the overall visual object patterns of words may be processed within the ventral visual processing stream along the fusiform gyrus (previously called the VWFA). This conceptualization is in keeping with the well known dissociation within the visual system of a dorsal pathway involved in the processing of spatial properties from a ventral pathway specialized for object recognition (Mishkin & Ungerleider, 1982; Ettlinger, 1990; Goodale & Milner, 1992). It is also supported by clinical evidence suggesting that the ventral occipito-temporal pathway is involved in early stages of reading, when words are detected quickly and at an unconscious level, whereas the dorsal parietal stream supports letter-by-letter assembly at a more conscious level (Gaillard et al., 2006).

Although, undoubtedly, the involvement of area PG in the left hemisphere of the human brain in the reading process is a uniquely human feature of area PG, it is of interest to note that the homologue of area PG in the non-human primate brain belongs to the dorsal stream of information processing. When this region is excised in nonhuman primates, specific visuo-spatial processing deficits can be demonstrated in the absence of impairment in the visual processing of objects in general (Petrides & Iversen, 1979; Mishkin & Ungerleider, 1982). Electrophysiological recording of neurons in area PG in macaque monkeys has also demonstrated that area PG is involved in specialized aspects of visuo-spatial processing, including the perception of spatial relations in complex visual stimuli (Mountcastle et al., 1975, 1987; Motter et al., 1987; Steinmetz et al., 1987). The results from the present study showing that area PG in the left hemisphere of the human brain is engaged during the reading of words, a process that requires the extraction of meaning from visuo-spatial forms are consistent with the known spatial properties of area PG.

The results presented here are also consistent with the pattern of results observed in a previously published study investigating the neural substrates of writing (Segal & Petrides, 2012a). That study demonstrates that activity in the angular gyrus is canceled out when two task conditions involving English words as stimuli are compared. However, when a task condition involving words as stimuli is compared with a task condition involving pictures as stimuli, activation is observed in the angular gyrus, strengthening the argument that this area is involved in orthographic processing, which is largely visuospatial analysis.

Additionally, the writing study shows that activity in the anterior portion of the superior parietal lobule (area PE) is associated with writing, and that area PE interacts with the angular gyrus when subjects write words that have just been read. Therefore, both the present study and the previous study are consistent in showing that activity in the angular gyrus is related to the reading of words.

In conclusion, the present study is the first to identify a specific morphological feature of the IPL, namely the cortex centred around the cSTS2 (area PG), that is related to word reading. This finding adds to a growing literature showing that specific morphological features of the human brain can reliably predict the location of functional activation (Dumoulin et al., 2000; Amiez et al., 2006, 2013). The results of the present investigation indicate that area PG between the cSTS2 and cSTS3 in the left hemisphere of the human brain may be an important region that is specialized for the extraction of meaning from the analysis of the spatial features pertinent to words and may contribute to word reading by supporting orthographic processing.

4.6 References

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4.7 Abbreviations

area PG cytoarchitectonic parietal area G; cSTS2 central branch of the caudal superior temporal sulcus; cSTS3 posterior branch of the caudal superior temporal sulcus; ILF inferior longitudinal fasciculus; IPL inferior parietal lobule; IPS intraparietal sulcus; ots occipital-temporal sulcus; SF Sylvian fissure; SLF superior longitudinal fasciculus; STS superior temporal sulcus; VWFA visual word form area

4.8 Acknowledgements

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4.9 Tables

Table 4.1. List of stimuli

Copy the English Words	**Writing the names of Pictured Objects**
alley	anchor
banjo	bananas
belly	bat
blouse	belt
building	books
candle	boxes
canteen	broom
carpet	cactus
cheetah	cane
clock	cap
cow	carrots
curtain	cat
doll	chair
easel	cigar
elbow	cookies
ferry	croissant
fox	cup
glass	dog
graph	ear
hook	egg
insect	envelope
jeans	fence
kangaroo	flowers
kite	folder

koala	giraffe
leaf	gloves
map	grapes
mill	hammer
mountain	harp
nails	horse
needle	kettle
nymph	kleenex
orchid	ladybug
paintbrush	lemon
phoenix	lion
pool	luggage
quay	monkey
quill	mushrooms
receipt	pants
rhubarb	peanuts
saddle	penguin
sand	pie
satyr	plant
school	pylon
skiis	rabbit
spatula	ring
stove	scissors
sugar	shell
symbol	shorts
tattoo	slide
toes	snake
town	socks
urn	spider
vault	squirrel

walker	stapler
whale	telephone
window	throne
worm	toilet
wrench	tooth
zoo	tree
	umbrella
	wallet

Table 4.2. Focal peaks of activation related to reading (multi-subject)

Left Hemisphere	*x*	*y*	*z*	*t-value*
Anterior temporal area, inferior	-50	-2	-34	4.99
Anterior temporal area, superior	-60	2	-10	5.53
Middle temporal area	-48	-38	0	4.45
Angular gyrus region (between cSTS2 and cSTS3)	-58	-64	26	5.29
posterior intermediate parietal sulcus (pips)	-50	-72	44	4.99
Midline/Medial	*x*	*y*	*z*	*t-value*
Medial area PG	0	-60	42	6.74
Right Hemisphere	*x*	*y*	*z*	*t-value*
Lateral prefrontal area 9	20	44	40	6.80
STG, anterior region	58	8	-28	5.23
Anterior temporal area, inferior	66	-4	-20	5.78
ITG, anterior region	66	-22	-26	5.66
Angular gyrus region (between cSTS2 and cSTS3)	58	-56	26	4.90
Posterior intermediate parietal sulcus (pips)	48	-72	42	6.56

All *t* statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system.

Table 4.3. Location of the functional peak observed between the cSTS2 and cSTS3 for each individual subject during reading

Subject	*x*	*y*	*z*	*t-value*
Subject 1	-48	-72	22	3.33
Subject 2	-62	-66	30	4.93
Subject 3	-56	-62	20	4.54
Subject 4	-58	-66	29	3.27
Subject 5	-46	-68	24	2.54
Subject 6	-34	-56	24	3.43
Subject 7	-54	-70	20	3.20
Subject 8	-44	-58	40	3.36
Subject 9	-62	-60	20	3.18
Average coordinates	-51.56	-64.22	25.44	
Standard deviation	9.32	5.52	6.62	

All t statistics are significant at $p < 0.05$ corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system.

Table 4.4 Functional Connectivity results of the cSTS2/cSTS3 peak during word reading

Left Hemisphere	*x*	*y*	*z*	*t-value*
ventral area 10	-28	60	-6	2.85
area 9	-30	28	38	2.66
anterior pars triangularis/area 45	-38	36	4	2.95
pars triangularis/area 45	-30	32	10	2.85
pars opercularis/area 44	-56	12	22	2.46
ventral premotor area 6	-52	4	0	2.95
dorsal premotor area 6	-36	0	50	2.36
ventral cingulate cortex	-2	8	34	2.56
dorsal cingulate cortex	-4	-24	72	2.66
primary motor cortex, area 4	-26	-18	76	2.95
superior temporal gyrus, middle region	-62	4	-6	2.95
inferior temporal gyrus, middle region	-56	-6	-26	2.46
temporal operculum of insula	-46	-12	-8	2.85
posterior region of superior temporal gyrus	-48	-38	16	2.56
AOCS-v	-56	-68	4	2.27
Fusiform, posterior and ventral part of area 37, dorsal to "VWFA"	-36	-56	-2	2.76
Fusiform, medial to OTS, anterior to "VWFA"	-32	-38	-18	2.85
extrastriate area 19, dorsal	-22	-80	44	2.46
extrastriate area 19, dorsal	-2	-82	48	2.56
extrastriate area 18, dorsal	-16	-74	28	2.66
retrosplenium	-8	-42	6	2.95
Midline	*x*	*y*	*z*	*t-value*
dorsal premotor 6	0	-6	70	4.61

Right Hemisphere	*x*	*y*	*z*	*t-value*
dorsal area 10	30	64	20	3.25
area 9	28	30	42	2.95
anterior insula	40	20	-8	3.24
pars triangularis/area 45	56	20	14	2.46
pars opercularis/area 44	60	6	30	3.54
anterior insula	30	20	-8	3.24
primary motor cortex, area 4	52	-8	56	3.05
ventral circular sulcus of insula	42	-18	-8	3.64
supramarginal gyrus, area 40	68	-32	24	2.95
posterior cingulate, ventral	6	-32	48	3.34
retrosplenium	8	-42	4	3.34
area 37	48	-74	8	2.76
AOCS-v	42	-68	12	2.76
SPL, area 7	24	-60	70	2.85
extrastriate area 19	12	-54	8	2.95
extrastriate area 18	12	-94	10	3.05
extrastriate area 18	4	-86	-10	2.66

All t statistics are significant at p <0.05 corrected for multiple comparisons. The stereotaxic coordinates are expressed in millimeters within the MNI stereotaxic proportional system.

4.10 Figures

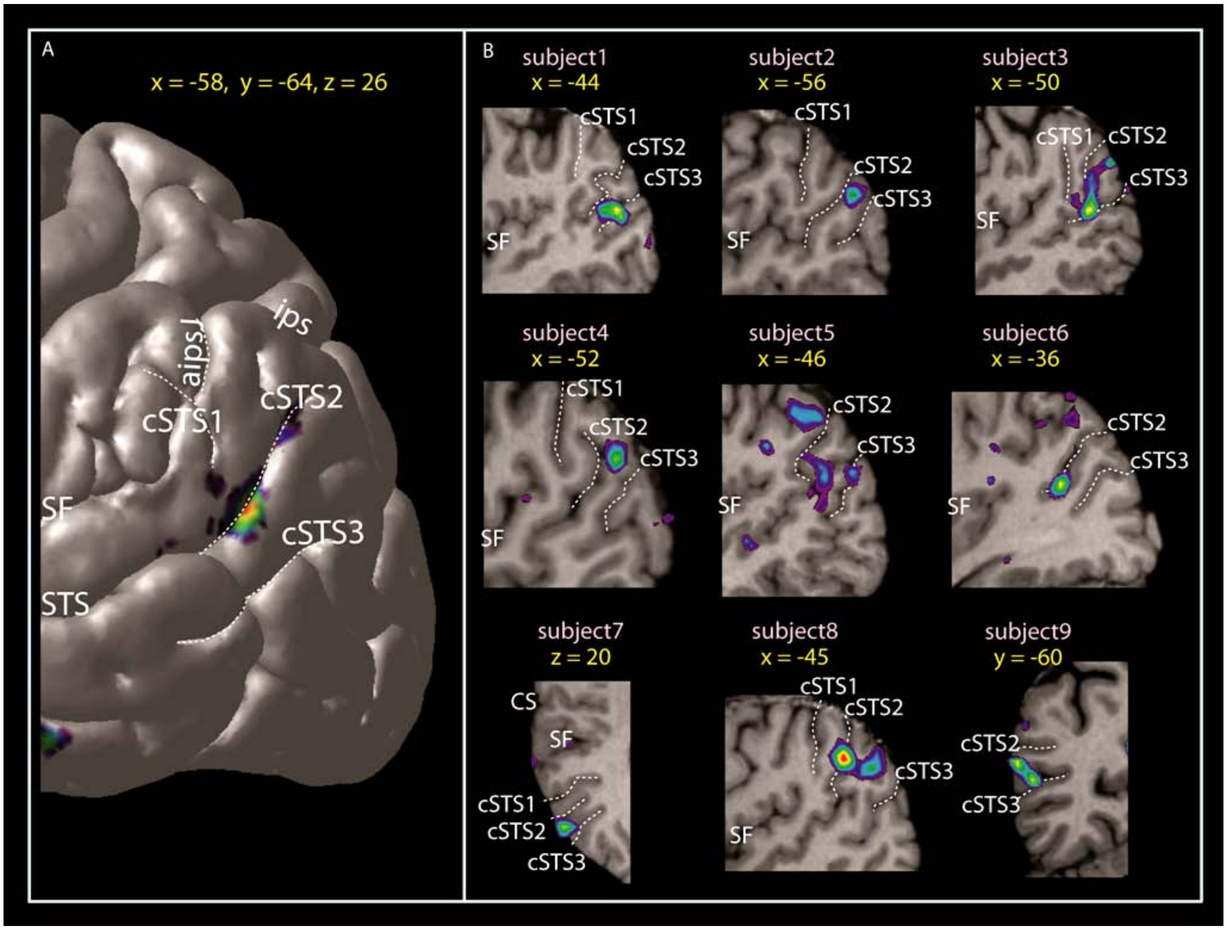

Figure 4.1. Reading-related Activation in the Angular Gyrus. Panel A. Multisubject average of the reading-related activation in the left angular gyrus, superimposed on the reconstructed 3D surface of the MNI average brain. The multi-subject average activation (xyz coordinates: -58, -64, 26, t = 5.29) falls within the central branch of the caudal superior temporal sulcus (cSTS2) and spreads towards the caudal branch (cSTS3). Thus, it is located in the central part of the angular gyrus. Panel B. 2D sections in the sagittal plane to show the reading-related functional data of each subject superimposed on his or her own anatomical MRI. Note that for subject 7 the activity is best displayed in a horizontal section (z = 20) and for subject 9 the activity is best displayed in a coronal section (y = -60). Abbreviations: aipsJ, anterior intermediate sulcus of Jensen; cSTS1, anterior branch of the caudal STS; cSTS2, central branch of the

cSTS; cSTS3, posterior branch of the caudal STS; IPS, intraparietal sulcus; SF, Sylvian fissure; STS, superior temporal sulcus.

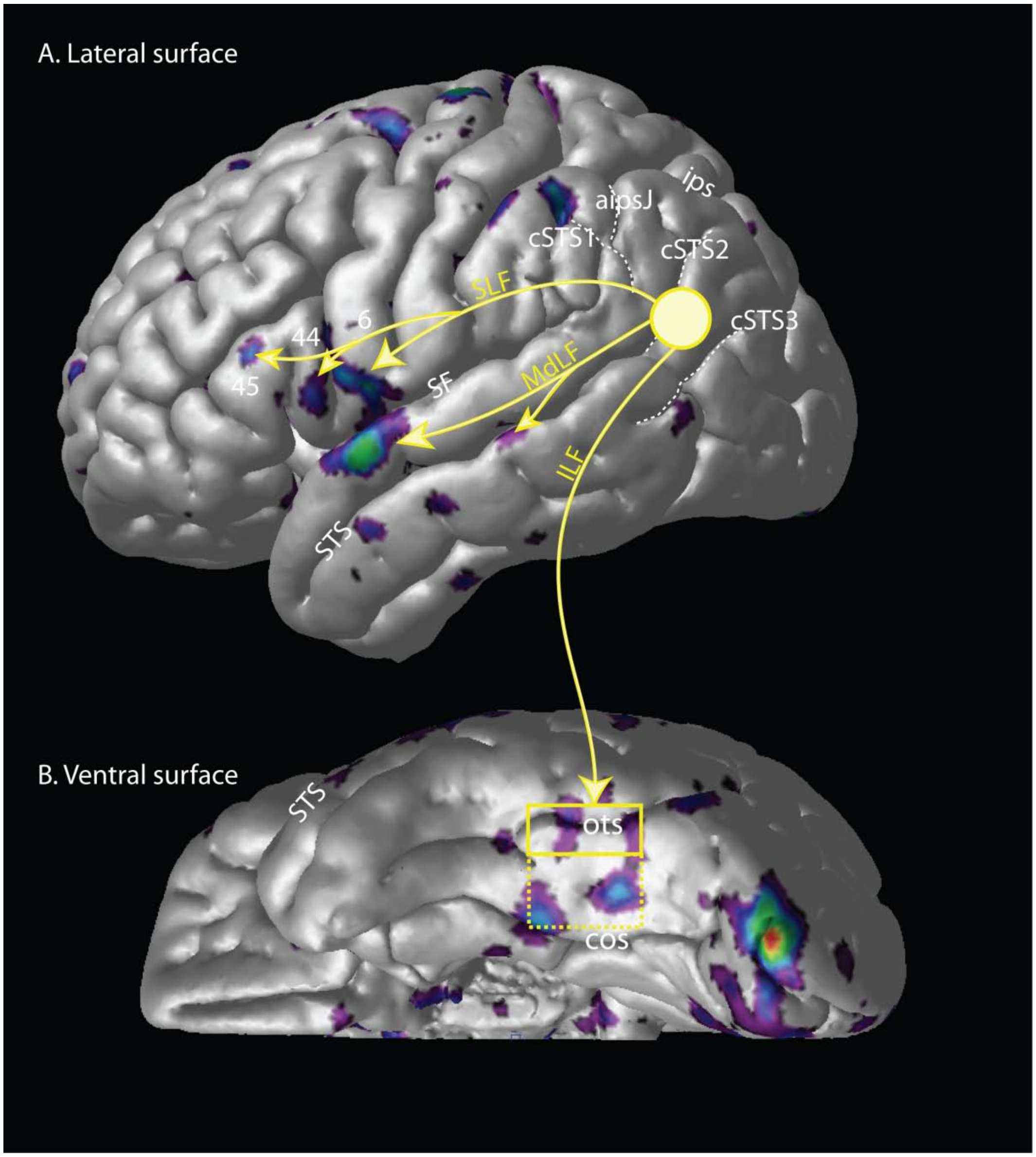

Figure 4.2. Functional interaction of the angular gyrus during reading. Panel A. The functional connectivity analysis demonstrated that, during reading, the region of the angular gyrus located between the cSTS2 and cSTS3 (indicated by the yellow circle) increased its interaction (i.e. functional connectivity) with the ventrolateral region of the frontal lobe that supports expressive language (Broca's region: areas 44 and 45) and the premotor region of the frontal lobe (area 6) that supports orofacial motor control. During reading, the angular gyrus also increased its interaction with parts of the superior temporal gyrus (Wernicke's receptive language temporal region) and with the mid-fusiform region, an area previously

described as VWFA. Panel B. The yellow boxes on the brain's ventral surface outline the extent of the coordinates that have been reported as representing the location of the VWFA. The coordinates associated with the maximum functional peak surround the ots, as outlined by the solid yellow box, but the functional activity spreads more medially and onto the middle part of the fusiform gyrus, as outlined by the dashed yellow box. The arrows indicate known anatomical connections from area PG in the angular gyrus to the regions showing increased interaction. Abbreviations: aipsJ, anterior intermediate sulcus of Jensen; cos, collateral sulcus; cSTS1, anterior branch of the caudal STS; cSTS2, central branch of the cSTS; cSTS3, posterior branch of the caudal STS; ILF, inferior longitudinal fasciculus; IPS, intraparietal sulcus; ots, occipital-temporal sulcus; MdLF, middle longitudinal fasciculus; SF, Sylvian fissure; SLF, superior longitudinal fasciculus; STS, superior temporal sulcus.

Chapter Five

5. General Discussion

The goal of this thesis was to investigate the neural basis of reading and writing in the human brain. We wished to examine the premise of the classic model (Dejerine, 1914; Damasio & Geschwind, 1984) whereby the posterior parietal cortex in the language dominant hemisphere, and in particular the angular gyrus region, is said to be critically involved in both reading and in writing. Evidence from the neurological case studies, on which the classic model is based, show that alexia and agraphia occur when the region of the angular gyrus is damaged. However, these case studies are of cerebrovascular accidents that involve extensive damage to the posterior parietal cortex that includes the region of the angular gyrus, and that may have affected also the white matter fiber tracts that run beneath the angular gyrus that serve to link posterior regions of the brain to frontal and temporal language areas. Accordingly, it remains inconclusive that the alexia and agraphia arose from damage to the white matter fiber pathways or from damage to the angular gyrus in and of itself.

The idea that there is only one neural structure that has evolved to support any single complex cognitive ability, including reading or writing, is unlikely. Rather, it is most probable that reading and writing depend on a network of areas, one of which is the region of the angular gyrus. However, while the classic model describes the angular gyrus as a critical neural structure, it does not tell us about the specific kinds of cognitive processing that the angular gyrus may be performing in its contribution to reading and writing. The functional magnetic resonance imaging studies presented in this thesis (Chapters two and four) were designed to test whether functional activation can be observed in the angular gyrus region during the performance of reading and writing tasks. As well, the functional neuroimaging studies were designed to explore the potential functional relationships between the angular gyrus and other brain regions that most likely are contributing together to the processes of reading and writing.

5.1 The morphology of the inferior parietal lobule

One of the major aims of this thesis was to achieve a better anatomical knowledge of the angular gyrus region (Chapter three). The morphology of the angular gyrus region was necessary to detail in order to study with greater precision the relationship between the angular gyrus and reading and writing functions that is based on the finding that cerebrovascular accidents involving the angular gyrus region produce alexia with agraphia. While cerebrovascular accidents are relatively large and extensive, they allow for structure-function relationships to be established, but on a more global level. By contrast, functional neuroimaging permits more detailed associations to be made between a particular function and a given neural structure that is being examined. However, in the case of reading and writing, few to no neuroimaging studies appear to find correlated functional activation peaks in the angular gyrus region during reading and writing tasks (Turkeltaub *et al.*, 2002), in contradiction with the classic neurological model of reading. Investigations of structure-function relationships using functional magnetic resonance imaging depend on the accurate identification of the neural structures around which functional activation peaks are found. Therefore, using functional neuroimaging to study the relationship between reading and writing and the angular gyrus region has been problematic in the past because the angular gyrus region has been characterized inadequately by the leading atlases of the human brain. The majority of leading atlases (Ono *et al.*, 1990; Watson, 1995; Duvernoy, 1999; Mai *et al.*, 2007; Haines, 2008; Woolsey *et al.*, 2008; Kiernan & Barr, 2009; Felten & Shetty, 2010) do not provide details about the caudal extent of the superior temporal sulcus, and those that do (Ono *et al.*, 1990; Duvernoy, 1999) illustrate two different pairs of caudal sulci that ascend into the inferior parietal lobule.

The results from our study in Chapter three clarify that there are three, rather than two, caudal branches of the superior temporal sulcus that ascend into the inferior parietal lobule (cSTS1, cSTS2, and cSTS3), and a fourth branch that occupies a ventral position in the posterior temporal-occipital lobe junction (the ventral anterior occipital sulcus, or AOCS-v). Importantly, we not only describe the morphology of the caudal superior temporal sulcus branches, but we also examine them in a sample of 45 human brains that had been registered to the Montreal Neurological Institute standard stereotaxic space in order to generate probability maps of these sulci in the same space (see Chapter three, Figure 3.10). By reporting the highest probable location of each caudal superior temporal sulcus branch in standard space xyz coordinates, we provide researchers using functional magnetic resonance imaging with the means to compare directly the location of their functional activation peaks to the probable location of each caudal superior temporal sulcus branch, since both the neuroimaging results and the caudal superior temporal sulcus probability maps are placed in the same Montreal Neurological Institute standard stereotaxic space. This allows for a more precise structure-function relationship between reading and writing and areas within the angular gyrus region to be investigated. Based on the findings from Chapter three, a revisiting of the functional neuroimaging results of past studies reveal that the functional peaks were in fact falling within the region of the angular gyrus, but were not being identified as such.

A key aim of the research presented in this thesis, that we believe has been achieved, was to understand better the morphology of the angular gyrus region. We were ultimately able to provide investigators with an anatomical map of this region so that they may approach the study of the angular gyrus region in a more precise way and may interpret their functional findings within a clearer anatomical context. We believe that we have addressed the need for a more comprehensive representation of the anatomy of the angular gyrus region so that functional activation observed in relation to reading and writing tasks can be localized with greater anatomical precision.

5.2 The angular gyrus and its involvement in reading

A greater anatomical knowledge of the morphology of the angular gyrus region permitted us to localize reading-related and writing-related activity to circumscribed parts within the angular gyrus region with greater specificity. In Chapter four, we demonstrate that the focus of activation that is correlated with reading (copying English words versus writing the names of pictured objects) is found within the angular gyrus region, and, furthermore, that this activation can be related with specificity to the cortex that lies between the middle and posterior branches of the caudal superior temporal sulcus (between the second and third branches, i.e. between cSTS2 and cSTS3) within the angular gyrus region. We therefore were able to relate the process of reading to a precise morphological entity within the angular gyrus region and to find support for the classic model of reading and writing using functional neuroimaging methods. This is the first time that reading-related activation has been associated with a well-defined morphological entity within the inferior parietal lobule, because prior to our anatomical investigation, the morphology of the parietal extent of the caudal superior temporal sulcus branches (i.e. the angular gyrus region) had not been clearly characterized.

Another major issue that this thesis aimed to address was the extent to which a region of the posterior inferior temporal cortex in the left hemisphere could be considered as a "visual word form area." According to several neuroimaging studies (Cohen *et al.*, 2000; Cohen *et al.*, 2002; Dehaene *et al.*, 2002; McCandliss *et al.*, 2003; Dehaene & Cohen, 2011; Szwed *et al.*, 2011) reading-related activation can be observed within the posterior part of the inferior temporal cortex in the left hemisphere. This activation is located close to the occipital-temporal sulcus and spreads medially into the middle part of the fusiform gyrus (see Chapter four, Figure 4.2). The observation of activation within this region has been interpreted as being consistent with Dejerine's account of pure word blindness, whereby damage to the area of the posterior-inferior temporal cortex of the left hemisphere produces reading problems (pure word blindness or pure alexia). However, what Dejerine actually maintained in his description of pure word blindness (Dejerine, 1914) is that damage to the area of the posterior-inferior temporal cortex of the left hemisphere leads to pure alexia insofar as it damages the underlying white matter tracts that carry visual information from visual processing areas within the occipital lobes to the angular gyrus area that supports reading; the posterior inferior temporal-occipital region in and of itself is not a word form area (Dejerine, 1914; Geschwind, 1965; Damasio & Geschwind, 1984).

The study presented in Chapter four of this thesis addresses the discrepancy between the classic model of reading that considers the angular gyrus region within the inferior parietal lobule of the left hemisphere to be the "center of the visual images of words" (Dejerine, 1914), and the more recent claim based on neuroimaging studies that it is the region of the mid-fusiform gyrus within the posterior inferior temporal cortex that functions as a visual word form area (Cohen *et al.*, 2000; Cohen *et al.*, 2002; Dehaene *et al.*, 2002; McCandliss *et al.*, 2003; Dehaene & Cohen, 2011; Szwed *et al.*, 2011). To isolate the brain areas associated with reading, we first compared the brain activity correlated with the copying of English words minus brain activity correlated with the writing of the names of pictured objects. Both of these conditions involve the lexical access of a word and require the same written output (i.e. writing down the word), but in the experimental condition of copying English words, the lexical access occurs via reading, whereas during the control condition of writing the names of pictured objects, the lexical access occurs via a picture. Therefore, a categorical comparison of correlated brain activity in the experimental condition minus that of the control condition should isolate areas of the brain that are associated with word reading. After the categorical subtraction of these two tasks there remains activation observed in the angular gyrus region, however, there is no activation observed in the fusiform gyrus or anywhere along the ventral visual processing stream (see Chapter four, Table 4.2). Interestingly, during the opposite comparison (brain activity correlated with the writing of the names of picture objects minus brain activity during the copying of English words), we see activation along the fusiform gyrus but no activation in the angular gyrus region. Therefore, we are able to determine that brain activation located within the middle part of the fusiform gyrus in the left hemisphere is not specific to reading words per se, but is related more generally to the visual processing of objects.

The idea that the middle part of the fusiform gyrus is a part of the brain that is dedicated expressly to the perception of words has been criticized by other investigators who argue that the so-called visual word form area is involved in reading because it is part of the ventral visual processing stream (Price & Devlin, 2003; Hillis *et al.*, 2005), and that it supports reading insofar as it receives top-down connections from other parts of the brain that are also involved in reading (Price & Devlin, 2011). To test specifically whether the angular gyrus region may be interacting with the region of the middle part of the fusiform gyrus of the left hemisphere during reading, we used an analysis of functional connectivity and demonstrated that during reading there is an increase in the functional coupling between the cortex bounded by the second and third branches of the caudal superior temporal sulcus within angular gyrus region, and the region of the middle part of the fusiform gyrus that has been called previously the visual word form area (see Chapter four, Figure 2). Therefore, our functional connectivity results support the idea that the so-called visual word form area is in a position to receive top-down connections from other parts of the brain that are also involved in reading, specifically the angular gyrus. We were able to show for the first time that during reading in healthy subjects there is an increased functional interaction between these two areas of the brain, among other language-related areas in the lateral prefrontal and temporal lobes.

It is interesting to consider that, on one hand, the functional connectivity results suggest that the middle part of the fusiform gyrus is involved in word reading, yet the categorical comparison used to isolate reading-related areas (i.e. the subtraction of copying English words minus writing the names of pictured objects) does not demonstrate functional activation in the fusiform gyrus. Rather, according to the results from the categorical comparison, we observe activation in the angular gyrus. The observed activation in the angular gyrus after categorical comparison may be explained by considering that the experimental condition of reading words has a strong spatial component to it, relative to the control condition of viewing pictures. For example, we view words in a pre-ordained directional manner, i.e. from left to right in the case of English words, whereas we have no such constraints when viewing a picture of an object. As well, words are distinguished from one another on the basis of spatial ordering of letters whereas pictures are not). Thus, the reason that we see activation in the angular gyrus region after the categorical comparison of copying English words minus writing the names of pictured objects may be due to the requirement of spatial processing, which may depend on the angular gyrus region as it is part of the dorsal visuo-spatial processing stream (Mishkin & Ungerleider, 1982). Similarly, the fusiform gyrus may participate in the processing visual forms, including words, because it is a neural structure that forms part of the ventral visual processing stream (Mishkin & Ungerleider, 1982). Both words and pictures are visual forms, yet there is less visual stimulus input during the viewing of single words than during the viewing of colored objects. Therefore, a lack of activation in the fusiform gyrus during the comparison of copying English words versus writing the names of pictured objects may reflect that the visual stimulus input provided by viewing words is of a lesser degree than is provided by viewing pictured objects. Therefore, in such a comparison, activation in the fusiform gyrus would be subtracted out. Additionally, we would expect also to see greater activation in the fusiform gyrus during the reverse comparison (i.e. viewing pictured objects minus the viewing words) and we do find this pattern of results.

5.3 The angular gyrus and its involvement in writing

The classic model of reading and writing suggests that the angular gyrus region is not only involved in reading, but that it supports both reading and writing as damage to the angular gyrus reading causes alexia *with* agraphia. We investigated the neural substrates of writing and were able to provide evidence that the region of the angular gyrus does in fact support the writing process, so long as writing occurs under the circumstance of reading (i.e. when writing is in response to a word that has just been read). The study presented in Chapter two showed that a specific region within the posterior parietal cortex of the left hemisphere, the anterior part of the superior parietal lobule (cytoarchitectonic area PE), is associated with the writing of words (see Chapter two, Figures 2.2-2.3). The activation in area PE is observed regardless of whether the words being written have just been read, or whether have just been generated by retrieving the names of pictured objects. Area PE, in and of itself, has been shown to be responsive to complex action (including hand orientation) of the hand and the arm, according to the results from electrophysiology studies of area PE in the brain of the macaque monkey (Sakata *et al.*, 1973; Georgopoulos, 1991; Clower *et al.*, 1996). It is reasonable to assume that the area of the brain that is anatomically homologous area PE in the human brain is also functionally homologous, and that understanding the functional properties of area PE in the macaque monkey has direct relevance to the understanding of the functional properties of human area PE. The coding of hand position and orientation would be very relevant to the human act of writing, as the hand takes on different orientations during the writing process the coding of which may be supported by area PE. Given the findings of the electrophysiological recordings from area PE neurons in the brains of the macaque monkey, the increased activation that we observe in area PE during writing in human subjects may reflect the fact that there is a greater range of and a greater variety of hand orientations that need to be computed during the execution of writing movements, compared to during the drawing of loops. A direct comparison of the activity observed during the two experimental writing tasks (i.e. brain activity during the copying of English words minus brain activity during the writing of the names of pictured objects, and vice versa) leads to the activation in area PE being canceled (subtracted) out. Therefore, activation in area PE of the language dominant hemisphere is associated with the act of writing.

However, although we found that the coordinated act of writing yields activation within a specific region of the anterior aspect of the superior parietal lobule (area PE) in the left hemisphere, we were able to show also that the writing-related activation in area PE is correlated with activation within the angular region of the left hemisphere when the words that were being written were accessed via reading (as opposed to being accessed via the naming of pictured objects). Our specific finding of an increased correlation of area PE with the angular gyrus region in particular when the writing is in response to words that have just been read is consistent with Dejerine's clinical observations of damage to the region of the angular gyrus as producing alexia with agraphia. Based on the results from our study, we would also expect that a lesion in the angular gyrus region would lead to problems of writing words that have just been read (i.e. agraphia with alexia). Not only would the lesion interfere with the aspects of the reading process that may be supported by the angular region proper, but also this reading deficit would deprive area PE of the knowledge of what has just been read, meaning that area PE would not be able to compute the hand action (e.g. orientation the hand and arm) required as output to the motor cortex. Although under these circumstances area PE would still be able to coordinate with the motor cortex in order to make markings on the page, these markings would not be the linguistic units that have just been read (i.e. not the letters, words, sentences). In fact, such neuropsychological clinical case reports do exist in the literature (Critchley, 1966).

Damage to the superior parietal lobule, including the region of area PE, in the language dominant hemisphere produces what is known clinically as apraxic agraphia or as pure agraphia: the impaired ability to write even with near-normal spoken output, and no deficits in receptive language, including both intact speech comprehension and intact reading ability (Auerbach & Alexander, 1981; Rajashekar *et al.*, 2009). Although there is clinical evidence to suggest that the SPL supports writing, the extent of the damage that produces the clinical syndrome of apraxic agraphia tends to be quite extensive, including areas within the superior parietal lobule (e.g. area PE), the intraparietal sulcus (e.g. AIP), as well as within the intraparietal sulcus (e.g. PF), parts of area 2, most of the SII and other SII related areas. Therefore, the clinical picture cannot tell us which part of the superior parietal lobule in particular is associated with the coordinated act of writing. As well, the clinical data do not provide details about which other parts of the brain the superior parietal lobule is functionally related to the act of writing.

The neuroimaging results from the writing study (Chapter two) are consistent with the clinical picture of apraxic agraphia. They suggest that damage to area PE would contribute to apraxic agraphia, not only because damage to area PE would lead to a deficit in the ability to direct the hand and arm in space, which would of course lead to writing problems, but also because damage to PE would lead to a functional disconnection of the inferior parietal language areas from the prefrontal areas that control motor output of the hand. Importantly, we were able show that area PE is functionally related to the region of the angular gyrus when writing is in response to reading a word. This is consistent with the classic model of reading and writing whereby the angular gyrus region is important for both reading and writing.

The results from the functional connectivity analysis of area PE, though, raise a question as to whether a lesion in the angular gyrus region would necessarily lead to problems in writing words that are derived from the retrieved names of pictured objects. This is because our results indicate that during the writing of pictured objects an increase in functional correlation is observed between area PE and the anterior aspect of the supramarginal gyrus (see Chapter two, Figure 2.5 and Figure 2.7). That the angular gyrus may not be involved in writing the names of pictured objects appears to stand in contradiction to Dejerine's classic model of reading and writing, as Dejerine's supposition is that the visual pictures of words (i.e. the visual forms of words and letters) are stored in the angular gyrus (Dejerine, 1914). As such, the angular gyrus is necessary for writing in general, regardless of whether the writing is generated spontaneously, is in response to dictation, is in response to reading words, or is in response to pictured objects, because it is where the word forms are stored. Since reading and writing emerged only recently in our evolutionary history, it is of course highly unlikely that any part of the brain is a dedicated "word area" per se. However, this does not preclude the region of the left angular gyrus from storing the general forms of complex shapes that require careful analysis of orientation, such as, but not limited to, words. It may very well be the case that the angular gyrus region is involved in reading and writing because it provides visuo-spatial processing of complex forms on which both reading and writing more generally depend.

5.4 Area PG

The region of the angular gyrus that is bordered by the second and third branches of the caudal superior temporal sulcus (cSTS2 and cSTS3) where we observe an increase in activation that is correlated with reading corresponds to cytoarchitectonic area PG. In the cytoarchitectonic map by Economo & Koskinas

(1925), there are three sulci that are depicted within the inferior parietal lobule. The sulci of Economo & Koskinas appear equivalent to the three caudal superior temporal sulcus branches that we have identified Chapter three, in terms of their relationship to adjacent sulci (such as the Sylvian fissure, the intraparietal sulcus, the transverse occipital sulcus, the lateral occipital sulcus, etc.). In the cytoarchitectonic map by Economo & Koskinas, the cortex lying between the second and third of these branches is comprised of cytoarchitectonic area PG, giving reason to believe that the cortex lying between what we have called the cSTS2 and the cSTS3 branches would be most likely to correspond to cytoarchitectonic area PG.

The homologue of cytoarchitectonic area PG has been established within the IPL of the brain of the macaque monkey (Bonin & Bailey, 1947; Pandya & Seltzer, 1982). Since monkeys do not possess the capacity to read and write, we have to ask ourselves: what process does area PG support in the brains of macaques? If we can understand the functional characteristics of area PG in the monkey then we may be able to understand the precursory cognitive process from which human beings evolved the capacity to read and write.

When the inferior parietal lobule, including area PG, of the monkey is lesioned bilaterally, monkeys are impaired on tasks that are dependent on spatial processing. For example, the classic double dissociation study of Mishkin and Ungerleider (Mishkin & Ungerleider, 1982) shows that monkeys with lesions to the inferior parietal lobule and the dorsal pre-occipital region, namely the dorsal visuo-spatial stream of processing, are impaired on a memory task that requires knowledge of *where* the object is located in space. By contrast, these monkeys are not impaired on a memory task that requires knowledge of *what* an object is. More precise lesions that were limited to the inferior parietal lobule in the monkey demonstrated a severe impairment in the ability to move a stimulus in various directions in space (Petrides & Iversen, 1979). Therefore, lesion studies in the macaque monkey have established that the dorsal occipito-parietal stream of information processing within the inferior parietal lobule in particular (including area PG) is critical for visuo-spatial processing. Electrophysiological recordings of neurons in the inferior parietal lobule of the macaque monkey brain, and specifically of neurons within area PG, confirm the involvement of area PG in visuo-spatial processing. PG neurons are observed to be sensitive to the direction of stimulus movement but not to stimulus speed, and they tend to increase their firing rate to the presence of a stimulus in peripheral space when the subject is fixated on a target in the central line of gaze (Mountcastle *et al.*, 1975; Motter *et al.*, 1987; Mountcastle *et al.*, 1987; Steinmetz *et al.*, 1987). Furthermore, these neurons appear to respond strongly to stimuli that move inward and outward along a particular meridian while the subject is fixated on a central point of gaze (Motter *et al.*, 1987; Mountcastle *et al.*, 1987; Steinmetz *et al.*, 1987). Although the receptive fields of area PG are bilateral (Motter *et al.*, 1987; Mountcastle *et al.*, 1987; Steinmetz *et al.*, 1987), they preferentially code for stimuli that move in and out of the contralateral visual field (Mountcastle *et al.*, 1975; Steinmetz *et al.*, 1987). Thus, the optimal stimuli for these neurons include stimuli that change direction as they cross the fixation point. Area PG neurons do not appear to be driven by eye movements per se because they are found to code for a location in space regardless of whether the location is attended to by a saccadic eye movement or whether the eyes remain still and a stimulus occurs in that same peripheral point in space (Andersen *et al.*, 1987; Crowe *et al.*, 2004). Taken together, the electrophysiological evidence fits well with the lesion data and suggests that area PG is involved in specialized aspects of visuo-spatial processing, including the perception of spatial relations in complex visual stimuli.

5.5 Reading and writing both depend on visuo-spatial processing

If we look at the way in which humans engage in reading and writing, we immediately appreciate the spatial nature of these two tasks. For example, in reading it is necessary for the brain to distinguish between letters on the basis of their spatial features. For example, the letters p, b, d, and q are similar in elemental form (i.e. they are composed of a circle element and a line element), but are differentiable by the spatial orientation of their elemental forms. Likewise, some written words are distinguishable from one another on the basis of different spatial relationships among the same letters. For example, the words "sack" and "cask" consist of the same elements (letters), but are differentiated from one another by the spatial arrangement of the letters. Another important spatial feature of reading is that we engage with the words in a spatially constrained way, for example in English from left to right.

In terms of writing, when we consider the execution of writing individual letters of the English alphabet we see a spatial bias of moving "to the right" as well. For example, consider how we write each of the letters of the English alphabet. In the case of the capital letters (A, B, C, D, etc.), the vast majority are executed "to the right" whereby one finishes to the right of where one starts. The same is true in the case of letters of the lower case alphabet (a, b, c, d, etc.). Children are specifically taught to write letters from the left to the right, but there is no good cognitive reason why, for example, we should teach them to write the letter "A" from left to right. The spatial nature of writing is even more striking when we consider the process of writing down whole words, where we order our letters such that sequentially they are placed on the page from the left to the right in order to form the words that we wish to write. Therefore, there is a strong spatial component to both reading and writing (Vernon, 1957).

However, the proposal that words and letters depend on an orientation "to the right" may be an oversimplification. In fact, when we write down letters we actually may be switching directions: for example writing the letter B, while in gross terms may be considered as going to the right, actually involves switching directions. Recall that monkeys who have bilateral lesions restricted to the inferior parietal lobule and including area PG are unimpaired making straight directional movements, either to the left or to the right; however, a severe impairment occurs in their ability to move a stimulus in complex directions in space (Petrides & Iversen, 1979). As well, recall that the electrophysiological recordings from neurons in area PG showed that the optimal stimuli for these neurons include stimuli that exhibit a directional change as they cross the fixation point. Therefore, it would seem logical to expect that area PG is involved in reading and writing because it supports a specialized aspect of visuo-spatial processing on which both reading and writing similarly depend.

5.6 Is the region of the angular gyrus more of a visual area or more of a language area?

"In 1892 I showed, always by the clinico-anatomical method, that 2 species of word blindness exist, with different symptoms and localized to different areas – word blindness with agraphia, *a variety of sensory aphasia*, and verbal blindness with writing intact – it is easy to distinguish one from the other clinically."

"There exists but one sensory aphasia, understanding at once disturbances of the comprehension of the spoken word and disturbances of reading."

- J. Dejerine, *Semiologie du Systeme Nerveux*, 1914

According to the above passages, it is clear that Dejerine classified alexia with agraphia as a variety of sensory aphasia and that he considered the region of the angular gyrus in the left hemisphere to be involved in language processing. Functionally speaking, the inferior parietal lobule was conceptualized by Dejerine as supporting receptive language in a gradation, with damage to the more posterior part (i.e. the angular gyrus) producing sensory aphasia in the visual modality (i.e. alexia with agraphia), and damage to the more anterior part (i.e. the supramarginal gyrus) producing sensory aphasia in the auditory modality (i.e. receptive aphasia of speech). However, he also attributed to the angular gyrus region the role as a center for the *visual* images of words (Dejerine, 1914), and clearly appreciated the visual nature of reading and writing.

More recent evidence from the field of neurolinguistics demonstrates that patients with damage to the posterior parts of the language dominant hemisphere, including the posterior parts of the temporal, parietal, and occipital lobes, exhibit a variety of reading impairments, including surface dyslexia, phonological dyslexia, and deep dyslexia (Beauvois & Dérouesné, 1979; Coltheart *et al.*, 1980; Hanley *et al.*, 1992; Coltheart, 2000; Price *et al.*, 2003). The literature provides differing conclusions about whether the nature of the deficit underlying these reading problems is due to an impairment of higher-order visual processing or whether it is due to an impairment of language processing (Warrington & Shallice, 1980; Patterson & Kay, 1982; Coltheart, 1998).

The same question applies to the reading deficit that is produced by damage involving the angular gyrus region of the left hemisphere: is it more linguistic in nature, or is it more visuo-spatial? To answer this question, it may be useful to consider a recent anatomical study of area PG and its connectivity with regions of the prefrontal cortex in the macaque monkey (Petrides & Pandya, 2009). The anatomical connectivity of area PG in the macaque monkey shows reciprocal connections between area PG and the homologues of Broca's language areas in the ventrolateral prefrontal lobe (cytoarchitectonic areas 44, and areas 45A and 45B) as well as regions in the mid-dorsolateral prefrontal cortex (area 9/46v). The dorsal part of area PG is reciprocally connected with areas of the prefrontal lobe that are involved in higher-order visual processing (cytoarchitectonic area 8Av) and also with the premotor area 6DR. The neurons in ventral PG have axons that form an arch and that may constitute the arcuate fasciculus, while neurons from dorsal PG have axons that may form part of the superior longitudinal fasciculus II. The connectivity study, therefore, reveals area PG to have connections with both visual attention areas and language-related areas in the prefrontal lobe, with a possible dissociation between dorsal PG and ventral PG. This research has been expanded recently in the human brain by Kelly et al. (2010) who showed a similar profile of connections between homologous regions of the prefrontal cortex and inferior parietal lobule in the human brain using functional resting state connectivity (Kelly *et al.*, 2010). Therefore, there is anatomical evidence to suggest that the angular gyrus region shares connections both with areas that are involved in higher-order visuo-spatial processing and in language processing, and the anatomical evidence therefore suggests that the nature of the reading impairment arising from damage to the angular gyrus region of language dominant hemisphere is neither exclusively visuo-spatial or exclusively linguistic, but rather that it is both.

5.7 Conclusion

The results from our functional neuroimaging studies demonstrate that when healthy subjects perform reading and writing tasks there is correlated activation that can be observed in various parts of the posterior parietal lobule in the language dominant hemisphere. Our results, by in large, support the classic model of the neural basis of reading and writing which presents the angular gyrus of the language dominant hemisphere as being critically involved in reading and in writing. Using parametric event-related functional neuroimaging, evidence was provided that the angular gyrus region is an important component of a network of areas that support reading and writing. The angular gyrus region is anatomically privileged to support reading and writing in that it appears to have connections with both language areas and visual processing areas of the prefrontal lobe. As well, there is evidence to suggest that area PG within the region of the angular gyrus supports particular aspects of visuo-spatial processing on which both reading and writing may critically depend. However, it is important to point out that even while we do find support for the involvement of the angular gyrus in both reading and writing, we do not wish to claim that any part of the brain in and of itself is "a reading area" or a "writing area," as such a claim is misleading. Reading and writing are complex abilities that are likely to depend on contributions from multiple brain regions, a key one of which is the region of the angular gyrus.

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Appendices

Appendix A

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