Investigating the contribution of the right hemisphere to language processing in the damaged and healthy brain

Andrea E. Gajardo-Vidal

May 2019

A dissertation submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Neuropsychology and Cognitive Neuroscience

Wellcome Centre for Human Neuroimaging
UCL Queen Square Institute of Neurology
University College London

Supervised by Professor Cathy J. Price,

Dr Mohamed L. Seghier and Dr Thomas M. H. Hope

Declaration of authorship

I, Andrea E. Gajardo-Vidal, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed declaration

Abstract

Acquired language disorders after stroke are strongly associated with left hemisphere damage. When language difficulties are observed after right hemisphere damage, patients are commonly considered to have atypical functional anatomy (i.e. crossed aphasia). On the other hand, fMRI studies have reported right hemisphere activation when neurologically-normal participants perform language tasks, and have shown that the right hemisphere contributes to recovery of language function after left hemisphere damage. In this thesis I investigated (i) the degree to which language difficulties after right hemisphere stroke can reflect disruption to typical functional anatomy and (ii) how the damaged areas contribute to normal language processing.

In Study 1 (Chapter 3), I investigated a group of patients with unilateral strokes that damaged either the right or the left hemisphere. The most frequently impaired language task was auditory sentence-to-picture matching after right hemisphere strokes, and spoken picture description after left hemisphere strokes. In 9 right hemisphere stroke patients, performance on the auditory sentence-to-picture matching task was selectively impaired and could not be explained by poor perceptual (visual or auditory) or linguistic processing (semantic, phonological or syntactic). I therefore hypothesised that the behavioural difficulties experienced by those patients arose as a consequence of impaired non-linguistic executive functions that are needed to support language processes.

In Study 2 (Chapter 4), I investigated the lesions of the 9 patients with selective deficits in the auditory sentence-to-picture matching task, and found that

they had significantly more damage to subcortical regions and parts of the superior longitudinal fasciculus impinging on the right inferior frontal sulcus compared to other right hemisphere stroke patients who were not impaired on the sentence comprehension task. Having identified these regions, their function (e.g. linguistic or executive) can be investigated using functional neuroimaging in neurologically-normal participants.

In Study 3 (Chapter 5), I used fMRI to investigate whether any parts of the right hemisphere regions associated with impaired sentence comprehension, in Study 2, were activated when neurologically-normal participants performed similar language tasks to those administered to right hemisphere stroke patients in Study 1 (including the auditory sentence-to-picture matching task). I found that, within the brain areas derived from Study 2, the right inferior frontal sulcus and right mediodorsal thalamus were normally activated by auditory sentence-to-picture matching but there was no evidence that these regions were exclusively performing linguistic functions.

In Study 4 (Chapter 6), I investigated the contribution of the identified regions further by using a new fMRI study of one-back matching tasks that varied demands on semantic and non-semantic working memory. By systematically integrating neuropsychological, lesion and fMRI data, I conclude that the right inferior frontal cortex and right mediodorsal thalamus contribute to non-semantic working memory capacity that is needed to accurately perform a range of language functions. This account helps to explain why auditory sentence-to-picture matching impairments occur after right hemisphere damage.

Impact Statement

Each year approximately 4 million stroke survivors are left with aphasia, which is an umbrella term used to refer to acquired difficulties in speech production, speech comprehension, writing and/or reading. Post-stroke aphasia is one of the most disabling behavioural consequences of stroke and is typically associated with damage to the left side of the brain. The role of the right hemisphere in the incidence of aphasia is, however, less well understood. This is because the dominant view portraits language abilities as being almost exclusively supported by brain regions in the left hemisphere. And when acquired language disorders are observed after damage to the right side of the brain, it is commonly assumed that the affected person had atypical language lateralisation prior to the stroke. An increasing number of functional neuroimaging studies of neurologically-intact individuals have, on the other hand, reported bilateral brain activation during language processing. This is, in turn, consistent with evidence suggesting an involvement of the right hemisphere in aphasia recovery.

The current thesis focused on the contribution of the right hemisphere to language processing by (A) investigating the speech and language abilities of a large sample of stroke survivors with unilateral right hemisphere damage, (B) identifying the brain regions associated with language impairments, and (C) using functional neuroimaging to characterise the functional role of the regions derived from step B in neurologically-normal subjects.

From a conceptual perspective, the relevance of the reported findings is that they highlight that impaired language function after right hemisphere damage is not necessarily the result of atypical functional anatomy or inter-subject variability. From a methodological perspective, the findings illustrate how functional neuroimaging of neurologically-intact individuals can be used to characterise the normal functional contribution of regions identified by unexpected lesion-deficit relationships. From a clinical perspective, the findings indicate that the detrimental impact of right hemisphere strokes on language (particularly on speech comprehension) is (a) much greater than expected; (b) frequently observed after damage to the right inferior frontal sulcus; (c) task dependent; (d) different to the type of impairments observed after left hemisphere strokes; and (e) can result in long-lasting deficits.

Given the high incidence of aphasia among stroke survivors, it is therefore reasonable to suspect that the number of patients with speech comprehension difficulties after right hemisphere damage is likely to be substantial. Clinicians should in consequence be aware of the possibility that patients with right hemisphere damage may suffer from long-lasting speech comprehension difficulties, rather than assuming that language impairments are only seen after left hemisphere damage. Finally, one key observation is that damage to the right inferior frontal sulcus is frequently associated with speech comprehension difficulties, and that these difficulties are plausibly the result of reduced working memory capacity. This suggests that training the working memory abilities of patient with speech comprehension difficulties in the context of unilateral left hemisphere damage in conjunction with neurostimulation delivered over the right inferior frontal sulcus may prove to be a promising treatment alternative.

Acknowledgments

I owe my deepest gratitude to my PhD supervisor, Prof Cathy Price, and my husband Diego.

Cathy, your guidance and support were crucial to complete my PhD. I would like to thank you for encouraging my research ideas and for allowing me to grow as a neuroscientist. Your advice on both research- as well as career-related aspects of my PhD have been invaluable.

Diego, there are no words to describe how important your company, love, help and advice have been throughout these five years. Thank you for being the best partner that life could give me and for your unconditional support.

Thank you to my parents (Grette and Andres), my sisters (Grette and Ingrid) and my lovely nieces (Amparo and Rafaela) for your love, encouraging conversations and for always being supportive. Also a big thank you to my parents in law (Liliana and Alejandro) for your wise advice.

I would also like to thank everyone in the language group, for being incredibly helpful and supportive during my PhD. Special thanks to Thomas Hope, Mohamed Seghier, Philipp Ludersdorfer, Marion Oberhuber and Louise Lim. Thank you to Prof David Green, for his insightful comments and advice. To the recruitment team, past and current members, for taking care of the patients and for being so kind and helpful throughout.

I am also extremely grateful to the Chilean National Commission for Scientific and Technological Research (CONICYT) for funding my PhD.

Finally, thank you to all the stroke survivors and research participants who took part in my studies. Without their commitment and patience this thesis would not have been possible.

Statement of publications

The work I have been involved in during my PhD has resulted in the following peer-reviewed publications:

Gajardo-Vidal, A., Lorca-Puls, D.L., Hope, T.M.H., Parker Jones, O., Seghier, M.L, Prejawa, S., Crinion, J.T., Leff, A.P., Green, D.W., Price, C.J., 2018. How right hemisphere damage after stroke can impair speech comprehension. Brain 141, 3389-3404.

Gajardo-Vidal, A., Lorca-Puls, D.L., Crinion, J.T., White, J., Seghier, M.L., Leff, A.P., Hope, T.M.H., Ludersdorfer, P., Green, D.W., Bowman, H., Price, C.J., 2018. How distributed processing produces false negatives in voxel-based lesion-deficit analyses. Neuropsychologia 115, 124-133.

Lorca-Puls, D.L., **Gajardo-Vidal, A**., Seghier, M.L., Leff, A.P., Sethi, V., Prejawa, S., Hope, T.M.H., Devlin, J.T., Price, C.J., 2017. Using transcranial magnetic stimulation of the undamaged brain to identify lesion sites that predict language outcome after stroke. Brain 140, 1729-1742.

Lorca-Puls, D.L., **Gajardo-Vidal, A.,** White, J., Seghier, M.L., Leff, A.P., Green, D.W., Crinion, J.T., Ludersdorfer, P., Hope, T.M.H., Bowman, H., Price, C.J., 2018. The impact of sample size on the reproducibility of voxel-based lesion-deficit mappings. Neuropsychologia 115, 101-111.

Loughnan, R., Lorca-Puls, D.L., **Gajardo-Vidal, A.,** Espejo-Videla, V., Gillebert, C.R., Mantini, D., Price, C.J., Hope, T.M.H., 2019. Generalizing post-stroke prognoses from research data to clinical data. Under review at Neuroimage Clinical.

Particularly important for the current thesis, the bulk of the findings presented in Chapters 3 to 6 has been reported in Gajardo-Vidal et al. (2018, Brain).

Table of Contents

Abbreviations

RH	Right hemisphere
LH	Left hemisphere
RHS	Right-hemisphere stroke
LHS	Left-hemisphere stroke
fMRI	Functional magnetic resonance imaging
MRI	Structural magnetic resonance imaging
PET	Positron emission tomography
TMS	Transcranial magnetic stimulation
EEG	Electroencephalography
MEG	Magnetoencephalography
TDCs	Transcranial direct stimulation
RH-BD	Right hemisphere brain damaged
IFG	Inferior frontal gyrus
SMG	Supramaginal gyrus
rTMS	Repetitive transcranial magnetic stimulation
PPC	Posterior parietal cortex
ERP	Event-related potential
CAT	Comprehensive aphasia test
RF	Radiofrequency
ALI	Automated lesion identification toolbox
SPM	Statistical parametric mapping software
GM	Grey matter
WM	White matter
LOM	Lesion overlap map
VBM	Voxel-based morphometry
VLSM	Voxel-based lesion-symptom mapping
HRF	Hemodynamic response function
BOLD	Blood oxygenation level dependent signal
EPI	Echo-planer imaging

GLM	General linear model
FWE	Family-wise error correction
ARTQ	Aphasia recovery and therapy questionnaire
Aud Sent-Pic	Auditory sentence-to-picture matching task
ITI	Inter-trial-interval
RTs	Response/Reaction times

List of figures

List of tables

CHAPTER 1: INTRODUCTION

1. 1. Motivation and aims

A crucial role for the left hemisphere in language processing was established as a result of the seminal works of Broca (1865) and Wernicke (1881) who discovered that brain damage to the left inferior frontal gyrus induced a reduced capacity for speech production whereas damage to the left superior posterior temporal gyrus was associated with language comprehension difficulties. A century later, Geschwind (1965a, b) reinterpreted these findings and added more evidence for the importance of white matter tracts in the left hemisphere for language processing. Together, these and other studies in brain-damaged patients led to the concept of “left hemispheric dominance” for language with little or no potential for language functions in the right hemisphere.

In the last thirty years, the rapid development of neuroimaging techniques has made it clear that the two cerebral hemispheres play cooperative roles in language and communication (Jung-Beeman, 2005; Bernal and Ardila, 2014). However, despite recent findings suggesting a more significant involvement of the right hemisphere in language, there are very few studies currently available which have investigated the anatomo-functional organization of language systems in the right hemisphere. Therefore, the aim of this thesis was to investigate the contribution of the right hemisphere to language processing by analysing data from a large sample of right hemisphere stroke (RHS) patients and neurologically-normal subjects. This thesis includes 4 studies which are introduced in the next section.

1.2. Summary of the core aims

In Study 1, I aimed to determine the most typical language processing impairments observed following right and left hemisphere damage in a large sample of stroke patients. The large data sets that were available to me provided a unique opportunity to compare language performance in left versus right hemisphere stroke patients and identify a range of concomitant behavioural impairments and the underlying processes that would help to explain why right hemisphere stroke (henceforth RHS) patients were impaired on any language tests.

In Study 2, I sought to investigate the lesion sites of the patients with right hemisphere lesions and impaired performance on the language tasks defined in Study 1. First, I used voxel-based lesion-deficit analysis to compare brain damage in patients with and without impaired performance. I then determined how frequently damage to the identified regions was observed in other patients with and without the deficit of interest and whether there were other regions that impaired performance but were not detected by the voxel-based lesion analysis.

In Study 3, I used functional MRI to define which parts of the regions of interest identified in Study 2 were activated when neurologically-normal participants perform a range of language tasks. This allowed me to examine how activation within the regions of interest responded to demands on visual, auditory, semantic, phonological and/or sentence level processing.

Finally, in Study 4, I aimed to investigate the function of the right hemisphere regions identified in Study 3 further by using a new fMRI paradigm in neurologically-normal subjects that determined whether the identified regions are responsive to demands on semantic or non-semantic working memory.

1.3. Background / Literature review

There is general consensus that the left hemisphere is dominant for language in most right-handed individuals (Toga and Thompson, 2003). In line with this, classic models of language – originated from the pioneering work of researchers in the late 19th century (for a review see Tremblay and Dick, 2016) - have traditionally proposed a left-lateralised language network composed of (i) an anterior inferior frontal area (referred to as "Broca's area"), (ii) a posterior temporal area (referred to as "Wernicke's area") and (ii) a single white-matter pathway that connects both regions (referred to as "the arcuate fasciculus"). However, in the last thirty years, the advent of functional neuroimaging techniques has extended the left-hemisphere-cortico-centric view of regions by also reporting activation in the right hemisphere when neurologically-normal subjects perform language tasks (Crosson et al., 2003; Jung-Beeman, 2005). More recently, transcranial magnetic stimulation (TMS) studies have added more evidence for a causal contribution of right hemisphere regions to language processing (see Hartwigsen et al., 2010a, b, 2013; Sollmann et al., 2014). However, in all these studies the precise role of the right hemisphere in language remains unclear; some have, for example, proposed that it may support domain-general cognitive functions (e.g. executive functions) that are required to perform language tasks (Vigneau et al., 2011). In this context, right hemisphere activation for language tasks could, for example, reflect visuospatial attention (Corbetta et al., 2005; Hillis et al., 2005; Bartolomeo et al., 2012), working memory (Ravizza et al., 2005), or inhibitory control (Aron et al., 2014).

In addition, findings from lesion and functional neuroimaging studies of left-hemisphere stroke patients have suggested an important role for the right hemisphere in the recovery of language functions (Crinion and Price, 2005; Baum et al., 2012). Nevertheless, there is an ongoing debate on this topic, with some studies showing that increased right hemisphere activation after left-hemisphere stroke may reflect a maladaptive strategy that negatively impacts on long-term recovery (Saur et al., 2010).

In what follows, I will review prior literature on the contribution of the right hemisphere to language processes in the damaged and healthy brain.

1.4. The role of the right hemisphere in language processing in the damaged brain

The right hemisphere has traditionally been associated with subtle aspects of language such as pragmatics, prosody, emotional expression, and discourse (Tompkins, 1998; Myers, 1999). Therefore, it is not rare to observe that, after right hemisphere brain damage, patients often present with a wide range of communication impairments that commonly have a negative impact on their functional performance in social contexts. In addition, right hemisphere brain damaged (RH-BD) patients may also exhibit cognitive disorders. These may include visuo-spatial neglect as well as difficulties with visual memory and executive functions (i.e. problem solving, reasoning, organization, planning, and self-awareness). Together, these difficulties are commonly referred to in the literature as “cognitive-communication disorder” (Myers, 1999; Tompkins 2011, 2012). Some of the most commonly observed cognitive and communicative disorders in RH-BD patients are listed in Table 1.1 (for a review see Tompkins et al., 2011).

Table 1.1. Most commonly observed impairments following right hemisphere damage (adapted from Tompkins et al., 2011)

I.- Language
1. Discourse production: Is disrupted, verbose, and tangential with abrupt topic shifting. 2. Discourse comprehension: Draw incorrect inferences/conclusions from what they read or are told 3. Conveying or interpreting things (pragmatics): Have difficulty catching on to hints from others
II.- Communication
1. Expressive aprosodia: Exhibit little modulation of vocal intonation 2. Receptive aprosodia: Have difficulty interpreting emotions or intentions from other people's voices 3. Inappropriate interpersonal communication: Exhibit communication that is inappropriate for the situation
III.- Cognition
1. Attention: Have difficulty following lengthy instructions or conversations 2. Visuo-spatial processing: Exhibit unilateral neglect 3. Memory: Have difficulty recalling information recently heard or read 4. Executive functions: Have difficulty planning daily activities, monitoring behaviour, sustaining appropriate behaviour and/or adjusting behaviour

In contrast, strokes to an extended network of regions in the territory of the left middle cerebral artery may lead to aphasia (Pedersen et al., 1995, 2004; McNeil and Pratt, 2001). Aphasia is defined as an acquired language disorder that typically produces devastating impairments in language production and/or comprehension, reading and/or writing that have an adverse effect on functional outcome, mood, quality of life and the ability to return to work (Ferro and Madureira, 1997). Acquired language disorders are frequently observed after left hemisphere stroke (in about a third of stroke survivors; Pedersen et al., 1995), but rarely reported following damage to the right hemisphere, and when they occur they are typically referred to as 'crossed aphasia'.

1.4.1. Is crossed aphasia the result of atypical language lateralisation?

Traditionally, the criteria for the diagnosis of crossed aphasia includes (i) evidence for a language disorder as a result of a lesion confined exclusively to the right hemisphere with a structurally intact left-hemisphere; (ii) absence of early brain damage; (iii) evidence of right-handedness, and (iv) no familiar history of left-handedness (Marien et al., 2004). The estimated incidence of crossed aphasia in dextrals varies between 1% and 13% (Alexander and Annett, 1996); and it is generally accepted that crossed aphasia represents no more than 3% of all cases of aphasia (Ha et al., 2012). The main reason for the low frequency of crossed aphasia cases is that language is predominantly left-lateralized in approximately 95% of right-handers and in 70% of left-handers (Knecht et al., 2000, 2002). Therefore, the presence of acquired language disorders after right hemisphere damage implies that language functions may had been atypically lateralised in these individuals prior to their stroke (Marien et al., 2004).

In the crossed aphasia literature, two major patterns of atypical language lateralisation have been traditionally cited: mirror and anomalous lateralisation of language functions (Henderson, 1983; Alexander et al., 1989; Alexander and Annett, 1996). The mirror image pattern proposed by Henderson (1983) involves a topographically identical migration of left hemispheric language functions to the right hemisphere regions such that the right hemispheric areas processing language are identical to the ones in the left hemisphere. According to this view, a lesion in the perisylvian language cortex of the right hemisphere will result in (crossed) aphasia, similar to that observed following damage to contralateral regions in the left hemisphere. Anomalous lateralisation, on the other hand, refers to a deviation from a mirror image functional migration where the allocation of language functions is assigned to non-homologous regions of the right brain such as prerolandic or perirolandic areas (Alexander et al., 1989).

In brief, all the evidence seems to suggest that crossed aphasia is the result of pre-morbid atypical lateralisation of language functions in the right hemisphere. However, despite the extensive investigations and case studies reported in the last three decades, there are still many unanswered questions about how and why language functions are predominantly lateralised to the left hemisphere in most right-handed neurologically-normal individuals.

1.5. Reviewing human hemispheric specialization for language

Converging findings from neuropsychological and neuroimaging studies in neurologically-normal individuals have supported the existence of behavioural (functional) and anatomical (structural) asymmetries between hemispheres. For example, the left hemisphere has been shown to be specialised for language and motor functions while the right hemisphere has been shown to be more specialised for visuospatial and attentional processing (Toga and Thompson, 2003; Herve et al., 2013).

1.5.1. Evidence from clinical studies

Over 40 years ago, Gazzaniga and colleagues published several articles on disconnection syndromes, in which they described a case series of patients who had undergone the surgical resection of their corpus callosum in order to treat epilepsy and other rare neurological conditions (Gazzaniga et al., 1962, 1963, 1979). These patients, who are typically referred to as ‘split-brain patients’, presented with a wide variety of cognitive and language disorders as a result of altered interhemispheric communication. Reports of split-brain patients (with a dissected corpus callosum) who could recognise words, pictures and abstract figures (Zaidel and Peters, 1981; Gazzaniga, 2000) but not use word order to understand sentences (Gazzaniga et al., 1984) have been informative to determine the extent to which the right hemisphere is able to process language.

Further evidence comes from clinical studies using the ‘WADA test’ in patients who were undergoing surgery to treat epilepsy. This procedure basically involves an anaesthetic injection (of sodium amytal) to one hemisphere, and is used to determine which hemisphere is dominant for a given language function (Rasmussen and Milner 1977; Zatorre et al., 1989). Transient anaesthesia was expected in the hemisphere ipsilateral to the injection. In the dominant hemisphere, anaesthesia typically results in transient naming difficulties, however, patients may be able to recite the days of the week. Together, these studies provided evidence that the right hemisphere was able to perform some tasks that involve semantic processing whereas the left hemisphere was needed to produce and comprehend all aspects of language, including syntax (Gazzaniga, 2000; Toga and Thompson, 2003). However, these findings also raised the possibility that different ‘language centres’ may be lateralised to either the left or right hemisphere.

1.5.2. Evidence from studies in neurologically-normal subjects

Hemispheric differences in speech and language processing capacity have also been investigated in neurologically-normal subjects using non-invasive techniques such as (i) dichotic-listening (Kimura, 1961; Cowell and Hugdahl, 2000), (ii) functional Transcranial Doppler ultrasonography (Knecht et al., 2000; Bishop et al., 2009), (iii) functional MRI (Arora et al., 2009; Seghier et al., 2011), and (iv) TMS (Knecht et al., 2003). Findings from these and other studies have consistently shown that the left hemisphere is specialised for language processing in more than 90% of right-handed individuals and in approximately 70% of left-handed subjects (Knecht et al., 2000, 2003; Josse et al., 2009), which in turn, has led to genetic theories linking hemispheric specialisation with handedness and the emergence of language (Crow, 2010). However, despite this irrefutable evidence, it has also been shown that language lateralisation may considerably vary in side and extent within individuals for different language functions as well as between subjects (Seghier et al., 2011; Bradshaw et al., 2017).

In the last fifty years, one of the most extensively used techniques to assess language lateralisation involves dichotic listening (Hugdahl, 2011; Kimura, 2011). Verbal dichotic listening paradigms basically involve the presentation of two slightly differing verbal stimuli (e.g. consonant–vowel syllables), whereby one stimulus is presented to the left ear and the other one is simultaneously presented to the right ear. Participants are instructed to report the syllable that was perceived best and usually report the right rather than the left-ear stimulus. This behavioural auditory laterality effect is used as a reliable indicator for determining left-hemispheric dominance for speech and language processing (see Kimura, 1967; Tervaniemi and Hugdahl, 2003; Toga and Thompson, 2003; Della Penna et al., 2007). Importantly, findings of these studies are consistent with those of clinical studies of patients (see section 1.5.1) showing that the left-hemisphere is dominant for most aspects of language. Nevertheless, a recent study challenged this notion by reporting, in a large group of 104 right-handed neurologically-normal participants, that both hemispheres – not only the left – are engaged by verbal dichotic listening, suggesting a more complex relationship between behavioural laterality and functional hemispheric activation asymmetry (Westerhausen et al., 2014). In line with this, a recent review of 76 papers that used fMRI to investigate language lateralisation, found that different language tasks show different levels of lateralisation (for details, see Bradshaw et al., 2017).

1.5.3. Structural asymmetries

In addition to functional differences between hemispheres, studies involving structural magnetic resonance imaging (MRI) techniques have reported significant anatomical differences between the left and right hemispheres. For instance, leftwards asymmetry has been reported for Broca's region using cytoarchitectonic analysis (Amunts et al., 1999), and for the pars opercularis using in vivo MRI-based measurements (Keller et al., 2007). Moreover, grey matter concentration differences in the pars opercularis have been found to correlate with language dominance as assessed by the Wada test (Dorsaint-Pierre et al., 2006).

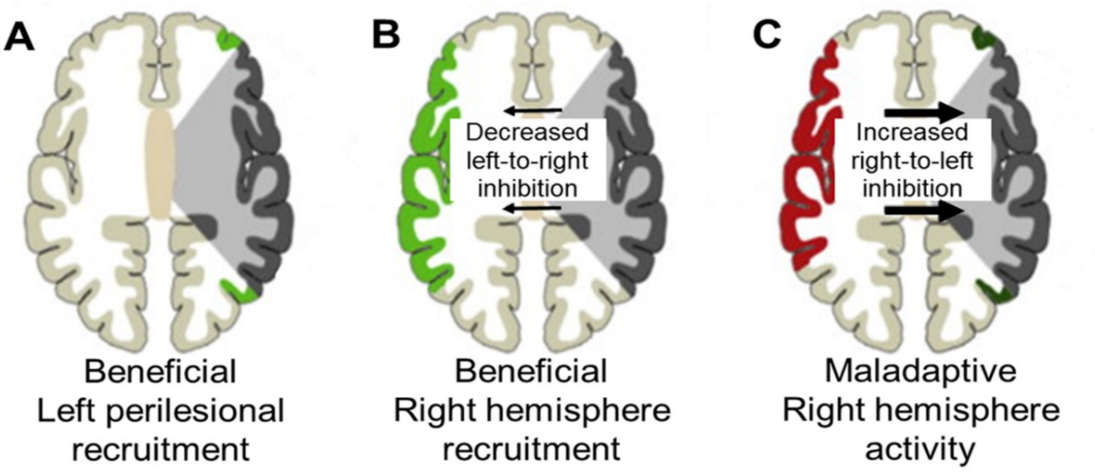
More recent methodological advances in diffusion imaging tractography (DTI) have permitted the study of asymmetries of white matter tracts including the arcuate fasciculus which connects temporal, parietal, and frontal language regions (Powell et al., 2006; Catani et al., 2007; Glasser and Rilling, 2008). For instance, it has been reported that there is substantial inter-subject variability in lateralisation patterns of the individual segments of the arcuate fasciculus across neurologically-normal individuals (Catani et al., 2007). The direct long segment of the arcuate fasciculus has been found to be bilaterally distributed in approximately 40% of the neurologically-normal population and extremely left lateralised in the remaining 60% (Catani et al., 2007; Forkel et al., 2014). Consistent with this, a resting state functional connectivity study found strong left-lateralisation of classical language regions (i.e. Broca’s and Wernicke’s areas) whereas right-lateralised hubs included the lateral intraparietal sulcus, anterior insula, and prefrontal cortex, that previous studies have associated with the attention control network (Nielsen et al., 2013).

To summarise, the left hemisphere specialization for language processing has been related to functional and structural grey matter asymmetries and more recently to differences in white matter and functional connectivity (Catani et al., 2007; Nielsen et al., 2013; Forkel et al., 2014). Despite the irrefutable advantage of the left hemisphere for language in right-handed neurologically-normal subjects, it has also been shown that the pattern of lateralisation of language functions varies with handedness, gender, age, and other factors (Toga and Thompson, 2013). This shows that language laterality is a multifactorial and complex process rather than unitary, with different language functions developing hemispheric lateralisation independently, and to varying degrees (Bishop, 2013).

1.6. The contribution of the right hemisphere to language recovery after left hemisphere stroke

Accumulating evidence from studies investigating patterns of reorganization after left hemisphere stroke have proposed three main theories to explain the plasticity mechanisms that may underlay language recovery in aphasic patients. The first one, known as the peri-lesional hypothesis, posits that the regions immediately adjacent to the damaged area play a relevant role in mediating compensatory activity after stroke (Warburton et al., 1999; Teasell et al., 2005; Heiss and Thiel, 2006). The second one, known as the laterality-shift hypothesis, suggests that right hemisphere homologue regions are recruited in order to compensate for functional loss in the left hemisphere. Finally, the third one, known as the disinhibition hypothesis, proposes that increased right hemisphere activation during language tasks in stroke survivors indicate a dysfunctional (maladaptive) reorganisation that negatively interfere with language recovery (Hamilton et al., 2011). See Figure 1.1 for an illustration of the three theories.

Figure 1.1. Illustration of three theories of reorganisation of the language system



The figure shows the three theories (A, B, C) accounting for different mechanisms of reorganisation and plasticity of the language system after left hemisphere stroke. Reproduced with permission (Elsevier) from Hamilton et al. (2011).

Consistent with the theories of re-organisation, there are currently two dominant views about the role of the right hemisphere in recovery; the first view argues that the right hemisphere plays a beneficial role in language recovery by assuming functions previously represented in the left hemisphere (Hamilton et al., 2011); whereas the second one suggests that activation of the right hemisphere during language tasks in patients with chronic aphasia is a reflection of inefficient mechanisms of language processing and may be detrimental to aphasia recovery. Finally, a third less known- view claims that functional activation of right hemisphere areas in aphasic patients during language tasks is epiphenomenal, and neither facilitates nor hinders language recovery (Thiel et al., 2001).

Supporting a beneficial role of the right hemisphere in language recovery but contrary to theories of hemispheric specialization for language (see section 1.5. above), there are a few previous studies suggesting that right hemispheric regions - homotopic to left perysilvian regions - have an inherent capacity to process language, but this capacity is usually masked by transcallosal interhemispheric inhibition from the dominant left-hemisphere (Karbe et al., 1998; Thiel et al., 2006a). From this perspective, language recovery after left hemisphere stroke is associated with a release from inhibition of latent right-hemisphere language functions (i.e. disinhibition). However, the extent to which right hemisphere networks may be engaged in language recovery following left hemisphere stroke would also depend on other factors such as lesion size and location (Hamilton et al., 2011).

In contrast, others have argued that increased right hemisphere activation during language tasks may not reflect an entirely beneficial change, but instead may reflect an inefficient or maladaptive mechanism in neural activity that could have emerged during the spontaneous reorganization of language functions (Belin et al., 1996; Hamilton et al., 2011). The latter has been reported to interfere with the efficient reacquisition of language abilities which seem to be better supported by perilesional areas of the left hemisphere. The other hypothesis (see Figure 1.1) extends the notion of maladaptive mechanisms, and suggests that abnormally increased transcallosal inhibition of the damaged left hemisphere may result in the upsurge of right hemisphere activity, which may in turn increase interhemispheric inhibitory influences from the right hemisphere on left hemisphere perisylvian areas, exacerbating language symptoms and obstructing the recovery of language function.

Functional neuroimaging studies of left-hemisphere stroke patients have added important evidence for a role of right hemisphere regions in language recovery, by showing increased activation in homotopic right hemisphere regions (in addition to classical left hemisphere language regions) during a range of different language tasks (Warburton et al., 1999; Gold and Kertesz, 2000; Crinion and Price, 2005; Warren et al., 2009).

Further evidence from a group of left-hemisphere stroke patients (Crinion and Price 2005), found that, irrespective of lesion site, auditory sentence comprehension ability was positively correlated with bilateral temporal activation when the temporal lobes were spared, while unilateral right anterior temporal activation was only observed when the left temporal lobe was damaged. Findings of this study support the role of the right temporal lobe in recovery of narrative speech and, in particular, auditory sentence comprehension function following left-hemisphere stroke, further suggesting that auditory sentence comprehension may rely on a bilaterally distributed system.

In another study, Wright and colleagues (2012) used multivariate analysis to discriminate structural–functional networks involved in syntactic and semantic processing in a group of chronic left-hemisphere stroke patients. It was found that syntactic performance correlated with tissue integrity and increased activity in a left frontotemporal network, whereas semantic performance was found to correlate with activity in right superior/middle temporal gyri regardless of tissue integrity. In additional imaging analyses, Wright et al. (2012) found that right temporal activity did not differ between left hemisphere stroke patients and a group of neurologically-normal subjects, suggesting that the semantic network is bilaterally organised, and regions in both hemispheres are able to perform similar computations. Supporting this view, van Oers et al. (2010) reported that in left hemisphere stroke patients, recovery of naming abilities was positively correlated with activation in the left inferior frontal gyrus (IFG) during semantic decision and verb generation tasks while recovery on the token test (an auditory comprehension task) was positively correlated with activation of both left and right inferior frontal gyri during the same tasks. The authors therefore concluded that in the chronic phase, activity in the left IFG is associated with improvement of picture naming and sentence comprehension, whereas activity in the right IFG may reflect up-regulation of non-linguistic cognitive processing (van Oers et al., 2010).

In summary, most evidence suggests that ipsilateral perilesional activation of left hemisphere regions in stroke patients is associated with an improvement of language skills. In this context, it has, for example, been suggested that most left-lateralised language functions such as syntax could not successfully reorganise in right hemisphere regions following damage to the left hemisphere (Tyler et al., 2010; Wright et al., 2012). Conversely, there is also growing evidence suggesting that the right hemisphere can potentially play a role in language recovery following left hemisphere stroke (Papanicolaou et al., 1987; Crinion and Price, 2005). Therefore, the debate on this topic is still open and more research is required to understand the nature of the contribution of right hemisphere regions to aphasia recovery.

1.6.1. Reorganisation of language functions following perinatal and childhood stroke

Important evidence for a role of the right hemisphere in functional compensation comes from cases studies of children with perinatal or childhood stroke (Vargha-Khadem et al., 1997; Staudt et al., 2002). Perinatal and childhood stroke occurs more frequently in the territory of the MCA (middle cerebral artery) and can therefore damage classical language regions, which may affect a range of language functions. However, it has been reported that the language deficits in children who suffer left-hemisphere strokes are more subtle than those of adults with comparable lesions (Funnell and Pitchford, 2010). This shows the remarkable plasticity of the developing brain and leads to the hypothesis that homologous areas in the right hemisphere have been able to compensate for left hemisphere damage (Max, 2004). Nevertheless, the role of the right hemisphere in functional compensation is inconsistent across children. For instance, some studies have shown that the cerebral plasticity of the right hemisphere differs according to: the extent of the lesion in the left hemisphere, the onset of structural damage and the complexity of the language process that needs to be subsumed (Helmstaedter et al., 1994; Tillema et al., 2008).

More recently, neuroimaging studies have shed new light on the implications of previous research findings by showing that the capacity for compensation depends on factors such as maturation of the brain which may be different in children with perinatal versus childhood stroke (Ilves et al., 2013). For example, some fMRI studies have reported that early left-side subcortical damage resulted in complete shift of language functions to the right hemisphere

(Staudt et al., 2001, Staudt et al., 2002), whereas other studies have reported less striking contralateral reorganization when the brain damage occurs at a later onset (Liegeois et al., 2004, Vikingstad et al., 2000).

Together, these results support the hypothesis that functionally homologous areas in the right hemisphere could in principle subsume language related functions following early injury of typical left hemisphere language areas. Nevertheless, findings of these studies also highlight that multiple other factors such time post stroke, the language process impaired and the lesion extent may influence post-stroke reorganization and recovery in the developing brain.

1.6.2. Reorganisation in other neurological conditions: evidence from brain tumour patients

Right-sided activations during language tasks have also been observed in studies of left hemisphere tumour patients (Thiel et al., 2001; Holodny et al., 2002; Schlosser et al., 2002; Meyer et al., 2003). For example, by combining transcranial magnetic stimulation (TMS) with positron emission tomography (PET), Thiel and colleagues (2005) demonstrated a relevant role for the right IFG in language function in a group of right-handed patients who had left hemisphere tumours. However, the authors of this study conclude that the left hemisphere remains essential in all patients, especially in those without right hemisphere activation, as demonstrated by greater susceptibility to TMS interference. Additional evidence comes from another study that found that only patients with slowly progressing tumours recovered right-sided language function as detected by TMS. In patients with rapidly progressive tumours, no right-sided language function was found and language performance was linearly correlated with the lateralisation of language-related brain activity to the left hemisphere (Thiel et al., 2006b).

In sum, prior literature on brain tumour patients has suggested a potential contribution of the right hemisphere to language recovery following left hemisphere damage. But more importantly, these studies have also pointed out that time is a critical factor which determines the successful integration of right hemisphere regions into the language network to compensate for the loss of left hemisphere language nodes.

1.7. The contribution of the right hemisphere to language processing in the neurologically-normal brain

The rapid development of non-invasive brain imaging techniques, such as functional MRI (fMRI) and EEG/MEG, have shifted the emphasis towards investigating the neural correlates of language processing in the neurologically-normal brain. More recently, non-invasive brain stimulation techniques such as TMS (transcranial magnetic stimulation) or TDCs (transcranial direct current stimulation) have also been used to test different hypotheses regarding the role of right hemisphere regions in language. There is also converging evidence from fMRI and TMS studies, that have suggested a relevant contribution of the right hemisphere to phonological and semantic processing (Hartwigsen et al., 2010a, b; Jung and Lambon Ralph. 2016).

1.7.1. Evidence from TMS studies

Findings from TMS studies of neurologically-normal subjects have shown that the right hemisphere is causally involved in different aspects of language processing including phonological decisions, reading, and the processing of paralinguistic features such as emotional prosody (see Hartwigsen and Siebner, 2012 for a review). For example, Hartwigsen et al. (2010a, b) – in two different studies - applied TMS over: (i) left, right and bilateral posterior inferior frontal gyrus (IFG; Hartwigsen et al., 2010a), and (ii) left, right and bilateral posterior supramarginal gyrus (SMG; Hartwigsen et al., 2010b). They found that TMS over IFG and SMG regions disrupted phonological processing (reflected in impaired accuracy and reaction times) to a similar degree. Importantly, the disruptive effect was identical for unilateral TMS over the right or left IFG/SMG regions. It was, therefore, suggested that intact function of the right posterior IFG and SMG is necessary for making accurate and efficient phonological decisions in neurologically-normal individuals. Based on these findings, Hartwigsen et al. (2010a, b) proposed that a bilateral network connecting the supramarginal gyri with the posterior inferior frontal gyri serves phonological aspects of word comprehension, challenging the notion that language is exclusively computed by the left hemisphere. At least for phonological decisions, the right and left hemisphere seem to have similar relevance in the neurologically-normal brain.

By using repetitive TMS (rTMS), Sollmann et al. (2014) added more evidence to this claim by showing that virtual lesions over the right opercular IFG and right pars triangularis (compared to other right hemisphere regions) significantly increased the overall error rates on a picture naming task (impaired behaviour was reflected in no-response and hesitation errors). As only one task was used in this study (i.e. picture naming), it could not be determined whether the right IFG contribution was linguistic or attentional (Sollmann et al., 2014). In another study, Hartwigsen et al. (2013) induced virtual lesions by applying continuous theta burst stimulation over the left IFG and then used fMRI to investigate acute changes in effective connectivity between the left and right hemispheres during repetition of auditory and visual words and pseudowords. Importantly, it was found that suppressed activity in the left posterior IFG increased activity in the homologous right IFG during repetition of pseudoword (compared to repetition of words) across modalities. In addition, it was shown that the right posterior IFG exerted a facilitatory influence over the left posterior IFG during pseudoword repetition. Critically, responses became faster as the influence of the right posterior IFG over the left posterior IFG increased, indicating that homologous areas in the right hemisphere may actively contribute to language function after a focal (virtual) left hemisphere lesion. The authors of this study conclude that the right IFG may potentially support aphasia recovery after left hemisphere damage (Hartwigsen et al., 2013).

A study by Braet and Humphreys (2006) showed that disruptive TMS over the right posterior parietal cortex (PPC) interfered with visual word recognition when neurologically-normal participants read aloud words presented either in lower case or in mixed case while task difficulty was increased by presenting stimuli at lower contrast and for shorter duration. It was found that the disruptive effect of TMS was more pronounced for mixed case than lower case words. Braet and Humpreys (2006) conclude that the right parietal lobe may mediate the recognition of words for unfamiliar formats (mixed case) by recruiting additional attentional processes needed for increased task demands.

In summary, TMS studies of neurologically-normal individuals have provided evidence for the involvement of right hemisphere regions in phonological, semantic and orthographic processing. However, more work is needed to understand the nature of this contribution and whether other right hemisphere regions may also be involved in other aspects of language.

1.7.2. Evidence from fMRI and EEG studies

There is growing evidence from functional neuroimaging studies of neurologically-normal subjects that bilateral activation is observed during a range of different language tasks (Meyer et al., 2002; Devlin et al., 2003; Ackermann & Riecker, 2004; Fiebach et al., 2004; Buchsbaum and D'Esposito, 2009), with the degree of right-sided recruitment depending on the complexity of the task (Indefrey et al., 2001). For example, bilateral inferior frontal and posterior parietal cortices have been shown to be significantly activated when neurologically-normal right-handed participants perform phonological tasks (Poldrack et al., 1999; Devlin et al., 2003; McDermott et al., 2003; Tremblay et al., 2004). In addition, fMRI activation in the inferior frontal cortex becomes increasingly right lateralised as semantic tasks become more demanding (Noonan et al., 2013). In the same vein, Lambon Ralph and colleagues (2017) provided converging evidence by showing increased activation within the anterior temporal lobes during verbal and non-verbal semantic tasks in both neurologically-normal and brain-damaged individuals (Jung and Lambon Ralph, 2016; Lambon Ralph et al., 2017).

In an extensive meta-analysis of functional neuroimaging studies which aimed to describe the role of the right hemisphere in different language processes (see Vigneau et al., 2011), it was found that across 59 studies reporting right hemisphere activation, most activation peaks were bilateral, with only a few studies reporting unilateral right hemisphere activation in the right frontal cortex. In view of these findings, Vigneau and colleagues (2011) suggested that the right hemisphere works in an inter-hemispheric manner in which left hemisphere participation for language tasks is crucial. Furthermore, it was concluded that increased activation observed in right frontal regions was not specific to language processing and appears to be related to attentional and working memory processes that are needed to perform more demanding language tasks (Vigneau et al., 2011).

In what follows, I will summarise the contribution of the right hemisphere to: phonological, semantic and sentence processing.

Functional neuroimaging studies investigating the neural basis of phonological processing in neurologically-normal participants have, for example, shown activation in right hemisphere regions for tasks that involved (i) passive listening to syllables (Poeppel et al., 2004), (ii) listening to sentences made of pseudowords compared to listening of normal sentences (Meyer et al., 2000); (iii) attending to visual pseudowords (Mechelli et al., 2000) and (iv) covert/overt repetition of pseudowords (Warbuton et al., 1996; McGettigan et al., 2011).

Studies investigating semantic processing reported activation of right hemisphere regions for task contrasts that involved (i) passive listening of words (Hagoort et al., 1999); (ii) semantic associations (Warbuton et al., 1996; Booth et al., 2002; McDermott et al., 2003), (iii) semantic retrieval (James and Gauthier, 2004); (iv) comprehension of words, pictures and sounds (Rice et al., 2015, Visser et al., 2010); and (v) noun/verb generation (Crescentini et al., 2010; Li et al., 2017).

Studies investigating sentence processing have reported right hemisphere activation for tasks that involved (i) comprehension of simple sentences (Crinion et al., 2003; Meyer et al., 2004), (ii) plausibility judgments on the sentence semantic content (Kuperberg et al., 2000; Zysset et al., 2002), and (iii) when complex sentences are compared to simpler ones (Ben Shachar et al., 2004; Constable et al., 2004). However, in most of these neuroimaging studies activation was typically stronger and more extensive in the left than the right hemisphere.

Event-related potential (ERP/EEG) studies of sentence processing have also shown that both hemispheres are broadly sensitive to basic manipulations of plausibility/expectancy as indicated by larger N400 amplitudes to implausible or unexpected endings as compared to expected endings (Coulson et al., 2005; Federmeier et al., 2005). The N400 component is a negative deflection in the ERP response that peaks around 400 milliseconds after stimulus presentation and has been linked to all potentially meaningful stimuli, including faces, auditory and visual words (for a review see Kutas and Federmeier, 2011). However, these studies have also indicated that the two hemispheres use context information differently. For instance, the left hemisphere seems to actively use context information to predict and prepare conceptual information of likely upcoming words. The right hemisphere, instead, seems to adopt a more “integrative” approach to processing, in which the fit of a given word to its context is assessed in a more bottom–up fashion (Wlotko and Federmeier 2007; Federmeier, 2008; Kutas and Federmeier, 2011).

In summary, there is an extensive number of functional MRI and EEG studies showing increased activation in right hemisphere regions when right-handed neurologically-normal subjects perform language tasks. However, the bilateral nature of these activations (observed in the majority of the studies) probably suggest that both hemispheres work in a highly interactive and complementary manner with left hemisphere regions playing a critical role in most aspects of language.

1.8. The role of the right hemisphere in other cognitive functions, bilateral systems and aging

Despite the growing evidence showing how the right hemisphere contributes to some aspects of language, there is a prevailing view that the right hemisphere activation is associated with other cognitive functions such as visuospatial attention (Corbetta et al., 2005; Hillis et al., 2005; Bartolomeo et al., 2012), visual memory (Salmon et al.,1996; Nagel et al., 2013) and executive/ inhibitory control mechanisms (Aron et al., 2004, 2014; Neef et al., 2018). For instance, visual spatial attention has been predominantly considered to be right hemisphere dominant (Corbetta and Shulman 2002; Shulman et al., 2010). Important evidence for this comes from studies of stroke patients with visual/spatial neglect. This is a failure to perceive and respond to stimuli on the contralesional side of space which is more severe and prolonged following right than left hemisphere lesions (Bowen et al., 1999; Ringman et al., 2004; Becker and Karnath, 2007). Visual neglect difficulties have been frequently associated with damage to a right fronto-parietal network as well as the right superior longitudinal fasciculus (Bartolomeo, 2007; Doricchi et al., 2008; Thiebaut de Schotten et al., 2008).

Several lines of evidence suggests that executive functions such as working memory, planning, inhibitory control and problem solving (Shallice and Burgess, 1991; Cooney et al., 2004) are anatomically associated with the prefrontal cortex in both hemispheres (Mesulam, 2002). For instance, patients with damage to the right inferior frontal cortex have been shown to present with impaired performance on inhibitory control tasks (Aron et al., 2003; Chambers et al., 2006; Cieslik et al., 2015). In particular, the posterior part of the right IFG has been associated with response inhibition during motor execution (Aron et al., 2014) as well as working memory control tasks (Marklund and Persson, 2012). In addition to its role in executive functions, neuroimaging studies have also associated the right frontal cortex with cognitive control processes, for example, right frontal regions have been shown to respond to increased demands on control during word comprehension (Lai et al., 2015) or when sentence comprehension requires inhibition and restructuring of information (Matchin and Hickok, 2016).

The extensive literature showing a critical role for right hemisphere regions in other cognitive functions is undeniable, however, a related question is whether right-lateralised cognitive systems interact with language domain-specific systems. There is important evidence from studies of semantic cognition and speech comprehension that have proposed the existence of bilateral interacting systems. For example, converging findings from studies of patients with semantic aphasia and semantic dementia and neuroimaging/TMS studies of neurologically-normal subjects (see Patterson et al. 2007; Jefferies, 2013; Lambon Ralph et al., 2017; Woollams et al., 2017) have shown that successful semantic cognition (i.e. the ability to use, manipulate and generalize knowledge that is acquired to support verbal and non-verbal behaviours) requires two-interacting systems: a ‘representational system’ that stores knowledge about items, their features and associations, and a ‘control system’ that has the ability to flexibly control the retrieval of information to suit our current goals and the situation (Jefferies and Lambon Ralph, 2006; Lambon Ralph et al., 2017). These two interacting systems have been shown to be supported by a distributed and bilateral brain network involving the anterior temporal lobes. In this context, right hemisphere regions have been indicated to contribute to executive aspects of semantic processing, e.g. controlled semantic retrieval.

Additional evidence comes from studies of speech comprehension which increase demands on a variety of cognitive functions (apart from language comprehension) including semantic and pragmatic as well as domain-general processes such as working memory and attention (Wright et al., 2012; Campbell and Tyler, 2018). Likewise, it has been found that domain-general systems can play a role in speech comprehension tasks whenever task demands increase (e.g. when participants listen to highly ambiguous sentences). In this context, Bozic and colleagues (2010) proposed a model of speech comprehension that differentiates between core linguistic functions, such as syntax, which are mainly supported by a left lateralised frontotemporal network (Tyler et al., 2011; Campbell and Tyler, 2018) and a broader cognitive system that involves semantic and pragmatic aspects that are bilaterally distributed (Bozic et al., 2010).

Finally, functional MRI studies investigating the effect of normal aging on language have added more evidence regarding the role of the right hemisphere in language by reporting that older adults showed a more bilateral pattern of prefrontal activity during verbal recall tasks compared to younger adults (Cabeza et al., 1997; Cabeza et al., 2003). The authors of these studies interpreted the change in prefrontal activity in older adults as reflecting functional compensation (Cabeza et al., 1997). Supporting these findings, Reuter-Lorenz and colleagues (2000; 2002) reported results of an fMRI study that used related verbal and spatial working memory tasks in a group of young and old neurologically-intact adults.

As expected, young participants activated left frontal regions for the verbal working memory task, whereas the spatial memory task activated homologous regions in the right hemisphere. Interestingly, in the older group it was found bilateral and indistinguishable activation in the frontal lobes for both tasks. The authors of these studies concluded that the change in hemispheric asymmetry in older adults during verbal recall and working memory tasks is indicative of a general aging phenomenon, whereby the increasing engagement of the right hemisphere acts as a mechanism to compensate for neural decline.

Conversely, Meunier et al (2014) found increased functional connectivity in the right hemisphere which was associated with worse (impaired) performance on spoken sentence comprehension (see also Tyler et al., 2011). This finding is consistent with a previous study on language processing which showed age-related decreases in the integrity of the left inferior frontal gyrus accompanied by increased functional activity in the right inferior frontal gyrus (Tyler et al., 2010), but without any improvement in language function. These findings suggest that less specialized activity in the non-dominant (right) hemisphere might have adverse effects, in particular for language functions (Cabeza et al., 2002; Persson et al., 2006).

In summary, there is growing evidence suggesting that right hemisphere regions may be part of bilateral language systems supporting semantically related processes, and also contributing to functional compensation in the normal aging brain. Furthermore, there is also prior literature showing that right hemisphere regions contribute to ‘domain-general processes’ (i.e. attention, executive, and cognitive control processes). Together, these findings have progressively started to change the left-hemisphere centric view of language processing that has dominated the literature in the last 150 years.

CHAPTER 2: GENERAL METHODS

2.1. Summary

This chapter outlines the experimental methods used to analyse the neuroimaging data presented in the current thesis. The chapter is divided into three parts. The first briefly describes the PLORAS database, a data repository of behavioural assessments, demographic information, and structural and functional neuroimaging data from stroke survivors. Analyses of the behavioural (language) data is presented in Chapter 3 of this thesis. The second part outlines the methods used to analyse the structural magnetic resonance imaging (MRI) data presented in Chapter 4. Structural MRI is a widely used imaging technique in research as well as in clinical practice, and was used in this thesis to (i) identify lesion sites associated with a given language impairment in RHS patients (i.e. lesion-deficit associations), and (ii) improve spatial normalisation of the functional MRI data. The third and final part describes the methods used to analyse functional MRI (fMRI) data presented in Chapters 5 and 6. Functional MRI is a non-invasive technique used to infer brain activity by detecting changes associated with blood flow, and in this thesis it was employed to investigate the patterns of brain activation in a group neurologically-normal subjects who performed similar language tasks to those administered to stroke patients.

2.2. The PLORAS Database: A data repository for Predicting Language Outcome and Recovery After Stroke

The PLORAS database is a repository for structural and functional scans and behavioural data that have primarily been acquired from stroke survivors, however, data from neurologically-normal subjects are also available. The latter is used to look at inter-subject variability in functional localisation and integration in both groups (Price et al., 2010; Seghier et al., 2016).

The main goal of this database is to Predict Language Outcome and Recovery After Stroke hence the acronym PLORAS. This is being tackled by: (a) acquiring a high resolution structural MRI scan and comparing the lesion site of a new patient with those of all other patients in the database; (b) selecting patients in the database who are most similar to the new patient (in terms of their lesion features and demographic measures); and (c) extracting language scores, over time, for these 'similar' patients.

Inclusion criteria to the PLORAS database include: (i) a demonstrable previous medical history of stroke; (ii) no history of concomitant neurological or psychiatric illness (e.g. dementia or depression); (iii) being able to provide written informed consent. At a minimum, the data currently available for more than 1200 stroke survivors include:

- The results of a standardised language assessment (the Comprehensive Aphasia Test; Swinburn et al., 2004),
- High-resolution structural T1-weighted scans,
- Demographic information (e.g. age, gender, handedness, time post-stroke, education and occupation), and
- Information about their stroke and other co-morbidities.

2.2.1. Author's contribution to the PLORAS database

During the course of my PhD, I have contributed (as part of a team effort) to the continuous expansion of the PLORAS database by participating in the recruitment and scanning of stroke patients. In addition, I have set up a project in Chile which aims to enable, in the medium term, the realization of studies investigating the effects of cultural (UK versus Chile) and linguistic (English versus Spanish) variables on language outcome and recovery after stroke. This has entailed translating the Comprehensive Aphasia Test into Spanish, sorting out the logistics of the project, securing ethical clearance, testing approximately 100 Chilean stroke survivors and obtaining their clinical CT (computerized tomography) scans. Although the Chilean data are not reported in this thesis, they provided me with extensive training and experience in all the PLORAS data acquisition procedures and underlying theory.

2.2.2. Ethical approval

All studies and analyses of stroke patients and neurologically-normal subjects presented in this thesis were approved by the London Queen Square Research Ethics Committee. All subjects gave written informed consent prior to participation and received financial compensation for their time.

2.2.3. Behavioural assessment

All stroke patients recruited to the PLORAS database (Seghier et al., 2016) are assessed with the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004). The CAT is a fully standardised test battery that was designed with three main purposes: to assess language comprehensively, to screen possible cognitive deficits associated with aphasia and to examine the disability associated with these impairments and how these can affect activities of daily living. Therefore, the CAT is divided into three parts: (i) the cognitive screen which includes 6 subtests; (ii) the language battery which includes 21 subtests; and (iii) the disability questionnaire that involves seven subtests that were not relevant to this thesis. The 6 cognitive and 21 language tasks administered as part of the CAT are fully described in Chapter 3. Behavioural analyses on the CAT data from 109 RHS patients are also presented in Chapter 3.

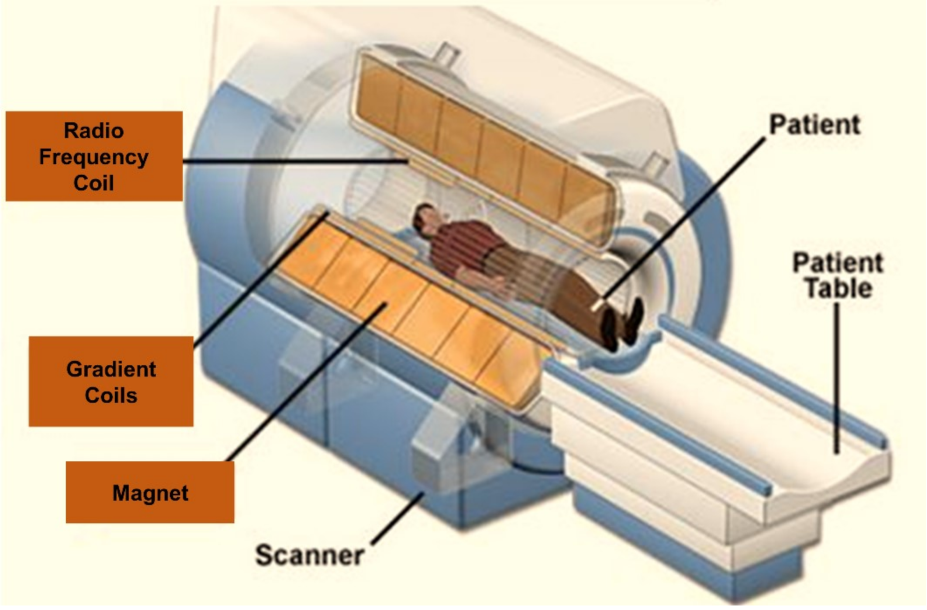
The CAT was selected from amongst, and in preference to, other competing alternatives mainly because: 1) it has been shown to have robust psychometric properties reflected in good validity and reliability measures, and 2) when designing the test stimuli the authors made an effort to control for some psycholinguistic parameters known to affect individual performance on language tasks such as word length, imageability, frequency as well as regularity (Bruce and Edmundson, 2010; Howard et al., 2010; Springer and Mantey, 2010).

2.3. Basic principles of structural MRI

Magnetic resonance imaging (MRI) is a non-invasive technique used to examine the anatomy of the brain. It is particularly useful in clinical settings for detecting abnormalities (e.g. damage to the brain after a stroke).

To acquire images, a person is positioned inside an MRI scanner that consists of: (i) a static electromagnet that produces a strong magnetic field (B_0); (ii) radiofrequency (RF) transmit and receive coils, which emit RF pulses and detect the reflected RF signal, and (iii) magnetic field gradients, which localise the source of the reflected signal by generating short-term spatial variations of the magnetic field strength across the person (see Figure 2.1).

Figure 2.1. An MRI scanner and its main components.



The principles of MRI scanning rely on detecting the presence of hydrogen protons (H+), which are abundant in the human body because most of the human body is made of water which accounts for 50-70% of total body weight.

Under normal circumstances hydrogen protons have two fundamental properties: (i) they spin around in random directions and (ii) have a positive electrical charge. These two properties are essential for a phenomenon known as "magnetic moment", which causes the proton to align the magnetic field created by its own spinning electrical charge with the much stronger magnetic field generated by the MRI scanner (Westbrook et al., 2011; see Figure 2.2). The speed at which the aligned protons spin depends on the strength of the static magnetic field of the scanner. This ranges from 1.5 Tesla to 7 Tesla.

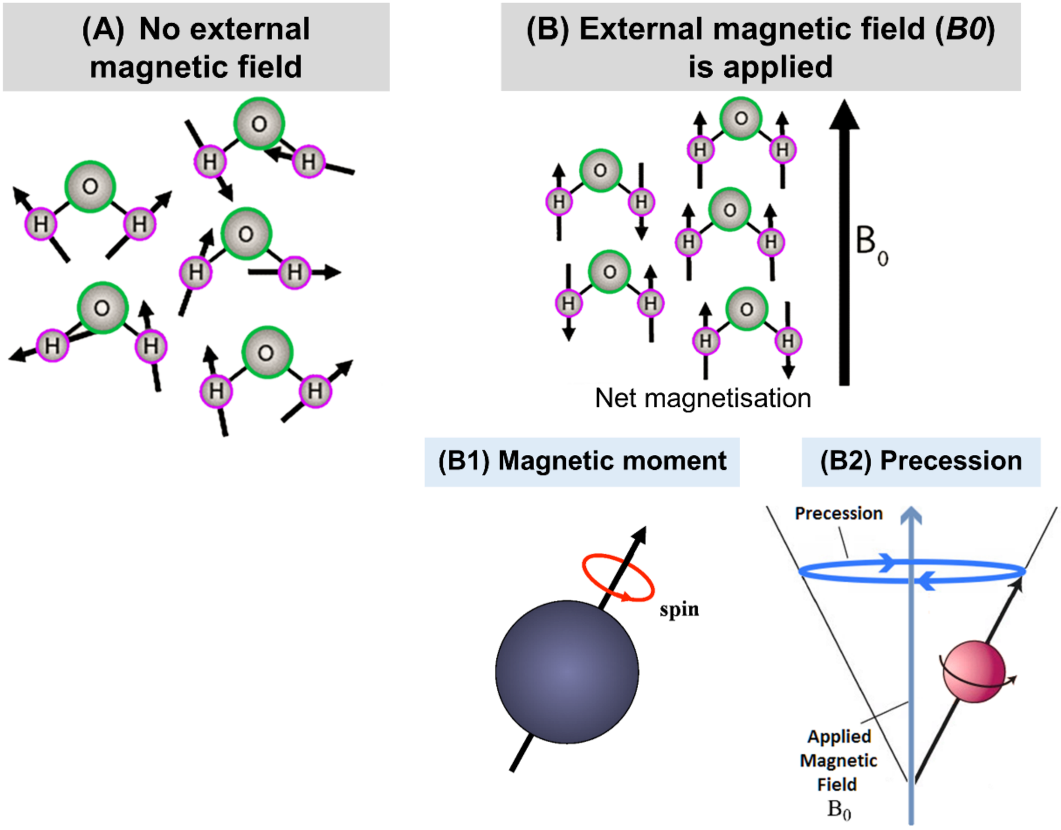
In the presence of a strong external magnetic field (B_0), some of the magnetic moments of the protons will tend to take one of two states: either aligned along (parallel to) or against (anti-parallel to) the magnetic field. More of the spins will enter the parallel state, resulting in a net magnetisation that is parallel to the scanner's magnetic field (see Figure 2.2).

Additionally, the protons "precess", i.e. the axis of their magnetic moments rotates around the magnetic field. The radiofrequency (RF) fields are applied at the same frequency as the frequency that the protons precess (see Figure 2.2). The application of RF causes resonance that perturbs or excites the nucleus as it absorbs the energy.

Once the RF is removed, the spin system loses energy, it recovers back to the same state it was in before excitation in two different ways: (i) the transverse magnetisation quickly loses coherence and (ii) the longitudinal magnetisation slowly recovers. Together, these changes in the MRI signal are called relaxation. The change in the transverse magnetisation is termed transverse decay (or T2 decay) while the longitudinal change is known as longitudinal relaxation (or longitudinal T1 recovery)

The recovery and relaxation properties vary across different tissue types (i.e. water or fat), and therefore the scanner can create contrasts that allow us to distinguish different anatomical structures. Different types of images are obtained by varying the parameters of the acquisition protocol (i.e. T1, T2 contrast and proton density). In T1-weighted images, fat loses longitudinal magnetization faster than water, therefore the T1 time for fat is shorter and its level of magnetization is higher after RF pulse. This results in high signal intensity from fat, showing bright fat (e.g. white matter) and dark water. For T2-weighted images fat loses transverse magnetization faster than water and its level of magnetization is lower, therefore fat produces low signal intensity, showing dark fat and bright water (Huettel et al., 2008).

Figure 2.2. A graphical illustration of the principles of the MRI signal



(A) The hydrogen protons in free space in the absence of an external magnetic field (they tend to align randomly). **(B)** When an external magnetic field is introduced, each proton's axis of spin will tend to enter one of two states: either aligned along (parallel to) or against (antiparallel) to the magnetic field. Net magnetization (M) is the sum of the magnetic moments of all spins within a spin system.

Finally, to reconstruct the MR signal into a high-resolution T1-weighted image, a computational mathematical process known as Fourier transform is necessary for conversion of the raw data from k-space (i.e. a notation scheme used to describe MRI data acquisition) to conventional image space (x,y,z). When several images need to be acquired sequentially to identify changes over time (time series) a different technique called fMRI is required, which I am going to explain in section 2.4.

2.3.1. MRI data acquisition

T1-weighted high resolution anatomical whole-brain volumes were available for all stroke patients. Three different MRI scanners (Siemens Healthcare, Erlangen, Germany) were used to acquire the structural images. Each of these T1-weighted images were then submitted to a fully automated lesion identification procedure for preprocessing, lesion detection and delineation (see below for details). This converts a scanner-sensitive raw image into a quantitative assessment of structural abnormality that should be independent of the scanner used.

For anatomical images acquired on the 1.5T Avanto scanner, a 3D magnetization-prepared rapid acquisition gradient-echo (MPRAGE; Mugler and Brookeman, 1990) sequence was used to acquire 176 sagittal slices with a matrix size of 256 × 224, yielding a final spatial resolution of 1 mm isotropic voxels (repetition time/echo time/inversion time = 2730/3.57/1000 ms). For anatomical images acquired on the other two scanners, an optimised 3D modified driven equilibrium Fourier transform (MDEFT; Deichman et al., 2004) sequence was used to acquire 176 sagittal slices with a matrix size of 256 × 224, yielding a final spatial resolution of 1 mm isotropic voxels: repetition time/echo time/inversion time = 12.24/3.56/530 ms and 7.92/2.48/910 ms at 1.5T and 3T, respectively.

2.3.2. The automated lesion identification toolbox (ALI)

In the context of patients with brain damage after stroke, each of the T1-weighted images was then submitted to our fully automated lesion identification procedure for preprocessing, lesion detection and delineation. The Automated Lesion Identification toolbox (ALI; Seghier et al., 2008) is implemented in the Statistical Parametric Mapping software (SPM; Wellcome Centre for Human

Neuroimaging, London, UK) running on Matlab 2014a (MathWorks, Natick, MA). It comprises 4 different steps that are described below:

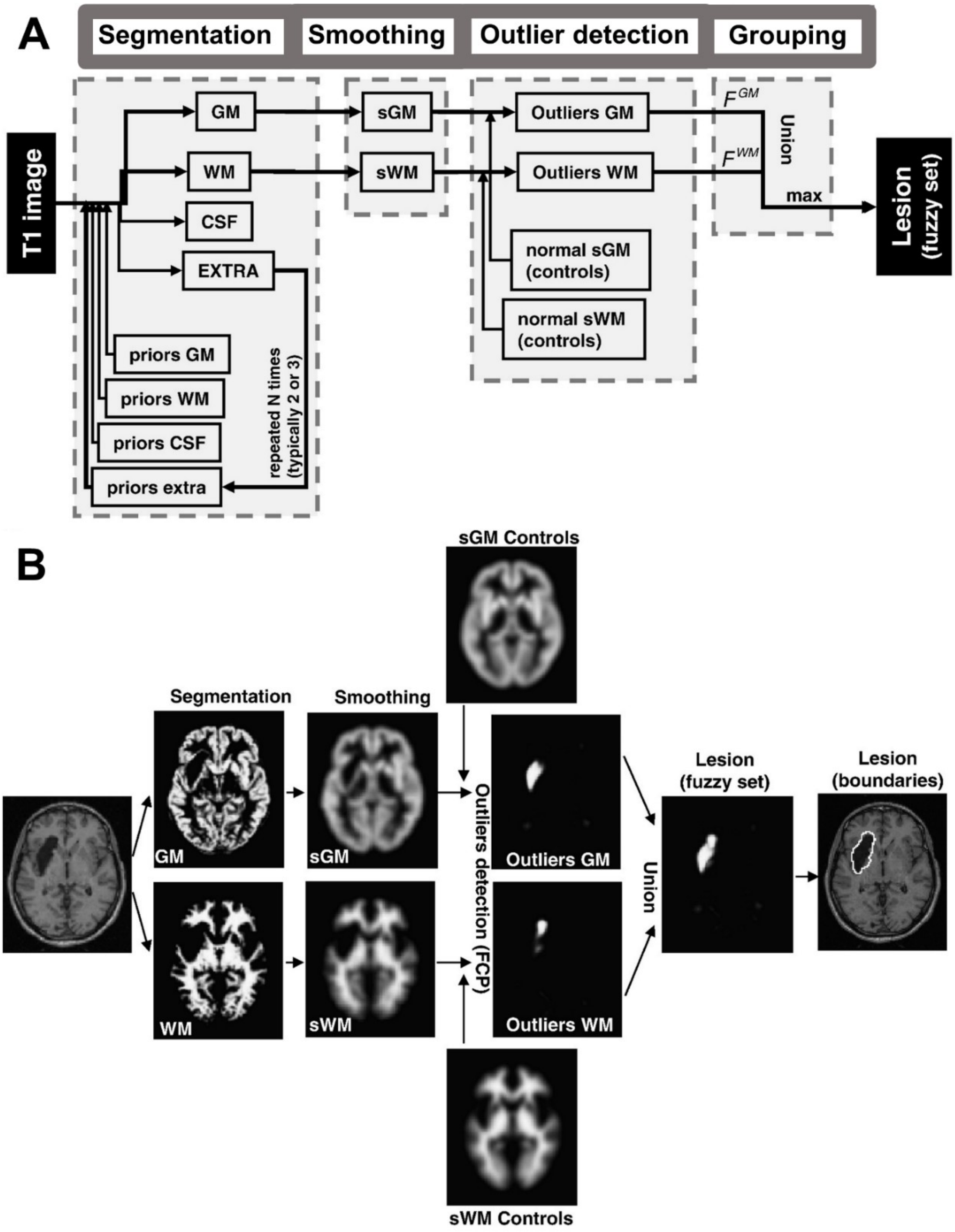
(i) Modified unified segmentation procedure: The modified segmentation procedure used here combines segmentation, bias correction and spatial normalisation (for more details see Seghier et al., 2008). The T1–weighted images of each stroke patient are segmented into four tissue classes: grey matter (GM), white matter (WM), cerebral spinal fluid (CSF), and ‘the extra tissue class’. The inclusion of an extra tissue class enables abnormal voxels (within the lesion) to be modelled explicitly. This procedure can be iterated several times and the estimated extra class acts as the prior for the next segmentation run, providing a more accurate tissue segmentation with minimal misclassification in GM and WM classes. The output is a set of 4 normalised and segmented images per subject (see Figure 2.3). For the purpose of lesion identification, only the normalised GM and WM images are used.

(ii) Smoothing: In order to supress fine-scale anatomical inter-subject variability, the normalised GM and WM images were smoothed (blurred) by replacing each voxel with the weighted average of the surrounding voxels using an Isotropic Gaussian Kernel of 8 mm full width at half maximum.

(iii) Outlier detection: abnormal (‘outlier’) voxels were identified by applying an outlier detection algorithm according to the fuzzy logic clustering principle (for details see Seghier et al., 2007). This algorithm assumes that a lesioned brain is an outlier in relation to neurologically-normal brains. For this purpose, smoothed GM (sGM) and WM (sWM) segments of each patient’s data are compared to those of neurologically-normal subjects by using normative data drawn from a sample of 64 neurologically-normal controls. The output is two fuzzy sets (one for GM and one for WM) representing the voxels in each patient's brain that had a very low probability of being GM and WM voxels, compared with neurologically-normal subjects (see Figure 2.3).

(iv) Lesion definition (grouping): in this step, both fuzzy GM and WM lesion images are combined to obtain a single lesion image that codes the degree of abnormality at each voxel of the brain. The output is two 3D lesion images: (i) a continuous (or fuzzy) lesion image coding at each voxel the degree of abnormality on a continuous scale from 0 (completely normal) to 1 (completely abnormal) relative to normative data from neurologically-normal controls; and (ii) a binary lesion image, which is simply a thresholded (i.e. lesion/no lesion) version of the abnormality (see Figure 2.3).

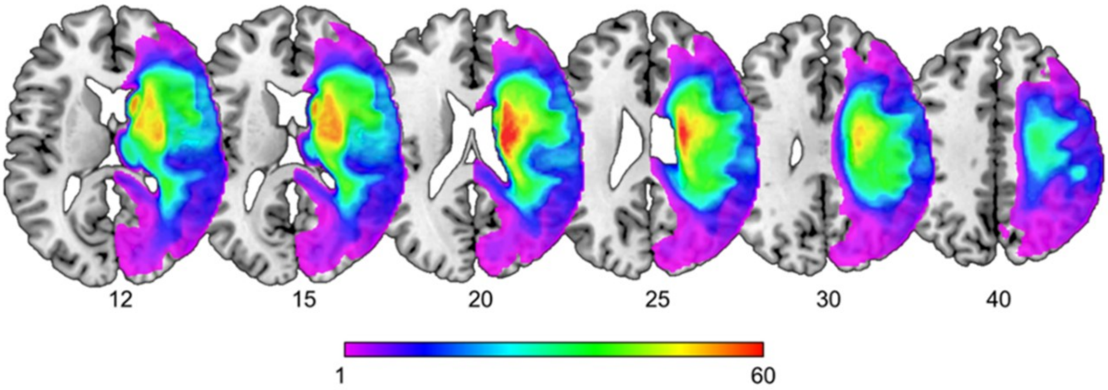
Figure 2.3. Illustration of ALI procedure



(A) A schematic view of the different steps that involve our lesion identification procedure. **(B)** An illustration of the resulting images for each step. Reproduced with permission (Elsevier) from Seghier et al. (2008).

The resulting 3D binary lesion of each patient was used in this thesis to (i) delineate the lesions, (ii) estimate lesion volume for each patient, and (iii) generate lesion overlap maps (LOMs; see Figure 2.4).

Figure 2.4. Lesion overlap map (LOM).



Lesion overlap map for a sample of 109 RHS patients, depicting voxels that were damaged in a minimum of 1 and a maximum of 60 patients. The colour scale indicates the number of patients with overlapping lesions at each given voxel.

2.3.3. Lesion-deficit mapping

Mapping lesions to their behavioural consequences remains a key goal in cognitive and clinical neuroscience. In the last decade and a half, the relationship between brain lesion data and behaviour has typically been assessed using mass-univariate techniques such as voxel-based morphometry (VBM, Ashburner and Friston, 2000; Mummery et al., 2000; Tyler et al., 2005) or voxel-based lesion-symptom mapping (VLSM, Bates et al., 2003; Rorden et al., 2007). These techniques perform thousands of statistical tests on a voxel-by-voxel basis. Voxels that surpass the threshold for statistical significance are then associated with a critical region that, when damaged, causes the deficit of interest.

In Study 2 (Chapter 4), the 3D binary images obtained from the automated lesion identification toolbox (ALI) were used for voxel-based lesion-deficit analyses with the aim of identifying which regions were significantly more damaged in RHS patients with impaired performance on a given language task than in other patients with RHS but with spared performance on that task. I have previously shown that when the same analyses are repeated with continuous measures of the lesion (i.e. the fuzzy lesion images), the results are very similar to those observed when binary lesion images are used instead (Gajardo-Vidal et al., 2018).

2.4. Functional Magnetic Resonance Imaging (fMRI)

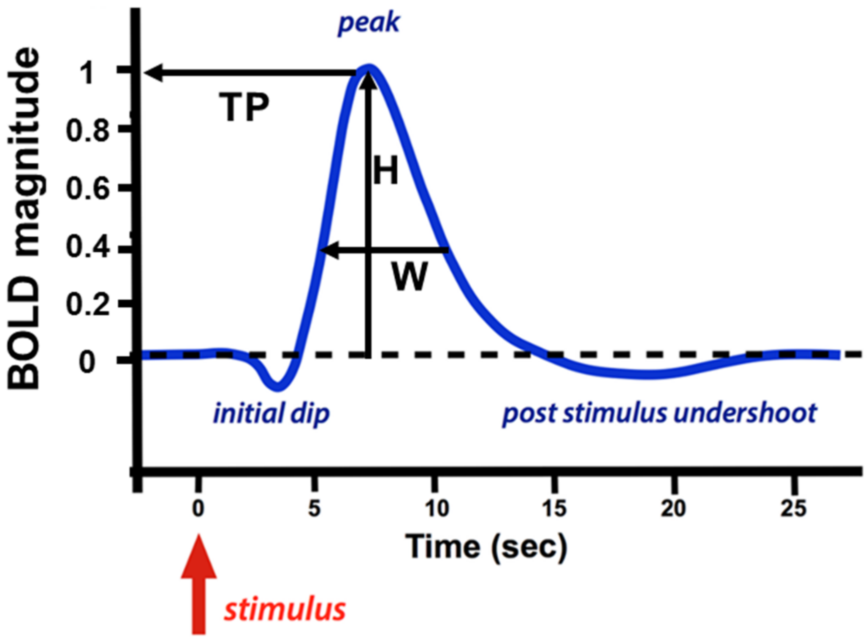
In Chapters 5 and 6 of this thesis I used fMRI data from neurologically-normal subjects. Functional MRI (fMRI) is a non-invasive technique used to infer brain activity by measuring changes in blood flow. During the course of an fMRI experiment, a series of brain images are acquired while the subject performs a set of language tasks. Changes in the measured signal between individual images are used to make inferences regarding task-related activations in the brain. The most common fMRI approach uses the Blood Oxygenation Level Dependent (BOLD) measure.

2.4.1. Basis of the BOLD signal

Functional MRI measures changes in the Blood Oxygen Level Dependent (BOLD) signal due to changing neural activity. When neurons fire in response to cognitive (e.g. language) processing a sequence of events happens resulting in an increase in local cerebral metabolism. An increase in neural activity (and metabolism) causes an increased demand for oxygen. To compensate for this demand, the vascular system increases the amount of oxygenated haemoglobin over and above the level of deoxygenated haemoglobin. Because the deoxygenated haemoglobin attenuates the MR signal, an increase in the relation between oxygenated haemoglobin and deoxygenated haemoglobin leads to an increase of the BOLD signal. This has an effect on the T2* signal which plays a critical role in the generation of the BOLD contrast. In brief, the T2* signal is the time constant that describes the decay of the transverse component of net magnetisation (for details see section 2.3 above).

For the purposes of estimating the BOLD signal in an experimental paradigm, SPM makes use of a canonical haemodynamic response function (HRF; Friston et al., 1995a, 1998), which mimics the shape and temporal dynamics of the blood flow changes in response to changes in neuronal activity. Some characteristics of the HRF response are shown in Figure 2.5.

Figure 2.5. The characteristics of the hemodynamic response function (HRF)



The shape of the HRF function can be described by a variety of characteristics including: (i) time to peak (TP): the peak of the HRF generally falls within 4-6 seconds of the stimulus onset; (ii) height of response (H); (iii) width (W): the HRF rises within 1-2 seconds and returns to baseline by 12-20 seconds after the stimulus onset; (iv) post stimulus undershoot: the HRF generally shows a late undershoot, which is relatively small in amplitude compared to the positive response and persists up to 20 seconds after the stimulus. Because the haemodynamic response lags behind changes in neuronal activity by several seconds, fMRI suffers from low temporal resolution relative to EEG or MEG.

In summary, fMRI exploits the fact that neural activity is tightly coupled to an increase in blood flow. The increased blood flow reduces the concentration of deoxygenated haemoglobin which in turn increases T2* signal. This allows the indirect measurement of neural activity simultaneously across the whole brain with high spatial resolution, although at the cost of low temporal resolution compared to EEG or MEG.

2.4.2. Scanning parameters

All functional MRI data described in this thesis were collected on one of two available 3T scanners (both Trio, made by Siemens, Erlangen, Germany), using a 12 channel head coil. In the following paragraph, I will explain the main parameters for the applied scanning sequence.

The most common technique for fMRI acquisition is ‘echo-planar imaging’ (EPI; see Mansfield, 1977), used here with a 3 x 3 mm in-plane spatial resolution and TR/TE/flip angle of 3080 ms/30 ms/90°. The repetition time (TR) refers to the amount of time required to collect a complete brain volume (i.e. the period of time between two successive radiofrequency pulses to the same brain region). The echo time (TE) describes the time in milliseconds (ms) between the radiofrequency pulse and MR signal sampling. Longer TR and TE result in higher resolution (measured in voxels, which are essentially 3D pixels) but at the cost of longer total scanning time. In this case, the TR was chosen to achieve whole brain coverage (i.e. 44 slices) and to ensure that slice acquisition onset was de-synchronized with each stimulus onset for distributed sampling of slice acquisition across each scanning session (Veltman et al., 2002). The flip angle determines the degree to which the net magnetization is rotated relative to the main magnetic field. The field of view (FOV), defined as the spatial encoding area of the image, was 192mm, when the matrix size was 64 × 64, and there were 44 slices, with a slice thickness of 2 mm and an inter-slice gap of 1 mm. A total of 61 and 85 volumes were acquired in Study 3 and 66 volumes were acquired in Study 4 (Chapters 5 and 6, respectively). Each set of volumes is referred to as a “time series”.

For anatomical reference, T1-weighted structural scans were acquired after the subjects completed the fMRI tasks, using a MDEFT sequence (Deichmann et al., 2004) with the parameters TR/TE/TI set at 7.92/2.48/910 ms, flip angle 16°, 176 slices and a voxel size of 1×1×1 mm.

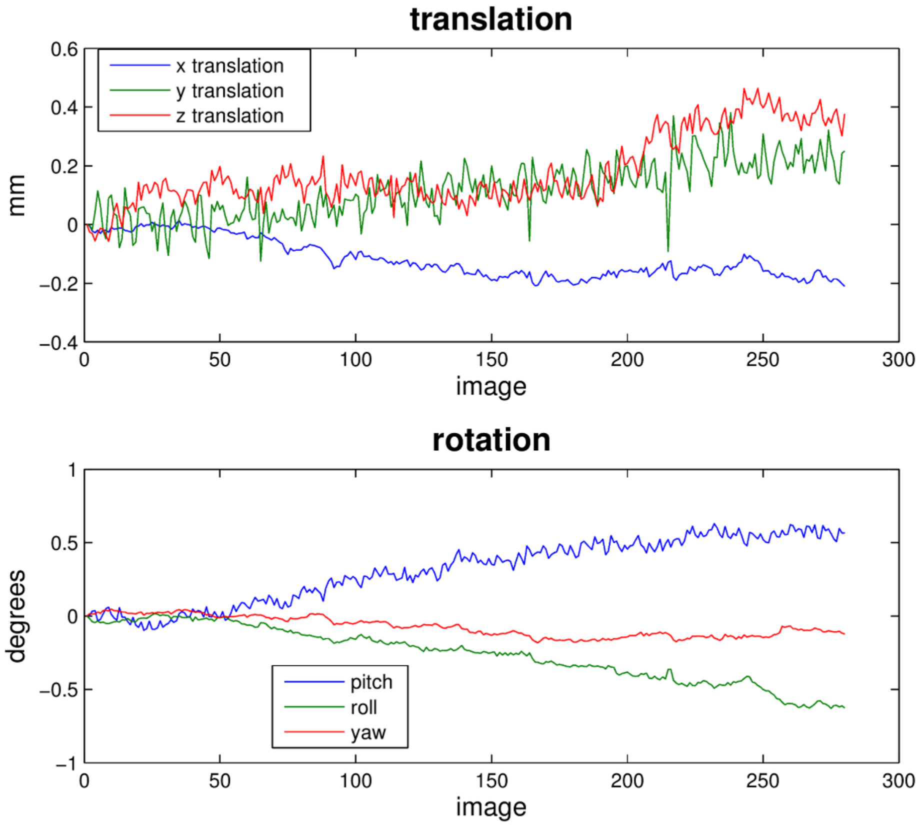
2.4.3. fMRI preprocessing

A typical fMRI experiment produces several hundred volumes of data, consisting of many different images collected at different time points in the experimental session. Before analytical methods for statistical inference are applied, four pre-processing steps were implemented on the whole time series to detect and repair potential artifacts in the data that may be caused either by the MRI scanner itself or non-task related movement or task-unrelated thought (i.e. mind-wandering) in the scanner.

For Studies 3 and 4 (Chapters 5 and 6), data pre-processing and statistical analyses were performed in SPM12 (Wellcome Centre for Human Neuroimaging, London, UK) running on MATLAB 2014a (MathWorks, Natick, MA). An overview of the preprocessing steps applied to the raw fMRI data are described below.

(i) Realignment/unwarping: In this step, time series were spatially realigned to a common reference scan (i.e. the first EPI volume) and unwarped to compensate for nonlinear distortions caused by head movement or magnetic field inhomogeneity. The unwarping procedure was used in preference to including the realignment parameters as linear regressors in the first-level analysis because unwarping accounts for nonlinear movement effects by modelling the interaction between movement and any inhomogeneity in the T2* signal. After realignment and unwarping, the realignment parameters are inspected to ensure that subjects moved less than one voxel (3 mm) within each scanning run (see Figure 2.6).

Figure 2.6. Motion correction (realignment)



The figure shows an example of motion estimates for an fMRI time series. The plots reflect the parameters of the rigid body transformation that are estimated by each time-point in comparison to a reference image.

(ii) Co-registration of functional and structural images: By matching the images from the same subject but in different modalities (i.e. the structural T1-weighted scan and the mean EPI image that was generated during the realignment step), this procedure provides (i) a more precise spatial normalisation of the functional images using the subject's anatomical image as reference and (ii) the anatomical localisation of single subject activations. SPM tries to optimise the shared information between the structural and mean functional image (mean EPI), and to minimize the amount of uncertainty between any two voxels between the two images. An established transformation matrix is then applied to all functional images to align them with the structural image.

(iii) Normalisation: Spatial normalisation aims to align images between different subjects to a common stereotactic standard space (i.e. the Montreal Neurological Institute, MNI, space). To normalise all EPI images to MNI space, deformation field parameters – obtained during the normalisation of the structural T1 scan – were applied. The original resolution of the images was maintained during normalisation (voxel size of 3mm^3 for EPI images and 1mm^3 for structural T1 images).

(iv) Smoothing: in the final preprocessing step, the normalised functional images were spatially smoothed with a 6-mm full-width half-maximum (FWHM) isotropic Gaussian kernel to compensate for residual anatomical variability and to satisfy the assumption of our statistical models (i.e. Gaussian random field theory). Each preprocessed functional volume was individually inspected for oddities before statistical analyses.

2.4.4. Statistical inference in fMRI

In general, the goal of fMRI data analysis is to analyse each voxel's time series to see whether the BOLD signal changes in response to known manipulations (e.g. linguistic and non-linguistic task conditions). The basis of statistical inference in SPM is achieved through a mass-univariate approach in which the entire time series for each voxel is modelled independently. Effects of interest were identified using the General Linear Model (GLM; Friston et al., 1995b) described as:

$$Y = \beta * x + \varepsilon$$

Where $\boldsymbol{Y}$ is a vector containing the BOLD signal in a single voxel across all acquired volumes and X is the design matrix describing hypothesised causes of changes in $\boldsymbol{Y}$ (Friston et al., 1994). A set of regression coefficients $\boldsymbol{\beta}$ is estimated to account for structure in the residual error $\boldsymbol{\varepsilon}$ (Glaser and Friston, 2004). After estimating a model for each voxel, the output is a set of estimated β values, one for each predictor of the model. This is then iterated over all voxels to obtain one beta image per predictor. The GLM helps to determine if there is a relationship between a dependent variable and one or more independent variables. The parameter estimates β for the predictor variables are also known as betas and can also be thought of as the slope of the regression line relating X to Y. The better the estimation of β, the better the model (fits the data) and the smaller the deviations ($\boldsymbol{\varepsilon}$) from the line (i.e. minimum sum of squared residuals). The neural response (HRF) is modelled in SPM using prior knowledge about haemodynamic, and convolved with the design matrix. The β at each voxel can then be transformed into a t-value by dividing it by the standard error.

In other words, the t-value gives a measure of the ratio of explained to unexplained variance of the entire model. In order to compare parameter estimates of interest (to test for a certain hypothesis), a contrast*,* or linear combination, of the parameter estimates can be created. To compare two parameters, one is assigned a ‘+1’ and the other a ‘-1’, written as [1 -1].

2.4.5. First-level analysis

Each pre-processed functional volume was entered into a subject specific fixed-effect analysis using the general linear model (Friston et al., 1995b)

All stimulus onset times, for all conditions, were all modelled as single events (Mechelli et al., 2003). For Study 3 (Chapter 5), 4 regressors per task were used, one modelling instructions, while the others distinguished correct, incorrect, and missing responses. For Study 4 (Chapter 6), 2 regressors per task were used, one modelling instructions, and the other modelling each stimulus.

Stimulus functions were then convolved with a canonical hemodynamic response function. To exclude low-frequency confounds, the data were high-pass filtered using a set of discrete cosine basis functions with a cut-off period of 128 s, and the contrasts of interest were generated for each of the conditions of interest (relative to fixation).

2.4.6. The multiple comparisons problem

The mass univariate approach used when analysing fMRI data involves modelling the several thousands of voxels in the brain as independent from each other. One limitation of using this approach alongside classical statistical inference is the problem of false positives that inevitably arises from multiple comparisons. The classical way to adjust the significant threshold (to control for Type I error) in the face of multiple comparisons is to use Bonferroni correction, in which the significance thresholds ($p = 0.05$) is divided by the number of statistical tests that are performed. However, the large number of voxels involved in fMRI analysis (~20,000) means that such an adjustment would result in a conservative statistical threshold, whereby the chance of Type II errors is dramatically increased. Nevertheless, in practice, voxels are not independent of each other (neighbouring voxels often belong to the same anatomical structure), therefore one method to control for the multiple comparison problem is to calculate the family-wise error (FWE) rate, i.e. the probability of type I errors. This method corrects for the number of statistical tests being performed by taking into account the smoothness of the data (Worsley et al., 1992).

CHAPTER 3: STUDY 1

Identifying the language task and processing level most frequently affected after right hemisphere damage

3.1. Summary

The right hemisphere has traditionally been associated with many aspects of social communication and cognitive functioning, however its involvement in language processing has not yet been clearly defined. The aim of my first experimental chapter was to investigate (i) the language task and (ii) the underlying processes that were most frequently impaired in a group of 93 stroke patients with unilateral right hemisphere lesions and normal performance on visual perceptual tasks (e.g. picture recognition and line bisection). The language task that was most sensitive to right hemisphere damage, in 12 of the 93 patients, involved matching a heard sentence to a picture (i.e. auditory sentence-to-picture matching). In contrast, the language task that was most sensitive to left hemisphere damage, in 167 out of 307 patients with unilateral left hemisphere damage, involved describing what was happening in a picture (i.e. spoken picture description).

To investigate the type of processing impairment that was causing errors on the auditory sentence-to-picture matching task after RHS, I analysed how the 12 patients with right hemisphere damage and auditory sentence-to-picture matching impairments performed on a battery of other cognitive and language tasks. The most frequently occurring behavioural profile was observed in 9

patients who had normal scores on other tasks involving speech recognition and auditory short-term memory (non-word repetition and digit span) and most critically the ability to perform sentence-to-picture matching when the same stimuli were presented in the visual modality. The underlying processing impairment could therefore not be explained by auditory or visual perception, semantic, phonological or syntactic processing, picture selection or decision making. On the basis of this behavioural analysis, I hypothesized that the auditory sentence-to-picture matching impairments after right hemisphere strokes were related to a breakdown in cognitive (e.g. executive) functions that were not specific to language processing.

3.2. Introduction

There has been a long history of research favouring the view that the left hemisphere is dominant for language processing in most right-handed subjects. In recent years, however, the assumption that language is solely processed in the left hemisphere has been challenged. The advent of neuroimaging techniques such structural and functional MRI, and more recently transcranial magnetic stimulation, have added new insights regarding the involvement of the right hemisphere in language processing. For instance, there is accumulating evidence that the right hemisphere contributes to language function in neurologically-normal individuals (Hartwigsen et al., 2010a, b). However, the precise role that the right hemisphere plays in language tasks has yet to be clearly defined. Some have proposed that the engagement of right hemisphere regions might reflect domain-general cognitive functions (e.g. executive processing) that are required to perform language tasks (van Oers et al., 2010; Vigneau et al., 2011; Baumgaertner et al., 2013). This emerging perspective is consistent with other literature that has associated right hemisphere activation/damage with selective attention (Corbetta et al., 2005; Hillis et al., 2005; Bartolomeo et al., 2012), inhibitory control (Aron et al., 2004, 2014), or working memory (Jonides et al., 1993; Ravizza et al., 2005). See Chapter 1 for a literature review. I contribute to the debate by investigating which language task and underlying processing are most frequently impaired after right hemisphere strokes.

3.2.1. The role of the right hemisphere in language processing: what we know so far

Historically, there has been a long-standing debate on the role that the right hemisphere plays in language functioning. For more than a century it was believed that the right hemisphere had little or no potential for processing language (Duffau et al., 2008). However, lesion studies of patients with unilateral right hemisphere damage have shown that structural damage in these patients may be associated with (i) discourse deficits (e.g. generating inferences, comprehending and producing main concepts or central themes; Johns et al., 2008) and (ii) prosodic deficits (e.g. interpreting and generating adequate prosodic intonation; Bryan, 1988; Myers, 1999). Other studies have reported that, although right hemisphere damage does not typically impair language functions, when it does linguistic deficits tend to be more subtle than in those with left hemisphere insults (Caplan et al., 1996; Johns et al., 2008).

Language impairments after right hemisphere damage

Patients who present with severe or mild language impairments after right hemisphere damage are commonly referred to as “crossed aphasics”. Bramwell (1899) was the first to coin the term “crossed aphasia” in an attempt to explain aphasic symptomatology resulting from a cerebral lesion ‘ipsilateral’ to the dominant hand. Crossed aphasia is considered as a rare and chronic disorder that may imply atypical lateralisation of language in the affected individuals prior to their stroke (see Chapter 1 for a literature review).

In what follows, I will review previous literature devoted to the investigation of the most common language deficits observed after damage to the right hemisphere.

Right hemisphere damage and speech comprehension difficulties

It has been traditionally accepted that sentence comprehension is sustained by a large network of left perisylvian brain regions (Caplan et al., 1996; Just et al., 1996; Cooke et al., 2006). However, several lines of evidence have suggested that in addition to the well-known role of the left hemisphere in language processing, the right hemisphere also contributes to language comprehension. Studies, for example, in split-brain patients (patients whose corpus callosum has been sectioned to relieve intractable epilepsy; see Chapter 1 for details) demonstrated that far from being nonverbal, the disconnected right hemisphere possesses significant receptive language ability and has a visual and auditory lexicon (Zaidel 1983; Baynes et al., 1992). In a more recent review of these surgical cases, Gazzaniga (2000) concluded that the right hemisphere possesses some passive recognition abilities but does not employ them productively. This is in line with the model of right hemisphere language proposed by Zaidel (1976), who suggested that the right hemisphere might be able to sustain speech comprehension better than speech production (Zaidel, 1976; Zaidel et al., 2000). Further evidence from Caplan and colleagues (1996) showed that the ability to process syntactically complex sentences was significantly lower after right hemisphere strokes than in neurologically-normal subjects. However, Caplan et al. (1996) also showed that the same RHS patients performed significantly better on the same task than left hemisphere stroke patients. In view of this, the authors concluded that the right hemisphere can play a role in assigning sentence structure and/or using it to determine sentence meaning. Likewise, another study has also reported that sentence comprehension or multi-command tasks without supporting context might be problematic after right hemisphere damage, especially if syntactic structure is complex (Van Lancker and Kempler, 1987).

Right hemisphere damage and semantic processing deficits

Anomia (the inability to find the correct words) is one of the most common symptoms following left hemisphere stroke. In contrast, RHS patients rarely present word findings difficulties and if they do, the deficits are either very mild (Jonanette et al., 1983) or due to co-occurring cognitive deficits that might indirectly impact on task performance. Nevertheless, a growing body of research investigating the hemispheric representations of semantics suggests that both cerebral hemispheres process word meaning (Chiarello and Church, 1986; Jung-Beeman, 2005), however, they do so in characteristically different ways (Beeman and Chiarello, 1998). In a study, investigating language performance in 27 right-hemisphere stroke patients, it was found that patients presented with significantly lower performance in semantic decision tasks compared to an age-matched group of neurologically-normal participants (Murteira and Santos, 2013). The authors interpreted the semantic deficits observed in RHS patients as a difficulty in accessing and judging semantic concepts and also establishing relations between them. Further evidence comes from a recent study reporting that right hemisphere damage can impair access to semantic processing, affecting both verbal comprehension and non-verbal tasks. The authors concluded that patients with right hemisphere damage have difficulties summating across meaning, which may be suggestive of subtle specialization between hemispheres (Thompson et al., 2016).

In contrast, others have supported the idea that difficulties performing language tasks after right hemisphere damage might be a consequence of disruption to domain-general executive processing that is necessary for normal language function (van Oers et al., 2010; Vigneau et al., 2011; Baumgaertner et al., 2013). This emerging perspective contrasts with the dominant view that when language impairments are observed in right-handed patients with unilateral right hemisphere damage, they necessarily imply atypical language lateralisation prior to the stroke (Marien et al., 2004).

In summary, the current study aimed to bridge this gap in the literature by (i) investigating which language task from a standard aphasia assessment battery was most frequently impaired in 109 stroke survivors who had unilateral right hemisphere damage, (ii) selecting a sample of patients with this task impairment in the context of spared performance on other tasks (e.g. line bisection, object recognition and semantic matching associations), and (iii) considering what underlying processing impairment could explain why the patients were impaired on the identified language task. By including data from 369 right-handed patients with unilateral left hemisphere strokes, I was also able to compare the language task that was most frequently impaired after right hemisphere strokes to the language task that was most frequently impaired after left hemisphere stroke.

3.2.1. Hypothesis

Based on the previous literature, I hypothesized that patients with right hemisphere damage were more likely to have impairments in speech comprehension than impairments in word finding or speech production.

3.3. Methods

All the data presented and analysed in this chapter were extracted from the PLORAS database (Seghier et al., 2016). This database is a repository for structural and functional scans and behavioural data from neurologically-normal controls and stroke patients (see Chapter 2 for more details).

3.3.1 Patient selection criteria

Patients were selected according to the following inclusion criteria:

(i) Right-hemisphere stroke (RHS) attested by a clinical neurologist and defined by an Automated Lesion Identification algorithm (see Chapter 2 and Seghier et al., 2008);

(ii) More than 1 cm^3 of right hemisphere damage and less than 1 cm^3 of left hemisphere damage;

(iii) Native speakers of English;

(iv) Right-handed prior to the stroke onset;

(v) Tested more than 3 months and less than 10 years after their stroke.

These criteria were met by 109 RHS patients (41 females) aged between 23 and 86 years old (Mean = 59.2, SD = 12.7). Table 3.1 provides demographic information for all participants. Data from all these 109 right stroke patients were included irrespective of the site of the lesion, the presence or absence of aphasia, or any other type of cognitive impairments (e.g. spatial neglect or short term memory problems). All individuals had undergone a full language assessment with the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004) and had a high-resolution structural brain image acquired with T1-weighted MRI scanning. This study was approved by the London Queen Square Research Ethics Committee and each patient was compensated for their time with £10 per hour.

In addition, to rule out the possibility that language impairments in RHS patients only reflected nonspecific differences in task difficulty, I also investigated language performance on 369 patients with unilateral left-hemisphere strokes aged between 21 and 90 years old (Mean = 59.6, SD = 12.7), who were selected using the same inclusion criteria described above (see Table 3.1).

Table 3.1. Summary of demographics details for all RHS and LHS patients included in the study.

Demographic details		**All RH patients N = 109**	**All LH patients N = 369**
Age at scan (years)	Mean	59.3	59.6
	SD	12.7	12.7
	Minimum	23.1	21.3
	Maximum	86.9	90.0
Years since stroke	Mean	3.3	3.3
	SD	2.3	2.5
	Minimum	0.3	0.3
	Maximum	9.2	10.0
Years of education	Mean	14.6	14.4
	SD	2.9	3.0
	Minimum	10.0	10.0
	Maximum	22.0	26.0
Gender	Number of males	68	105
	Number of females	41	264

3.3.2. Language assessment

All participants were assessed with the Comprehensive Aphasia Test (CAT; Swinburn et al., 2004). The 27 tasks administered as part of the CAT are listed in Table 3.2. The functions tapped by each of these tasks are considered in Table 3.3. What constitutes impaired performance on each task was defined according to the standard criteria in the CAT. For more details, see Swinburn et al. (2004).

For ease of comparison across tasks, the authors of the CAT encourage the conversion (through a non-linear transformation) of raw scores into T-scores, which represent how well the patient performed relative to a reference population of 113 patients with aphasia, 56 of whom were tested more than once. For example, a T-score of 50 indicates the mean of the patient sample used to standardise the CAT, whereas a T-score of 60 represents one standard deviation above the mean. Most people without post-stroke aphasia would therefore be expected to score above the average of the patient standardisation sample on any given task from the CAT. The threshold for impairment is defined relative to a second reference population of 27 neurologically-normal controls. Specifically, it is the point below which the score would place the patient in the bottom 5% of the control population (Swinburn et al., 2004). Lower scores indicate poorer performance.

Test description

The CAT consists of 27 tasks divided into two main parts: the cognitive screen and the language battery. Each task is described below, in the same order as administered in the assessment.

I.- The cognitive screen: the first part of the CAT screens for cognitive deficits associated with language impairment (aphasia) that might influence language performance of the patient with aphasia. The presence of associated cognitive deficits may have a profound influence on language performance. Excluding the possibility of associated cognitive deficits may help researchers to narrow down the number of potential hypotheses regarding the underlying processes that caused the observed language performance.

Task 1: the CAT line bisection task visually presents three lines of different lengths. The instructions are to bisect the horizontal lines by drawing small vertical lines through the midpoints. The results are compared with a standard template located on the scoring book of the CAT manual that estimated the deviance from the centre, to give a description of normal (-0.5 to +0.5), mild (-1 to +1), or severe (-2 to +2) visual field defects (i.e. neglect). T-scores equal to or below 40 constitute the impaired range.

Task 2: the CAT picture-to-picture semantic association matching task visually presents five pictures of objects simultaneously on each trial. The instructions are to match the picture at the centre (e.g., mitten) with one of four possible alternatives according to the strongest semantic association (e.g., hand, sock, jersey, and lighthouse). The inclusion of a semantically-related distractor (e.g., sock) encouraged deeper levels of semantic processing. There are a total of ten test trials plus a practice one at the beginning. Correct responses were given a score of 1; incorrect responses were given a score of 0. T-scores equal to or below 50 constitute the impaired range.

Task 3: the CAT recognition memory task visually presents (one at a time) each of the ten central items from Task 2 along with three unrelated distractors. The instructions were to indicate which of the four pictures on display had just been seen in the previous task. There are a total of ten test trials plus a practice trial at the beginning. The scoring system for this task was identical to that used in Task 2. T-scores equal to or below 47 constitute the impaired range.

Task 4: the CAT word fluency task requires the participant to verbally produce as many words as possible within the category “animals” within a period of 1 minute. This is then repeated with instructions to produce as many words as possible that begin with the letter “s”. Correct responses were given a score of 1. T-scores equal to or below 57 constitute the impaired range.

Task 5: the CAT gesture object use task visually presents six pictures of common objects with instructions to gesture how each item would be used. There are a total of six test trials plus a practice one at the beginning. Correct responses were given a score of 2. A score of 1 was given if the action, orientation or gesture are incorrect or if a body part is used as the object itself. Incorrect responses were given a score of 0. T-scores equal to or below 54 constitute the impaired range.

Task 6: the CAT arithmetic task involves six simple calculations. The instructions are to point to the correct answer for each sum (multiple choice) and underline the response made. Correct answers were given a score of 1. Incorrect responses were given a score of 0. T-scores equal to or below 43 constitute the impaired range.

II.- The language battery: the second part of the CAT assesses language performance on 21 tasks. In general terms, the language battery is subdivided into two broad sections: receptive language (part 1) and expressive language (part 2).

Part 1: Receptive language

Task 7: the CAT auditory word-to-picture matching task involves hearing a word and selecting the picture, among four possible alternatives, that best matched the meaning of the heard word. There are a total of fifteen test trials plus a practice one at the beginning. Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1.T-scores equal to or below 52 constitute the impaired range.

Task 8: the CAT auditory sentence-to-picture matching task involves hearing a sentence produced by the examiner and selecting the picture, among four possible alternatives, that best matched the meaning of the sentence. There are a total of sixteen test trials plus a practice one at the beginning. The task spans a wide range of syntactic structures such as reversible, active, passive and embedded sentences (e.g. the apple is under the shoe, the singer hits the soldier, the policeman is painted by the dancer). Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after self-correction or a delay (> 5 seconds) were given a score of 1. A total T-score equal to or below 60 signals impaired performance.

Task 9: the CAT auditory paragraph task aurally presents two short and unrelated stories. The instructions are to listen to the stories and then respond to yes/no questions relating to information given in the story. Answering appropriately relied on understanding the information given. Patients were asked 8 questions in total (4 questions per story). Questions are paired, if both responses were correct, a score of 1 was given. If only one of each pair was correct, no point was given. The points are then totalled (maximum score was 4). A total T-score equal to or below 48 signals impaired performance.

Task 10: the CAT written word-to-picture matching task involves reading a visually presented word and selecting the picture, among four possible alternatives, that best matched the meaning of the written word. There are a total of fifteen test trials plus a practice one at the beginning. Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. T-scores equal to or below 54 constitute the impaired range.

Task 11: the CAT written sentence-to-picture matching task involves reading a visually presented sentence and selecting the picture, among four possible alternatives, that best matched the meaning of the sentence. There are a total of sixteen test trials plus a practice one at the beginning. Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after self-correction or a delay (> 5 seconds) were given a score of 1. T-scores equal to or below 58 constitute the impaired range.

Part 2: Expressive language

Task 12: the CAT repetition of words task aurally presents sixteen single words (e.g. table), one at a time, with instructions to repeat them aloud. There are a total of sixteen test trials plus one practice trial at the beginning. Immediate correct responses were given a score of 2. Correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. Articulatory errors (e.g., dysarthric distortions) not affecting the perceptual identity of the target were scored as correct. Incorrect responses (i.e. verbal, phonemic, neologistic and dyspraxic errors) were given a score of 0. T-scores equal to or below 56 constitute the impaired range.

Task 13: the CAT repetition of complex words task aurally presents three morphologically complex words (e.g. unthinkable), one at a time, with instructions to repeat them aloud. Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. Verbal, phonemic, neologistic and apraxic errors were scored as incorrect. T-scores equal to or below 61 constitute the impaired range.

Task 14: the CAT repetition of nonwords task aurally presents five nonsense words (e.g., gart), one at a time, with instructions to repeat them aloud. Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. T-scores equal to or below 52 constitute the impaired range.

Task 15: the CAT repetition of digit strings task involves hearing digit strings and repeating what has been heard. There are six progressive levels of difficulty that start with two digits and build up to seven digits. The total score is obtained by multiplying the number of digits in the digit string of maximum length successfully repeated by two. Phonemic, apraxic and dysarthric errors were not penalized. T-scores equal to or below 54 constitute the impaired range.

Task 16: the CAT repetition of sentences task presents a series of sentences in ascending length, with the instruction to repeat them aloud. The examiner asks the participant to repeat out the first of each pair of sentences. If the participant repeats them correctly, they proceed to the next level. If the response is incorrect, the examiner asks the patient to repeat the second sentence of the pair in that same level. They stop when both trials from the same level are incorrect. The score is the number of content words in the longest sentence correctly repeated multiplied by 2. T-scores equal to or below 62 constitute the impaired range.

Task 17: the CAT naming objects task visually presents 24 line drawing pictures of objects (e.g., knife), one at a time, with instructions to name them aloud. There are a total of twenty four test trials plus one practice trial at the beginning. Immediate correct responses are given a score of 2. Correct responses after a self-correction or a delay (> 5 seconds) were given a score of

1. Incorrect responses (e.g. verbal, phonemic, neologistic and apraxic errors) were given a score of 0. T-scores equal to or below 61 constitute the impaired range.

Task 18: the CAT naming actions visually presents five line drawing pictures of an action being performed, for example, a picture of a man eating an apple, with instructions to say what the person (in the picture) is doing. There are a total of five test trials plus one practice trial at the beginning. Correct naming responses spoken within 5 seconds, were given a score of 2. Correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. Incorrect responses are given a score of 0. T-scores equal to or below 62 constitute the impaired range.

Task 19: the CAT spoken picture description task visually presents a picture of a complex scene, with instructions to say what is happening in the scene. There are five scored parameters in this task:

(i) Appropriate information carrying words: each word conveying exact meaning in the correct context was given a score of 1. Dysarthric distortions are not penalised here.

(ii) Inappropriate information carrying words: each word incorrectly selected (e.g. verbal paraphasias, neologisms, semantically related/unrelated words) was given a score of 1. The total number of inappropriate carrying words is deducted from the total number of appropriate carrying words.

The others parameters scored are: (iii) the variety of syntactic structures used which was scored on a 0-6 scale; (iv) the grammatical well-formedness of sentences/phrases which was scored on a 0-6 scale; and finally (v) the speed of speech production which was scored on a 0-3 scale. T-scores equal to or below 60 constitute the impaired range.

Task 20: the CAT reading words task visually presents 24 written words, one at a time, with instructions to read them aloud. There are a total of twenty four test trials plus one practice trial at the beginning. Immediate correct responses were given a score of 2. Correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. Incorrect responses were given a score of 0. T-scores equal to or below 61 constitute the impaired range.

Task 21: the CAT reading complex words task visually presents three morphologically complex words (e.g. recooked) one at a time, with instructions to read them aloud. Immediate correct responses were given a score of 2. Correct responses after a self-correction or a delay (> 5 seconds) were given a score of 1. Incorrect responses were given a score of 0. T-scores equal to or below 60 constitute the impaired range.

Task 22: the CAT reading function words task visually presents three function words (e.g. and), one at a time, with instructions to read each word aloud. Correct responses were given a score of 2. Correct responses after a delay and/or self-correction were given a score of 1. Incorrect responses were given a score of 0. T-scores equal to or below 48 constitute the impaired range.

Task 23: the CAT reading nonwords task: visually presents five nonsense words (e.g. fask), one at a time, with instructions to read them aloud. Immediate correct responses were given a score of 2; incorrect responses were given a score of 0; correct responses after a self-correction or a delay (>5 seconds) were given a score of 1. Articulatory errors (e.g. dysarthric distortions) not affecting the perceptual identity of the target were scored as correct. Verbal, phonemic, neologistic and apraxic errors were scored as incorrect. T-scores equal to or below 57 constitute the impaired range.

Task 24: the CAT copying letters task visually presents 10 letters (five from upper to upper case, and five from lower to upper case); and 3 words, with instructions to copy all letters and words with every letter in upper case. Each correct letter (all must be upper case) were given a score of 1. T-scores equal to or below 51 constitute the impaired range.

Task 25: the CAT written picture naming task visually presents five line drawing pictures (e.g., tank), one at a time, with instructions to write their names on paper. Letters in the correct position were given a score of 1 each. Substitutions, omissions and transpositions were given a score of 0. One point was deducted from the total score if one or more letters were added to the target word. T-scores equal to or below 54 constitute the impaired range.

Task 26: the CAT written to dictation task aurally presents five items, one at a time, with the instruction to write each word on paper. There are a total of five test trials plus one practice trial at the beginning. As above, 1 point was scored for every correct letter in the correct position (relative to the adjacent letters). Substitutions, omissions, or transpositions were given a score of 0. Any additional letter within a word was deducted from the total. T-scores equal to or below 58 constitute the impaired range.

Task 27: the CAT written picture description task: is the same as the spoken picture description task (task 19) except that the examiner asks the participant to write down on paper what is happening in the picture. Time allowed for this task is 3 minutes. T-scores equal to or below 65 constitute the impaired range.

Table 3.2. Sections and tasks in the Comprehensive Aphasia Test (CAT)

Sections	Tasks	Abbreviations
I. – The Cognitive Screen		
	1. Line bisection 2. Match pic-to-pic (semantic) 3. Recognition memory 4. Word fluency (letter) Word fluency (category) 5. Gesture object use 6. Arithmetic	Line bisection Pic-Pic Recognition Letter Fluency Animal Fluency Gesture Arithmetic
II.- The Language Battery		
Language comprehension	7. Match auditory word-to-picture 8. Match auditory sentence-to-picture 9. Match auditory paragraphs 10.Match written words-to-picture 11.Match written sentence-to-picture	Aud-Wd-Pic Aud-Sen-Pic Aud-Par Wr-Wd-Pic Wr-Sen-Pic
Repetition	12.Repetition of heard words 13.Repetition of complex words 14.Repetition of nonwords 15.Repetition of digit strings 16.Repetition of sentences	Repetition Wd Repetition CWd Repetition NWd Repetition DS Repetition Sen
Spoken output	17.Naming objects 18.Naming Actions 19.Spoken picture description	Naming Obj Naming Act Spoken PicDis
Reading aloud	20.Reading words 21.Reading complex words 22.Reading function words 23.Reading nonwords	Read Wd Read CWd Read FWd Read NWd
Writing	24.Copying letters 25.Written picture naming 26.Writing to dictation 27.Written picture description	Copy Letters Write ObjName Write Dictation Written PicDis

3.3.3. Co-occurring deficits and group assignment

109 patients met the inclusion criteria but 16 of these patients were excluded from the main analyses because they had poor performance on (i) line bisection (Task 1) - indicative of perceptual (visual attention) impairments; or (ii) semantic memory (which is a combined score from picture-to-picture semantic association and recognition memory tasks (tasks 2 and 3) - indicative of object recognition and/or semantic memory impairments. Following the same criteria, 62 (out of 369) left-hemisphere stroke patients were excluded from the main analyses.

The rationale for excluding patients with perceptual/semantic matching deficits was based upon the fact that right hemisphere damage has previously been associated with a high incidence of visuoperceptual deficits (Corbetta et al., 2005; Hillis et al., 2005; Bartolomeo et al., 2012), which in turn could influence the patient's performance on a range of language tasks (see Table 3.3 for a functional analysis of the 27 tasks from the CAT). For instance, if a patient has difficulty sustaining visual attention (as measured by line bisection in Task 1), this would impact upon all tasks that involve matching speech (or other stimuli) to complex pictures because picture recognition will be compromised when visual spatial attention is also compromised. Therefore, and in order to accurately investigate the underlying processes that may have caused language deficits in right-hemisphere stroke patients, I will focus my analysis on the remaining 93 right-hemisphere stroke patients (and 307 left-hemisphere stroke patients).

Table 3.3. Analysis of 27 tasks from the Comprehensive Aphasia Test

Task	Comprehension					Production					Executive Function		
	Perception			Semantics		Retrieve		Articulate					
	Pic	Wr	Sp	Con	Act	Wd	Sen	Cov	Seq	Ovt	WM	VSA	O
1. Line bisection												Y	
2. Pic-Pic	Y			Y								Y	
3. Letter Fluency						Y		Y	Y	Y	Y		Y
Animal Fluency				Y		Y		Y	Y	Y	Y		Y
4. Recognition	Y			Y								Y	Y
5. Gesture	Y			Y								Y	Y
6. Arithmetic		Y						Y			Y	Y	Y
7. Aud-Wd-Pic	Y		Y	Y				Y			Y	Y	
8. Aud-Sen-Pic	Y		Y	Y	Y			Y			Y	Y	
9. Aud-Par				Y	Y			Y			Y		
10. Wr-Wd-Pic	Y	Y	Y	Y								Y	
11.Wr-Sen-Pic	Y	Y	Y	Y	Y							Y	
12. Repetition Wd			Y	Y				Y	Y	Y			
13. Repetition CWd			Y	Y				Y	Y	Y			
14. Repetition NWd			Y					Y	Y	Y	Y		
15. Repetition DS			Y					Y	Y	Y	Y		
16. Repetition Sen			Y	Y	Y			Y	Y	Y	Y		
17. Naming Obj	Y			Y		Y			Y	Y		Y	
18. Naming Act	Y			Y	Y	Y			Y	Y		Y	
19. Spoken PicDis	Y			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
20. Read Wd		Y		Y		Y		Y	Y	Y		Y	
21. Read CWd		Y		Y		Y		Y	Y	Y		Y	
22. Read FWd		Y				Y		Y	Y	Y		Y	
23. Read NWd		Y				Y		Y	Y	Y		Y	
24. Copy Letters		Y										Y	
25. Write ObjName	Y			Y				Y			Y	Y	
26. Write Dictation			Y	Y							Y	Y	
27. Written PicDis	Y			Y	Y			Y	Y		Y	Y	Y

Key to abbreviations in Table 3.3.

- Y = yes this function is involved in the task.
- Pic = pictures of object,
- Wr = writing, Sp = heard speech,
- Con = concept,
- Act = action, Wd = words, Sen = sentences,
- Cov = covert, Seq = sequences, Ovt = overt,
- WM = working memory,
- VSA = visuo-spatial-attention,
- O = other executive functions such as suppressing other responses.

3.3.4. Self-reported measures

The Aphasia Recovery and Therapy Questionnaire (AR&TQ) is an unpublished assessment of aphasia symptoms and recovery in the first weeks and months after their stroke. The questionnaire captures the patient's perceived abilities across four language domains (speaking, understanding, reading and writing). For each domain the respondent must retrospectively rate their ability at one week, one month and one year post stroke.

The questionnaire is scored using a 7 point scale (0 = unable to attempt, 7 = as normal). If a patient reported themselves as in between two points, a half score was provided. The questionnaire is an aphasia friendly document with pictorial representations as well as text. When required, the examiner helps patients to respond, for example by reading the questions, and using a range of communication strategies to clarify the questions and facilitate communication.

3.4. Results

3.4.1. The most frequently impaired language task

The language task that was most frequently impaired after RHS damage was auditory sentence-to-picture matching (Task 8; for stimuli details see Table 3.4 and Figure 3.1). Even after excluding all patients with visual perceptual/semantic memory deficits, the incidence of impairments on the auditory sentence-to-picture matching task was 13% (12/93) compared to 0-9% (mean = 4%) on all other language tasks (see Table 3.5). In contrast, in patients with left-hemisphere stroke damage, the most frequently impaired task (in those who did not have visual perceptual impairments) was spoken picture description, with an incidence of 54% (167/307) compared to 1-50% (mean = 30%) on all other tasks and 46% (140/307) on auditory sentence-to-picture matching.

Table 3.4. The auditory sentence-to-picture matching task.

Sentence Number	Sentence Type	Number of predicates	Example
1, 2, 3	NP	1	The woman is walking
4, 5	NP VP NP A	2	The man is eating the apple
6	NP VP PP	2	The dog is sitting on the table
7	NP VP NP	2	The apple is under the shoe
8, 9, 12	NP VP NP A	2	The singer hits the soldier
10, 11	NP VP NP P	2	The policeman is painted by the dancer
13	NP (*PP) VP NP E	2	The shoe under the pencil is blue
14	NP(*clause) VP NP E	2	The carpet the cat is on is red
15	NP VP PP	2	The red pencil is under the shoe
16	NP (*PP) VP NP	1	The flower in the cup is blue

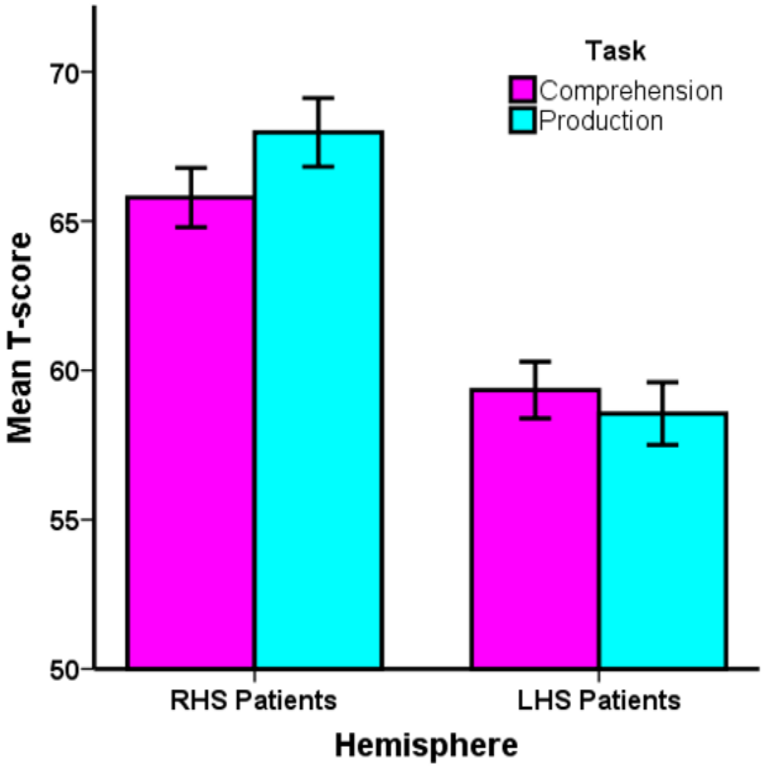
Abbreviations: NP = noun phrase, VP = verb phrase, PP = prepositional phrase, A = active sentence, P = passive sentence, E = embedded sentence, * = post-modifying. Sentences 1-6 were non-reversible, sentences 7-16 were reversible.

Figure 3.1. An example stimulus from the CAT auditory sentence-to-picture matching task

The figure shows sentence number 1 from the CAT auditory sentence-to-picture matching task. Patients were instructed to hear a sentence (produced by the examiner), and selects the picture, from a set of 4, that best illustrates the sentence. The target sentence was "the woman is drinking" (right upper corner).

To further characterise differences in performance between language comprehension (i.e. auditory sentence-to-picture matching task) and production (i.e. spoken picture description task) in left-hemisphere versus right-hemisphere stroke patients, a 2×2 mixed factorial ANOVA was conducted on task scores with Task (Production versus Comprehension) as a within-subjects factor and Hemisphere Damaged (Left versus Right) as a between-subjects factor (see Figure 3.2). I found a main effect of Hemisphere Damaged ($F(1,398) = 87.70$, $P < 0.001$), indicating that left-hemisphere stroke patients performed, on average (mean = 58.9), significantly worse than right-hemisphere stroke patients (mean = 66.9). The main effect of Task was not significant (F(1,398) = 2.48, P = 0.116) but there was a significant Hemisphere Damaged by Task interaction (F(1,398) = 11.26, P = 0.001). Post-hoc tests confirmed that patients with unilateral right-hemisphere lesions had poorer language comprehension (mean = 65.8; SE = 0.79) than production (mean = 68.0; SE = 0.88; P = 0.005), while a trend in the opposite direction was observed in patients with unilateral left-hemisphere lesions (mean Comprehension = 59.3; SE = 0.44 versus Production = 58.6; SE = 0.48; P = 0.066). The number of patients with impaired performance on any of the 27 tasks from the CAT is reported in Table 3.5.

Figure 3.2. Mean T-scores for the comprehension and production tasks for RHS and LHS patients



The figure shows the mean T-scores for the comprehension and productions tasks of the CAT for 93 patients with right hemisphere strokes (RHS) and 307 patients with left hemisphere strokes (LHS). Error bars represent the standard error of the mean (SE).

Table 3.5. Incidence of impaired performance for all right hemisphere and left hemisphere stroke patients.

		RH patients		LH patients	
Sections	**Tasks**	**All patients (n = 109)**	**Without VPI (n= 93)**	**All patients (n = 369)**	**Without VPI (n = 307)**
I.-The Cognitive Screen					
	1. Line Bisection	12 (11%)	0	23 (6%)	0
	2. Match pic-to-pic (semantic)	8 (7%)	2 (2%)	23 (6%)	6 (2%)
	3. Recognition Memory	6 (6%)	3 (3%)	18 (5%)	10 (3%)
	* Memory Score	7 (6%)	0	24 (7%)	0
	4. Word fluency	3 (3%)	1 (1%)	57 (15%)	90 (29%)
	5. Gesture Object Use	5 (5%)	2 (2%)	28 (8%)	452(14%)
	6. Arithmetic	1 (1%)	0	8 (2%)	3 (1%)
II.-The Language Battery					
Comprehension	7. Match Aud word-to-pic	10 (9%)	2 (2%)	41 (11%)	54 (18%)
	8. Match Aud sentence-to-pic	**21 (19%)**	**12 (13%)**	**197 (53%)**	**140 (46%)**
	9. Match Aud paragraph	2 (2%)	0	32 (9%)	44(14%)
	10.Match Written word-to-pic	16 (15%)	8 (9%)	53 (14%)	91 (30%)
	11.Match Written sentence-to-pic	12 (11%)	2 (2%)	61 (17%)	109 (36%)
Repetition	12.Repetition of heard words	11 (10%)	5 (5%)	59 (16%)	151(49%)
	13.Repetition of complex words	8 (7%)	4 (4%)	56 (15%)	120 (39%)
	14.Repetition of pseudowords	13 (12%)	7 (8%)	58 (16%)	104 (34%)
	15.Repetition of digit strings	2 (2%)	2 (2%)	60 (16%)	125 (41%)
	16.Repetition of sentences	2 (2%)	1 (1%)	64 (17%)	137 (45%)
Spoken output	17.Naming objects	12 (11%)	5 (5%)	65 (18%)	146(48%)
	18.Spoken picture description	**18 (17%)**	**7 (8%)**	**219 (59%)**	**167 (54%)**
Reading aloud	19.Reading words	12 (11%)	3 (3%)	60 (16%)	153 (50%)
	20.Reading complex words	8 (7%)	2 (2%)	61 (17%)	133 (43%)
	21.Reading function words	0	0	36 (10%)	37 (12%)
	22.Reading pseudowords	6 (6%)	1 (1%)	61 (17%)	142 (46%)
Writing	23.Copying letters	7 (6%)	3 (3%)	25 (7%)	26 (8%)
	24.Written picture naming	4 (4%)	0	40 (11%)	61 (20%)
	25.Writing to dictation	10 (9%)	4 (4%)	59 (16%)	125 (41%)
	26.Written picture description	12 (11%)	6 (6%)	58 (16%)	154 (50%)

Abbreviations: RH = right-hemisphere stroke patients; LH = left-hemisphere stroke patients, VPI = visual perceptual impairments; * = Memory score is a combined score from match picture-to-picture semantic matching and recognition memory. The action naming task was not included in the table due to the high variability in scores across neurologically-normal controls (i.e. low specificity).

3.4.2. The most frequently impaired functional process

In total, 12 of the 93 right-hemisphere stroke patients with normal perceptual skills had impaired performance on the auditory sentence-to-picture matching task (i.e. the most frequently impaired task). Out of 12 patients, 9 had consistent behavioural profiles that indicated “selective” impairments in auditory sentence-to-picture matching, particularly on trials with reversible sentences (see Table 3.6). The remainder of the study therefore sought to explain what type of processing impairment was causing these 9 patients to make errors when they matched auditory sentences, with reversible syntactic structures, to pictures. See Tables 3.7 and 3.8 for patient’s performance across the 27 tasks of the CAT.

The most striking result was that all 9 patients of interest could perform the sentence-to-picture matching within normal limits when the stimuli were presented in the visual modality (Task 11) even when the visually presented sentences were semantically reversible. This makes it unlikely that their impairments matching reversible sentences to pictures in the auditory modality could be explained by a breakdown in processes that are shared by auditory and visual sentence-to-picture matching, such as syntactic processing (as proposed by Grodzinsky et al., 1999) or the integration of the syntactic structure of a sentence with semantic information (as proposed by Saffran, et al., 1998) or decision making (see Table 3.9 for a task analysis).

Table 3.6. Type of errors made by the nine patients of interest in the auditory sentence-to-picture matching task

Type of sentences	**Patient ID**									**Stim Loc.**
Non-reversible sentences	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**	
1. The woman is drinking			▒			■			▒	RU
2. The man is walking		▒				▒	■	▒		LB
3. She is laughing										LB
4. The man is eating the apple										RB
5. The woman is painting the wall				▒			▒			RU
6. The dog is sitting on the table										LU
Reversible sentences										
7. The apple is under the shoe										RU
8. The nurse shoots the butcher	■	▒		■	▒					RU
9. The singer hits the soldier	■	■	■	■	■	▒	■	■	■	LB
10. The policeman is painted by the dancer						■	▒		■	LU
11. The butcher is chased by the nurse					■	▒				RB
12. The dancer paints the policeman										LU
13. The shoe under the pencil is blue	■	■	■	▒	▒		▒	■	▒	RB
14. The carpet the cat is on is red			▒							LU
15. The red pencil is under the shoe										LB
16. The flower in the cup is blue										RB

Type of errors made by the nine patients with selective impairments on the auditory sentence-to-picture matching task. Light grey denotes a score of 1 for an accurate but delayed response, repetition of the target by the examiner and/or self-correction. Black denotes a score of 0 for incorrect responses. Importantly, all incorrect responses on reversible sentences corresponded to instances where the subject-verb-object relationship was reversed. For example, in sentence number 13, patients chose alternative (C): The pencil under the shoe is blue. The last column shows the location in which the target sentences were displayed: Stim Loc = Stimulus Location; R/L = Right/Left; B/U = Bottom/Upper. Patients had to select a picture, from a set of 4 (2x2 array) that best illustrated the sentence that they heard (see Figure 3.1 for an example stimulus). Patients Numbers 1-9 refers to the following IDs in the PLORAS database: PS0316, PS0383, PS0448, PS0670, PS0870, PS1172, PS1211, PS1550 and PS2627.

In addition, all 9 patients of interest were able to repeat nonwords and digit strings (tasks 14 and 15; two classic tests of speech perception and short-term memory). This makes it unlikely that the difficulty these patients had matching reversible sentences in the auditory domain were due to phonological working memory deficits (as proposed by Richardson et al., 2010).

An alternative hypothesis is that greater difficulties with reversible sentences (during auditory sentence-to-picture matching) arose as a consequence of a reduction in the overall domain general processing capacity available for syntactic, interpretive, and task-related operations (Caplan et al., 2007). There were not sufficient behavioural data from the 9 patients of interest to test this hypothesis, nor were any of the 9 patients available for further testing. Therefore, I used lesion analyses (in Study 2) and functional neuroimaging in neurologically-normal participants (Chapters 5 and 6) to explore this hypothesis further. Importantly, however, I was able to establish that 6 out of 9 patients of interest indicated that they were aware that their everyday auditory speech comprehension had been impaired by their stroke. See Table 3.10 for information on the self-assessment questionnaire.

Table 3.7. Performance of the patients of interest across the 6 cognitive tasks of the CAT

Task	P1	P2	P3	P4	P5	P6	P7	P8	P9
Line Bisection	66	66	44	53	53	66	53	59	48
Match Pic-to-Pic	60	60	60	60	60	60	60	51	**47**
Recognition Memory	48	59	48	48	59	59	**43**	48	59
Memory Score *	54	62	54	54	62	62	50	50	50
Word Fluency	71	69	67	69	72	70	69	70	75
Gesture	60	60	68	60	60	60	55	68	60
Arithmetic	65	65	57	57	53	65	44	53	65

The table displays for every patient in the group of interest the test scores on the 6 cognitive tasks of the Comprehensive Aphasia Test (see Table 3.2 for details). * = Memory score is a combined score from picture-to-picture semantic matching and recognition memory tasks. Grey denotes impaired performance. Patients 1-9 refer to the following IDs in the PLORAS database: PS0316, PS0383, PS0448, PS0670, PS0870, PS1172, PS1211, PS1550 and PS2627.

Table 3.8. Performance of the 9 patients of interest on 21 CAT tasks.

Task	**P1**	**P2**	**P3**	**P4**	**P5**	**P6**	**P7**	**P8**	**P9**
Match Aud wtASKord-to-pic	55	55	60	65	60	65	60	65	53
Match Aud sentence-to-pic	**57**	**58**	**58**	**58**	**58**	**58**	**58**	**60**	**57**
Match Aud paragraphs	60	49	60	60	49	60	60	60	49
Match Written word-to-pic	55	59	65	65	65	65	59	**51**	**47**
Match Written sentence-to-pic	62	64	62	65	65	64	67	59	62
Repetition of heard words	57	57	57	65	57	57	**56**	57	57
Repetition of complex words	62	62	62	62	62	62	62	62	62
Repetition of nonwords	55	53	67	67	55	53	62	67	67
Repetition of digit strings	55	66	55	66	55	59	55	55	59
Repetition of sentences	63	63	63	63	63	63	63	63	63
Naming objects	**60**	74	66	70	64	74	74	66	**60**
Naming Actions	69	**59**	69	69	69	69	69	59*	69
Spoken picture description	66	62	62	72	74	61	66	68	**58**
Reading words	69	62	64	62	69	69	62	**57**	64
Reading complex words	67	67	67	67	67	67	67	**51**	67
Reading function words	62	62	62	62	62	62	62	49	62
Reading nonwords	68	68	61	64	68	68	68	58	68
Copying letters	61	61	61	61	61	61	52	61	61
Written picture naming	67	67	62	67	67	67	58	55	67
Writing to dictation	**57**	63	59	63	61	61	63	**54**	68
Written picture description	68	69	67	75	75	75	68	**64**	70

The table displays for every patient in the group of interest the test scores (i.e. T-scores) on the 21 language tasks of the Comprehensive Aphasia Test. Grey denotes impaired performance; Aud = auditory stimuli (heard speech); pic = picture.

Table 3.9. Task analysis comparing the auditory and visual sentence-to-picture matching tasks

Process of interest	**Auditory sentence-to-picture matching**	**Visual sentence-to-picture matching**
Auditory processing	▓	
Visual processing	▓	▓
Lexical-semantic processing	▓	▓
Syntactic processing	▓	▓
Working memory	■	░
Attention (monitoring)	■	░
Matching/Decision-making	▓	▓
Finger response	▓	▓

The levels of processing hypothesized to be required for completing the CAT sentence comprehension tasks. Black is used to highlight the processes that are differentially engaged by the auditory and visual sentence-to-picture matching tasks. Dark grey indicates necessary/explicit processes. Light grey signifies supporting/implicit processes.

Table 3.10. Self-report questionnaires data for RHS and LHS patients

Stroke patients	**Difficulty understanding 1 week**	**Difficulty understanding 1 month**	**Difficulty understanding 1 year**
RHS patients	37/93	27/93	19/93
Group of Interest	6/9	5/9	2/9
LHS patients	212/290	183/290	130/290
	Difficulty speaking 1 week	**Difficulty speaking 1 month**	**Difficulty speaking 1 year**
RHS patients	51/93	39/93	21/93
Group of Interest	5/9	4/9	2/9
LHS patients	274/290	259/290	213/290

The table provides a summary of the self-report data from the 93 patients with right hemisphere stroke (RHS) and 290 patients with left hemisphere stroke (LHS) included in this study. In total, 93 out of 109 RHS patients and 290 out of 369 LHS patients had information on the self-assessment questionnaire available. The differences in performance between language comprehension and production in LHS versus RHS patients reported above (see Figure 3.2) were not apparent in the self-reported questionnaires data.

3.5. Discussion

As previous lesion studies have shown that right hemisphere damage does not cause language impairments the focus of the literature to date has been on the role of the left hemisphere and thus much less is known about the contribution of the right hemisphere to language processing. This study sought to investigate which language task and processing level were the most frequently impaired following right hemisphere damage. The behavioural data from 109 right-hemisphere stroke patients allowed me to identify a group of patients who had right hemisphere damage and poor scores on one or more language tasks, and generate hypotheses to explain what level of processing impairment (e.g. perceptual, semantic, syntactic or executive) might underlie their poor language scores. Based on the previous literature, I hypothesized that patients with right hemisphere damage were more likely to have impairments in speech comprehension than impairments in word finding or speech production.

Previous studies have reported that the incidence of acquired language disorders is approximately 1-13% for right-handed right-hemisphere stroke patients (Alexander and Annett, 1996; Coppens et al., 2002) and 18-38% for right-handed left-hemisphere stroke patients (Pedersen et al., 1995). The results from this study are consistent with these prior studies but also show how the incidence of language impairments is task dependent even after controlling for visual perceptual/memory abilities. For patients with unilateral right-hemisphere damage, the highest incidence of impaired performance (13%) was recorded for auditory sentence-to-picture matching which tests spoken sentence comprehension abilities. This cannot simply be explained in terms of task difficulty, because, in patients with left hemisphere damage, the most frequently impaired task was spoken picture description (see Table 3.5).

By examining how the patients with right hemisphere damage and impaired auditory sentence-to-picture matching performed on other cognitive and language tasks, I identified a group of 9 patients with selective deficits who were not impaired on tasks that collectively place similar demands on visual and auditory perception, phonological, semantic, and syntactic processing and verbal working memory. Interestingly, 6 out of 9 patients with selective deficits indicated through self-reports (see Table 3.4) that they were aware of difficulties comprehending every day speech after their stroke.

Analysis of the errors made by the 9 patients with selective impairments in the task of interest (see Table 3.6), indicated that they had most difficulty when auditory sentences were semantically reversible. For example, they all had difficulties with the sentence “The singer hits the soldier”. This short simple sentence is challenging to understand because when its subject-verb-object word order is reversed, another meaningful sentence is created: “The soldier hits the singer”. If the patient hears the words but does not remember the order of the lexical items, they may mistakenly decide that they heard the other semantically plausible version, in this case that “The soldier hits the singer” (pictures of both these interpretations are included in the response selection). A previous study (Caplan et al., 1996) has also reported sentence comprehension impairments after right hemisphere damage, particularly when sentences have complex syntactic structures.

Many previous studies have reported and investigated the particular challenge that semantically reversible sentences pose in those with normal, aphasic and developing language skills. This has led to appreciation that semantically reversible sentences place enhanced demands on syntactic processing (Grodzinsky et al., 1999), the integration of the syntactic structure of a sentence with semantic information (Saffran et al., 1998), phonological working memory (Richardson et al., 2010), and general processing capacity (Caplan et al., 2007). Since the patients of interest (i.e. those with selective deficits in the task of interest) were not impaired when they were matching visually presented reversible sentences-to-pictures (i.e. visual sentence-to-picture matching), I hypothesised that their difficulties matching auditory sentences to pictures might be related to instances when word order needed to be held in memory or the task placed high demands on executive (working memory) functions. These types of processing may be more heavily taxed during auditory than visual sentence-to-picture matching, because the auditory sentences are only heard once, before decisions and responses are required, whereas the patients can continue reading the sentence while making a decision with written sentence-to-picture matching. Although it was not possible to assess patients' deficits further, I concluded, that their difficulties with auditory sentence-to-picture matching were more likely to be the consequence of disrupted executive processing than impairments in linguistic or perceptual processing. It is also possible that mild executive-semantic impairments, paired with disrupted connectivity from auditory input, gives rise to semantic 'access' deficits affecting the auditory modality only (Thompson and Jefferies, 2013).

I can also discount the possibility that selective difficulties in auditory sentence-to-picture matching were the consequence of impaired verbal short – term memory because these patients were not impaired on the digit span (i.e. repeating back a string of numbers) or nonword repetition tasks, which are both classic tests of verbal short-term memory and speech perception. Unlike these verbal short-term memory tasks, auditory sentence-to-picture matching requires the patient not only to hold word order in memory but to match the representation to one of a set of pictures with competing semantic interpretations. Together, verbal working memory load and picture selection may be overburdening the demands on general processing capacity or executive function in those patients.

Abnormally low auditory sentence-to-picture matching scores, in the context of good perceptual skills (as observed in the 9 patients of interest) are likely to reflect impaired speech comprehension in everyday conversations, even if the patients were not fully aware of their own limitations. This is because the auditory sentence-to-picture matching task includes constructions (e.g. “the woman is drinking” or “the flower in the cup is blue”) mirrored in everyday relative clauses (Roland et al., 2007).

3.6. Limitations

The results of this study have generated support for the hypothesis that right hemisphere damage can impair sentence comprehension. The main limitation of this study is that the behavioural data available were not able to directly indicate whether selective difficulties in auditory sentence-to-picture matching were the consequence of impaired executive functions. Future studies of patients with right hemisphere damage and sentence comprehension impairments are therefore required to evaluate the relationship between sentence comprehension and executive function. This could be achieved using standardised tests designed such as the Raven’s Standard Progressive Matrices (Raven, 2003), the Trail-Making test (Tombaugh, 2004), the Verbal Stroop test (Stroop, 1935), the Wisconsin Card-Sorting test (Stuss et al., 2000), and the Letter–Number Sequencing test to examine working memory (Wechsler, 2008). However, as I will demonstrate in Studies 2-4 (Chapter 4-6), the hypothesis can be indirectly investigated by examining how neurologically-normal participants typically use the regions that are damaged in patients with sentence comprehension impairments.

Another point to highlight is that this study has focused only on impaired accuracy when right hemisphere patients were performing tasks from the Comprehensive Aphasia Test (Swinburn et al., 2004). Perhaps I would have been able to find more patients with impaired performance on the task of interest (and other language tasks) if I used more sensitive behavioural measures such as reaction times (which are not currently available from our assessments). It is highly likely that right hemisphere damage also impairs language processing that was not assessed in the current patients. For example, right hemisphere damage has been shown to impair prosodic components and the pragmatic aspects of speech (Myers, 1999; Lindell, 2006). Standardise language and communication assessments for use with RHS patients such as the Montreal Protocol for the Evaluation of Communication (Joanette et al., 2015) or the Right Hemisphere Language Battery (RHLB; Bryan, 1995)), are therefore needed to evaluate more subtle alterations in language processing after right hemisphere injury.

3.7. Conclusions

The results presented here provide some initial and needed information regarding the frequency of occurrence of language deficits in patients with right hemisphere damage after stroke. The careful analysis of the patients' behavioural data allowed me to:

(i) find the most frequently impaired language task (i.e. auditory sentence-to-picture matching)

(ii) generate hypotheses to explain what level of processing impairment (e.g. perceptual, semantic, syntactic or executive) might explain their poor language scores.

Also by investigating language performance in a large sample of left hemisphere patients, I discarded the possibility that language impairments in right-hemisphere stroke patients would only reflect differences in task difficulty. At the end of this study, I hypothesized that the selective difficulties in the 9 patients of interest were likely to be the consequence of a disruption to domain-general executive processing rather than linguistic or perceptual processing. In the next experimental chapters, I systematically investigate this hypothesis by identifying which right hemisphere regions were damaged in patients with selective impairments in auditory sentence-to-picture matching (lesion-deficit mapping) and then linking the identified regions to their normal functions using functional neuroimaging studies of neurologically-normal participants.

Finally, findings from the current study offer a perspective on how and why language processes can be affected after RHS. They also highlight the importance of including detailed behavioural assessments when investigating cognitive functioning in brain-damaged patients.

CHAPTER 4: STUDY 2

Identifying right hemisphere regions where damage impairs auditory sentence-to-picture matching

4.1. Summary

In my first Study (Chapter 3), I identified 9 patients who had very selective impairments in auditory sentence-to-picture matching after right hemisphere strokes. Examination of the available behavioural data suggested that these patients had speech comprehension difficulties that were a consequence of a disruption to non-linguistic (domain-general) executive processing rather than linguistic or perceptual processing.

The aim of my second study was to investigate the lesion sites of the 9 patients identified in Study 1. First, I used voxel-based lesion-deficit analyses to find the regions that were significantly more damaged in the 9 patients with selective auditory sentence-to-picture matching impairments compared to other patients with right hemisphere damage who did not have auditory sentence-to-picture matching impairments. Then, in post-hoc tests, I determined how frequently damage to the identified regions was observed in other patients with and without auditory sentence-to-picture matching impairments, and whether the effect of the lesions was typical or atypical.

I found that 6 out of the 9 patients with selective deficits in auditory sentence-to-picture matching (4 of whom also self-reported speech comprehension deficits) had significantly more damage to dorsal parts of the

superior longitudinal fasciculus impinging on the right inferior frontal sulcus compared to other patients without auditory sentence-to-picture matching impairments. The remaining three patients had relatively small subcortical lesions in the vicinity of the right putamen, thalamus and caudate. The results of this study therefore identify a set of right hemisphere regions where damage can impair speech comprehension. Having identified these regions, their function (e.g. linguistic or executive) can be investigated using functional neuroimaging in neurologically-normal participants (Chapters 5 and 6).

4.2. Introduction

In Study 1, I identified 9 patients who had auditory sentence-to-picture matching impairments in the context of preserved performance on other tasks that placed similar demand on perceptual, semantic, phonological and syntactic processing. Therefore, I concluded that the selective impairments in these patients were explained by domain-general executive processing that contribute to auditory sentence-to-picture matching and may also be important for other cognitive tasks that were not part of the behavioural assessment used in Study 1.

The aim of the current study was to identify which right hemisphere regions were damaged in the 9 patients from Study 1 who had selective impairments in the auditory sentence-to-picture matching task. The function of the regions identified here can then be investigated in subsequent fMRI studies of neurologically-normal participants.

The right hemisphere lesions that selectively impaired auditory sentence-to-picture matching were investigated in four successive steps. First, I used voxel-based morphometry (VBM) to assess lesion-deficit relationships and identify the regions where damage was significantly greater in the group of 9 patients of interest compared to a group of 75 control patients who had right hemisphere damage that did not result in impaired auditory sentence to picture matching. This group comparison identifies regions that are more damaged in the group of interest than the control group but significant results cannot necessarily be interpreted to imply that the identified regions are either (i) damaged in all patients of interest or (ii) preserved in all control patients. In the second step, I conducted post-hoc tests to examine how frequently the regions identified by VBM were observed in the 9 patients of interest. In the third step, I investigated which right hemisphere regions were damaged in patients of interest who did not have damage to the regions identified with VBM. These additional lesions (sparing the VBM regions) might either be rare but consistently cause speech comprehension deficits or they might be common but seldom cause speech comprehension deficits. The final (fourth) step examined how frequently the VBM and additional regions were damaged in the control non-impaired group. Based on prior evidence showing that the association between lesion site and deficit is inconsistent across left-hemisphere stroke patients (Gajardo-Vidal et al., 2018), I expect to find inconsistent lesion-deficit mappings after right hemisphere damage.

4.2.1. Speech comprehension and domain-general executive functions in the right hemisphere

Although prior studies have suggested that right hemisphere damage may cause subtle deficits in comprehending language (Beeman and Chiarello, 1998; Bookheimer, 2002), right hemisphere regions that might be critical for speech comprehension have not yet been identified. For example, Caplan et al. (1996) reported sentence comprehension impairments after right hemisphere damage, particularly when sentences have complex syntactic structure; they did not, however, identify any right hemisphere lesion site associated with the deficit of interest. Dewarrat and colleagues (2009), suggested that damage to the right but not left inferior frontal gyrus induced speech comprehension disorders in the acute stage after stroke, however, their conclusions were mainly based on the analysis of data from left rather than right-handed right-hemisphere stroke patients, which may suggest atypical language lateralisation in those subjects.

Evidence from functional neuroimaging studies of neurologically-normal subjects has typically shown that the right hemisphere is less strongly activated by sentence comprehension than the left hemisphere (Indefrey et al., 2001). Nevertheless, demanding sentence comprehension tasks activate both the left and right hemispheres. For example, Xu et al. (2005) examined brain responses to individual sentences, and connected narratives and found that, as task complexity increased, activation became increasingly bilateral in many brain regions, including perisylvian, extrasylvian, and premotor cortical areas and the cerebellum. Meyer et al. (2000) provided further evidence for this claim by showing that activation in the right inferior frontal gyrus (pars opercularis and pars triangularis) and the right temporal transverse gyrus increased with task demand when subjects had to mentally transform ungrammatical sentences into grammatical ones - but not when they had to perform grammaticality judgments.

On the other hand, a great deal of evidence has suggested that the right hemisphere is also part of a bilateral domain-general cognitive control network. This system includes (i) a fronto-parietal control network (involved in executive attention; Hampshire et al., 2010; 2012), and (ii) a cingulo-opercular network (involved in cognitive control; Geranmayeh et al., 2014), with right dorsolateral prefrontal cortex (within the inferior frontal cortex) playing a crucial role in cognitive control and inhibitory processing (Duncan, 2010; Aron et al., 2014). One dominant view is that a set of these regions can rapidly adapt to exert top-down control during a wide range of tasks (Duncan, 2010; 2013) including language (Fedorenko, 2014; Fedorenko and Thompson-Schill, 2014). For example, in a meta-analysis of 59 studies reporting right hemisphere activation during language tasks, Vigneau and colleagues (2011) concluded that right frontal activation (in addition to many other regions) reflected the recruitment of attentional and working memory functions needed to perform language tasks (Vigneau et al., 2011).

In summary, the review of the literature does not clearly demonstrate which right hemisphere regions are associated with persistent impairments in sentence comprehension or domain-general executive processes. Therefore, the current study aimed to: (i) identify the right hemisphere regions damaged in stroke patients who have selective impairments in the auditory sentence-to-picture matching task (defined in Study 1), and (ii) determine how frequently damage to the identified right hemisphere regions was observed in other patients and thus, to establish whether the effect of the lesion sites was typical or atypical. By determining the frequency with which the identified regions were damaged in other patients, I will be able to single out any unexplained patients that can be used to detect additional lesion sites associated with the deficit of interest.

4.2.1. Hypotheses

(i) In the context of distributed neural networks, whereby multiple brain regions contribute to any given cognitive function, damage to any part of the sentence comprehension system might impair the function of interest. Therefore, I would expect that selective deficits in the auditory sentence-to-picture matching task will be associated with anatomically distinct right (and left) hemisphere lesion sites.

(ii) As the extent to which the right hemisphere is involved in language varies across neurologically-normal participants (see Bozic et al., 2010), and the effect of left hemisphere lesions have been shown to be very inconsistent

(Gajardo-Vidal et al., 2018), I hypothesised that there would also be high inter-patient variability in the effect of right hemisphere damage on auditory sentence-to-picture matching scores.

4.3. Methods

4.3.1. Patient selection criteria

This study focused on a subset of 84 right-hemisphere stroke patients (32 females) aged between 23 and 86 years old (Mean = 58.2, SD = 13.1) from the full sample of 109 patients included in Study 1 (Chapter 3). The 84 patients included in this study were split into those who had:

(i) Selective deficits in the auditory sentence-to-picture matching task (“the group of interest”; n = 9) and;

(ii) Non-impaired performance on the auditory sentence-to-picture matching task (“the control group”; n = 75).

All 84 patients had normal performance on the following tasks from the Comprehensive Aphasia Test (CAT): (a) line bisection, semantic matching and recognition memory (part of the cognitive screen of the CAT); (b) repetition of nonwords and digit strings (classic tests of speech perception and verbal short-term memory); and (c) the visual sentence-to-picture matching task (see Chapter 3 for exclusion criteria). Table 4.1 provides demographic information for all participants.

Table 4.1. Summary of demographics details for 84 RHS patients included in this study.

Demographic details		All RH Patients N = 84	Group of interest N = 9	Control Patients N = 75
Age at scan (years)	Mean	58.2	72.3	56.5
	SD	13.1	8.2	12.6
	Minimum	86.9	61.8	23.1
	Maximum	23.1	86.9	80.3
Years since stroke	Mean	3.1	4.4	3.0
	SD	2.1	1.8	2.1
	Minimum	0.3	1.6	0.3
	Maximum	9.2	7.9	9.2
Years of education	Mean	15.0	14.1	15.1
	SD	2.9	3.7	2.8
	Minimum	11.0	12.0	11.0
	Maximum	22.0	22.0	22.0
Gender	Number of females	32	2	30
	Number of males	52	7	45

4.3.2. MRI data acquisition and lesion identification

T1-weighted high resolution anatomical whole-brain volumes were available for all patients (n = 84). Three different MRI scanners (Siemens Healthcare, Erlangen, Germany) were used to acquire the structural images: 45 patients were imaged on a 3T Trio scanner, 15 on a 1.5T Sonata scanner, and 24 on a 1.5T Avanto scanner. Each of these T1-weighted images was then submitted to our fully automated lesion identification procedure for lesion detection and delineation (see below for details).

All T1-weighted images were converted to 3D lesion images in standard MNI space as described in Seghier et al. (2008). Two types of 3D lesion images were obtained from our automated lesion identification procedure: (i) a fuzzy lesion image and (ii) a binary lesion image – used here to delineate the lesions, to estimate lesion volume, and to generate lesion overlap maps. Scanning parameters and preprocessing steps of the imaging data are described in the general methods chapter (Chapter 2).

The presence of a lesion and lesion volume were based on binary lesion images generated by thresholding the fuzzy images. The threshold used to convert the fuzzy to binary images was 0.3 as recommended in Seghier et al. (2008). Each binary lesion image was visually inspected by the operator. The boundaries of the lesion may differ slightly from what is seen by eye but provide an objective rather than subjective measure of structural abnormality. There is no gold standard of true abnormality. As a result classification errors are treated as "noise" in the analysis and therefore bias towards false negatives rather than false positives.

4.3.3. Lesion-deficit analysis

There were four steps to my lesion-deficit analysis. These are described in detail below and illustrated in Figure 4.1.

Step 1: Voxel based morphometry (VBM)

The first step of my lesion-deficit analysis (Step 1), used voxel-based morphometry (VBM, Ashburner and Friston, 2000; Mummery et al., 2000) implemented in SPM12 with, an unequal variance two sample t-test, to identify which regions were significantly more damaged in the 9 patients of interest (those with selective impairments to the auditory sentence-to-picture matching task) compared to the 75 non-impaired control patients. As in Price et al. (2010), Gajardo-Vidal et al. (2018) and Lorca-Puls et al. (2018), the lesion images entered into the VBM analysis were continuous measurements of structural "abnormality" at each and every voxel. The advantages of utilising the fuzzy lesion images are that they: (i) provide a quantitative measure of the degree of abnormality, at each and every voxel of the brain, relative to neurologically-normal controls; (ii) are based on a spatial normalisation and an accurate tissue segmentation with minimal misclassification; (iii) combine grey and white matter into one image which allows the whole brain to be considered in each analysis (see Seghier et al., 2008 for more details).

The analysis included lesion volume as a covariate of no-interest and the search volume was limited to voxels that were classified as lesioned in at least five patients (as in Fridriksson et al., 2016; for rationale, see Sperber and Karnath, 2017). Given that large lesions are more likely to damage critical regions, the inclusion of lesion of volume as a covariate of no interest in voxel-based analyses might have a negative impact on the identification of lesion-deficit associations (for more details, see Butler et al., 2014). Firstly, I performed the same analysis after removing the lesion volume regressor. In a second and third analysis, I controlled for age as a confound that could have influenced the results of my lesion-deficit analysis. The reason for this is that the group of interest was significantly older (mean = 72.3, SD = 8.2) compared to the control group (mean = 56.5, SD = 12.6; $p < 0.001$). I therefore performed two separate analyses (i.e. analyses 2 and 3), where I firstly included age as an additional covariate of no interest; and secondly I statistically matched the group of interest and the control group for age by including 9 and 40 patients (instead of 9 and 75 patients) in the voxel-based lesion-deficit analysis.

The statistical output from the comparison of brain structure in the group of interest versus the control group was thresholded at $p < 0.05$ after family-wise error (FWE) correction for multiple comparisons across the whole search volume (estimated using random field theory as implemented in SPM; Flandin and Friston, 2015). Having identified a significant lesion-deficit, I then examined the extent of the effect at a voxel-level threshold of $p < 0.001$ uncorrected, $p < 0.05$ FWE-corrected cluster-level. All voxels that met these criteria became our "VBM region". Within this region, I report the x,y,z MNI co-ordinates corresponding to the peak Z scores.

Step 2: How frequently are the VBM regions damaged in the 9 patients with auditory sentence-picture matching difficulties?

After running the VBM analysis, the second step of my lesion-deficit analysis (Step 2) examined (i) how frequently the regions identified from the VBM analyses (henceforth "VBM regions") were damaged in the 9 patients of interest; and (ii) how much of the VBM regions were damaged (measured in percentage) in each of the 9 patients.

For those who did not have damage to the regions identified by VBM, I created a lesion overlap map to examine whether patients with selective deficits who preserved the VBM regions had damage to different regions (i.e. no lesion overlap) or to the same regions (i.e. lesion overlap).

If this lesion overlap map showed any regions that were damaged in more than one patient, I planned to repeat Steps 1 and 2 above. Repeating Step 1 involved a second VBM analysis that compared (i) all the patients who had auditory sentence-to-picture matching impairments with lesions that spared the regions identified in the VBM analysis to (ii) all the patients in the control group (who do not have auditory sentence-to-picture matching impairments). This might identify regions that were missed in the first VBM analysis due to false negatives rather than false positives. Specifically, Gajardo-Vidal and colleagues (2018) showed that univariate voxel-based analyses might not detect some or all of the lesion-deficit mappings when the same deficit can be the consequence of multiple lesion sites (i.e. distributed processing). Importantly, the authors also demonstrated that some of the missed effects can be unveiled by adopting an iterative approach that repeats the same lesion-deficit analysis multiple times while systematically excluding patients with damage to regions identified in previous steps.

Repeating Step 2, involved (i) examining how many of the patients of interest in the second VBM analysis had damage to regions identified by the second VBM analysis and (ii) whether there was any overlap in the lesion sites in patients who did not have damage to regions identified in either VBM analysis 1 or VBM analysis 2. I planned to iteratively repeat Steps 1 and 2, until the VBM analysis revealed no significant effects (Gajardo-Vidal et al., 2018). Given that there were only 9 patients of interest, I did not expect many iterations and would not have been surprised if there was insufficient power to detect significant effects in VBM analysis 1 (Lorca-Puls et al., 2018).

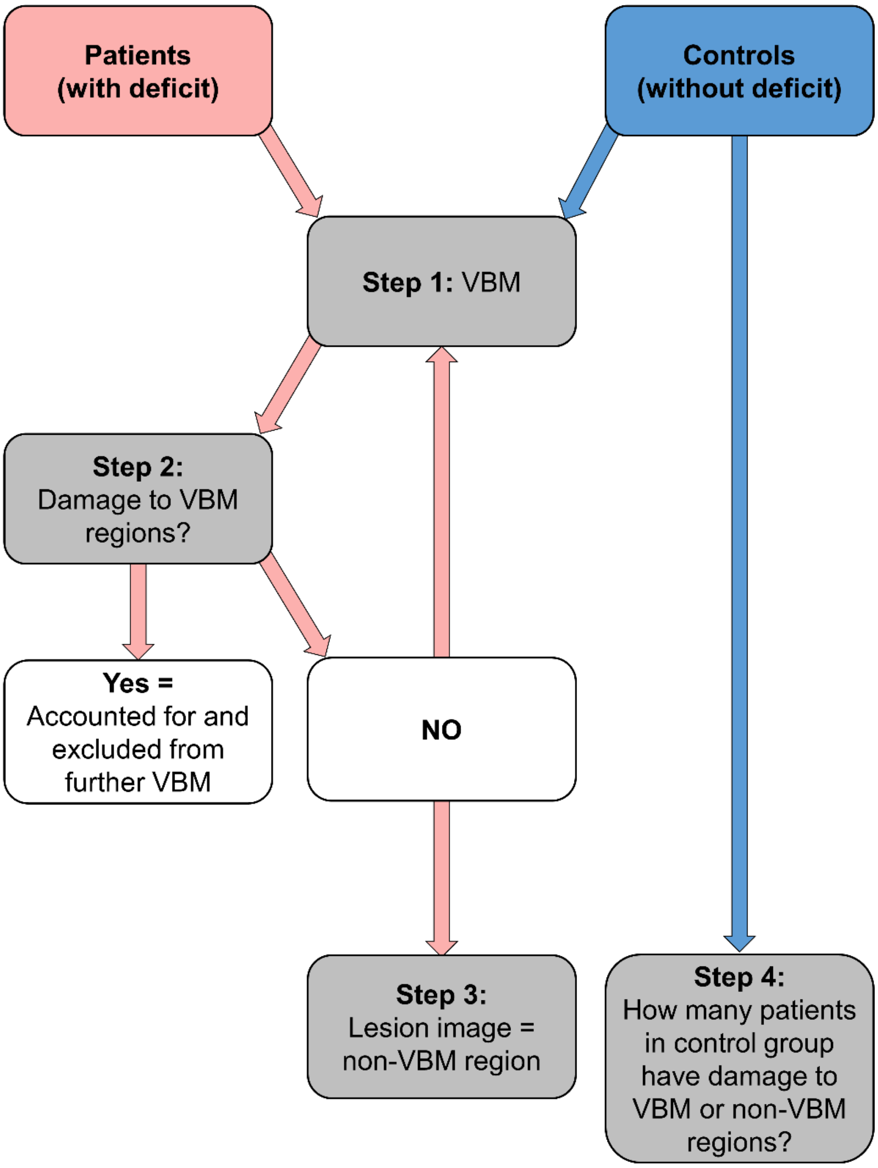
Step 3: Regions not detected by VBM

When the iterative VBM analyses revealed no significant effects, the third step of my lesion-deficit analysis (Step 3) examined the lesion sites in each patient who had auditory sentence-to-picture matching impairments but did not have damage that was identified by VBM. The full extent of damage (i.e. the 3D binary lesion image) in each of these patients became a “non-VBM region of interest”. By using the full extent of damage, I ensured that all the parts that contribute to the deficit were accounted for.

Step 4: How frequently are the lesion sites associated with auditory sentence-to-picture matching impairments damaged in the control group

Finally, in Step 4, I examined (i) how frequently the VBM and non-VBM regions of interest were damaged in the control group (who did not have impaired auditory sentence-to-picture matching) and (ii) the proportion of damage to the VBM region in each of the control patients.

Figure 4.1. The four-step approach for lesion-deficit identification

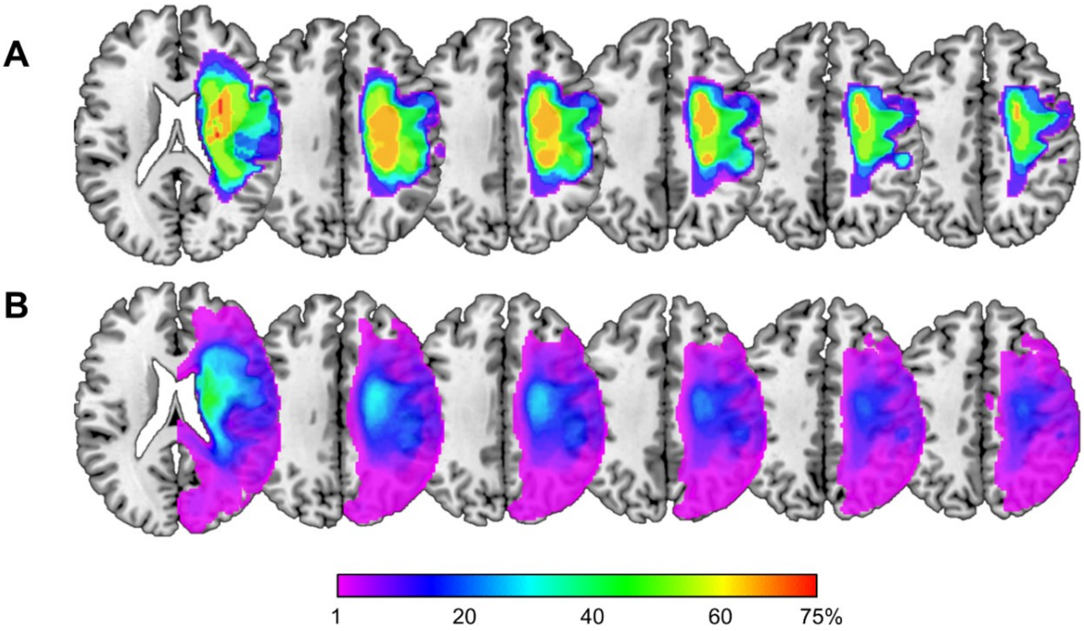


The figure shows the four-step approach that was used in the current study for lesion-deficit identification.

4.4. Results

The lesion overlap maps of the 9 patients of interest (those with impaired auditory sentence-to-picture matching and preserved cognitive skills) and 75 patients from the non-impaired control group are illustrated in Figure 4.2. The lesion sites of the 9 patients of interest are shown in Figure 4.4.

Figure 4.2. The lesion overlap map of the 9 patients of interest and 75 control patients.



(A) The top row shows the lesion overlap map for the 9 patients of interest with selective impairments in the auditory sentence-to-picture matching task. The area of maximum lesion overlap was 7/9 (78%).

(B) The bottom row shows the lesion overlap map for the 75 non-impaired control patients (i.e. those who had spared performance on the auditory sentence-to-picture matching task). The area of maximum lesion overlap was 42/75 (56%). The colour bar on the bottom indicates the percentage (0-75%) of patients who have a lesion including that particular voxel.

4.4.1. Lesion analysis Step 1

The VBM analysis (see Methods for details) yielded one significant cluster (782 contiguous voxels) centred on the dorsal aspect of the superior longitudinal fasciculus at peak co-ordinates +22, +8, +40 and impinging on the inferior frontal sulcus at co-ordinates +32, +4, +34. This region is referred to as the “VBM region” (see Figure 4.3 and Table 4.2). The same analysis was repeated three times (i) first, without including lesion volume as a covariate of no-interest (see Methods)

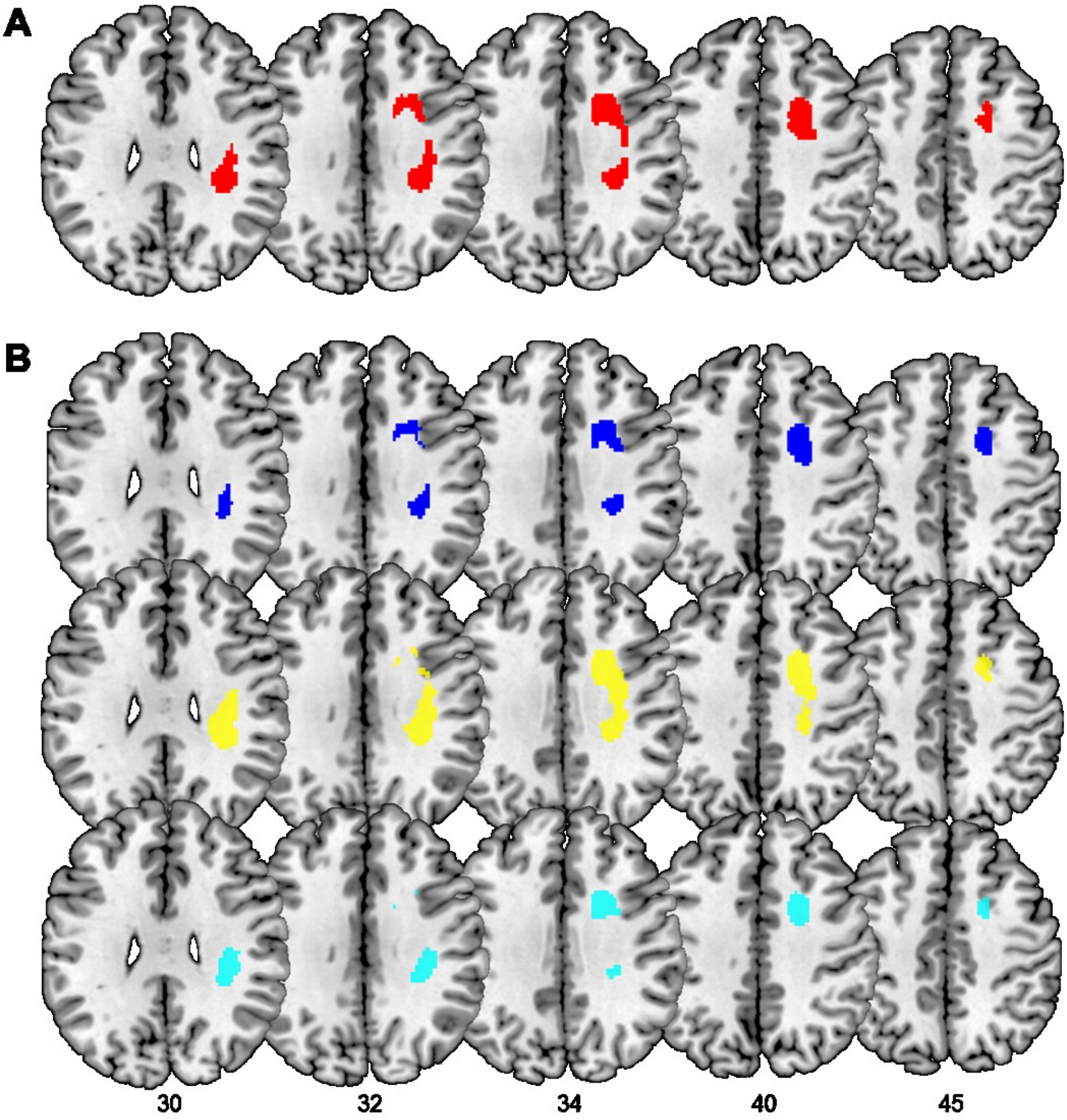
(ii) second, including age as a covariate of no interest and (iii) third, after matching the group of interest and the control group for age. For all the performed replications virtually the same lesion-deficit associations were identified. Henceforth, I focus on the results of the first VBM analysis that factored out linear effects from lesion size (see Figure 4.3 and Table 4.2).

Table 4.2. Location and significance of voxel-based analysis for Study 2

Contrast of interest	Region	k	x	y	z	Z-score	$P_{FWE\text{-}corr}$
Main analysis: Group of Interest > Control Group (with lesion volume)	R Fronto-Parietal white matter	782	22	8	40	6.7	< 0.05
	R Inferior Frontal sulcus (IFS)		32	4	34	3.3	
Analysis 1: Group of Interest > Control Group (without lesion volume)	R Frontal white matter	411	22	8	40	6.0	< 0.05
	R Inferior Frontal sulcus (IFS)		30	2	36	3.9	
	R Parietal white matter	117	26	-32	36	4.5	< 0.05
Analysis 2: Group of Interest > Control Group (with lesion volume and age as covariates)	R Frontal white matter	902	22	8	40	6.0	< 0.05
	R Inferior Frontal sulcus (IFS)		30	4	34	3.8	
Analysis 3 Group of Interest > Control Group (statiscally matched by age)	R Frontal white matter	232	22	6	40	5.3	< 0.05
	R Parietal white matter	292	34	-32	20	4.0	< 0.05

Abbreviations: R = right hemisphere; x y z = MNI coordinates, $P_{FWE\text{-}corr}$ = p-value corrected (family-wise error correction) for multiple comparisons across the whole search volume, k = region extent.

Figure 4.3. The VBM region of interest



(A) The top row shows the region identified (in red) in the voxel-based lesion-deficit mapping analysis ("the VBM region of interest), where the lesion sites of the 9 patients of interest were compared with the lesion sites of 75 control subjects (non-impaired performance on the task of interest). Numbers below indicate the corresponding MNI co-ordinates.

(B) The bottom row shows the region identified (in blue, yellow and cyan) when I repeated the same VBM analysis after removing the lesion volume regressor, including age a as covariate of no interest and matching the group of interest with the control group for age.

4.4.2. Lesion analysis Step 2

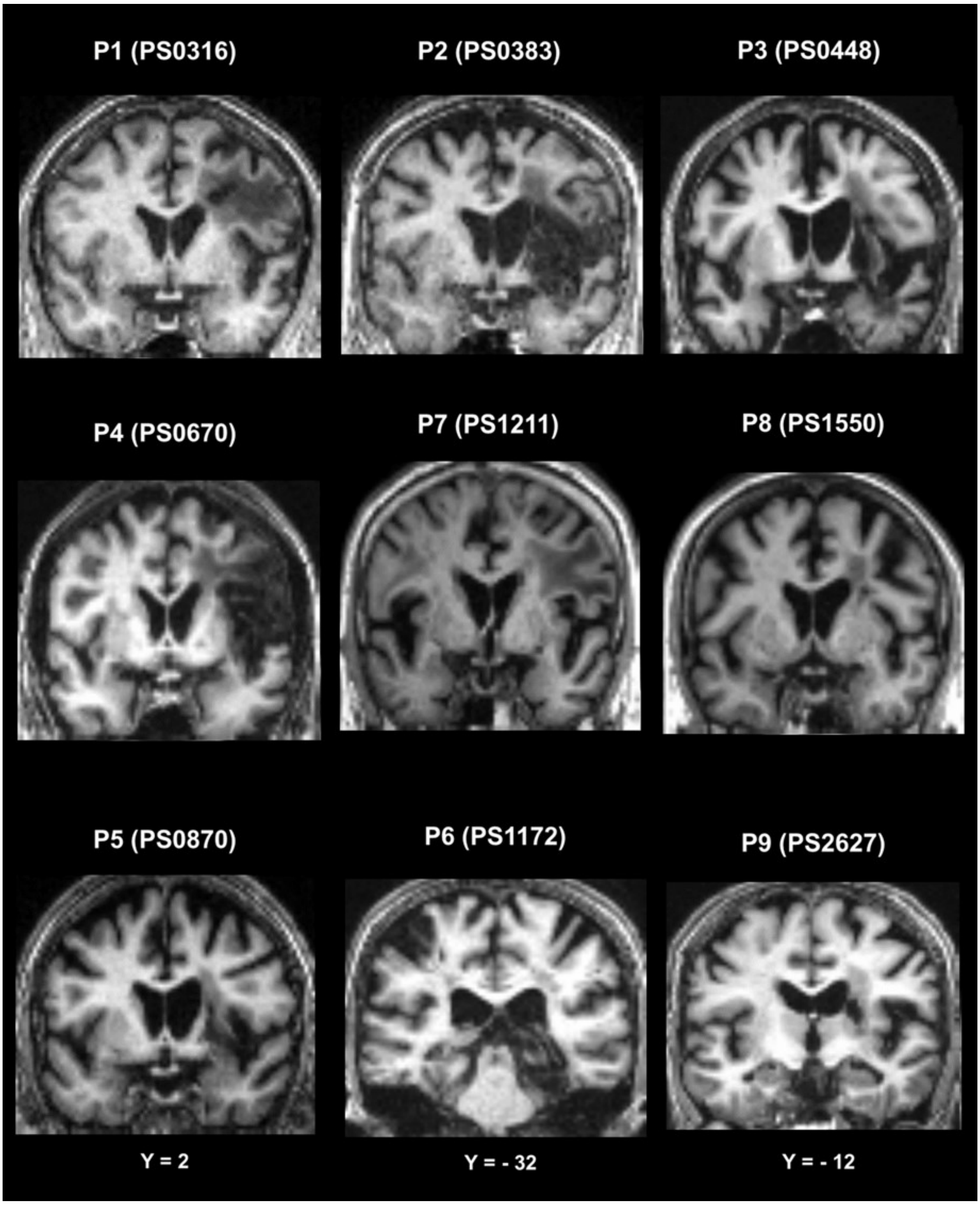
Here I examined the frequency of damage to the VBM region in the 9 patients with selective deficits in the auditory sentence-picture matching task. The proportion of the VBM region that was damaged in each of the 9 patients of interest was: 100%, 100%, 98%, 86%, 84%, 71%, 0%, 0% and 0%. In other words, 6/9 of the patients of interest had more than 70% damage to the VBM region. See Figure 4.4 for the Individual T1-weighted scans for the 9 patients of interest.

The lesion overlap of the 3 patients with no damage to the VBM region showed that the lesion sites of two patients overlapped in a small area centred on the right mediodorsal thalamus and right posterior putamen (see Figure 4.5). I therefore repeated Step 1 by running a second VBM analysis where I compared the lesion sites of the 3 patients of interest with no damage to the VBM region (identified in Step 1) to the lesion sites of the 75 non-impaired control patients. As expected, no other significant voxels were identified at FWE-corrected p values and therefore my VBM analysis stopped here (see Methods for details).

4.4.3. Lesion analysis Step 3

All the 3 patients where the VBM region was completely preserved (0% damage) had relatively small lesions (i.e. non-VBM regions A, B and C in Figure 4.5). Non-VBM region A (1.97 cm^3) included parts of the right dorsolateral putamen, caudate and globus pallidus. Non-VBM region B (12.7 cm^3) included portions of the right dorsolateral putamen, right caudate, mediodorsal thalamus, posterior insular cortex and surrounding white matter. Non-VBM region C (25.6 cm^3) included the posterior middle temporal lobe.

Figure 4.4. Individual T1-weighted scans for the 9 patients of interest



The figure shows the extent of the lesion sites in MNI space of the 9 patients of interest in coronal views of the normalised high-resolution T1-weighted images. The first two rows show the patients with damage to the VBM-region at y = 3. The last row shows the two patients with focal damage to subcortical regions (P5 and P9) and the patient with damage to the right posterior temporal lobe (P6).

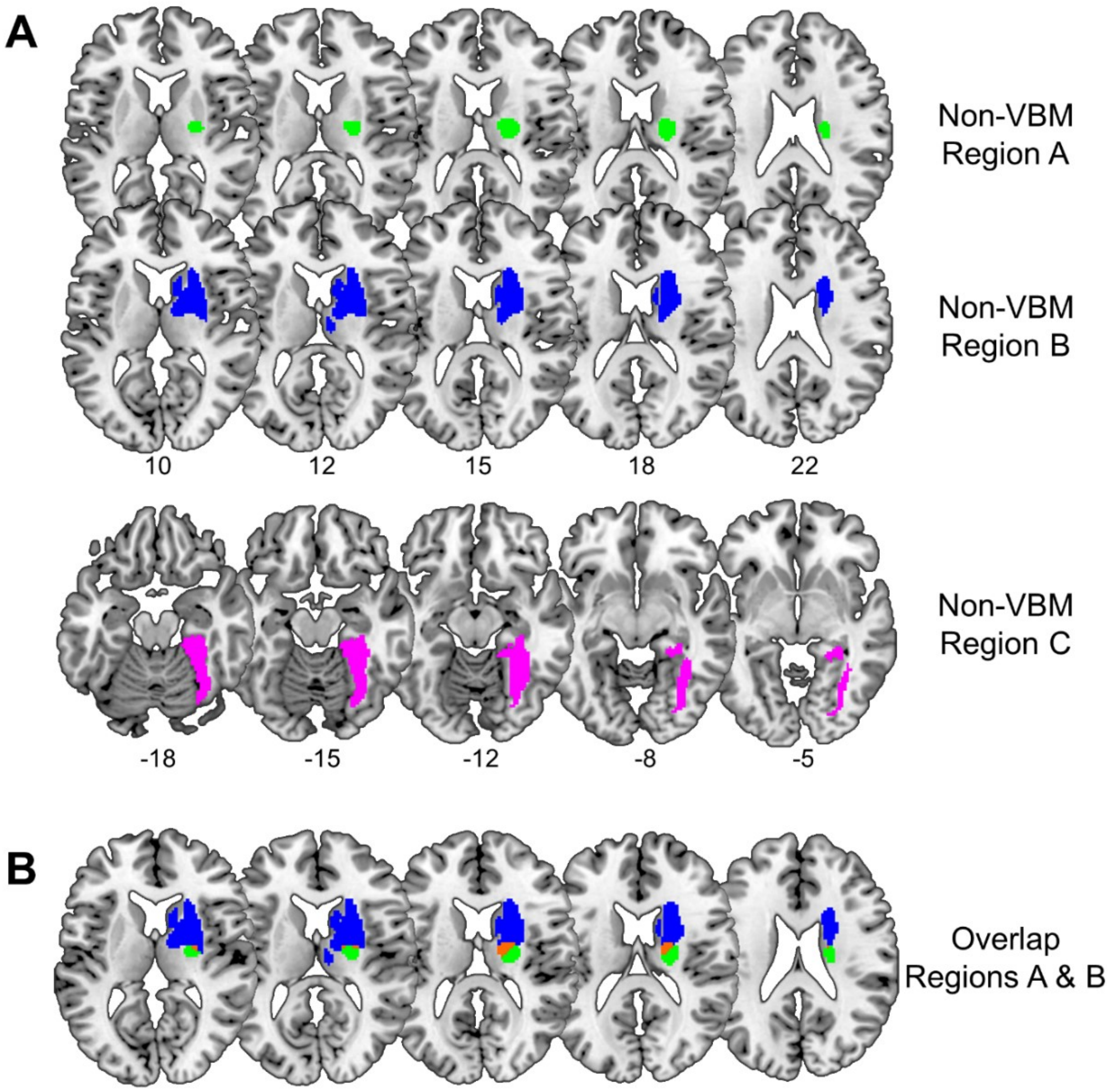
4.4.4. Lesion analysis Step 4

Finally, I examined how frequently the VBM and non-VBM regions (from Steps 1 and 3) were damaged in the control group (who did not have impaired auditory sentence-to-picture matching).

i. I found that only 3/75 (4%) patients from the control group had more than 70% damage to the VBM region (compared to 67% (6/9) of the patients of interest).
ii. Non-VBM region A was more than 95% damaged in 14/75 (19%) control patients compared to 33% (3/9) patients of interest.
iii. Non-VBM region B was more than 95% damaged in 5/75 (7%) control patients, compared to 33% (3/9) patients of interest. The overlap between non-VBM regions A&B was more than 95% damaged in 20/75 (27%) controls patients compared to 4/9 (44%) patients of interest. The overlap between these regions was not considered further.
iv. Non-VBM region C was rare and only damaged in the patient of interest defining it, and therefore it was not considered in further experimental chapters.

Taking into account all regions of interest together (VBM and non-VBM), above threshold damage was observed in a total of 14/75 patients in the control group (see Table 4.3).

Figure 4.5. Non-VBM regions A, B and C



The figure shows the “non-VBM regions A, B and C” identified in 3 patients with selective impairments in the auditory sentence-to-picture matching task and no damage to the VBM region (see Table 4.3). The bottom row shows the overlap (in orange) between the non-VBM regions A and B. Numbers below indicate the corresponding MNI co-ordinates.

Table 4.3. Clinical and behavioural characteristics of patients with impaired performance on the task of interest and/or extensive damage to the identified regions of interest

	ID	Years since stroke	Age at scan	Lesion size (cm^3)	% Damage VBM region	% Damage region A	% Damage region B	% Damage overlap regions A & B	% Damage region C	Aud Sent-Pic
Group of Interest	PS2627	1.60	74.36	1.97	0	**100***	4	100	0	58
	PS0870	5.17	64.08	12.72	0	24	**100***	100	0	58
	PS1172	2.61	75.11	25.62	0	0	0	0	**100***	57
	PS0316	5.18	61.82	65.30	98	20	11	0	0	58
	PS0670	3.14	80.5	86.07	100	74	39	72	0	58
	PS0383	5.35	72.2	141.32	100	100	100	100	0	58
	PS0448	7.91	86.85	89.93	86	100	97	100	1	58
	PS1550	4.33	63.59	35.18	84	37	35	24	0	60
	PS1211	3.99	72.15	61.31	71	9	2	0	3	57
Control Group	PS0195	6.15	58.31	195.14	100	100	100	100	0	72
	PS0544	5.79	66.81	266.75	100	100	99	100	0	65
	PS0607	5.04	62.59	204.71	70	100	100	100	0	65
	PS1763	1.53	60.95	95.77	60	100	61	100	0	65
	PS1003	2.17	49.88	150.96	32	100	96	100	0	65
	PS0402	4.92	52.19	88.70	32	100	73	100	2	72
	PS2127	2.73	41.01	55.74	31	98	62	97	1	63
	PS0037	2.95	80.33	54.54	31	96	76	98	0	72
	PS2321	4.47	46.08	70.25	16	100	98	100	0	63
	PS0093	4.88	57.53	53.70	1	100	94	100	0	65
	PS0682	2.49	54.42	29.67	0	100	78	100	0	72
	PS0028	3.08	58.76	10.93	0	100	55	100	0	72
	PS0004	0.30	36.19	17.26	0	96	51	91	0	72
	PS1190	0.80	25.36	26.52	0	95	73	98	0	72
	PS2280	3.29	56.74	11.31	0	94	54	100	0	65
	PS0669	6.01	68.04	24.67	7	93	81	100	0	72
	PS0942	2.35	42.39	12.80	0	93	60	100	0	61
	PS1081	1.78	63.75	10.85	0	78	61	100	0	63
	PS0993	5.59	74.99	120.92	22	70	83	98	3	65
	PS0294	8.10	68.03	37.86	13	42	84	98	0	72
Total number impaired (task of interest)										9
Total number with substantial damage to VBM and non-VBM regions										29

The table displays for 29 right-hemisphere stroke patients the degree of damage to the ROIs (i.e. VBM and non-VBM regions) as well as the test scores on the auditory sentence-to-picture matching task from the CAT. For the auditory sentence-to-picture matching (Aud Sent-Pic) task, a total T-score equal to or below 60 signals impaired performance. * = patients with small lesions and no damage to the VBM region where regions A, B and C were identified.

4.5. Discussion

There are only a few studies that have mapped language deficits onto lesions in the right hemisphere but findings from those studies were based on left- rather than right-handed right-hemisphere stroke patients (Basso et al., 1990; Dewarrat et al., 2009). The present study sought to identify right hemisphere regions associated with selective deficits in auditory sentence-to-picture matching in the 9 patients of interest identified in Study 1 (Chapter 3).

A four-step approach was used to investigate the right hemisphere lesions that selectively impaired auditory sentence-to-picture matching. First, a voxel-based lesion-deficit analysis was used to identify the first region ("the VBM region") which included dorsal aspects of the superior longitudinal fasciculus impinging on the inferior frontal sulcus. Second, post-hoc analyses tested how frequently the VBM region was damaged in those with auditory sentence-to-picture matching impairments. This revealed that 6/9 patients had damage to the VBM region but 3/9 patients preserved the VBM region. The third step identified two additional regions (the non-VBM regions of interest A and B) that primarily involved right subcortical regions (in the vicinity of the caudate, putamen and mediodorsal thalamus), and a third region (involving the right temporal lobe) that was rare and only damaged in the patient of interest defining it. Finally, examination of the frequency of the identified regions in the control group showed that damage to either of these regions was associated with impaired performance on the auditory sentence-to-picture matching task in less than 50% of the cases.

Altogether, I identified three distinct regions of interest (i.e. the VBM region and non-VBM regions A and B) associated with selective deficits in auditory sentence-to-picture matching. And, as expected (see above), high across-subject variability was observed in the extent to which damage to these right hemisphere regions was associated with impaired performance on the task of interest. In what follows, I will discuss previous literature showing (i) how damage to the identified right hemisphere regions can affect behaviour, and (ii) inter-patient variability when deficits are mapped onto discrete lesion sites.

4.5.1. Damage to the right superior longitudinal fasciculus and inferior frontal gyrus

Damage to right fronto-parietal white matter has previously been related to difficulties in sustained attention tasks (expressed in longer reaction times; Klarborg et al., 2013). Further evidence has associated damage to the right superior longitudinal fasciculus in the inferior parietal lobe with (i) visuospatial attention deficits (i.e. hemispatial neglect; Shinoura et al., 2009; Thiebaut de Schotten et al., 2014), and (ii) stuttering severity (Neef et al., 2018). Of particular relevance to my findings, I note that damage to the right ventrolateral prefrontal cortex (i.e. BA 44-45 and 47) has been related to difficulties in inhibiting responses, task coordination, attentional control, and working memory (Courtney et al., 1998a, b; Aron et al., 2004, 2014; Hampshire et al., 2010). Interestingly, a recent study of 132 stroke patients that used multivariate machine learning algorithms to correlate different behavioural measures with damaged voxels, found that the right inferior frontal gyrus was part of a distributed and bilateral language network (Corbetta et al., 2015).

4.5.2. Damage to right subcortical regions

Lesion studies have reported executive processing difficulties after focal damage to the right basal ganglia (Giroud et al., 1997; Newsome et al., 2015) while damage to the right thalamus has been reported to produce memory difficulties along with transient impairments in language processing and visual perception (Schmahmann and Pandya, 2008). Studies of patients with Parkinson's disease have added more evidence by associating bilateral damage to the putamen and caudate with executive and cognitive control difficulties (Skeel et al., 2001), while unilateral damage to the putamen (either right- or left-side) has also been related to executive dysfunction, particularly after disruption to the dorsolateral-striato-pallido-thalamic circuit (Kokubo et al., 2015). These observations are in line with previous functional neuroimaging studies showing that right basal ganglia activity plays an inhibitory role, by suppressing or lessening the activation of the non-dominant right frontal cortex (Crosson et al., 2003).

Together, the evidence is consistent with the role of the right subcortical regions in a distributed neural network that supports executive/cognitive control processes. It is therefore not surprising that these regions contribute to more demanding language tasks - such as the comprehension of reversed sentences (see Chapter 3). However, further investigation is still needed to show that the regions that contribute to the comprehension of reversible sentences (i.e. during language processing) are the same as the regions that contribute to non-linguistic executive processing.

4.5.3. Inter-patient variability after right hemisphere damage

The four step lesion-deficit analysis identified a set of regions that were completely or partially damaged in the patients who had auditory sentence-to-picture matching impairments. However, Step 4 of this analysis showed that damage to the identified regions was also observed in 14/75 of those who did not have auditory sentence-to-picture matching impairments. In other words, there was inter-patient variability in the effect of damage to these right hemisphere regions. Similar observations have also been made when considering the effect of damage to left hemisphere regions (Corbetta et al., 2015; Gajardo-Vidal et al., 2018).

Plausibly, damage to the VBM and non-VBM regions identified in this study might have been more consistently associated with impaired sentence comprehension if all the patients had been tested earlier after their stroke. Unfortunately, the data were not available to test this hypothesis. Alternatively, the effect of damage to the VBM and non-VBM regions identified here might reflect pre-morbid differences in the degree to which the patients used the right hemisphere for language. This is in line with prior explanations of inter-subject variability in the contribution that the right hemisphere makes to language processing in neurologically-normal right-handed subjects (Knecht et al., 2000; Toga and Thompson, 2003; Josse et al., 2009; Seghier et al., 2011; Forkel et al., 2014); see Chapters 1 and 7 for detailed discussion.

4.6. Limitations and future directions

This study identified right hemisphere regions that are damaged in patients with selective deficits on the auditory sentence-to-picture matching task, however, it cannot fully discount the possibility that the patients had atypical functional anatomy for sentence comprehension. What it can show is that damage to these regions is not infrequently associated with sentence comprehension impairments. To establish whether the regions identified in this study are normally involved in sentence comprehension, I examined (in my next experimental chapters) how they responded when neurologically-normal participants were performing sentence comprehension and other language tasks (see Chapter 5). I also examined how these regions responded when participants were engaged in one-back matching tasks that increase the demands on domain-general working memory (see Chapter 6).

A second limitation of this study is the lack of spatial specificity of lesion-deficit mappings derived from stroke patients, which does not allow me to demonstrate that the regions identified in the lesion-deficit analysis are exactly the same as the regions that have been reported in previous studies of language processing or executive functions. This is because naturally occurring lesions are not limited to functional boundaries and may therefore conflate critical regions with areas that are susceptible to vascular damage (see Mah et al., 2014; Price et al., 2017). Of note, some of the regions of interest identified in this study (i.e. right subcortical regions) have been found to be frequently damaged in right-hemisphere stroke patients - which is not surprising considering that lesion topography in middle cerebral artery infarcts is mainly determined by the architecture of the vascular tree (see Sperber and Karnath, 2016). I will address the limitations identified above in Chapters 5 and 6 by (i) using regions of interest from the current study to report activation during sentence comprehension and other language tasks and (ii) testing whether there is a correspondence between the results of the lesion-deficit analysis reported here and the activation peaks observed during functional neuroimaging of neurologically-normal participants.

4.7. Conclusions

By focusing on a carefully selected group of 9 patients who had the most consistent language impairment after RHS, the current study showed that the patients of interest had significantly more damage to dorsal parts of the superior longitudinal fasciculus and right inferior frontal sulcus than other patients who also had RHS but were not impaired on the auditory sentence-to-picture matching task. Post-hoc tests showed how frequently damage to the identified regions was observed in other patients with and without auditory sentence-to-picture matching impairments, and whether the effect of the lesions was commonly observed or not. I found that damage to these right hemisphere regions was associated with deficits in the auditory sentence-to-picture matching task in less than 50% of the cases. Plausibly this could reflect across-subject variability in lesion-deficit mappings, as previously reported in studies of left-hemisphere stroke patients (see Chapter 7 for discussion).

From a neural network perspective, whereby multiple regions contribute to any given function, this study identified a set of three right hemisphere regions (the VBM region and non-VBM regions A and B) where damage can selectively impair auditory sentence-to-picture matching. The results of the lesion analyses can therefore inform subsequent fMRI studies (Chapter 5 and 6) by providing regions of interest for investigations of how the right hemisphere responds to language and executive processing in neurologically-normal subjects.

CHAPTER 5: STUDY 3

Which parts of the regions identified in Study 2 are involved in normal sentence comprehension?

5.1. Summary

The aim of the current functional MRI study was to investigate whether any parts of the right hemisphere regions associated with impaired sentence comprehension in Study 2 (Chapter 4) were activated when neurologically-normal participants performed similar language tasks to those administered to RHS patients in Study 1 (including the auditory sentence-to-picture matching task). This allowed me to (a) identify which parts of the regions of interest, if any, contribute to auditory sentence-to-picture matching and (b) determine the functional role of these regions by examining their response during different task/conditions that factorially varied the demands on auditory, visual, phonological, semantic and sentence processing and verbal short-term memory.

I found that the right inferior frontal sulcus and right mediodorsal thalamus were significantly activated by auditory sentence-to-picture matching. However, activation within the same regions was also observed for all other language tasks with no significant main effects of speech input, semantic associations, naming, articulation or sentence processing. The observation that regions where damage was associated with impaired auditory sentence to picture matching after stroke were normally activated during auditory sentence to picture matching and during other language tasks demonstrates that: (i) sentence comprehension impairments can be explained by disruption to normal functional anatomy rather being indicative of crossed aphasia/atypical language lateralisation and also (ii)

the activation observed in these regions was not specific to language functions, such as phonology, semantics or syntax.

Having discounted a specific role of the right inferior frontal sulcus and mediodorsal thalamus in language processing, I can further investigate the contribution of these right hemisphere regions using data of a new fMRI study of working memory (an executive function) in neurologically-normal participants (see Chapter 6).

5.2. Introduction

In my second Study (Chapter 4), I identified a set of right hemisphere regions where damage can selectively impair sentence comprehension. In the present study, I investigated whether the association between the identified right hemisphere regions and language functions was likely to reflect atypical language lateralisation (i.e. crossed aphasia; for a literature review see Chapter 1) or whether the same right hemisphere regions were involved in normal language processing. If the patients with right hemisphere damage and impaired sentence comprehension have atypical language lateralisation, then I would not expect to see activation in the right hemisphere regions when right-handed neurologically-normal participants were matching auditory sentences to pictures. On the other hand, if some parts of the regions of interest are normally involved in auditory sentence-to-picture matching, then a functional neuroimaging experiment may indicate which grey matter parts of the region of interest are important. Such a finding would indicate that sentence comprehension impairments following damage to these regions are not necessarily the result of atypical functional anatomy.

By using a multi-task fMRI paradigm, I was also able to investigate how the right hemisphere regions of interest might be contributing to auditory sentence-to-picture matching (i.e. the functional role). This required a task analysis of the auditory sentence-to-picture matching task and a literature review.

5.2.1. Task analysis

According to my task analysis (see Table 5.1), matching auditory sentences to pictures involves (A) auditory and phonological processing of heard speech, (B) visual and semantic processing of objects and events in pictures, (C) verbal short-term memory to hold the speech in memory while (D) matching the semantic content of the speech to the semantic content of the picture, (E) response selection and motor control of the fingers to press the corresponding response button. To tap each of these processing levels, I used an fMRI experiment that factorially manipulates the demands on: auditory input; speech input, sentence processing, pictures that present objects or events; semantic matching and verbal short-term memory (see Methods section).

Table 5.1. Task analysis of the auditory sentence-to-picture matching task

Auditory sentence-to-picture matching
Auditory processing
Visual processing
Phonological processing
Semantic processing
Syntactic processing
Short-term memory
Attention (monitoring)
Matching/Decision-making
Finger response (motor response)

The levels of processing hypothesized to be required for completing the fMRI auditory sentence-to-picture matching task.

5.2.2. Literature review

In what follows, I will review the literature on the contribution of the right frontal and subcortical regions to phonological, lexical-semantic and sentence processing in right-handed neurologically-normal subjects. The majority of the reported studies used functional neuroimaging but there were also a handful of studies that used transcranial magnetic stimulation (TMS).

The right inferior frontal gyrus and language processing in the healthy brain

There is accumulating evidence from functional neuroimaging studies reporting right inferior frontal activation during auditory or visual language tasks (Chee et al., 1999; Poldrack et al., 1999; Devlin et al., 2003). For example, increased activation within the right inferior frontal gyrus (IFG) has been observed for: (i) vowel processing, with higher activation during syllable discriminations when vowel tone pitch is spectrally varied compared to rapid temporal variation in consonant tone sweep (Joanisse and Gati, 2003); (ii) mapping from sound to lexical meaning (Bozic et al., 2010) and (iii) auditory processing of sentences (Ben Shachar et al., 2004; Constable et al., 2004). Moreover, activation within this region has also been observed during phonological decisions on visually presented words (Poldrack et al., 1999; Devlin et al., 2003; Shibahara, 2004). Together, these findings are in line with another study suggesting that the right IFG is equally activated by auditory and visual phonological decision tasks (Baumgaertner et al., 2013).

Further evidence from fMRI studies has also shown that the right inferior frontal cortex is more sensitive to the demands on non-linguistic than linguistic processing when stimulus are words (e.g. when subjects focused their attention on perceptual changes in font size in the visual stimuli; Baumgaertner et al., 2013) or sentences (Bozic et al., 2010). Likewise, Meyer and colleagues (2002) found that activation within the right inferior frontal cortex was higher when subjects had to listen to sentences with non-sense words compared to sentences with real words. Therefore, it can be concluded that non-linguistic processing demands (e.g. attention or working memory) may also explain some of the observations reported above. Indeed, this was the conclusion of a meta-analysis of 128 fMRI studies (Vigneau et al., 2011) that observed right frontal activation was more likely to be observed during more demanding language tasks.

TMS studies have added more evidence by showing that the right inferior frontal gyrus may contribute to phonological and lexical processing. For example, Hartwigsen et al. (2010a, b) showed that TMS over the right (and left) inferior frontal gyrus increased reaction times and error rates during phonological decisions on both auditory and visually presented pseudowords; whereas Sollmann et al. (2014) reported increased error rates when TMS was applied over the right pars opercularis and right pars triangularis (within the IFG) during a picture naming task.

In summary, together all the evidence suggests that the right inferior frontal cortex is actively contributing to language tasks - independently of stimulus modality. However, it is not clear whether the involvement of this region is specific to a given language component or is contingent upon the overall processing demands of the task.

Right subcortical regions and language processing in the healthy brain

In contrast to several studies showing activation within right frontal regions during language processing, there are only a few functional neuroimaging studies reporting activation in right subcortical regions when neurologically-normal individuals perform language tasks. In fact, the particular role that subcortical regions play in language still remains unclear. A small number of functional neuroimaging studies have reported significant activation within the right basal ganglia during (i) word/sentence generation tasks (Fu et al., 2002; Crosson et al., 2003; Gauthier et al., 2009) and (ii) the production of automated/recited speech (Sörös et al., 2006; Bridges et al., 2013). Crosson and colleagues (2003) have, for example, suggested that the right basal ganglia plays an inhibitory role by supressing or lessening the activation of the right frontal cortex during word generation tasks. Similar interpretation was given by Ketteler et al. (2008) to explain the increased activation observed in the right putamen and caudate during a semantic ambiguity resolution task. The right putamen, in particular, has been associated with broader semantic processes, such as memory and visual imagery (Viñas-Guasch and Wu, 2017) whereas the right (and left) thalamus has been shown to have a role in processes that involve manipulations of lexical information, especially, during more challenging task conditions (Llano, 2013).

In summary, prior literature does not seem to suggest that right subcortical structures are directly involved in language processing. Instead, it has been proposed that subcortical regions might operate in coordination with cortical language brain regions (as part of distributed cortico-striatal networks) to support the execution of more cognitively demanding language tasks.

5.2.3. Research question and hypothesis

In brief, the current study used fMRI of neurological-normal participants to answer the following research questions:

(i) Do regions where right hemisphere damage impairs sentence comprehension activate when neurologically-normal participants perform the auditory sentence-to-picture matching task?

(ii) Do regions where right hemisphere damage impairs sentence comprehension activate when neurologically-normal participants perform similar language/tasks conditions to those administered to patients in Study 1?

Based on prior literature, I expected that the right inferior frontal region identified in Study 2, would be significantly activated by a range of language tasks including auditory sentence-to-picture matching, but that activation would also be observed in other language tasks with auditory and visual stimuli, particularly when task demands were high (e.g. for sentence compared to word processing).

5.3. Methods

5.3.1. Participants

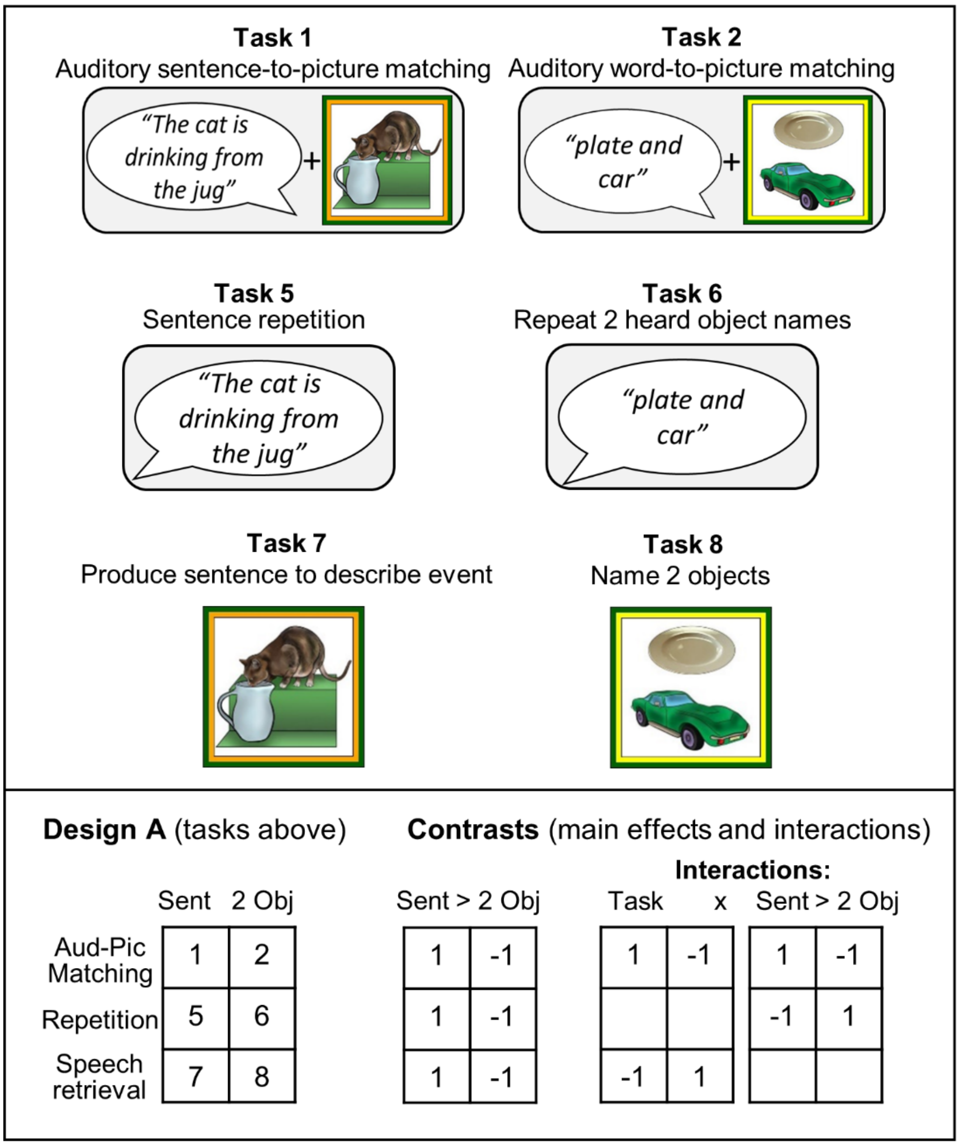
A total of 25 neurologically-normal, right-handed, native-English speakers with normal or corrected-to-normal vision (15 females, aged 23–37 years with a mean and standard deviation of 30.35 ± 3.90 years) were included in this fMRI study.

5.3.2. Experimental Design

Brain activation related to each type of processing involved in the auditory sentence-to-picture matching tasks (Task 1) was investigated using sets of tasks that factorially manipulated the demands on one type of processing while controlling the demands on another type of processing. In total, this involved three factorial designs.

The first factorial design (Design A) was used to investigate whether auditory sentence-to-picture matching activation was related to matching the semantic content of the heard speech to the semantic content of the picture and/or sentence/event processing. This design combined 6 conditions to compare sentences to objects during (i) speech-to-picture matching, (ii) auditory repetition and/or (iii) speech retrieval. The six conditions are illustrated in Figure 5.1.

Figure 5.1. Task conditions included in factorial Design A



Design A (tasks above)

	Sent	2 Obj
Aud-Pic Matching	1	2
Repetition	5	6
Speech retrieval	7	8

Contrasts (main effects and interactions)

Sent > 2 Obj

1	-1
1	-1
1	-1

Interactions:

Task x Sent > 2 Obj

Task		Sent > 2 Obj	
1	-1	1	-1
		-1	1
-1	1		

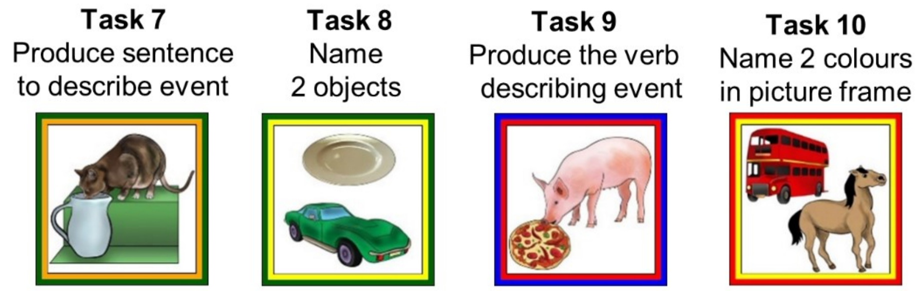
Key to abbreviation in Figure 5.1 (Design A)

- Aud-Pic Matching = auditory sentence-to-picture matching (sentences or 2 objects)
- Repetition = auditory repetition of sentences or 2 objects names
- Speech retrieval = producing a sentence to describe the interaction (event) between 2 objects in a picture or naming unrelated objects.
- Sent = hearing or producing a sentence
- 2 Obj = hearing 2 unrelated object names or seeing 2 unrelated objects in a picture.

If activation was related to matching the semantic content of the heard speech to the semantic content of the pictures, it should be higher for this task than auditory repetition and picture naming/description which controlled for all stimulus inputs. If activation was related to sentence/event processing, it should be greater for matching heard sentences to events than heard object names to seen objects.

A second factorial design (Design B) combined 4 naming conditions to isolate sentence processing from the presence or absence of (i) object names and (ii) verbs. The first factor manipulated the presence or absence of event stimuli. The second factor manipulated the presence or absence of object stimuli. This comprised four speech production tasks: producing a sentence to describe the event between two objects in a picture (production of nouns and verbs), naming the event between two objects (verbs not nouns), naming two unrelated objects (nouns not verbs) and naming the colour surrounding a meaningless pattern (no object names or verbs). The four conditions are illustrated in Figure 5.2).

Figure 5.2. Task conditions included in factorial Design B



Design B (tasks above)

	2 Obj	Not Obj
Verbs	7	9
Not Verbs	8	10

Contrasts (main effects and interactions)

2 Obj > not

1	-1
1	-1

Verbs > not

1	1
-1	-1

Sentences > Obj/Vb

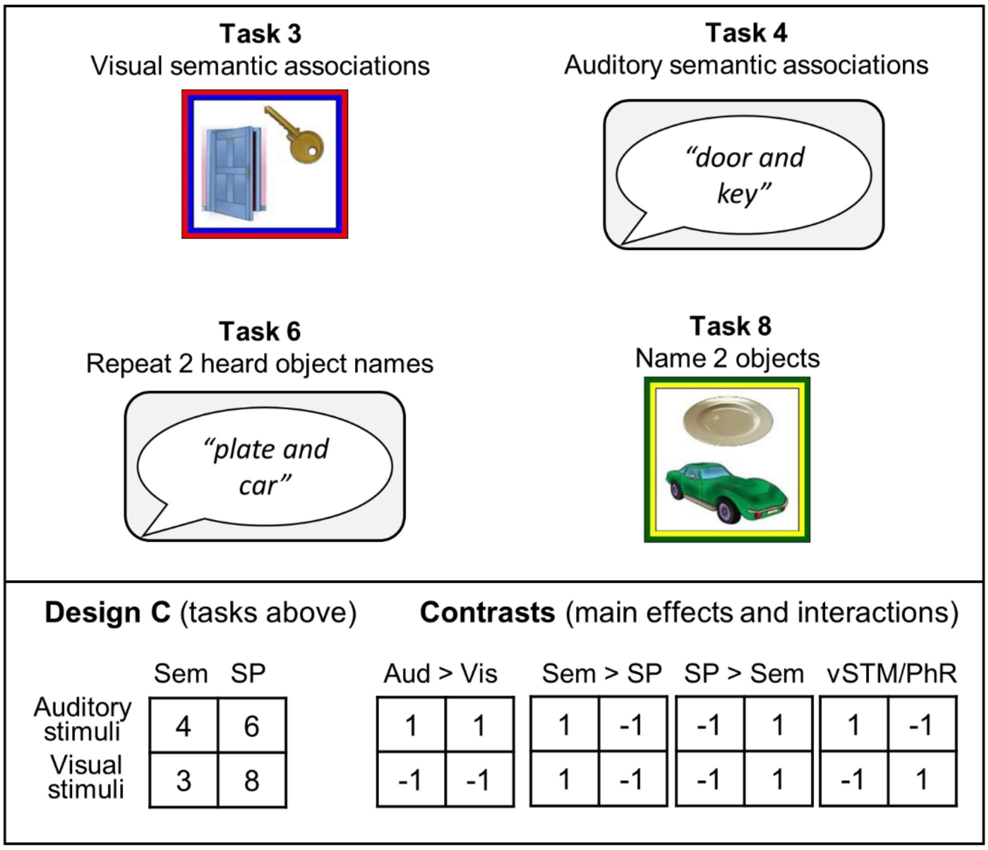
1	-1
-1	1

Key to abbreviation in Figure 5.2 (Design B)

- Verbs = producing a sentence or verb that describes the event between 2 objects (e.g. eating)
- Verbs > not = naming verb (or producing sentence) > object and colour naming.
- 2 Obj = naming two objects in a picture or a sentence describing the event between 2 objects.
- 2 Obj > not = naming two objects (unrelated or in event) > verb and colour naming.
- Sentences > Obj/Vb = producing a sentence > naming objects or verbs without sentence.

Finally, the third factorial design (Design C) compared semantic associations to speech production tasks in the auditory and visual modalities (4 conditions) while keeping stimuli constant within modality and the task constant across modality. In this third design, the interaction of task and stimulus modality tests the demand on: (i) Phonological (name) retrieval which is greater for speech production than semantic decisions when the stimuli are pictures of objects than when the stimuli are heard objects names; and (ii) verbal short-term memory which is greater for semantic decisions than speech production when the stimuli are auditory object names (which need to be held in memory while a semantic association is assessed) than when the stimuli are visually presented objects (that do not require auditory memory). The four conditions are illustrated in Figure 5.3.

Figure 5.3. Task conditions included in factorial Design C



	Sem	SP
Auditory stimuli	4	6
Visual stimuli	3	8

Aud > Vis	
1	1
-1	-1

Sem > SP	
1	-1
1	-1

SP > Sem	
-1	1
-1	1

vSTM/PhR	
1	-1
-1	1

Key to abbreviations in Figure 5.3 (Design C)

- Sem = semantic associations of two objects in picture (visual) or 2 heard object names (auditory).
- SP = speech production (naming objects in pictures, or repeating heard objects names).
- Aud = auditory stimuli (e.g. 2 heard object names).
- Vis = visual stimuli (e.g. pictures of 2 unrelated objects).
- vSTM = verbal short-term memory (highest for semantic association on heard object names).
- PhR = phonological retrieval (highest when naming objects from pictures).

If activation was related to auditory and phonological processing of heard speech, it was expected to be higher in the main effect of stimulus modality (auditory > visual). If activation was related to visual and semantic processing of objects in pictures, it was expected to be higher for the reverse contrast (visual > auditory). If activation was related to response selection and motor processing, it was expected to be higher for the main effect of task (semantic decision > speech production). If activation was related to verbal short-term memory, it was expected to be higher for semantic associations on auditory object names than the other three conditions which collectively controlled for auditory input, semantic association, response selection and motor processing. This is because semantic decisions on two heard object names requires the participant to hold the object names in memory while the semantic association is assessed. In contrast, in the visual version of this task the pictures of the two objects stay on the screen while the semantic association is being assessed.

5.3.3. Task details

In total, the three factorial designs required 10 tasks/conditions, because four conditions (repetition and naming) were used in two different designs.

The semantic matching tasks (with finger press response)

Task 1, auditory sentence-to-picture matching: In this task, subjects were simultaneously presented with a depicted event and its spoken sentence description. Subjects pressed a button to indicate whether the sentence they heard correctly described the picture. They pressed one button if the sentence they heard ‘matched’ the one they saw (i.e. when the visual drawing of an event completely matched the meaning of the heard sentence), or pressed another button if the stimuli did ‘not match’ (i.e. when a picture of an event did not match the meaning of the heard sentence at all). The assignment of buttons to responses was counter-balanced across subjects.

Task 2, auditory word-to-picture matching: In this task subjects were simultaneously presented with a picture of two non-interacting objects and their spoken names. Subjects pressed a button to indicate whether the two names they heard correctly defined the pictures. They pressed one button if the two names they heard ‘matched’ the two pictures that they saw, or pressed another button if the stimuli did ‘not match’. The same pictures and recording were used in this task as well as in task 8 (noun production), task 4 (word-to-word semantic matching) and task 6 (auditory repetition of nouns).

Task 3, picture-to-picture matching association: In this task, subjects saw pictures of two objects. Half of the stimuli were semantically related (e.g., ‘door’ and ‘key’) while the other half were unrelated (‘clock’ and ‘pumpkin’). Subjects were instructed to indicate whether the objects were related or unrelated by button press. One button was designated for ‘related’ stimuli, while another button was designated for ‘unrelated’ stimuli. Buttons were counterbalanced between subjects and semantic relatedness was determined in a pilot experiment, in which participants were asked whether two objects presented in a pair were semantically related (e.g. ‘tree’ and ‘log’) or not (e.g. ‘bread’ and ‘log’).

Task 4, word-to-word semantic matching: This task was the same as picture-to-picture matching association (task 3), except that the stimuli were auditory recordings instead of pictures (as in tasks 2 and 6). Subjects were instructed to keep their eyes open and focused on the fixation cross throughout the task.

The speech production tasks

Task 5, auditory repetition of sentences: In this task, subjects heard a sentence (e.g. ‘The goat is eating the hat’) and were instructed to overtly repeat it. The same sentences were used in this task as well as in task 7 (i.e. sentence production). As with the other auditory tasks, subjects were instructed to keep their eyes open and focused on the fixation cross throughout the task.

Task 6, auditory repetition of nouns: In this task, subjects heard the two object names in a conjunctive phrase (e.g., ‘clock and pumpkin’) and were instructed to overtly repeat the words. The same object names were used in this task as well as in task 8 (noun production). Subjects kept their eyes open and focused on a fixation cross throughout the task.

Task 7, sentence production: In this task, subjects were presented with coloured drawings (‘pictures’) of events. The task required subjects to describe the picture in a spoken response. Prior to scanning, participants were instructed to respond using sentences of the form *The noun is verbing the noun* (e.g., ‘The goat is eating the hat’) or *The noun is verbing preposition the noun* (e.g., ‘The zebra is drinking from the pool’), where the first noun in each case was the grammatical *subject* and the second was the *object*. Subjects were additionally instructed to use one of four pre-specified verbs in their responses: ‘eating’, ‘drinking’, ‘jumping’, or ‘falling’. The set of acceptable verbs were explicitly restricted in order to minimise inter-subject variability in verb selection, limiting the use of synonyms or near-synonyms (e.g. ‘sipping’ vs. ‘licking’). Further constraints were placed on word ordering with instructions to produce the subject (‘goat’) before the object (‘hat’) (‘The goat is eating the hat’), ruling out passive constructions (‘The hat is being eaten by the goat’). The instructions were confirmed to be reasonable and could be followed prior to scanning in a pilot study for which a separate group of subjects was recruited. The same pictures were used in this task as well as in task 9 (verb production).

Task 8, noun production: In this task, subjects were presented with a picture of two non-interacting objects and instructed to produce both nouns linking them together with the conjunction ‘and’ (e.g. ‘clock and pumpkin’) to create a more meaningful phrase and increase the word count closer to that involved in sentence production. In contrast to task 7 (sentence production), the stimuli were drawings of two objects that were not interacting with one another. The same two pictures were used in this task as well as in tasks 2 and 10 (word-to-picture matching and colour naming).

Task 9, verb production: In this task, subjects were presented with a picture of an event and instructed to identify the action on the scene and name the relevant verb in the form of a gerund (e.g. ‘eating’).

Task 10, colour production: In this task, subjects were presented with pictures of two unrelated and non-interacting objects and instructed to name the two colours in the frame around the picture (e.g. ‘orange and green’). The format of the response ‘orange and green’ was intended to match the format of the noun production response ‘clock and pumpkin’. The same picture of objects were used in this task as well as in tasks 2 and 8 (word-to-word to picture matching and noun production).

5.3.4. Stimulus selection, creation and counterbalancing

Over the 10 conditions, a total of 120 objects concepts were used. The objects were easy to recognise and name when presented in picture format (using high definition pictures drawn by a professional artist). Each of the 120 objects was paired in three different ways (180 different pairs in total) making sure that no pairings were repeated. The first pairing involved 2 objects interacting with one another to indicate an event, with a corresponding sentence (e.g. the cat is drinking from the jug). These were used for sentence production, sentence repetition, verb naming and auditory sentence-to-picture matching. The second pairing presented 2 unrelated objects (e.g. “car” and “plate”) that were used for object naming, auditory repetition, colour naming or auditory word-to-picture matching. The third pairing involved semantic pairs that were half related (e.g. door and key) and half unrelated (e.g. deer and barrel). Pairing repetitions, within subject, were avoided by repeating objects (i) with a different pair, (ii) in different stimulus modalities (auditory versus visual or both) or (iii) with a change in task and response (matching versus spoken). Over participants each object was seen an equivalent number of times in each condition.

Compared to Study 1 (Chapter 3), the auditory sentence-to-picture matching in the fMRI study was less demanding in several ways. Specifically, it included sentences with simpler structure (i.e. object-verb-subject) and only four possible actions/verbs (jumping, falling, eating or drinking). The limited number of verbs was to minimise inter-subject variability in word choice (or syntactic structure) during production. In addition, each heard sentence was matched to one picture in the fMRI version of the task (with a yes/no response) and one of four pictures (with 3 distractors) in the CAT version of the task (with a pointing response). See Figure 5.4 for an example stimulus from the CAT auditory sentence-to-picture matching task (Chapter 3) and from the auditory sentence-to-picture matching used in the current study. The differences in the CAT and fMRI versions of the auditory sentence-to-picture matching task might decrease sensitivity in the fMRI experiment to processing related to the CAT task. However, because the fMRI version of the task was easier than the CAT task, it is less likely to identify activation related to processing that is not also involved in the CAT task.

5.3.5. Procedure

Prior to scanning, subjects were trained on an independent set of stimuli until they understood the tasks. Once in the scanner, subjects performed 10 tasks one after another in one of the 12 counterbalanced orders.

Each of the 10 tasks described above started with the instructions “Get Ready” written on the in-scanner screen while five dummy scans were collected. This was followed by 5 blocks of 4 stimuli, interleaved with resting with eyes open. The length of blocks varied across subjects, for about half the subjects (n = 12) an inter-trial-interval (ITI) of 5s was used, for the other half (n = 13), an ITI of 7s was used. Using two different ITIs allowed us to replicate the experiment over two different groups and showed that the paradigm can be used in different circumstances. For example, one might want a longer ITI for studies of patients who have difficulty with sentence production and a shorter ITI when time in the scanner is the most important issue. The two different subject cohorts (i.e., 5s and 7s ITI groups) were modelled separately in the data analyses. See Table 5.2 and Figure 5.4 for study details.

The acquisition of functional images for all 10 conditions took at least 33.88 minutes for subjects with 5s ITIs; and 41.07 minutes for subjects with 7s ITIs. These times do not include out-of-scanner training, setting up and getting the subject into the scanner, collecting structural images, and any unplanned technical issue. On average the experiment lasted approximately 60–80 minutes.

Visual stimuli were all presented via an LCD projector and an adjustable head-coil mirror onto a screen that was clearly visible to the subject, subtending a visual angle of 7.4° with a screen resolution of 1024 × 768.

Auditory stimuli were presented via MRI compatible headphones (MR Confon, Magdeburg, Germany), which filtered out ambient in-scanner noise. Volume levels were adjusted to suit each subject before scanning. During auditory trials, including sentence repetition, participants kept their eyes open and fixated on a central cross. Using ANOVAs, multiple comparison tests, and Bonferroni corrected t-tests for 10 comparisons (i.e. number of tasks), confirmed that, as expected, the duration of heard speech was longer in the sentence conditions than the word conditions (i.e. sentence tasks 1 and 5 versus word tasks 2, 4 and 6; $t > 13$, $p < 0.001$ for all pairs).

Subjects finally responded in one of two ways. For auditory and visual semantic decision tasks, they used two fingers on their right hands to press one of two buttons on an fMRI compatible button box. For the production tasks, spoken responses were recorded via a noise-cancelling MRI microphone (FORMI IITM Optoacoustics, Or-Yehuda, Israel). These auditory recordings were then transcribed manually for off-line analysis and to record in-scanner accuracy.

Table 5.2. Experimental details for Study 3

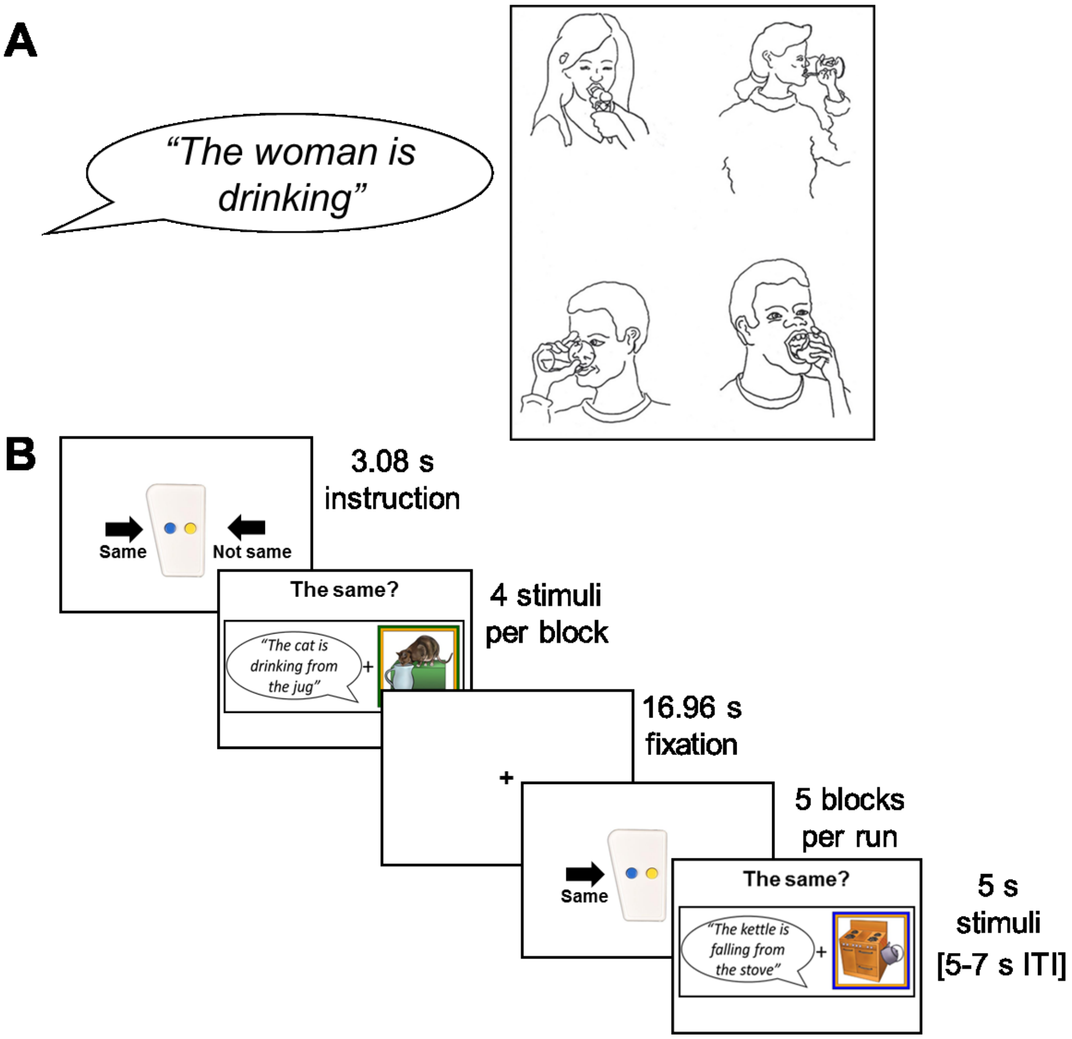
Partcipants	
Number	25
Gender (females / males)	15/10
Mean age in years (+/-SD)	30.4 (3.9)
Timing parameters	
Stimulus duration in sec	
Visual stimuli	2.5
Auditory stimuli/words[a]	1.8 - 2.5
ITI (sec)[b]	5 / 7
Block length (sec)[c]	20/28
Total time for each run (min)[d]	3.4 / 4.1
Total acquisition time (min)	33.9 / 41.1
Number of stimuli per block	4
Number of blocks per run	5
Total number of stimuli per run	20
Number of runs	10
Scanning parameters	
TR (sec)	3.1
Number of slices	44
Number of volumes per run	61 / 85
Number of dummy acquisitions	5

(a) Auditory stimuli included single words and sentences

(b) Each block began with instructions for 3.1 seconds.

(c) Each run ended with a resting period of 16.96/18.2 seconds for 5s/7s ITI, respectively.

Figure 5.4. Example stimuli from the CAT auditory sentence-to-picture matching task (Chapter 3) and from the fMRI auditory sentence-to-picture matching task



(A) The top row shows sentence number 1 from the CAT auditory sentence-to-picture matching task. Patients were instructed to hear a sentence (produced by the examiner), and selects the picture, from a set of 4, that best illustrates the sentence. The target sentence was "the woman is drinking" (right upper corner). **(B)** The bottom row shows the fMRI auditory sentence-to-picture matching task used in the current study. Participants were instructed to press a button to indicate whether the sentence they heard correctly described the picture. They pressed one button if the sentence they heard 'matched' the one they saw, or they pressed another button if the stimuli (i.e. the heard sentence and the seen picture) did 'not match' (sentences in the bubble were presented aurally).

5.3.6. Analysis of in-scanner behaviour

The accuracy and speed of response was measured by button-presses for tasks 1–4. A response was categorised as ‘correct’ if it matched the expected target and as ‘incorrect’ if the response did not match the target, took longer than the allotted time, or was self-corrected.

For tasks 5–10, the accuracy and response times (RTs) were measured from audio recordings of the spoken response. These audio recordings were transcribed, checked for errors, and subjected to a signal processing analysis that automatically extracted the spoken RTs for each stimulus (using an in-house script implemented in Matlab 2014a). A trial was considered to be ‘correct’ if >10% of other subjects made the equivalent response, even if it was not the same as our intended target (e.g. if >10% of subjects said ‘mug’ when our expected response was ‘cup’). This flexibility was built into the design because the set of possible responses was open-ended for both sentence production and noun production tasks (i.e. tasks 7 and 8). Only ‘correct’ trials were used in the fMRI analyses.

Reaction times (RTs) for correct spoken responses were measured using an adaptive-window-moving-average filter that was customised to remove noise for each subject and task. The optimal window length (i.e., the width of the maximally smoothed audio stream) was based on a sample of the audio file collected during rest. Once the whole audio recording was smoothed to remove high-frequency noise, the onset of speech was defined as the first rise in absolute amplitude above one standard deviation from the mean amplitude of a stimulus event. See Figure 5.5 for an overview of all reaction time and accuracy results.

No data were excluded. Head movement during the speech production tasks was limited and corrected using unwarping during image realignment. Consequently, there were no noticeable movement-related artefacts.

Data acquisition, preprocessing and first–level analyses steps of the imaging data are explained in the general methods chapter (Chapter 2)

5.3.7. Second-level analysis

The aim of the second-level analysis was to identify whether the right hemisphere regions of interest from Study 2 (Chapter 4) were activated: (i) during auditory sentence-to-picture matching, and (ii) the processing probed by the three different factorial designs. Each result is reported from a single second level analysis that included the parameter estimates comparing activation for each task to rest in the first level analyses. As the inter-trial-interval (ITI) was 5s for 12 subjects and 7s for 13 subjects, the second level analysis included a between subjects factor modelled as a 2x10 repeated measures ANOVA. However, the second level contrasts described below summed over inter-trial interval because it had no effect on the results in our search volume (i.e. P > 0.001 uncorrected).

Second-level contrasts (see Table 5.3)

1) Auditory sentence-to-picture matching (task 1 compared to rest)
2) Main effect of auditory speech stimuli (tasks 4 & 6 > 3 & 8)
3) Main effect of picture processing (tasks 3 & 8 > 4 & 6)
4) Verbal short term memory (tasks 4 & 8 > 3 & 6 and 4 > 8)
5) Auditory to picture object matching (tasks 1& 2 > 5,6,7,8)

6) Auditory to picture sentence matching (tasks (1>2) > (5 & 7 > 6 & 8)

7) Verb processing (tasks 7 & 9 > 8 & 10).

The statistical threshold for the second-level contrasts was corrected for multiple comparisons (i.e. family-wise error correction, FWE) within the regions of interest identified in Study 2 (Chapter 4) and also for whole brain analyses (see Table 5.4). Peak co-ordinates (x,z,y) are reported in MNI space.

Table 5.3. Experimental design and second level contrasts for Study 3

Paradigm Details					**Second Level Contrasts**									
ID	**Task name**	**Stimulus**		**Response**	**(A) Sentences > 2 Obj**			**(B) Sentences Obj/Verbs**			**(C) Stimulus/task vSTM / PhR**			
		Hear	See	Finger / Speech	Main effect	Inter		2 Obj	Vb	Inter	Aud	Sem	SP	Inter
1	Aud-Pic Match	Sent	Event	finger	1	1	1	0	0	0	0	0	0	0
2	Aud-Pic Match	2 Obj	2 Obj	finger	-1	-1	-1	0	0	0	0	0	0	0
3	Vis Sem Assoc	~	2 Obj	finger	0	0	0	0	0	0	-1	1	-1	-1
4	Aud Sem Assoc	2 Obj	~	finger	0	0	0	0	0	0	1	1	-1	1
5	Aud Rep Sent	Sent	~	SP sent	1	0	-1	0	0	0	0	0	0	0
6	Aud Rep 2 Obj	2 Obj	~	SP names	-1	0	1	0	0	0	1	-1	1	-1
7	Produce Sentence	~	Event	SP sent	1	-1	0	1	1	1	0	0	0	0
8	Name 2 Objects	~	2 Obj	SP names	-1	1	0	1	-1	-1	-1	-1	1	1
9	Produce Verb	~	Event	SP verbs	0	0	0	-1	1	-1	0	0	0	0
10	Name Colours	~	Pattern	SP colour	0	0	0	-1	-1	1	0	0	0	0

Details of each of the 10 tasks (illustrated in Figures 5.1-5.3) and the weighting that each task was given in the factorial analysis of the 3 embedded designs.

Key to Abbreviations in Table 5.3

- Aud = auditory presentation of object names or sentences
- Vis = visual presentation of pictures
- Aud-Pic Match = matching an auditory stimulus to a picture
- Sem Assoc = matching two objects according to whether they are semantically related or not
- SP = speech production
- Aud Rep = auditory repetition
- Sent = sentences
- 2 Obj = pictures of two objects or 2 object names
- Vb = verbs
- vSTM = verbal short-term memory (highest for auditory semantic associations)

- PhR = phonological retrieval (highest for object naming/sentence production)
- Inter = interaction between 2 effects. **In Design A:** sentences > 2 Obj on Aud-Pic Match > other tasks. **In Design B**: sentences (object names and verbs) > object names or verbs. **In Design C**: vSTM/PhR.

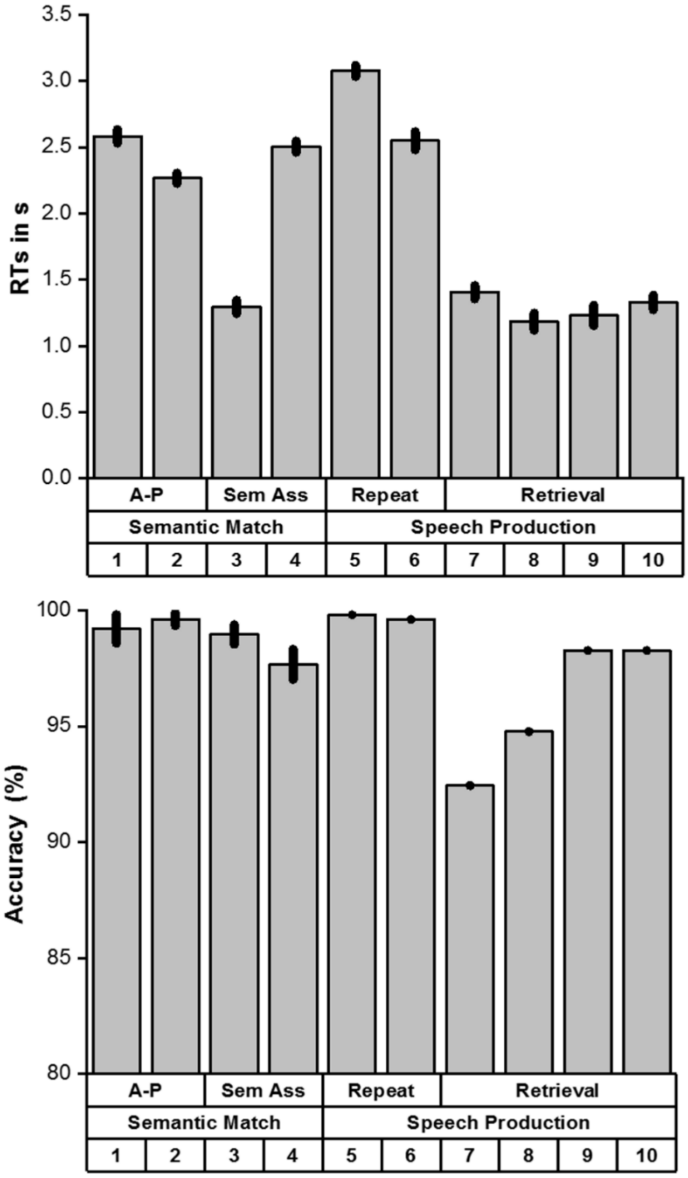
5.4. Results

5.4.1. In-scanner behavioural results

All participants performed well and contributed a consistently high number of correct trials to all the effects of interest (mean accuracy was over 90% for all tasks). Together, accuracy was notably lowest for speech production tasks 7 and 8, although still above 90%. Performance on the remaining tasks was generally at ceiling except for the semantic matching tasks (3 and 4). See Figure 5.5 for all accuracy and reaction times results.

Reaction times (RTs) for the auditory tasks were notably slower than for the visual tasks but this was expected because auditory stimuli take longer to present than visual stimuli (see Table 5.2 for experimental details).

Figure 5.5. In-scanner behavioural data for all tasks in Study 3



The figure shows reaction times (in seconds, top row) and accuracy (mean and SE, bottom row) averaged across both groups (i.e. 5s and 7s ITI groups; see Methods for details). Errors bars show standard error.

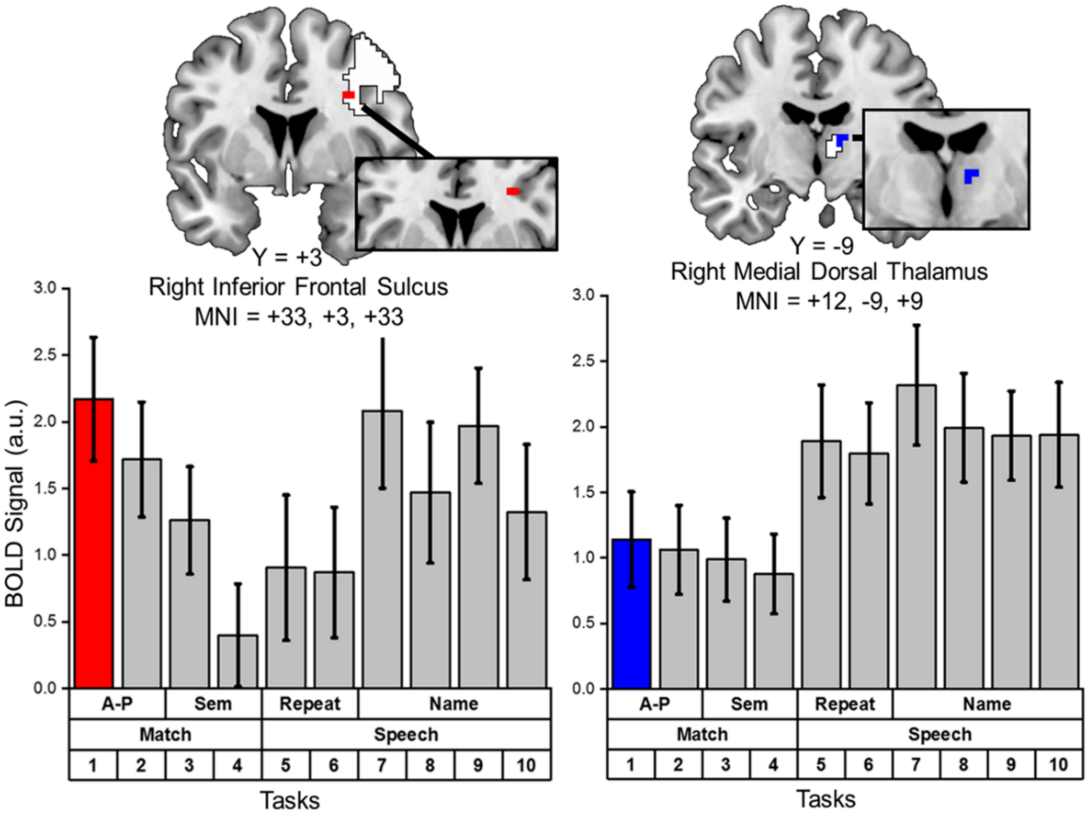
5.4.2. fMRI results

Regions activated when participants match auditory sentences to pictures

Within the region of interest (encompassing the VBM region and non-VBM regions A and B; see Chapter 3), I found significant activation for auditory sentence-to-picture matching (relative to rest) in the right inferior frontal sulcus at peak co-ordinates +33, +3, +33, $P < 0.05$, and in the right mediodorsal thalamus at peak co-ordinates +12, -9, +9, $P < 0.05$; see Table 5.4.

The same regions were also activated during all other conditions (see Figure 5.6) with no significant differences ($P > 0.001$ uncorrected and $P > 0.05$ corrected for multiple comparisons within the search volume) for any of the effects of interest (see Table 5.4) including sentences compared to objects during any of the three task manipulations (Design A); sentences, verbs or objects names (Design B); auditory stimuli, semantic associations, verbal short-term memory, speech production or phonological (name) retrieval (Design C), or any of the reverse contrasts.

Figure 5.6. Illustration of right hemisphere activation within the regions of interest



The figure shows coronal slices depicting peak activations for auditory sentence-to-picture matching relative to rest in the right inferior frontal sulcus (in red, **A**) and right medial dorsal thalamus (in blue, **B**) at co-ordinates [x = +33 y = +3 z = +3] and [x = +12 y = -9 z = +9], respectively. White regions show the full extent of activation, after family-wise error correction for multiple comparisons across the whole brain (see Table 5.4 and results). Bar plots show the contrast estimate (with confidence interval) for all 10 tasks averaged across groups (i.e. 5s and 7s ITI groups). See Figures 5.1-5.3 for task numbers. **Abbreviations:** A-P = auditory-to-picture matching tasks; Sem = semantic association tasks.

5.4.3. Whole brain analyses

When I conducted a whole brain search, I found that other right- and left-hemisphere regions were activated for auditory sentence-to-picture matching task relative to rest ($P < 0.05$ FWE-corrected across the whole brain).

Significant activation was found in (i) the right inferior frontal gyrus and thalamus (including the regions reported above in the region of interest analysis) at peak co-ordinates +39, +6, +33 and +9, -12, +6, respectively; (ii) the left inferior frontal gyrus and left thalamus at co-ordinates -42, +6, +30 and -12, -18, +6, respectively; and (iii) the insula (bilaterally; see Table 5.4). In addition, bilateral activation was observed in the superior temporal lobe and occipital regions that were also activated by the auditory and visual object processing conditions respectively. However, I do not report the details of these effects as they are superfluous to the aims of the study.

Table 5.4. Location and significance of fMRI activations within predefined ROIs (A) and in whole brain analyses (B)

(A) Region of interest analysis								
Contrast of interest	**Region**	**Peak-Level**						
		k	**x**	**y**	**z**	Z_{score}	P_{uncorr}	$P_{FWE-corr}$
Aud-Pic Sent > Rest	R IFS	5	33	3	33	6.30	< 0.001	< 0.001
	R MD thalamus	9	12	-9	9	4.31	< 0.001	0.005
(B) Whole brain analyses								
Aud-Pic Sent > Rest	L Temp-Occ	3406	-45	-21	6	Inf	< 0.001	< 0.001
	R Temp-Occ	1011	51	-12	3	Inf	< 0.001	< 0.001
	L IFG	223	-42	6	30	Inf	< 0.001	< 0.001
	R IFG	361	39	6	33	Inf	< 0.001	< 0.001
	L Thalamus	21	-12	-18	6	6.17	< 0.001	< 0.001
	R Thalamus	15	9	-12	6	4.60	< 0.001	0.040
	L insula	39	-33	24	3	6.33	< 0.001	< 0.001
	R insula	35	33	24	0	6.13	< 0.001	< 0.001

Abbreviations: Aud-Pic Sent = auditory sentence-to-picture matching; R = right hemisphere; L = left hemisphere; IFS = inferior frontal sulcus; MD = medial dorsal thalamus; Temp-Occ = temporal occipital brain regions; IFG = inferior frontal gyrus.

In summary, the results of Study 3 provide evidence that parts of the right hemisphere regions that were damaged in patients with auditory sentence-to-picture matching impairments (Study 2) were activated when neurologically-normal participants are matching auditory sentences to pictures and during other language tasks. However, despite manipulating the demands on several different linguistic and non-linguistic functions, the results of the current experiment do not indicate how activation in the regions of interest is contributing to language tasks.

5.5. Discussion

The aim of the current fMRI study was to identify which parts of the right hemisphere regions of interest (identified in Study 2) were activated when 25 neurologically-normal subjects performed the auditory sentence-to-picture matching task and other language tasks conditions that varied demands on auditory, visual, phonological, semantic, sentence processing and verbal short-term memory.

Within the regions of interest from Study 2, I found significant activation for auditory sentence-to-picture matching in the right inferior frontal sulcus and right mediodorsal thalamus. However, the same right hemisphere regions were also activated during all other conditions with no significant differences in these regions for any of the linguistic manipulations that I investigated.

This observation is informative in three ways. First, it shows that the regions of interest that I have associated with selective impairments in sentence comprehension (in Chapters 3 and 4) are normally involved in auditory sentence-to-picture matching. I can therefore discount the possibility that sentence comprehension impairments after right hemisphere lesions necessarily reflect atypical functional anatomy (i.e. crossed aphasia). Second, fMRI of neurologically-normal participants allowed me to identify which parts of the regions of interest are involved in normal auditory sentence-to-picture matching. Particularly, I found that auditory sentence-to-picture matching activates the right inferior frontal sulcus and right mediodorsal thalamus (in addition to other left hemisphere regions that are already known to be involved in sentence comprehension; see Table 5.4). While focusing on the function of these right hemisphere regions I am not dismissing the likely contribution of the surrounding white matter, which is expected to play the important role in propagating activity to and from other task related regions. Third, activation in the right inferior frontal sulcus and right mediodorsal thalamus was not limited to auditory sentence-to-picture matching; it was also observed during other semantic and speech production tasks that did not involve auditory sentence processing.

In order, to further clarify the actual role of the right inferior frontal sulcus and right mediodorsal thalamus in auditory sentence-to-picture matching, in what follows I will discuss prior literature on the contribution of the identified right hemisphere regions to language processing.

5.5.1. The right inferior frontal sulcus and language processing

Previous fMRI studies have shown increased activation within the right inferior frontal sulcus for a wide range of linguistic conditions including: (i) simple compared to more-demanding grammaticality judgments (Cooke et al., 2006), (ii) response inhibition across perceptual and semantic (conceptual) decisions (Gonzalez Alam et al., 2018) and (iii) when new instructions are implemented compared to when new instructions are memorised (Demanet et al., 2016).

Willems and colleagues (2016) added more evidence by showing significant activation in the right inferior frontal sulcus (in addition to other left and right brain regions) when subjects listen to reverse speech versions of stories compared to the real speech stories. The authors of this study concluded that activation in the right frontal sulcus was more strongly modulated when the surprise value was high, i.e. when subjects perceive words deviated from what was predicted (Willems et al., 2016). Furthermore, an fMRI study in patients with left hemisphere stroke and a history of aphasia, found that better performance on a sentence comprehension task was significantly correlated with increased activity in more dorsal portions of the right inferior frontal sulcus and right parietal regions, particularly during a memory delay period (Meltzer et al., 2013).

Together, these findings suggest that the right inferior frontal sulcus (i) plays an important role during the formation of procedural representations in working memory, and (ii) is more sensitive to the demands on non-linguistic than linguistic processes that are needed to accurately perform more complex tasks.

5.5.2. The right mediodorsal thalamus and language processing

Although, in general, the right thalamus has not been directly associated with language processing, there are a few fMRI studies that have reported significant activation within the right mediodorsal thalamus during (i) word fluency (Halari et al., 2006) and (ii) verb/sentence generation tasks (Warburton et al., 1996). Increased activation in this region has also been found during task conditions involving the simultaneous presentation of picture and words compared to the presentation of words only (Kraut et al., 2002). Importantly, two meta-analyses of fMRI studies investigating the contribution of the thalamus to language processing reported activation within the right mediodorsal thalamus during a wide range of linguistic conditions; nonetheless, most of these studies reported bilateral thalamic activation with a left-sided preponderance for linguistic violations effects and the degree of right-sided recruitment depending on stimulus complexity (Indefrey et al., 2001; Llano, 2013).

In summary, I found increased activation in two right hemisphere regions when neurologically-normal participants performed an in-scanner version of the auditory sentence-to-picture matching task. However, the same regions also responded to the demands on a wide range of language functions (see Figure 5.6). This observation does not allow to establish the type of computational processing that causes activation in these regions during auditory sentence-to-picture matching, nor does it explain why I found in Study 2 (Chapter 4) that damage to the regions of interest in nine patients with selectively impaired auditory sentence-to-picture matching while preserving other semantic/phonological functions.

5.6. Limitations

The main limitation of this study is that it only focused on the function of the grey matter regions within the right hemisphere, which means that I have not been able to assess the likely contribution of the surrounding white matter tracts, which are expected to play the important role of propagating activity to and from other task-related regions. Future studies using anatomical connectivity analyses (i.e. Diffusion Tensor Imaging Tractography) are therefore required to evaluate the likely contribution of white matter tracts across sentence comprehension networks.

5.7. Conclusions

Using a multi-task fMRI study, I set out to investigate whether any parts of the regions of interest from Study 2 (Chapter 4) were activated when a group of 25 neurologically-normal subjects were performing the auditory sentence-to-picture matching task and other language tasks/conditions. Within the regions of interest (identified in Chapter 4), I found significant activation in the right inferior frontal sulcus and right mediodorsal thalamus during auditory sentence-to-picture matching, however, the same regions were also responsive to a wide range of language tasks that taxed phonological, semantic, sentence and verbal short-term memory processing. Findings of this study are informative because they show that increased activation within these regions was observed during normal sentence comprehension (language processing), and thus make it unlikely that selective impairments in auditory sentence-to-picture matching found in nine RHS patients in Study 1 reflect atypical language lateralisation. Based on prior literature highlighting the role of right frontal and thalamic regions in non-linguistic executive functions, in my final fMRI study (Chapter 6), I investigated the role of these regions further by using data of a new sample of 25 neurologically-normal participants who performed a range of one-back matching tasks that varied demands on semantic and non-semantic working memory (executive function) without involving sentence comprehension.

CHAPTER 6: STUDY 4

Unravelling the role of the right inferior frontal sulcus and right mediodorsal thalamus in a fMRI study of semantic and non-semantic working memory

6.1. Summary

The current study aimed to further investigate the functional role of the right inferior frontal sulcus and right mediodorsal thalamus by reporting a fMRI study of neurologically-normal participants that examined how activation varied over a range of conditions that differed in their demands on semantic and non-semantic working memory (executive processing). I found that the right inferior frontal sulcus and right mediodorsal thalamus were significantly more activated when one-back matching tasks were performed in the absence of semantic information, irrespective of whether the stimuli were speech-like (e.g. pseudowords) or non-speech (e.g. coloured patterns). I therefore concluded that these right hemisphere regions were contributing to non-semantic executive functions (i.e. working memory) that are normally required to support a range of language tasks, especially when task demands are increased.

Findings of this study allowed me to illustrate (i) how functional neuroimaging of neurologically-normal participants can be used to investigate the functional contribution of regions identified by lesion-deficit relationships, and (ii) how seemingly domain-specific cognitive deficits (e.g. language processing) may

arise from disruption to domain-general cognitive mechanisms (e.g. non-semantic executive processing).

6.2. Introduction

In my previous fMRI experiment (Chapter 5), the right inferior frontal sulcus and mediodorsal thalamus were activated for auditory sentence-to-picture matching. However, the same right hemisphere regions were also activated during all tasks and conditions with no significant main effects of any of the linguistic manipulations tested. Therefore, although I found that these right hemisphere regions were associated with auditory sentence-to-picture matching during lesion-deficit mapping (see Chapter 4) and during fMRI (see Chapter 5), I concluded that their functional contribution is not specific to sentence or even semantic processing.

Building on prior literature showing the importance of executive functions (e.g. working memory) to sentence comprehension (Ye and Zhou, 2009; Colman et al., 2011; Key-DeLyria and Altmann, 2016), and the contribution of the right inferior frontal sulcus and right mediodorsal thalamus to executive processing (i.e. planning, monitoring, switching and inhibition; Aron et al., 2004, 2014; Halassa and Kastner, 2017), the aim of the current study is to elucidate the functional role of the regions identified in Study 3 (Chapter 5) by using fMRI of a new set of 25 neurologically-normal, right-handed participants who performed a wide range of one-back matching tasks that varied the demands on semantic and non-semantic working memory (an executive function).

6.2.1. The use of N-back matching tasks for the study of working memory

There are many prior reports showing that working memory is required for the short-term storage and online manipulation of information necessary for higher cognitive functions, such as language, planning and reasoning (Baddeley, 1983; Cohen et al., 1997; Baddeley, 2010). Due to its relevance in cognition, the concept of working memory has been increasingly studied in the last 20 years. One of the most popular experimental paradigms for investigating the neural basis of working memory is ‘the N-back matching tasks’ in which subjects are asked to monitor the identity or location of a series of verbal or nonverbal stimuli and to indicate when the currently presented stimulus is the same as the one presented ‘N’ trials before (Owen et al., 2005).

N-back matching tasks require online monitoring, updating, and manipulation of remembered information and are therefore assumed to place great demands on a number of key processes within working memory (Owen et al., 2005). Importantly, experimental designs comparing the load ‘N’ factor (i.e. N = 1, N = 2, and N= 3) are often employed to manipulate task complexity as an experimental condition. In the current study, I used an fMRI paradigm with eight 1-back-matching conditions that involved viewing or listening to a series of stimuli and pressing a yes/no button box to indicate whether the stimulus was the same or different to the previous one.

6.2.2. Task analysis

According to my task analysis (see Table 6.1) all one-back matching task conditions involved working memory capacity (N load = 1) and motor control of the fingers to press the corresponding response button. The tasks differed in the demands that they posed on (i) perceptual processing (ii) semantic content and

(iii) sublexical phonological processing. To tap each of these processing levels, I used an fMRI experiment that factorially manipulates the demands on: stimulus modality (auditory versus visual), the presence or absence of semantic content, and the presence or absence of sublexical phonological inputs.

Table 6.1. Task analysis of the eight one-back matching tasks included in the current fMRI study

One-back matching tasks	**Visual processing**	**Auditory processing**	**Semantic Content**	**Sublexical Phonological Processing**
Matching pictures of objects	■		■	▒
Matching written words	■		■	■
Matching written pseudowords	■		▒	■
Matching colours	■		▒	▒
Matching sounds of objects		■	■	▒
Matching heard words		■	■	■
Matching heard pseudowords		■	▒	■
Matching gender		■	▒	▒

Dark grey indicates necessary/explicit processes. Light grey signifies supporting/implicit processes. All one-back matching tasks involved the same working memory load and button pressing.

6.2.3. Literature review

In what follows, I will review previous fMRI studies of the contribution of the right inferior frontal sulcus and right mediodorsal thalamus to executive functions and cognitive control processes.

The role of the identified right hemisphere regions in executive processing: evidence from fMRI

The role of the right inferior frontal sulcus and right mediodorsal thalamus in executive functions and memory processes has been demonstrated in previous functional neuroimaging studies of neurologically-normal participants (Derrfuss et al., 2004; 2005; Aron et al., 2014). For instance, activation within the right inferior frontal sulcus has been reported during (i) object-recall tasks (Assaf et al., 2006), (ii) encoding of letter strings and (iii) associative memory formation tasks (Fletcher et al., 1999, 2005; Becker et al., 2017). Likewise, Thompson-Schill et al. (1997) reported right inferior frontal activity (in addition to more extensive left frontal activity) during semantic tasks that involved different competing responses. There is also accumulating evidence suggesting that the right inferior frontal cortex plays a key role in response inhibition (Aron et al., 2003; Aron and Poldrack, 2006) and the cognitive control processes that are needed during (i) speech production (Neef et al., 2016) and (ii) sentence comprehension tasks (Lai et al., 2015). Furthermore, right Broca's area has been associated with motor imagery (Guillot et al., 2008) and working memory control (Marklund and Persson, 2012).

The mediodorsal thalamic nuclei, on the other hand, have been associated with various executive functions (e.g. guided/sustained attention) as well as memory processing (Van der Werf et al., 2003; Mitchell and Chakraborty, 2013; Browning et al., 2015; Parnaudeau et al., 2015). In addition, increased activation within the right mediodorsal thalamus has been observed in task conditions requiring shifts in behavioural strategy such as the Wisconsin card-sorting task (Monchi et al., 2001). In a review article, Saalmann and Kastner (2015) proposed that mediodorsal thalamic regions regulate synchrony between neurons in the prefrontal cortex and, consequently, information exchange according to cognitive control demands imposed by a given cognitive task.

Together, previous findings from functional neuroimaging studies of neurologically-normal participants suggest a relevant contribution of the right inferior frontal sulcus and right mediodorsal thalamus to executive and cognitive control processes.

6.2.4. Research question and hypothesis

In brief, the current study attempted to address the following research question:

(i) Are the right inferior frontal sulcus and mediodorsal thalamus involved in semantic or non-semantic (executive) working memory functions?

Based on prior literature and findings from my previous fMRI study (see Chapter 5), where I found that the involvement of the right inferior frontal sulcus and mediodorsal thalamus was not specific to sentence or even semantic processing (i.e. language processing), I expected to find increased activation in these regions for one-back matching on non-semantic stimuli compared to semantic stimuli.

6.3. Methods

6.3.1. Participants

A total of 25 neurologically-normal, right-handed, native speakers of English, with normal or corrected-to-normal vision (12 females, aged 20–45 years with a mean and standard deviation of 31.4 ± 5.9 years) were included in this fMRI study.

6.3.2. Experimental design

Study 4 was a 2x2x2 factorial design that manipulated: (1) auditory versus visual stimuli, with (2) speech versus non-speech content and (3) high versus low semantic content. The conditions of interest in the current study were eight one-back matching tasks that required participants to press a button box in response to each stimulus to indicate if the stimulus was the same or different to the previous one (for stimuli example see Figure 6.1). In addition, the same 8 types of stimuli were also presented with a speech production task. The speech production conditions are not relevant to the current study but have been reported in a previous study of phonological processing in the left supramarginal gyrus (for details see Oberhuber et al., 2016).

6.3.3. Task details

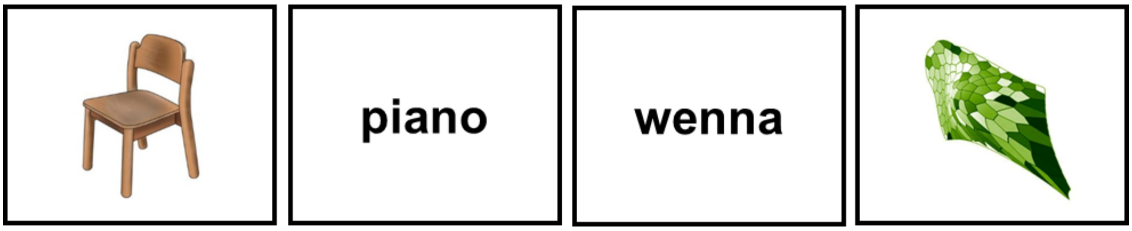
Stimuli with high semantic content were:

1) Heard object names in the auditory speech condition.
2) Written object names in the visual speech condition.
3) Heard object sounds in the auditory nonverbal condition.
4) Pictures of objects in the visual nonverbal condition.

Stimuli with low semantic content were:

5) Heard pseudowords in the auditory speech condition.
6) Written pseudowords in the visual speech condition.
7) Heard humming sounds in the auditory nonverbal condition.
8) Pictures of coloured patterns in the visual nonverbal condition.

Figure 6.1. Example stimuli for visual conditions



The figure shows example stimuli for the four visual tasks, i.e. matching pictures of objects (O), matching written words (W), matching written pseudowords (P) and matching coloured patterns (B).

6.3.4. Stimulus selection, creation and counterbalancing

Stimulus selection started by generating 128 pictures of easily recognizable animals and objects (e.g., cow, bus, elephant, plate) with one to four syllables (mean = 1.59; SD = 0.73). Visual word stimuli were the written names of the 128 objects, with 3–12 letters (mean = 5 letters; SD = 1.8). Auditory word stimuli were the spoken names of the 128 objects (mean duration = 0.64 s; SD = 0.1), recorded by a native speaker of English. Pseudowords were created using a non-word generator (Duyck et al., 2004) and matched to the real words for bigram frequency, number of orthographic neighbours, and word length. The same male speaker recorded the auditory words and pseudowords.

The non-verbal objects sounds associated with objects were available and easily recognizable for a quarter (32) of the stimuli, and taken from the NESSTI sound library (http://www.imaging.org.au/Nessti; Hocking et al., 2013). The duration of the environmental sounds needed to be significantly longer (mean length = 1.47 s, SD = 0.13) than the duration of the words ($t(158) = 40.28$; $p < 0.001$) because shorter sounds were not recognizable. The auditory baseline stimuli were recorded by both a male and female voice humming novel pseudowords, thereby removing any phonological or semantic content (mean duration = 1.04 s, SD = 0.43). Half of these stimuli were matched to the length of the auditory words; the other half, to the length of the environmental sounds. The visual baseline stimuli were meaningless object pictures, created by scrambling both global and local features, and then manually edited to accentuate one of 8 colours (brown, blue, orange, red, yellow, pink, purple, and green).

The 128 object stimuli were divided into four sets of 32 stimuli (A, B, C, and D). Set D was always presented as environmental non-verbal sounds. Sets A, B, and C were rotated across pictures, visual words, and auditory words in different participants. Half the subjects performed all eight speech production tasks first (not of interest for this study) followed by all eight one-back-matching tasks (the tasks of interest for this experimental chapter). The other half performed all eight one-back-matching tasks first followed by all eight speech production tasks. Within each task, half the subjects were presented auditory stimuli first, followed by visual stimuli; and the other half were presented visual stimulus first followed by auditory stimuli. The order of the four stimulus types was fully counterbalanced across subjects.

6.3.5. Procedure

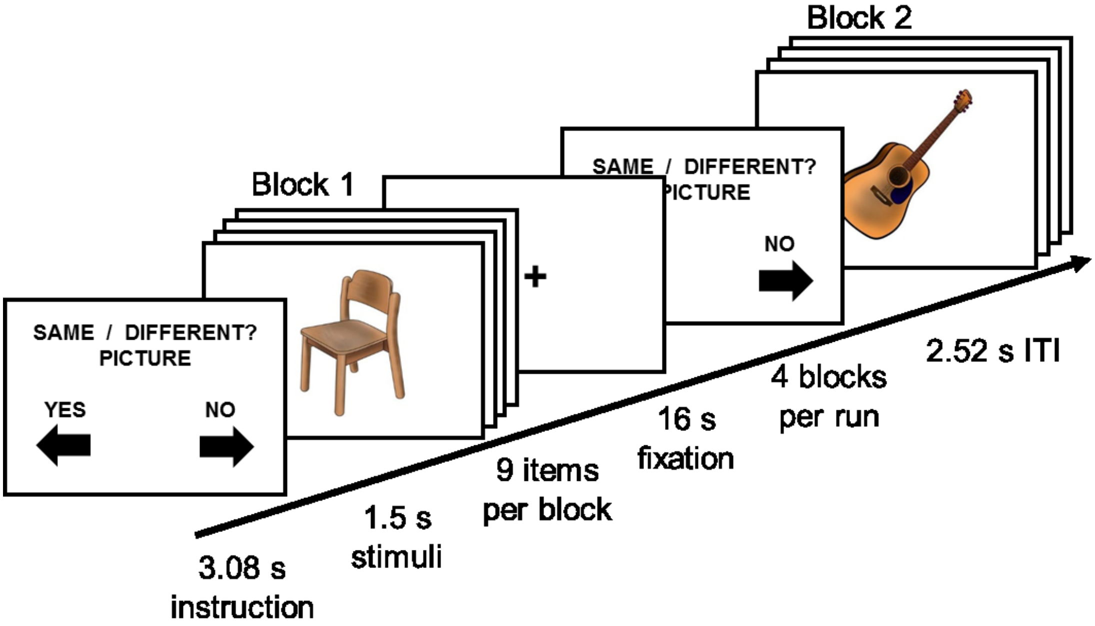
Each participant was trained on all tasks in a quiet testing room, using stimulus materials that were not used in the scanner, except the environmental sounds which remained the same for the training and in-scanner tests because environmental sound naming was more difficult and required more practice than the other conditions.

The one-back matching tasks required a button-press to indicate whether the present stimulus was the same as the one preceding it. Participants held their hand over two buttons with instructions to press the left button if the stimulus was the “same” as the previous one and the right button if the stimulus was “different” from the previous one. The participants were instructed to keep their head and body as still as possible and to keep their eyes open throughout. Total scanning time was approximately 1.5 hours per subject, including 10 min set-up time and a 12 min structural scan.

Scanning started with the instructions “Get Ready” written on the in-scanner screen while five dummy scans were collected. This was followed by 4 blocks of 9 stimuli interleaved with 16 s of resting with eyes open. Every stimulus block was preceded by a written instruction slide (e.g. “Repeat”), lasting 3.08 s each, which indicated the start of a new block and reminded subjects of the task. Experimental details are provided in Table and Figure 6.2.

Visual stimuli were each displayed for 1.5 s. Each image was scaled to 350 × 350 pixels and subtended a visual angle of 7.4°, with a screen resolution of 1024 × 768. Words and pseudowords were presented in lower case Helvetica. Their visual angle ranged from 1.47 to 4.41° with the majority of words (with five letters) extending 1.84–2.2°. The length of sound files varied across stimuli and tasks, ranging from 0.64 to 1.69 s (see stimulus creation above). Auditory stimuli were presented via MRI compatible headphones (MR Confon, Magdeburg, Germany), which filtered ambient in-scanner noise. Volume levels were adjusted for each subject before scanning. Each subject’s spoken responses were recorded via a noise-cancelling MRI microphone (FOMRI IIITM Optoacoustics, Or-Yehuda, Israel), and transcribed manually for off-line analysis. See Table 6.2 for experimental details and Figure 6.2 for a schematic illustration of one task.

Figure 6.2. Schematic illustration of the timing of one task ("matching pictures of objects").



The participants were instructed to indicate (by pressing the Yes or NO button) if the current stimulus was the same as the one before (i.e. "Is the picture on screen the same as that immediately before it?") ITI = inter-stimulus interval (i.e. the time between the presentation of 2 successive stimuli).

Table 6.2. Experimental details for Study 4

Partcipants	
Number	25
Gender (females / males)	12/13
Mean age in years (+/-SD)	31.4 (5.7)
Timing parameters	
Stimulus duration in sec	
Visual stimuli	1.5
Auditory stimuli/words[a]	0.64
Auditory pseudowords	0.68
ITI (sec)	2.5
Block length (sec)[b]	22.5
Total time for each run (min)[c]	3.2
Total acquisition time (min)	51.2
Number of stimuli per block	9 (incl. one repeat)
Number of blocks per run	4
Total number of stimuli per run	36
Number of runs	16
Scanning parameters	
TR (sec)	3.1
Number of slices	44
Number of volumes per run	62
Number of dummy acquisitions	5

(a) Auditory stimuli included single words.

(b) Each block began with instructions for 3.1 seconds.

(c) Each run ended with a resting period of 16 seconds.

6.3.6. Analysis of in-scanner behaviour

The accuracy and speed of response was measured by button-presses for all 8 one-back matching tasks. A response was categorised as ‘correct’ if it matched the expected target and as ‘incorrect’ if the response did not match the target, took longer than the allotted time, or was self-corrected. Only ‘correct’ trials were used in the fMRI analyses.

Statistical analyses involved 2 × 4 ANOVAs in SPSS manipulating stimulus modality (visual versus auditory) with stimulus type (word, pseudoword, sound/picture, and gender/colour). All ANOVAs were corrected for potential violations of sphericity, adjusting their degrees of freedom using the Greenhouse–Geisser correction (Greenhouse and Geisser, 1959). These corrections result in more conservative statistical tests (i.e. decreasing the risk of false positives while increasing the risk of false negatives).

Three subjects' behavioural data were excluded because their button press responses were not consistently detected (due to technical failure) in one of the following one-back-matching conditions: written pseudowords, environmental sounds, and/or spoken words.

Data acquisition, preprocessing and first–level analyses steps of the imaging data are explained in the general methods chapter (Chapter 2).

6.3.7. Second-level analysis

The aim of the second-level analysis was to identify whether the right hemisphere regions associated with auditory sentence-to picture matching in Studies 2 and 3 were activated when neurologically-normal participants were making one-back matching decisions (i.e. is the stimulus currently displayed the same as the previously presented stimulus?) on semantic and non-semantic stimuli.

The contrasts from the first level – one for each task relative to rest – were entered into a one-way ANOVA and reported the main effect of:

1. semantic content (i.e. words and objects compared to pseudowords and meaningless baselines),

2. sublexical phonological cues (words and pseudowords compared to pictures of objects and their nonverbal sounds), and
3. the interaction of these variables with stimulus modality (visual versus auditory; see Tables 6.3 and 6.4).

The search volume was restricted to only include voxels that were part of two spheres (radius 3 mm) centred on the peak co-ordinates obtained from the contrast of interest in Study 3 (Chapter 5). I report effects that survived a voxel-level threshold of $p < 0.05$, after FWE-correction for multiple comparisons within the regions of interest (see Table 6.4). Peak co-ordinates (x,y,z) are reported in MNI space.

Table 6.3. Experimental design and second level contrasts

Paradigm Details		**Second Level Contrasts**							
ID	**Task**	**Stimulus**		***Semantic Content (S)**		**Sublexical Phonology(Ph)**		**Interaction (S & Ph)**	
		Vis	Aud	Pr	Ab	Pr	Ab	Pr	Ab
O	See pictures of objects	1	-1	1	-1	-1	1	-1	1
W	See written object names	1	-1	1	-1	1	-1	1	-1
P	See written pseudowords	1	-1	-1	1	1	-1	-1	1
B	See coloured patterns	1	-1	-1	1	-1	1	1	-1
O	Heard sounds of objects	-1	1	1	-1	-1	1	-1	1
W	Heard names of objects	-1	1	1	-1	1	-1	1	-1
P	Heard pseudowords	-1	1	-1	1	1	-1	-1	1
B	Heard male/female voice	-1	1	-1	1	-1	1	1	-1

There were 8 one-back matching with finger press response tasks that factorially manipulated the presence or absence of semantic content [S], the presence or absence of sublexical phonology [Ph], using heard or written pseudowords [P], words [W] objects [O] or baselines [B], see text for details. **Abbreviations:** * = task/condition of interest; Vis = visual; Aud = Auditory; Pr = present; Ab = absent; S & Ph = semantic and phonology.

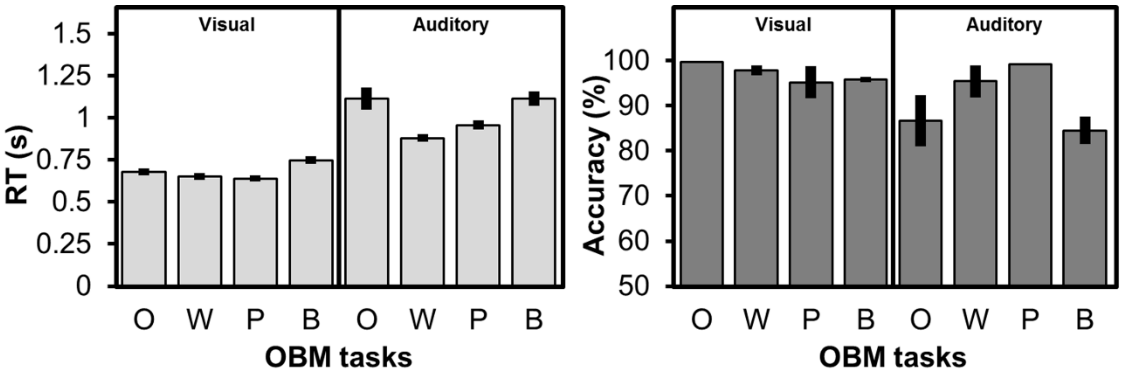
6.4. Results

6.4.1. In-scanner behavioural results

The 22 participants (three subjects were excluded because of measurement error; see Methods) performed well and contributed a consistently high number of correct trials to all the effects of interest (mean average of 95% or above per task). The exceptions, in which accuracy dipped below 95%, were the auditory and visual baseline conditions. See Figure 6.3 for an overview of all accuracy and reaction time results. The lower accuracy for the baseline conditions may have arisen because some participants attempted to match these stimulus on their visual or auditory forms rather than their colour or pitch. The following main effects were statistically significant: (i) stimulus type ($F(2.25, 47.32) = 29.94$; $p < 0.001$, Greenhouse–Geisser) and (ii) stimulus modality ($F(1, 21)=4.89$; $p=0.038$, Greenhouse–Geisser). There also was a significant stimulus modality by stimulus type interaction ($F(2.08, 43.65) = 6.54$; $p = 0.003$, Greenhouse–Geisser).

Reaction times (including correct trials only) showed a main effect of modality, i.e. longer response times for auditory stimuli than visual stimuli ($F(1,21) = 150.51$, $p < 0.001$). This is likely due to longer stimulus durations for auditory than visual stimuli (see Table 6.2).

Figure 6.3. In-scanner behavioural data for all one-back matching task



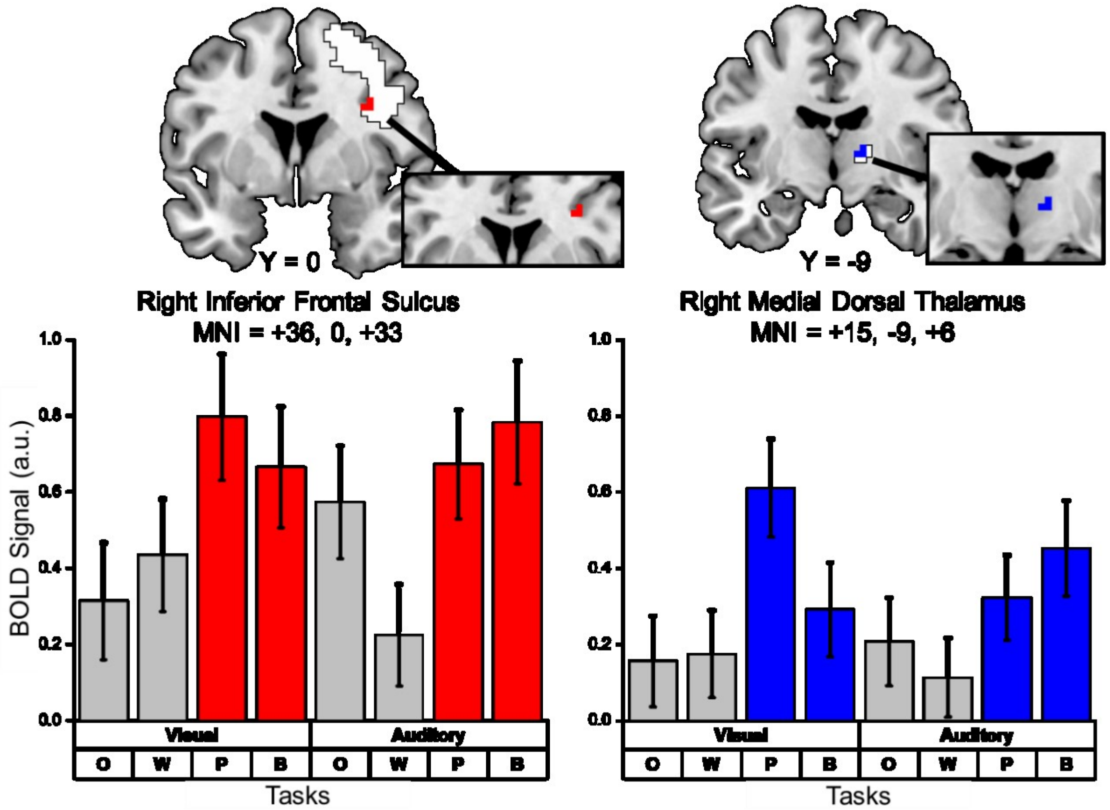
The figure shows accuracy and RTs (mean and SE) for the eight one-back matching tasks that comprised Experiment 4. Behavioural results for one-back matching tasks are based on 22 subjects because button-press responses were lost in one or more one-back matching tasks for 3 subjects (see Methods).

6.4.2. fMRI results

Effect of interest (second level analysis)

I found that the right inferior frontal and thalamic regions, that were engaged by auditory sentence-to-picture matching in neurologically-normal subjects (see Chapter 5) and damaged in patients with auditory sentence-to-picture matching (see Chapter 4), were significantly more activated (Z scores = 3.9 and 3.8, respectively) when one-back matching was performed in the absence of semantic information (i.e. pseudowords and baselines compared to words and objects across modalities; see Figure 6.4 and Table 6.4).

Figure 6.4. Illustration of right hemisphere activations within the regions of interest



Top panel shows coronal slices showing peak activations for one-back matching on pseudowords [P] and baselines [B] more than words [W] or objects [O] in the right inferior frontal sulcus (5 voxels in red) and the right medial dorsal thalamus (5 voxels in blue) at coordinates [x = +36 y = 0 z = +33] , Z score = 3.9, P = 0.001, and [x = +15 y = -9 z = +6], Z score = 3.8, P = 0.001, respectively. White regions show the full extent of activation from whole brain analysis; P < 0.001, uncorrected. Bottom plots showing the contrast estimate (with confidence interval) for all one-back matching tasks. Abbreviations: [O] = objects, [W] = words, [P] = pseudowords, [B] = baseline tasks.

Whole brain analysis

Increased and significant activation for the absence more than presence of semantic information was also observed in the following brain regions:

(i) the right inferior and superior inferior frontal gyri and thalamus (including the regions reported above in the region of interest analysis) at peak co-ordinates +24, -3, +66 and +18, -12, +6, respectively;

(ii) the left inferior frontal cortex at co-ordinates -48, 0, +33;

(iii) and left/right supramarginal gyrus at co-ordinates -39, -42, +39 and +42, -36, +39, respectively.

There were no significant effects in any part of the right hemisphere that could be attributed to the demands on phonological or semantic processing or the interaction between semantic and phonological processing. In other words, the response in the right hemisphere, including the regions of interest, was more consistent with non-semantic (driven by stimuli that lacked semantic content) than semantic processing demands.

Table 6.4. Location and significance of fMRI activations within the predefined ROIs (A) and in whole brain analyses (B)

(A) Region of interest analysis								
Contrast of interest	**Region**	**Peak-Level**						
		k	x	y	z	Z_{score}	P_{uncorr}	$P_{FWE-corr}$
P + B > O + W	R IFS	5	36	0	33	3.94	< 0.001	0.001
	R MD thalamus	5	15	-9	6	3.79	< 0.001	0.001
(B) Whole brain analyses								
P + B > O + W	L IFG	252	-48	0	33	5.58	< 0.001	< 0.001
	R SFG	510	24	-3	66	5.06	< 0.001	0.009
	L thalamus	14	-12	-12	3	3.40	< 0.001	0.994
	R thalamus	24	18	-12	6	3.90	< 0.001	0.622
	L SMG	850	-39	-42	39	6.53	< 0.001	< 0.001
	R SMG	950	42	-36	39	6.47	< 0.001	< 0.001

Abbreviations: P + B > O + W = matching pseudowords and baseline tasks compared to matching objects of pictures and words (across modalities); R = right hemisphere; L = left hemisphere; IFS = inferior frontal sulcus; MD = mediodorsal thalamus; IFG = middle frontal gyrus; SFG = superior frontal gyrus; SMG = supramarginal gyrus.

6.5. Discussion

In my previous fMRI studies (Chapter 5), I found that the functional contribution of two right-hemisphere regions (the right inferior frontal sulcus and mediodorsal thalamus) was not specific to sentence comprehension, sentence production or even semantic processing. In this study, I investigated whether activation within the identified right-hemisphere regions was observed during one-back matching tasks that differed in their the demands on semantic and non-semantic working memory (an executive function).

I found significant activation in the right inferior frontal sulcus and mediodorsal thalamus for one-back matching on stimuli that lacked semantic content (pseudowords and baseline conditions) compared to perceptually matched and semantically rich stimuli (words and pictures of objects). This result shows that the right-hemisphere regions identified in Studies 2 and 3 (Chapters 4 and 5) were more sensitive to the demands on non-semantic working memory executive capacity (i.e. responded to stimuli with low semantic content; see Figure 6.4).

Therefore, the behavioural (Chapter 3), lesion (Chapter 4) and fMRI data (Chapters 4 and 5) collectively support the hypothesis that difficulties performing the auditory sentence-to-picture matching task – observed in nine right-hemisphere stroke patients – could result from a disruption to executive processing capacity that is necessary for normal language functions, especially when task difficulty is increased. This is consistent with prior literature showing a role for the right inferior frontal sulcus and right mediodorsal thalamus in executive processing (i.e. working memory, planning, monitoring and switching; Aron et al., 2004, 2014; Halassa and Kastner, 2017).

By integrating findings from four studies, I was able to link three unrelated observations in the prior literature: (a) right inferior frontal sulcus and mediodorsal thalamic activity increases during (non-semantic) executive processing, (b) executive processing is required for sentence comprehension and (c) right frontal and thalamic activity increases during sentence comprehension. In what follows, I will discuss points (a) and (b). A more extensive discussion of the findings from my four studies can be found in Chapter 7 of this thesis.

6.5.1. The role of right fronto-thalamic regions in executive processing

Together, the results of the current fMRI study have associated the right inferior frontal sulcus and right mediodorsal thalamus regions with non-semantic working memory. As I showed in Study 2 (Chapter 4), the link between damage to the right frontal and thalamic regions and impaired auditory sentence-to-picture matching was entirely novel. However, there is accumulating evidence from functional and lesion studies that right fronto-thalamic regions are involved in non-semantic executive processing. Neuropsychological studies have, for example, reported difficulties in working memory and inhibitory control after focal damage to either the mediodorsal thalamus (Halassa and Kastner, 2017; Pergola et al., 2018) or the right inferior frontal cortex (Szczepanski and Knight, 2014). These findings are consistent with fMRI studies that have shown increased activation in the right inferior frontal sulcus (Sebastian et al., 2016) and mediordorsal thalamic regions (Andrews et al., 2006; Minzenberg et al., 2009) under a variety of tests conditions that taxed executive functions.

Damage to the right prefrontal cortex (including BA 44-45 and 47 and the inferior frontal sulcus) has been, for example, associated with difficulties in inhibiting responses, task coordination, attentional control, and working memory

(Courtney et al., 1998a, b; Aron et al., 2004, 2014; Hampshire et al., 2010; Szczepanski and Knight, 2014). The right inferior frontal sulcus has also been proposed to be part of a multiple-demand system (i.e. a distributed set of cortical regions) that have been shown to rapidly adapt to exert top–down control during a broad range of tasks that require, for example, cognitive flexibility, behavioural inhibition, and attentional/executive control (Hampshire et al., 2012). Importantly, several lines of evidence have also suggested that the right inferior frontal sulcus is important for the hierarchical organization and planning of actions required by multi-component (cascading) behaviour (Duncan, 2010; Binkofski and Buccino, 2006; Koechlin and Jubault, 2006).

The mediodorsal thalamus, on the other hand, has been shown to be part of several cortico-subcortical networks, primarily, in those involving the prefrontal cortex (Parnaudeau et al., 2013; Golden et al., 2016; Parnaudeau et al., 2018) and considered an important high-order thalamic relay nucleus for cognitive processing (Mitchell et al., 2015; Golden et al., 2016). Animal lesion studies have added more evidence by showing that bilateral ablation of the mediodorsal thalamus may result in impaired performance on (non-spatial) working memory tasks with more severe impairment observed if task difficulty is increased (Mitchell, 2007; Watanabe and Funahashi, 2012).

6.5.2. Reciprocal fronto-thalamic connections

Growing evidence that the right inferior frontal cortex and right mediodorsal thalamus work as part of a neural system for executive functions is further provided by anatomical connectivity studies that have identified reciprocal fronto-thalamic connections (Behrens et al., 2003; Hwang et al., 2010; Eckert et al., 2012; Jeon et al., 2014). This is in line with findings from animal studies showing dense connections between the mediodorsal thalamic nuclei and frontal cortical regions such as prefrontal, anterior cingulate and premotor cortex (Goldman-Rakic and Porrino, 1985; Browning et al., 2015).

Neuropsychological studies have added more support to a functional link between these regions, by showing that focal damage to the mediodorsal thalamus can produce symptoms similar to those observed after prefrontal damage, including executive dysfunction and difficulties in organising behaviour (Daum and Ackermann, 1994; Van der Werf et al., 2003). It has also been suggested that lesions to the mediodorsal thalamic nuclei (in rhesus monkeys) could disrupt pathways leading to the prefrontal cortex affecting in turn processes that are typically governed by prefrontal regions, including attention, inhibition, planning, coordination, and strategy selection (Gaffan and Parker, 2000).

In summary, the literature seems to suggest that both the right inferior frontal sulcus and right mediodorsal thalamus could both be part of a neural network contributing to non-semantic executive processes but, more importantly, required during more demanding stimulus conditions that involve planning and organising sequential behaviour.

6.5.3. The link between executive functions and sentence comprehension

In keeping with the association of the right inferior frontal and thalamic regions with non-semantic executive functions, there is also prior literature showing a link between sentence comprehension and executive functions, especially when task demands increase.

The association between sentence comprehension and verbal (linguistic) working memory has been extensively reported (see Caplan and Waters, 1999; Rogalsky et al., 2015, 2018). Previous studies have also shown that sentences with non-canonical order such as passive or reversible sentences are generally considered to be more complex and difficult to understand (Amici et al., 2007) because words and phrases need to be held in memory and manipulated in order to understand the actual meaning of the sentence (Baddeley and Hitch, 1974; Grodzinsky, 2000). This is consistent with previous studies showing that in addition to verbal working memory, sentence comprehension also requires an active involvement of (i) domain-general executive capacity, particularly when sentences have ambiguous content (Key-DeLyria and Altmann, 2016), and (ii) cognitive control processes that may operate when a revision of the sentence structure and meaning is necessary (del Rio et al., 2011).

Prior aphasia literature has added more evidence by suggesting that brain regions involved in domain-general executive processing – either in the left or right-hemisphere – can play a relevant role in recovery from language impairments after left hemisphere brain damage. This inference is based on previous reports that language performance is not only dependent on brain regions that display language-related functions (Hickok and Poeppel, 2007; Price, 2012), but also on widely distributed and often overlapping brain regions that make domain-general contributions to cognition and particularly to language processing (Fedorenko, 2014; Geranmayeh et al., 2014). Importantly, there is evidence from therapy studies in patients with aphasia showing that the status of attentional-executive skill may predict therapy gains in aphasic patients (Fillingham et al., 2005; Lambon Ralph and Fillingham, 2007)

In summary, there are a few previous studies showing a link between sentence comprehension and executive/cognitive control processes. There is also accumulating prior literature suggesting that right inferior frontal and mediodorsal thalamic regions play a functional role in domain-general executive functions that are generically involved in many language/cognitive functions, especially for more demanding task conditions. While the contribution of the right mediodorsal thalamus to sentence comprehension is entirely novel, more investigation and evidence is still required to fully characterise the role of thalamic regions in language and executive processing.

6.6. Limitations

Some limitations are noted. Ideally, the same RHS patients with impaired auditory sentence-to-picture matching and damage to the regions of interest identified in Study 2 (Chapter 4) should have been tested with a battery of neuropsychological tasks designed to measure executive functions (see Chapter 3 for details). However, by systematically integrating findings from neuropsychological studies in right-hemisphere stroke patients with functional neuroimaging studies of neurologically-normal participants, I was also able to demonstrate alternative ways by which the association between sentence comprehension impairments and executive processing can be investigated.

6.6. Conclusions

In this study, I sought to investigate the contribution of the right inferior frontal sulcus and right mediodorsal thalamus further, by reporting a fMRI study that examined whether activation within these right hemisphere regions was observed when a new sample of 25 neurologically-normal subjects performed a range of conditions that differed in their demands on semantic and non-semantic working memory. Findings of this study confirmed my working hypothesis that the identified right hemisphere regions might have a functional role in executive functions (e.g. working memory) that are generically involved in many language tasks including auditory sentence-to-picture matching.

Future neuropsychological studies are needed to assess whether damage to the right inferior frontal sulcus and mediodorsal thalamus impairs domain-general (non-linguistic) executive functions. By testing a new sample of right hemisphere patients with damage to the identified regions of interest, I would be able to (a) confirm the link between sentence comprehension and executive functions, and (b) identify other brain regions that may be associated with executive processing and sentence comprehension impairments.

CHAPTER 7: GENERAL DISCUSSION AND CONCLUSION

In this thesis I sought to investigate the contribution of the right hemisphere to language processing in RHS patients and neurologically-normal subjects. By systematically integrating findings from four experiments (i.e. Chapters 3-6), I argue below that one of the reasons that sentence comprehension can be impaired after RHS is because (i) normal sentence comprehension increases the demands on non-linguistic working memory, and (ii) non-linguistic working memory (an executive function) is partly supported by right hemisphere regions.

In brief, the behavioural data (see Chapter 3), allowed me to (i) identify a group of patients who had right hemisphere damage and poor scores on one or more language tasks, and (ii) generate hypotheses to explain what level of processing impairment (e.g. perceptual, semantic, syntactic or executive) might underlie their poor language scores. The lesion analyses (see Chapter 4), enabled me to create regions of interest by comparing the lesion sites in patients with right hemisphere damage and poor language task scores to the lesion sites in other patients who had right hemisphere damage in the absence of impaired language task scores. Finally, functional neuroimaging (see Chapters 5 and 6) allowed me to show that parts of the regions identified in the lesion study were activated when neurologically-normal participants performed language tasks and moreover activation in these regions was more responsive to non-semantic than semantic working memory demands. Below, I consider the results of my behavioural, lesion and functional neuroimaging experiments in the context of prior literature in order to demonstrate their importance.

7.1. Behavioural data: The language task, and processing level, most frequently affected by right hemisphere damage

The results from my first study (Chapter 3) were consistent with prior studies reporting the prevalence of acquired language impairments in right-handed RHS patients and right-handed left-hemisphere stroke patients (Pedersen et al., 1995; Alexander and Annet, 1996). But in addition, the results of Study 1 also showed how the incidence of language impairments after RHS damage was highest on auditory sentence-to-picture matching even after excluding patients with visual perceptual deficits. Such a finding cannot simply be explained in terms of task difficulty, because in a sample of left hemisphere stroke patients, the most impaired language task was spoken picture description. My findings are, therefore, consistent with prior literature in post-stroke aphasia showing that the right hemisphere might contribute to speech comprehension more than speech production (Zaidel, 1976; Crinion and Price, 2005).

By additionally identifying a group of 9 patients who had impaired auditory sentence-to-picture matching in the context of spared visual and auditory perception, phonological and semantic processing and verbal short-term memory, I was able to hypothesise that their difficulty matching auditory sentences-to-pictures might be the consequence of disrupted executive processing rather than impairments in linguistic or perceptual processing.

7.2. Lesion analyses: The right hemisphere lesion sites associated with impaired auditory sentence-to-picture matching

In Study 2 (Chapter 4), I identified three distinct right hemisphere regions of interest that were damaged in patients with impaired auditory sentence-to-picture matching. However, damage to the identified regions was also observed in some of those who did not have auditory sentence-to-picture matching difficulties. In other words, there was inter-patient variability in the effect of damage to these right hemisphere regions. Below I discuss the possible sources that caused the observed inconsistencies.

7.2.1. Sources of inter-patient variability in lesion-deficit associations

Variability in the effects of lesions to regions that show highly significant effects in group-level voxel-based analyses has also been observed in studies of patients with left hemisphere damage. For example, in Gajardo-Vidal et al. (2018), I reported that the incidence of long-term word finding impairments following damage to regions identified in group-level voxel-based analyses (with very conservative statistical thresholds) was less than 50%.

In a recent paper, Price and colleagues (2017) discussed different sources of inter-patient variability in lesion-deficit mappings and differentiated those related to the patients themselves such as demographic factors, time post-stroke and effect of therapy, from those related to basic principles of functional organisation and re-organisation. They argue that the effect of damage to a region will depend on (i) whether other regions can potentially compensate for the lost function or (ii) the degree to which language functions were left lateralised prior to the stroke.

There is general consensus that language is more impaired after lesions to the left than right hemisphere, and language functions activate left more than right hemisphere regions in right-handed neurologically-normal subjects.

Nonetheless, the degree to which language is left lateralized significantly varies across subjects, with some individuals showing bilateral or right hemisphere lateralisation (Springer et al., 1999; Knecht et al., 2000). But more importantly, there is also evidence showing how the representation of language functions also differs between and within subjects (Seghier et al., 2011; Bradshaw et al., 2018). For instance, syntactic functions have been shown to be supported by left-lateralised fronto-temporal networks (Tyler et al., 2011, Wright et al., 2012) whereas semantic and phonological input processes have been reported to be bilaterally represented (Hartwigsen et al., 2010a, b; Lambon Ralph et al., 2017). In this context, the inter-patient variability observed in the lesion-deficit associations in Study 2 (Chapter 4) may also be related to underlying anatomical patterns of lateralisation of language networks (Knecht et al., 2002; Baynes and Long, 2007), and therefore the effect of damage to the identified set of regions could have reflected pre-morbid differences in the degree to which patients used their right hemisphere for language. Alternatively, if the observed inter-patient variability was due to differences in the ability to recover, future studies should find that variability is less when patients are tested in the acute stage of stroke before recovery from initial deficits has occurred.

Although future research is required to understand which patients are more versus less affected by right hemisphere damage, the key point here is that the effect of damage to these right hemisphere sites was not atypical. However, it is clear that (i) the degree to which language functions are represented in both hemispheres varies across subjects, and (ii) the interaction of many other factors may impact on the consistency of lesion-deficits associations.

7.3. Functional neuroimaging data: the contribution of the right hemisphere regions associated with auditory sentence-to-picture matching abilities to language functions

Formal evidence that the right hemisphere is normally involved in matching spoken sentences-to-pictures is provided by Study 3 (Chapter 5). Within the regions that were damaged in patients with auditory sentence-to-picture matching impairments, activation was observed in the right inferior frontal sulcus and right mediodorsal thalamus. In addition, these regions responded during a range of language tasks, with no evidence to suggest that they were particularly responsive to perceptual, semantic, phonological or syntactic processing. The results of a second functional neuroimaging study (Chapter 6) explain this finding by showing that the right inferior frontal sulcus and right mediodorsal thalamus are sensitive to the demands on non-semantic working memory capacity because they were significantly more activated when one-back matching was performed on stimuli that lacked semantic content. The data thus complement and extend the results of previous studies of semantic cognition (Jefferies, 2013; Thompson et al., 2016) that have shown that regions in the right middle cerebral artery territory contribute to executive aspects of semantic processing (i.e. controlled semantic retrieval). Using functional neuroimaging of neurologically-normal participants, I show the most critical region is likely to be the right inferior frontal sulcus and that the function of this region is not limited to semantic tasks.

The neuropsychological, lesion and fMRI data therefore collectively support the hypothesis that difficulties performing the auditory sentence-to-picture matching task after right hemisphere damage could result from disruption to non-linguistic executive processing that is necessary for normal language function.

7.4. Scientific novelty

Findings from my four studies add to previous literature in several ways. First, I demonstrate that damage to the right inferior frontal sulcus and right mediodorsal thalamus can impair spoken sentence comprehension. Second, I show that the effect of damage to these regions can be explained by disruption to normal functional anatomy. Third, I experimentally link the literature on three unrelated topics (summarised below) by identifying a right inferior frontal region that is (i) damaged in patients who have auditory sentence-to-picture matching impairments; (ii) activated when neurologically-normal participants are performing auditory sentence-to-picture matching; and (iii) sensitive to the demands on non-linguistic working memory. This provides the first evidence that the same right hemisphere regions are contributing to both sentence comprehension and executive function.

As I discussed in Chapter 6, the role of the right inferior frontal and right mediodorsal thalamic regions in executive functions has been demonstrated in many previous neuropsychological and functional neuroimaging studies (Van der Werf et al., 2003; Aron et al., 2004, 2014; Szczepanski and Knight, 2014; Halassa and Kastner, 2017; Neef et al., 2018). In addition, the importance of good executive functions for speech comprehension has also been suggested. For example, individuals with higher IQ scores and faster processing were more likely to answer ambiguous sentence comprehension questions correctly (Engelhardt et al., 2017), and older adults with good inhibition skills showed better sentence comprehension than those with poor inhibition skills (Yoon et al., 2015). Interestingly, syntactic interference effects during sentence comprehension were found to be predicted by general working memory capacity but not by phonological memory capacity as measured by digit span (Tan et al., 2017). This highlights a role for non-linguistic working memory in sentence comprehension that is over and above the contribution of verbal working memory capacity and may explain why my patients of interest were not found to have abnormally low digit spans (see Chapter 3).

The role of the right inferior frontal lobe in sentence comprehension has also been shown previously, particularly for older compared to younger neurologically-normal participants (Wingfield and Grossman, 2006), when words are ambiguous (Mason and Just, 2007), when sentences are reversible (Meltzer et al., 2010) or indeterminate (de Almeida et al., 2016), and when patients with aphasia after left hemisphere strokes are recovering their sentence comprehension abilities (van Oers et al., 2010; Mohr et al., 2014; Kielar et al., 2016). Finally, it has been previously proposed that the right hemisphere may be playing a non-linguistic executive role in normal speech comprehension (Bozic et al., 2010; Vigneau et al., 2011; Baumgaertner et al., 2013). Together, these studies provide abundant evidence that non-linguistic executive processing in the right hemisphere is important for speech comprehension. Nonetheless, I am not dismissing the potential contribution of right hemisphere regions to language processing itself. For instance, there is accumulating evidence showing that bilateral anterior temporal lobes are involved in the representation of conceptual knowledge (Rice et al., 2015; Jung and Lambon Ralph, 2016; Lambon Ralph et al., 2017). Nor am I dismissing prior conclusions that some right hemisphere lesion or activation effects can be driven by people who are right hemisphere dominant for language.

7.5. Future directions

In neurologically-normal participants, I have identified a right inferior frontal region and a right mediodorsal thalamic region that are both activated during auditory sentence-to-picture matching and also when the demands on non-linguistic working memory are increased. Future studies of patients are needed to complement findings of this thesis by determining whether a new sample of patients with damage to these right hemisphere regions have difficulties with both sentence comprehension and tasks that are specifically designed to test non-linguistic executive functions. Furthermore, such a finding would still necessitate subsequent investigation with neurologically-normal participants to determine whether the same brain regions were activated by sentence comprehension and non-linguistic executive functions (a co-occurrence in patients could be due to damage to different regions).

A larger patient sample will also allow me to quantify and understand inter-patient variability in the lesion-deficit associations after both left and right hemisphere strokes. This will necessitate tight control of time post stroke and other factors (e.g. age, gender, education, and therapeutic interventions) that might influence how patient behaviour evolves after brain damage.

It would also be useful to understand the relative contribution of right hemisphere grey and white matter damage to the incidence of impaired language and executive functions and how these structures, and associated neural activity, change in the course of recovery after RHS. Additionally, in a follow-up study of neurologically-intact participants, I would like to investigate the behavioural effect of disruptive TMS delivered over the right inferior frontal sulcus (by inducing a virtual lesion in this region).

7.6. Conclusions

To conclude, by combining behavioural, lesion and fMRI data from four studies, I was able to demonstrate that (1) long lasting speech comprehension impairments were frequently observed in right-handed patients with right frontal and thalamic damage; (2) this can be explained by disruption to normal functional anatomy rather than being indicative of crossed aphasia/atypical language lateralisation; and (3) the same right hemisphere regions contribute to both sentence comprehension and executive functions. Seemingly domain-specific cognitive deficits (e.g. language processing) can therefore be explained by disruptions to domain-general cognitive mechanisms (e.g. non-linguistic executive processing). Furthermore, these findings are consistent with previous reports that attribute increased right inferior frontal activity during speech comprehension, in patients with left hemisphere lesions, to a greater reliance on domain-general cognitive processing (van Oers et al., 2010; Geranmayeh et al., 2014). Finally, findings of this thesis also show how functional neuroimaging of neurologically-normal participants can be used to investigate the normal functional contribution of regions identified by unexpected lesion-deficit relationships.

REFERENCES

Ackermann H, Riecker A. The contribution of the insula to motor aspects of speech production: a review and a hypothesis. Brain Lang 2004; 89(2): 320-8.

Alexander MP, Annett M. Crossed aphasia and related anomalies of cerebral organization: case reports and a genetic hypothesis. Brain Lang 1996; 55(2): 213-39.

Alexander MP, Fischette MR, Fischer RS. Crossed aphasias can be mirror image or anomalous. Case reports, review and hypothesis. Brain 1989; 112 (Pt 4): 953-73.

Amici S, Brambati SM, Wilkins DP, Ogar J, Dronkers NL, Miller BL, et al. Anatomical correlates of sentence comprehension and verbal working memory in neurodegenerative disease. J Neurosci 2007; 27(23): 6282-90.

Amunts K, Schleicher A, Burgel U, Mohlberg H, Uylings HB, Zilles K. Broca's region revisited: cytoarchitecture and intersubject variability. J Comp Neurol 1999; 412(2): 319-41.

Andrews J, Wang L, Csernansky JG, Gado MH, Barch DM. Abnormalities of thalamic activation and cognition in schizophrenia. Am J Psychiatry 2006; 163(3): 463-9.

Aron AR, Fletcher PC, Bullmore ET, Sahakian BJ, Robbins TW. Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. Nat Neurosci 2003; 6(2): 115-6.

Aron AR, Poldrack RA. Cortical and Subcortical Contributions to Stop Signal Response Inhibition: Role of the Subthalamic Nucleus. J Neurosci 2006; 26(9): 2424.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex. Trends Cogn Sci 2004; 8(4): 170-7.

Aron AR, Robbins TW, Poldrack RA. Inhibition and the right inferior frontal cortex: one decade on. Trends Cogn Sci. 2014; 18(4): 177-85.

Arora J, Pugh K, Westerveld M, Spencer S, Spencer DD, Todd Constable R. Language lateralization in epilepsy patients: fMRI validated with the Wada procedure. Epilepsia 2009; 50(10): 2225-41.

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. NeuroImage 2000; 11(6 Pt 1): 805-21.

Assaf M, Calhoun VD, Kuzu CH, Kraut MA, Rivkin PR, Hart J, Jr., et al. Neural correlates of the object-recall process in semantic memory. Psychiatry Res 2006; 147(2-3): 115-26.

Baddeley A. Working memory. Phil Trans R Soc Lond B 1983; 302(1110): 311.

Baddeley A. Working memory. Curr Biol 2010; 20(4): 136-40.

Baddeley AD, Hitch G. Working Memory. In: Bower GH, editor. Psychology of Learning and Motivation: Academic Press; 1974. p. 47-89.

Bartolomeo P, Thiebaut de Schotten M, Chica AB. Brain networks of visuospatial attention and their disruption in visual neglect. Front Hum Neurosci 2012; 6: 110.

Bartolomeo P, Thiebaut de Schotten M, Doricchi F. Left unilateral neglect as a disconnection syndrome. Cereb Cortex 2007; 17(11): 2479-90.

Basso A, Farabola M, Grassi MP, Laiacona M, Zanobio ME. Aphasia in left-handers: Comparison of aphasia profiles and language recovery in non-right-handed and matched right-handed patients. Brain Lang 1990; 38(2): 233-52.

Bates E, Reilly J, Wulfeck B, Dronkers N, Opie M, Fenson J, et al. Differential effects of unilateral lesions on language production in children and adults. Brain Lang 2001; 79(2): 223-65.

Bates E, Wilson SM, Saygin AP, Dick F, Sereno MI, Knight RT, et al. Voxel-based lesion-symptom mapping. Nat Neurosci 2003; 6(5): 448-50.

Baum SH, Martin RC, Hamilton AC, Beauchamp MS. Multisensory speech perception without the left superior temporal sulcus. NeuroImage 2012; 62(3): 1825-32.

Baumgaertner A, Hartwigsen G, Roman Siebner H. Right-hemispheric processing of non-linguistic word features: implications for mapping language recovery after stroke. Hum Brain Mapp 2013; 34(6): 1293-305.

Baynes K, Long DL. Three Conundrums of Language Lateralization. Lang Linguist Compass 2007; 1(1-2): 48-70.

Baynes K, Tramo MJ, Gazzaniga MS. Reading with a limited lexicon in the right hemisphere of a callosotomy patient. Neuropsychologia 1992; 30(2): 187-200.

Becker E, Karnath H-O. Incidence of visual extinction after left versus right hemisphere stroke. Stroke 2007; 38(12): 3172-4.

Becker N, Kalpouzos G, Persson J, Laukka EJ, Brehmer Y. Differential Effects of Encoding Instructions on Brain Activity Patterns of Item and Associative Memory. J Cogn Neurosci 2017; 29(3): 545-59.

Beeman MJ, Chiarello C. Complementary right- and left-hemisphere language comprehension. Curr Dir Psychol Sci 1998; 7(1): 2-8.

Behrens TEJ, Johansen-Berg H, Woolrich MW, Smith SM, Wheeler-Kingshott CAM, Boulby PA, et al. Non-invasive mapping of connections between human thalamus and cortex using diffusion imaging. Nat Neurosci 2003; 6(7): 750-7.

Ben-Shachar M, Palti D, Grodzinsky Y. Neural correlates of syntactic movement: converging evidence from two fMRI experiments. NeuroImage 2004; 21(4): 1320-36.

Bernal B, Ardila A. Bilateral representation of language: A critical review and analysis of some unusual cases. J Neurolinguistics 2014; 28: 63-80.

Binkofski F, Buccino G. The role of ventral premotor cortex in action execution and action understanding. Journal of Physiology-Paris 2006; 99(4): 396-405.

Bishop DVM. Cerebral asymmetry and language development: cause, correlate, or consequence? Science 2013; 340(6138): 1230531.

Bishop DVM, Watt H, Papadatou-Pastou M. An efficient and reliable method for measuring cerebral lateralization during speech with functional transcranial Doppler ultrasound. Neuropsychologia 2009; 47(2): 587-90.

Bookheimer S. Functional MRI of language: new approaches to understanding the cortical organization of semantic processing. Annu Rev Neurosci 2002; 25: 151-88.

Booth JR, Burman DD, Meyer JR, Gitelman DR, Parrish TB, Mesulam MM. Modality independence of word comprehension. Hum Brain Mapp 2002; 16(4): 251-61.

Bowen A, McKenna K, Tallis RC. Reasons for variability in the reported rate of occurrence of unilateral spatial neglect after stroke. Stroke 1999; 30(6): 1196-202.

Bozic M, Tyler LK, Ives DT, Randall B, Marslen-Wilson WD. Bihemispheric foundations for human speech comprehension. Proc Natl Acad Sci USA 2010; 107(40): 17439-44.

Bradshaw AR, Thompson PA, Wilson AC, Bishop DVM, Woodhead ZVJ. Measuring language lateralisation with different language tasks: a systematic review. PeerJ 2017; 5: e3929.

Braet W, Humphreys GW. Case mixing and the right parietal cortex: evidence from rTMS. Exp Brain Res 2006; 168(1-2): 265-71.

Bramwell B. On "crossed" aphasia and the factors which go to determine whether the "leading" or "driving" speech-centres shall be located in the left or in the right hemisphere of the brain. Lancet 1899; 153(3953): 1473-9.

Bridges KA, Van Lancker Sidtis D, Sidtis JJ. The role of subcortical structures in recited speech: Studies in Parkinson's disease. J Neurolinguistics 2013; 26(6): 591-601.

Broca P. Sur la faculte du langage articule. Paris Bull Soc Anthr 1865; 6: 337–93.

Browning PG, Chakraborty S, Mitchell AS. Evidence for Mediodorsal Thalamus and Prefrontal Cortex Interactions during Cognition in Macaques. Cereb Cortex 2015; 25(11): 4519-34.

Bruce C, Edmundson A. Letting the CAT out of the bag: A review of the Comprehensive Aphasia Test. Commentary on Howard, Swinburn, and Porter, oPutting the CAT out: What the Comprehensive Aphasia Test has to offero. Aphasiology 2010; 24(1): 79-93.

Bryan KL. Assessment of language disorders after right hemisphere damage. Br J Disord Commun 1988; 23(2): 111-25.

Buchsbaum BR, D'Esposito M. Repetition Suppression and Reactivation in Auditory-Verbal Short-Term Recognition Memory. Cereb Cortex 2009; 19(6): 1474-85.

Butler RA, Lambon Ralph MA, Woollams AM. Capturing multidimensionality in stroke aphasia: mapping principal behavioural components to neural structures. Brain 2014; 137(Pt 12): 3248-66.

Cabeza R, Grady CL, Nyberg L, McIntosh AR, Tulving E, Kapur S*, et al.* Age-Related Differences in Neural Activity during Memory Encoding and Retrieval: A Positron Emission Tomography Study. J Neurosci 1997; 17(1): 391.

Cabeza R, Locantore JK, Anderson ND. Lateralization of Prefrontal Activity during Episodic Memory Retrieval: Evidence for the Production-Monitoring Hypothesis. J Cogn Neurosci 2003; 15(2): 249-59.

Campbell KL, Tyler LK. Language-related domain-specific and domain-general systems in the human brain. Curr Opin Behav Sci 2018; 21: 132-7.

Caplan D, Hildebrandt N, Makris N. Location of lesions in stroke patients with deficits in syntactic processing in sentence comprehension. Brain 1996; 119 (Pt 3): 933-49.

Caplan D, Waters G, Dede G, Michaud J, Reddy A. A study of syntactic processing in aphasia I: behavioral (psycholinguistic) aspects. Brain Lang 2007; 101(2): 103-50.

Caplan D, Waters GS. Verbal working memory and sentence comprehension. Behav Brain Sci 1999; 22(1): 77-94; discussion 5-126.

Catani M, Allin MP, Husain M, Pugliese L, Mesulam MM, Murray RM, et al. Symmetries in human brain language pathways correlate with verbal recall. Proc Natl Acad Sci USA 2007; 104(43): 17163-8.

Chambers CD, Bellgrove MA, Stokes MG, Henderson TR, Garavan H, Robertson IH, et al. Executive "brake failure" following deactivation of human frontal lobe. J Cogn Neurosci 2006; 18(3): 444-55.

Chee MWL, O'Craven KM, Bergida R, Rosen BR, Savoy RL. Auditory and visual word processing studied with fMRI. Hum Brain Mapp 1999; 7(1): 15-28.

Chiarello C, Church KL. Lexical judgements after right- or left-hemisphere injury. Neuropsychologia 1986; 24(5): 623-32.

Cieslik EC, Mueller VI, Eickhoff CR, Langner R, Eickhoff SB. Three key regions for supervisory attentional control: Evidence from neuroimaging meta-analyses. Neurosci Biobehav Rev 2015; 48: 22-34.

Cohen JD, Perlstein WM, Braver TS, Nystrom LE, Noll DC, Jonides J, et al. Temporal dynamics of brain activation during a working memory task. Nature 1997; 386: 604.

Colman KSF, Koerts J, Stowe LA, Leenders KL, Bastiaanse R. Sentence Comprehension and Its Association with Executive Functions in Patients with Parkinson's Disease. Parkinsons Dis. 2011: 15.

Constable RT, Pugh KR, Berroya E, Mencl WE, Westerveld M, Ni W, et al. Sentence complexity and input modality effects in sentence comprehension: an fMRI study. NeuroImage 2004; 22(1): 11-21.

Cooke A, Grossman M, DeVita C, Gonzalez-Atavales J, Moore P, Chen W, et al. Large-scale neural network for sentence processing. Brain Lang 2006; 96(1): 14-36.

Cooney LM, Kennedy GJ, Hawkins KA, Hurme SB. Who can stay at home? Assessing the capacity to choose to live in the community. Arch Intern Med 2004; 164(4): 357-60.

Coppens P, Hungerford S, Yamaguchi S, Yamadori A. Crossed aphasia: an analysis of the symptoms, their frequency, and a comparison with left-hemisphere aphasia symptomatology. Brain Lang 2002; 83(3): 425-63.

Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. Nat Neurosci 2005; 8(11): 1603-10.

Corbetta M, Ramsey L, Callejas A, Baldassarre A, Hacker CD, Siegel JS, et al. Common behavioral clusters and subcortical anatomy in stroke. Neuron 2015; 85(5): 927-41.

Corbetta M, Shulman GL. Control of goal-directed and stimulus-driven attention in the brain. Nat Rev Neurosci 2002; 3(3): 201-15.

Coulson S, Federmeier KD, Van Petten C, Kutas M. Right hemisphere sensitivity to word- and sentence-level context: evidence from event-related brain potentials. J Exp Psychol Learn Mem Cogn 2005; 31(1): 129-47.

Courtney SM, Petit L, Haxby JV, Ungerleider LG. The role of prefrontal cortex in working memory: examining the contents of consciousness. Philos T Roy Soc B 1998a; 353(1377): 1819-28.

Courtney SM, Petit L, Maisog JM, Ungerleider LG, Haxby JV. An Area Specialized for Spatial Working Memory in Human Frontal Cortex. Science 1998b; 279(5355): 1347.

Cowell P, Hugdahl K. Individual differences in neurobehavioral measures of laterality and interhemispheric function as measured by dichotic listening. Dev Neuropsychol 2000; 18(1): 95-112.

Crescentini C, Shallice T, Macaluso E. Item Retrieval and Competition in Noun and Verb Generation: An fMRI Study. J Cogn Neurosci 2010; 22(6): 1140-57.

Crinion J, Price CJ. Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. Brain 2005; 128(Pt 12): 2858-71.

Crinion JT, Lambon-Ralph MA, Warburton EA, Howard D, Wise RJS. Temporal lobe regions engaged during normal speech comprehension. Brain 2003; 126(Pt 5): 1193-201.

Crosson B, Benefield H, Cato MA, Sadek JR, Moore AB, Wierenga CE, et al. Left and right basal ganglia and frontal activity during language generation: Contributions to lexical, semantic, and phonological processes. J Int Neuropsych Soc 2003; 9(7): 1061-77.

Crow TJ. A theory of the origin of cerebral asymmetry: epigenetic variation superimposed on a fixed right-shift. Laterality 2010; 15(3): 289-303.

Daum I, Ackermann H. Dissociation of Declarative and Nondeclarative Memory After Bilateral Thalamic Lesions: A Case Report. Int J Neurosci 1994; 75(3-4): 153-65.

de Almeida RG, Riven L, Manouilidou C, Lungu O, Dwivedi VD, Jarema G, et al. The Neuronal Correlates of Indeterminate Sentence Comprehension: An fMRI Study. Front Hum Neurosci 2016; 10: 614.

Deichmann R, Schwarzbauer C, Turner R. Optimisation of the 3D MDEFT sequence for anatomical brain imaging: technical implications at 1.5 and 3 T. NeuroImage 2004; 21(2): 757-67.

del Rio D, Maestu F, Lopez-Higes R, Moratti S, Gutierrez R, Maestu C, et al. Conflict and cognitive control during sentence comprehension: recruitment of a frontal network during the processing of Spanish object-first sentences. Neuropsychologia 2011; 49(3): 382-91.

Della Penna S, Brancucci A, Babiloni C, Franciotti R, Pizzella V, Rossi D, et al. Lateralization of dichotic speech stimuli is based on specific auditory pathway interactions: neuromagnetic evidence. Cereb Cortex 2007; 17(10): 2303-11.

Demanet J, Liefooghe B, Hartstra E, Wenke D, De Houwer J, Brass M. There is more into ‘doing’ than ‘knowing’: The function of the right inferior frontal sulcus is specific for implementing versus memorising verbal instructions. NeuroImage 2016; 141: 350-6.

Derrfuss J, Brass M, Neumann J, von Cramon DY. Involvement of the inferior frontal junction in cognitive control: Meta-analyses of switching and Stroop studies. Hum Brain Mapp 2005; 25(1): 22-34.

Derrfuss J, Brass M, Yves von Cramon D. Cognitive control in the posterior frontolateral cortex: evidence from common activations in task coordination, interference control, and working memory. NeuroImage 2004; 23(2): 604-12.

Devlin JT, Matthews PM, Rushworth MFS. Semantic processing in the left inferior prefrontal cortex: a combined functional magnetic resonance imaging and transcranial magnetic stimulation study. J Cogn Neurosci 2003; 15(1): 71-84.

Dewarrat GM, Annoni JM, Fornari E, Carota A, Bogousslavsky J, Maeder P. Acute aphasia after right hemisphere stroke. J Neurol 2009; 256(9): 1461-7.

Doricchi F, Thiebaut de Schotten M, Tomaiuolo F, Bartolomeo P. White matter (dis)connections and gray matter (dys)functions in visual neglect: gaining insights into the brain networks of spatial awareness. Cortex 2008; 44(8): 983-95.

Dorsaint-Pierre R, Penhune VB, Watkins KE, Neelin P, Lerch JP, Bouffard M, et al. Asymmetries of the planum temporale and Heschl's gyrus: relationship to language lateralization. Brain 2006; 129: 1164-76.

Duffau H, Leroy M, Gatignol P. Cortico-subcortical organization of language networks in the right hemisphere: an electrostimulation study in left-handers. Neuropsychologia 2008; 46(14): 3197-209.

Duncan J. The multiple-demand (MD) system of the primate brain: mental programs for intelligent behaviour. Trends Cogn Sci 2010; 14(4): 172-9.

Duncan J. The Structure of Cognition: Attentional Episodes in Mind and Brain. Neuron 2013; 80(1): 35-50.

Duyck W, Desmet T, Verbeke LP, Brysbaert M. WordGen: a tool for word selection and nonword generation in Dutch, English, German, and French. Behav Res Methods Instrum Comput 2004; 36(3): 488-99.

Eckert U, Metzger CD, Buchmann JE, Kaufmann J, Osoba A, Li M, et al. Preferential networks of the mediodorsal nucleus and centromedian-parafascicular complex of the thalamus--a DTI tractography study. Hum Brain Mapp 2012; 33(11): 2627-37.

Engelhardt PE, Nigg JT, Ferreira F. Executive function and intelligence in the resolution of temporary syntactic ambiguity: an individual differences investigation. Q J Exp Psychol (Hove) 2017; 70(7): 1263-81.

Federmeier KD, Mai H, Kutas M. Both sides get the point: hemispheric sensitivities to sentential constraint. Mem Cognit 2005; 33(5): 871-86.

Federmeier KD, Wlotko EW, Meyer AM. What's "right" in language comprehension: ERPs reveal right hemisphere language capabilities. Lang Linguist Compass 2008; 2(1): 1-17.

Fedorenko E. The role of domain-general cognitive control in language comprehension. Front Psychol 2014; 5(335).

Fedorenko E, Thompson-Schill SL. Reworking the language network. Trends Cogn Sci 2014; 18(3): 120-6.

Ferro JM, Madureira S. Aphasia type, age and cerebral infarct localisation. J Neurol 1997; 244(8): 505-9.

Fiebach CJ, Vos SH, Friederici AD. Neural correlates of syntactic ambiguity in sentence comprehension for low and high span readers. J Cogn Neurosci 2004; 16(9): 1562-75.

Fillingham JK, Sage K, Lambon Ralph MA. Treatment of anomia using errorless versus errorful learning: are frontal executive skills and feedback important? Int J Lang Commun Disord 2005; 40(4): 505-23.

Flandin G, Friston KJ. Topological Inference A2 - Toga, Arthur W. Brain Mapping. Waltham: Academic Press; 2015. p. 495-500.

Fletcher PC, Dolan RJ. Right prefrontal cortex responds to item familiarity during a memory encoding task. Memory 1999; 7(5-6): 703-13.

Fletcher PC, Zafiris O, Frith CD, Honey RAE, Corlett PR, Zilles K, et al. On the Benefits of not Trying: Brain Activity and Connectivity Reflecting the Interactions of Explicit and Implicit Sequence Learning. Cereb Cortex 2005; 15(7): 1002-15.

Forkel SJ, Thiebaut de Schotten M, Dell'Acqua F, Kalra L, Murphy DG, Williams SC, et al. Anatomical predictors of aphasia recovery: a tractography study of bilateral perisylvian language networks. Brain 2014; 137(Pt 7): 2027-39.

Fridriksson J, Yourganov G, Bonilha L, Basilakos A, Den Ouden D-B, Rorden C. Revealing the dual streams of speech processing. Proc Natl Acad Sci USA 2016; 113(52): 15108-13.

Friston KJ. Testing for anatomically specified regional effects. Hum Brain Mapp 1997; 5(2): 133-6.

Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. Event-related fMRI: Characterizing differential responses. NeuroImage 1998; 7(1): 30-40.

Friston KJ, Frith CD, Turner R, Frackowiak RS. Characterizing evoked hemodynamics with fMRI. NeuroImage 1995a; 2(2): 157-65.

Friston KJ, Holmes AP, Poline JB, Grasby PJ, Williams SCR, Frackowiak RSJ, et al. Analysis of Fmri Time-Series Revisited. NeuroImage 1995b; 2(1): 45-53.

Friston KJ, Worsley KJ, Frackowiak RS, Mazziotta JC, Evans AC. Assessing the significance of focal activations using their spatial extent. Hum Brain Mapp 1994; 1(3): 210-20.

Fu CHY, Morgan K, Suckling J, Williams SCR, Andrew C, Vythelingum GN, et al. A Functional Magnetic Resonance Imaging Study of Overt Letter Verbal Fluency Using a Clustered Acquisition Sequence: Greater Anterior Cingulate Activation with Increased Task Demand. NeuroImage 2002; 17(2): 871-9.

Funnell E, Pitchford NJ. Reading disorders and weak Verbal IQ following left hemisphere stroke in children: No evidence of compensation. Cortex 2010; 46(10): 1248-58.

Gaffan D, Parker A. Mediodorsal thalamic function in scene memory in rhesus monkeys. Brain 2000; 123(4): 816-27.

Gajardo-Vidal A, Lorca-Puls DL, Crinion JT, White J, Seghier ML, Leff AP, et al. How distributed processing produces false negatives in voxel-based lesion-deficit analyses. Neuropsychologia 2018; 115: 124-33.

Gauthier CT, Duyme M, Zanca M, Capron C. Sex and performance level effects on brain activation during a verbal fluency task: A functional magnetic resonance imaging study. Cortex 2009; 45(2): 164-76.

Gazzaniga MS. Cerebral specialization and interhemispheric communication: does the corpus callosum enable the human condition? Brain 2000; 123 (Pt 7): 1293-326.

Gazzaniga MS, Nass R, Reeves A, Roberts D. Neurologic Perspectives on Right Hemisphere Language Following Surgical Section of the Corpus-Callosum. Seminars in neurology 1984; 4(2): 126-35.

Gazzaniga MS, Volpe BT, Smylie CS, LeDoux JE, Wilson DH. Plasticity in speech organization following commissurotomy. Brain 1979; 102: 805–15.

Gazzaniga MS, Bogen JE, Sperry RW. Laterality effects in somesthesis following cerebral commissurotomy in man. Neuropsychologia 1963; 1: 209–15.

Gazzaniga MS, Bogen JE, Sperry RW. Some functional effects of sectioning the cerebral commissures in man. Proc Natl Acad Sci USA 1962; 48: 1765–9.

Geranmayeh F, Brownsett SL, Wise RJ. Task-induced brain activity in aphasic stroke patients: what is driving recovery? Brain 2014; 137(Pt 10): 2632-48.

Geschwind N. Disconnexion syndromes in animals and man. I. Brain 1965a; 88(2): 237-94.

Geschwind N. Disconnexion syndromes in animals and man. II. Brain 1965b; 88(3): 585-644.

Giroud M, Lemesle M, Madinier G, Billiar T, Dumas R. Unilateral lenticular infarcts: radiological and clinical syndromes, aetiology, and prognosis. J Neurol Neurosurg Psychiatry 1997; 63(5): 611-5.

Glasser MF, Rilling JK. DTI tractography of the human brain's language pathways. Cereb Cortex 2008; 18(11): 2471-82.

Gold BT, Kertesz A. Right hemisphere semantic processing of visual words in an aphasic patient: an fMRI study. Brain Lang 2000; 73(3): 456-65.

Golden EC, Graff-Radford J, Jones DT, Benarroch EE. Mediodorsal nucleus and its multiple cognitive functions. Neurology 2016; 87(20): 2161-8.

Goldman-Rakic PS, Porrino LJ. The primate mediodorsal (MD) nucleus and its projection to the frontal lobe. J Comp Neurol 1985; 242(4): 535-60.

Gonzalez Alam T, Murphy C, Smallwood J, Jefferies E. Meaningful inhibition: Exploring the role of meaning and modality in response inhibition. NeuroImage 2018; 181: 108-19.

Greenhouse SW, Geisser S. On methods in the analysis of profile data. Psychometrika 1959; 24(2): 95-112.

Grodzinsky Y. The neurology of syntax: language use without Broca's area. Behav Brain Sci 2000; 23(1): 1-21; discussion -71.

Grodzinsky Y, Pinango MM, Zurif E, Drai D. The critical role of group studies in neuropsychology: comprehension regularities in Broca's aphasia. Brain Lang 1999; 67(2): 134-47.

Guillot A, Collet C, Nguyen VA, Malouin F, Richards C, Doyon J. Functional neuroanatomical networks associated with expertise in motor imagery. NeuroImage 2008; 41(4): 1471-83.

Ha J-W, Pyun S-B, Hwang YM, Sim H. Lateralization of cognitive functions in aphasia after right brain damage. Yonsei Med J 2012; 53(3): 486-94.

Hagoort P, Indefrey P, Brown C, Herzog H, Steinmetz H, Seitz RJ. The neural circuitry involved in the reading of German words and pseudowords: A PET study. J Cogn Neurosci 1999; 11(4): 383-98.

Halari R, Sharma T, Hines M, Andrew C, Simmons A, Kumari V. Comparable fMRI activity with differential behavioural performance on mental rotation and overt verbal fluency tasks in healthy men and women. Exp Brain Res 2006; 169(1): 1-14.

Halassa MM, Kastner S. Thalamic functions in distributed cognitive control. Nat Neurosci 2017; 20(12): 1669-79.

Hamilton RH, Chrysikou EG, Coslett B. Mechanisms of aphasia recovery after stroke and the role of noninvasive brain stimulation. Brain Lang 2011; 118(1-2): 40-50.

Hampshire A, Chamberlain SR, Monti MM, Duncan J, Owen AM. The role of the right inferior frontal gyrus: inhibition and attentional control. NeuroImage 2010; 50(3): 1313-9.

Hampshire A, Chaudhry AM, Owen AM, Roberts AC. Dissociable roles for lateral orbitofrontal cortex and lateral prefrontal cortex during preference driven reversal learning. NeuroImage 2012; 59(4): 4102-12.

Hartwigsen G, Baumgaertner A, Price CJ, Koehnke M, Ulmer S, Siebner HR. Phonological decisions require both the left and right supramarginal gyri. Proc Natl Acad Sci USA 2010a; 107(38): 16494-9.

Hartwigsen G, Price CJ, Baumgaertner A, Geiss G, Koehnke M, Ulmer S, et al. The right posterior inferior frontal gyrus contributes to phonological word decisions in the healthy brain: evidence from dual-site TMS. Neuropsychologia 2010b; 48(10): 3155-63.

Hartwigsen G, Saur D, Price CJ, Ulmer S, Baumgaertner A, Siebner HR. Perturbation of the left inferior frontal gyrus triggers adaptive plasticity in the right homologous area during speech production. Proc Natl Acad Sci USA 2013; 110(41): 16402-7.

Hartwigsen G, Siebner HR. Probing the involvement of the right hemisphere in language processing with online transcranial magnetic stimulation in healthy volunteers. Aphasiology 2012; 26(9): 1131-52.

Heiss WD, Thiel A. A proposed regional hierarchy in recovery of post-stroke aphasia. Brain Lang 2006; 98(1): 118-23.

Helmstaedter C, Elger CE, Linke DB, Kurthen M. Right hemisphere restitution of language and memory functions in right hemisphere language-dominant patients with left temporal lobe epilepsy. Brain 1994; 117(4): 729-37.

Henderson VW. Speech fluency in crossed aphasia. Brain 1983; 106 (Pt 4): 837-57.

Herve PY, Zago L, Petit L, Mazoyer B, Tzourio-Mazoyer N. Revisiting human hemispheric specialization with neuroimaging. Trends Cogn Sci 2013; 17(2): 69-80.

Hickok G, Poeppel D. The cortical organization of speech processing. Nat Rev Neurosci 2007; 8(5): 393-402.

Hillis AE, Newhart M, Heidler J, Barker PB, Herskovits EH, Degaonkar M. Anatomy of spatial attention: insights from perfusion imaging and hemispatial neglect in acute stroke. J Neurosci 2005; 25(12): 3161-7.

Hocking J, Dzafic I, Kazovsky M, Copland DA. NESSTI: norms for environmental sound stimuli. PloS one 2013; 8(9): e73382.

Holodny AI, Schulder M, Ybasco A, Liu W-C. Translocation of Broca's area to the contralateral hemisphere as the result of the growth of a left inferior frontal glioma. J Comput Assist Tomogr 2002; 26(6): 941-3.

Howard D, Swinburn K, Porter G. Putting the CAT out: What the Comprehensive Aphasia Test has to offer. Aphasiology 2010; 24(1): 56-74.

Huettel SA, Song AW, McCarthy G. Functional Magnetic Resonance Imaging. 2nd edition ed. Sunderland, MA: Sinauer Associates Inc; 2008.

Hugdahl K. Fifty years of dichotic listening research - still going and going and. Brain Cogn 2011; 76(2): 211-3.

Hwang K, Velanova K, Luna B. Strengthening of top-down frontal cognitive control networks underlying the development of inhibitory control: a functional magnetic resonance imaging effective connectivity study. J Neurosci 2010; 30(46): 15535-45.

Ilves P, Tomberg T, Kepler J, Laugesaar R, Kaldoja M-L, Kepler K*, et al.* Different Plasticity Patterns of Language Function in Children With Perinatal and Childhood Stroke. J Child Neurol 2013; 29(6): 756-64.

Indefrey P, Hagoort P, Herzog H, Seitz RJ, Brown CM. Syntactic processing in left prefrontal cortex is independent of lexical meaning. NeuroImage 2001; 14(3): 546-55.

James TW, Gauthier I. Brain areas engaged during visual judgments by involuntary access to novel semantic information. Vision Res 2004; 44(5): 429-39.

Jefferies E. The neural basis of semantic cognition: converging evidence from neuropsychology, neuroimaging and TMS. Cortex 2013; 49(3): 611-25.

Jefferies E, Lambon Ralph MA. Semantic impairment in stroke aphasia versus semantic dementia: a case-series comparison. Brain 2006; 129(Pt 8): 2132-47.

Jeon HA, Anwander A, Friederici AD. Functional network mirrored in the prefrontal cortex, caudate nucleus, and thalamus: high-resolution functional imaging and structural connectivity. J Neurosci 2014; 34(28): 9202-12.

Joanette Y, Lecours AR, Lepage Y, Lamoureux M. Language in right-handers with right-hemisphere lesions: A preliminary study including anatomical, genetic, and social factors. Brain Lang 1983; 20(2): 217-48.

Joanisse MF, Gati JS. Overlapping neural regions for processing rapid temporal cues in speech and nonspeech signals. NeuroImage 2003; 19(1): 64-79.

Johns CL, Tooley KM, Traxler MJ. Discourse Impairments Following Right Hemisphere Brain Damage: A Critical Review. Lang Linguist Compass 2008; 2(6): 1038-62.

Johnson AF, Vikingstad EM, Cao Y, Thomas AJ, Malik GM, Welch KMA. Language Hemispheric Dominance in Patients with Congenital Lesions of Eloquent Brain. Neurosurgery 2000; 47(3): 562-70.

Jonides J, Smith EE, Koeppe RA, Awh E, Minoshima S, Mintun MA. Spatial working memory in humans as revealed by PET. Nature 1993; 363(6430): 623-5.

Josse G, Kherif F, Flandin G, Seghier ML, Price CJ. Predicting language lateralization from gray matter. J Neurosci 2009; 29(43): 13516-23.

Jung-Beeman M. Bilateral brain processes for comprehending natural language. Trends Cogn Sci 2005; 9(11): 512-8.

Jung J, Lambon Ralph MA. Mapping the Dynamic Network Interactions Underpinning Cognition: A cTBS-fMRI Study of the Flexible Adaptive Neural System for Semantics. Cereb Cortex 2016; 26(8): 3580-90.

Just MA, Carpenter PA, Keller TA, Eddy WF, Thulborn KR. Brain activation modulated by sentence comprehension. Science 1996; 274(5284): 114-6.

Karbe H, Thiel A, Weber-Luxenburger G, Kessler J, Herholz K, Heiss WD. Reorganization of the cerebral cortex in post stroke aphasia studied with positron emission tomography. Neurology 1998; 50(4): A321-A.

Keller SS, Highley JR, Garcia-Finana M, Sluming V, Rezaie R, Roberts N. Sulcal variability, stereological measurement and asymmetry of Broca's area on MR images. J Anat 2007; 211(4): 534-55.

Ketteler D, Kastrau F, Vohn R, Huber W. The subcortical role of language processing. High level linguistic features such as ambiguity-resolution and the human brain; an fMRI study. NeuroImage 2008; 39(4): 2002-9.

Key-DeLyria SE, Altmann LJP. Executive Function and Ambiguous Sentence Comprehension. Am J Speech Lang Pathol 2016; 25(2): 252-67.

Kielar A, Deschamps T, Jokel R, Meltzer JA. Functional reorganization of language networks for semantics and syntax in chronic stroke: Evidence from MEG. Hum Brain Mapp 2016; 37(8): 2869-93.

Kimura D. Functional Asymmetry of the Brain in Dichotic Listening. Cortex 1967; 3(2): 163-78.

Kimura D. From ear to brain. Brain Cogn 2011; 76(2): 214-7.

Klarborg B, Skak Madsen K, Vestergaard M, Skimminge A, Jernigan TL, Baaré WFC. Sustained attention is associated with right superior longitudinal fasciculus and superior parietal white matter microstructure in children. Hum Brain Mapp 2013; 34(12): 3216-32.

Knecht S, Deppe M, Drager B, Bobe L, Lohmann H, Ringelstein E, et al. Language lateralization in healthy right-handers. Brain 2000a; 123 (Pt 1): 74-81.

Knecht S, Drager B, Deppe M, Bobe L, Lohmann H, Floel A, et al. Handedness and hemispheric language dominance in healthy humans. Brain 2000b; 123 Pt 12: 2512-8.

Knecht S, Floel A, Drager B, Breitenstein C, Sommer J, Henningsen H, et al. Degree of language lateralization determines susceptibility to unilateral brain lesions. Nat Neurosci 2002; 5(7): 695-9.

Koechlin E, Jubault T. Broca's Area and the Hierarchical Organization of Human Behavior. Neuron 2006; 50(6): 963-74.

Kokubo K, Suzuki K, Hattori N, Miyai I, Mori E. Executive Dysfunction in Patients with Putaminal Hemorrhage. J Stroke Cerebrovasc Dis 2015; 24(9): 1978-85.

Kraut MA, Kremen S, Moo LR, Segal JB, Calhoun V, Hart J, Jr. Object activation in semantic memory from visual multimodal feature input. J Cogn Neurosci 2002; 14(1): 37-47.

Kuperberg GR, McGuire PK, Bullmore ET, Brammer MJ, Rabe-Hesketh S, Wright IC, et al. Common and distinct neural substrates for pragmatic, semantic, and syntactic processing of spoken sentences: an fMRI study. J Cogn Neurosci 2000; 12(2): 321-41.

Kutas M, Federmeier KD. Thirty years and counting: finding meaning in the N400 component of the event-related brain potential (ERP). Annu Rev Psychol 2011; 62: 621-47.

Lai V, van Dam W, Conant LL, Binder J, Desai RH. Familiarity differentially affects right hemisphere contributions to processing metaphors and literals. Front Hum Neurosci 2015; 9.

Lambon Ralph MA, Jefferies E, Patterson K, Rogers TT. The neural and computational bases of semantic cognition. Nat Rev Neurosci 2017; 18(1): 42-55.

Lambon Ralph, M, Lambon, RMA, Fillingham, JK, Meyer, A (ed.), Wheeldon, LR (ed.) & Krott, A (ed.).The importance of memory and executive function in aphasia: evidence from the treatment of anomia using errorless and errorful learning. in Automaticity and control in language processing. Psychology Press, Hove; 2007. pp. 193-216.

Liégeois F, Connelly A, Cross JH, Boyd SG, Gadian DG, Vargha-Khadem F*, et al.* Language reorganization in children with early-onset lesions of the left hemisphere: an fMRI study. Brain 2004; 127(6): 1229-36.

Li Y, Li P, Yang QX, Eslinger PJ, Sica CT, Karunanayaka P. Lexical-Semantic Search Under Different Covert Verbal Fluency Tasks: An fMRI Study. Front Behav Neurosci 2017; 11(131).

Lindell AK. In your right mind: right hemisphere contributions to language processing and production. Neuropsychol Rev 2006; 16(3): 131-48.

Llano DA. Functional imaging of the thalamus in language. Brain Lang 2013; 126(1): 62-72.

Lorca-Puls DL, Gajardo-Vidal A, White J, Seghier ML, Leff AP, Green DW, et al. The impact of sample size on the reproducibility of voxel-based lesion-deficit mappings. Neuropsychologia 2018; 115: 101-11.

Mah YH, Husain M, Rees G, Nachev P. Human brain lesion-deficit inference remapped. Brain 2014; 137: 2522-31.

Marien P, Paghera B, Dedeyn P, Vignolo L. Adult Crossed Aphasia in Dextrals Revisited. Cortex 2004; 40(1): 41-74.

Marklund P, Persson J. Context-dependent switching between proactive and reactive working memory control mechanisms in the right inferior frontal gyrus. NeuroImage 2012; 63(3): 1552-60.

Mason RA, Just MA. Lexical ambiguity in sentence comprehension. Brain Research 2007; 1146: 115-27.

Matchin W, Hickok G. 'Syntactic Perturbation' During Production Activates the Right IFG, but not Broca's Area or the ATL. Front Psychol 2016; 7: 241.

McDermott KB, Petersen SE, Watson JM, Ojemann JG. A procedure for identifying regions preferentially activated by attention to semantic and phonological relations using functional magnetic resonance imaging. Neuropsychologia 2003; 41(3): 293-303.

McGettigan C, Warren JE, Eisner F, Marshall CR, Shanmugalingam P, Scott SK. Neural correlates of sublexical processing in phonological working memory. J Cogn Neurosci 2011; 23(4): 961-77.

McNeil MR, Pratt SR. Defining aphasia: Some theoretical and clinical implications of operating from a formal definition. Aphasiology 2001; 15(10-11): 901-11.

Mechelli A, Friston KJ, Price CJ. The effects of presentation rate during word and pseudoword reading: A comparison of PET and fMRI. J Cogn Neurosci 2000; 12: 145-56.

Mechelli A, Henson RNA, Price CJ, Friston KJ. Comparing event-related and epoch analysis in blocked design fMRI. NeuroImage 2003; 18(3): 806-10.

Meltzer JA, McArdle JJ, Schafer RJ, Braun AR. Neural aspects of sentence comprehension: syntactic complexity, reversibility, and reanalysis. Cereb Cortex 2010; 20(8): 1853-64.

Meltzer JA, Wagage S, Ryder J, Solomon B, Braun AR. Adaptive significance of right hemisphere activation in aphasic language comprehension. Neuropsychologia 2013; 51(7): 1248-59.

Mesulam MM. The human frontal lobes: transcending the default mode through contingent encoding. In: RT SDK, editor. Principles of frontal lobe functioning: Oxford: Oxford University Press; 2002. p. 8-30.

Meunier D, Stamatakis EA, Tyler LK. Age-related functional reorganization, structural changes, and preserved cognition. Neurobiol Aging 2014; 35(1): 42-54.

Meyer M, Alter K, Friederici AD, Lohmann G, von Cramon DY. FMRI reveals brain regions mediating slow prosodic modulations in spoken sentences. Hum Brain Mapp 2002; 17(2): 73-88.

Meyer M, Friederici AD, von Cramon DY. Neurocognition of auditory sentence comprehension: event related fMRI reveals sensitivity to syntactic violations and task demands. Brain Res Cogn Brain Res 2000; 9(1): 19-33.

Meyer M, Steinhauer K, Alter K, Friederici AD, von Cramon DY. Brain activity varies with modulation of dynamic pitch variance in sentence melody. Brain Lang 2004; 89(2): 277-89.

Meyer PT, Sturz L, Schreckenberger M, Spetzger U, Meyer GF, Setani KS, et al. Preoperative mapping of cortical language areas in adult brain tumour patients using PET and individual non-normalised SPM analyses. Eur J Nucl Med Mol Imaging 2003; 30(7): 951-60.

Minzenberg MJ, Laird AR, Thelen S, Carter CS, Glahn DC. Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. Arch Gen Psychiatry 2009; 66(8): 811-22.

Mitchell AS. The mediodorsal thalamus as a higher order thalamic relay nucleus important for learning and decision-making. Neurosci Biobehav Rev 2015; 54: 76-88.

Mitchell AS, Baxter MG, Gaffan D. Dissociable Performance on Scene Learning and Strategy Implementation after Lesions to Magnocellular Mediodorsal Thalamic Nucleus. J Neurosci 2007; 27(44): 11888-95.

Mitchell AS, Chakraborty S. What does the mediodorsal thalamus do? Front Syst Neurosci 2013; 7: 37.

Mohr B, Difrancesco S, Harrington K, Evans S, Pulvermuller F. Changes of right-hemispheric activation after constraint-induced, intensive language action therapy in chronic aphasia: fMRI evidence from auditory semantic processing. Front Hum Neurosci 2014; 8: 919.

Monchi O, Petrides M, Petre V, Worsley K, Dagher A. Wisconsin Card Sorting Revisited: Distinct Neural Circuits Participating in Different Stages of the

Task Identified by Event-Related Functional Magnetic Resonance Imaging. J Neurosci 2001; 21(19): 7733.

Mugler JP, Brookeman JR. Three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE). Magn Reson Med 1990; 15(1): 152-7.

Mummery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR. A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. Ann Neuro 2000; 47(1): 36-45.

Murteira A, Santos ME. Language processing in right hemisphere stroke patients: Response speed and quality. Aphasiology 2013; 27(2): 145-56.

Myers PS. Right Hemisphere Damage: Disorders of Communication and Cognition. San Diego, CA: Singular Publishing Group, Inc; 1999.

Nagel BJ, Herting MM, Maxwell EC, Bruno R, Fair D. Hemispheric lateralization of verbal and spatial working memory during adolescence. Brain Cogn 2013; 82(1): 58-68.

Neef NE, Anwander A, Butfering C, Schmidt-Samoa C, Friederici AD, Paulus W, et al. Structural connectivity of right frontal hyperactive areas scales with stuttering severity. Brain 2018; 141(1): 191-204.

Neef NE, Bütfering C, Anwander A, Friederici AD, Paulus W, Sommer M. Left posterior-dorsal area 44 couples with parietal areas to promote speech fluency, while right area 44 activity promotes the stopping of motor responses. NeuroImage 2016; 142(15): 628-44.

Newsome MR, Durgerian S, Mourany L, Scheibel RS, Lowe MJ, Beall EB, et al. Disruption of caudate working memory activation in chronic blast-related traumatic brain injury. NeuroImage Clin 2015; 8(8): 543-53.

Nielsen JA, Zielinski BA, Ferguson MA, Lainhart JE, Anderson JS. An evaluation of the left-brain vs. right-brain hypothesis with resting state functional connectivity magnetic resonance imaging. PloS one 2013; 8(8): e71275.

Noonan KA, Jefferies E, Visser M, Lambon Ralph MA. Going beyond inferior prefrontal involvement in semantic control: evidence for the additional contribution of parietal and posterior middle temporal cortex. J Cogn Neurosci 2013; 25(11): 1824-50

Oberhuber M, Hope TM, Seghier ML, Parker Jones O, Prejawa S, Green DW*, et al.* Four Functionally Distinct Regions in the Left Supramarginal Gyrus Support Word Processing. Cereb Cortex 2016; 26: 4212-26

Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. Neuropsychologia 1971; 9(1): 97-113.

Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. Hum Brain Mapp 2005; 25(1): 46-59.

Papanicolaou AC, Moore BD, Levin HS, Eisenberg HM. Evoked potential correlates of right hemisphere involvement in language recovery following stroke. Arch Neurol 1987; 44(5): 521-4.

Parnaudeau S, Bolkan SS, Kellendonk C. The Mediodorsal Thalamus: An Essential Partner of the Prefrontal Cortex for Cognition. Biol Psychiatry 2018; 83(8): 648-56.

Parnaudeau S, O'Neill P-K, Bolkan Scott S, Ward Ryan D, Abbas Atheir I, Roth Bryan L, et al. Inhibition of Mediodorsal Thalamus Disrupts Thalamofrontal Connectivity and Cognition. Neuron 2013; 77(6): 1151-62.

Parnaudeau S, Taylor K, Bolkan SS, Ward RD, Balsam PD, Kellendonk C. Mediodorsal Thalamus Hypofunction Impairs Flexible Goal-Directed Behavior. Biol Psychiatry 2015; 77(5): 445-53.

Patterson K, Nestor PJ, Rogers TT. Where do you know what you know? The representation of semantic knowledge in the human brain. Nat Rev Neurosci 2007; 8: 976.

Pedersen PM, Jorgensen HS, Nakayama H, Raaschou HO, Olsen TS. Aphasia in acute stroke: incidence, determinants, and recovery. Ann Neuro 1995; 38(4): 659-66.

Pedersen PM, Vinter K, Olsen TS. Aphasia after stroke: type, severity and prognosis. The Copenhagen aphasia study. Cerebrovasc Dis 2004; 17(1): 35-43.

Pergola G, Danet L, Pitel A-L, Carlesimo GA, Segobin S, Pariente J, et al. The Regulatory Role of the Human Mediodorsal Thalamus. Trends Cogn Sci 2018; 22(11): 1011-25.

Persson J, Nyberg L, Lind J, Larsson A, Nilsson LG, Ingvar M, Buckner RL. Structure–Function Correlates of Cognitive Decline in Aging. Cereb Cortex 2005; 16(7): 907-15.

Poeppel D, Guillemin A, Thompson J, Fritz J, Bavelier D, Braun AR. Auditory lexical decision, categorical perception, and FM direction discrimination differentially engage left and right auditory cortex. Neuropsychologia 2004; 42(2): 183-200.

Poldrack RA, Wagner AD, Prull MW, Desmond JE, Glover GH, Gabrieli JD. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. NeuroImage 1999; 10(1): 15-35.

Powell HWR, Parker GJM, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CAM, et al. Hemispheric asymmetries in language-related pathways: a combined functional MRI and tractography study. NeuroImage 2006; 32(1): 388-99.

Price CJ. A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. NeuroImage 2012; 62(2): 816-47.

Price CJ, Crinion JT, Leff AP, Richardson FM, Schofield TM, Prejawa S, et al. Lesion sites that predict the ability to gesture how an object is used. Arch Ital Biol 2010a; 148(3): 243-58.

Price CJ, Hope TM, Seghier ML. Ten problems and solutions when predicting individual outcome from lesion site after stroke. NeuroImage 2017; 145(Pt B): 200-8.

Price CJ, Seghier ML, Leff AP. Predicting language outcome and recovery after stroke: the PLORAS system. Nat Rev Neurol 2010b; 6(4): 202-10.

Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. Ann N Y Acad Sci 1977; 299: 355-69.

Raven J. Raven Progressive Matrices. In: McCallum RS, editor. Handbook of Nonverbal Assessment. Boston, MA: Springer US; 2003. p. 223-37.

Ravizza SM, Behrmann M, Fiez JA. Right parietal contributions to verbal working memory: spatial or executive? Neuropsychologia 2005; 43(14): 2057-67.

Reuter-Lorenz PA. New visions of the aging mind and brain. Trends Cogn Sci 2002; 6(9): 394-400.

Reuter-Lorenz PA, Jonides J, Smith EE, Hartley A, Miller A, Marshuetz C*, et al.* Age Differences in the Frontal Lateralization of Verbal and Spatial Working Memory Revealed by PET. J Cogn Neurosci 2000; 12(1): 174-87.

Rice GE, Lambon Ralph MA, Hoffman P. The Roles of Left Versus Right Anterior Temporal Lobes in Conceptual Knowledge: An ALE Meta-analysis of 97 Functional Neuroimaging Studies. Cereb Cortex 2015; 25(11): 4374-91.

Richardson FM, Thomas MS, Price CJ. Neuronal activation for semantically reversible sentences. J Cogn Neurosci 2010; 22(6): 1283-98.

Ringman JM, Saver JL, Woolson RF, Clarke WR, Adams HP. Frequency, risk factors, anatomy, and course of unilateral neglect in an acute stroke cohort. Neurology 2004; 63(3): 468-74.

Rogalsky C, LaCroix AN, Chen K-H, Anderson SW, Damasio H, Love T, et al. The Neurobiology of Agrammatic Sentence Comprehension: A Lesion Study. J Cogn Neurosci 2018; 30(2): 234-55.

Rogalsky C, Poppa T, Chen K-H, Anderson SW, Damasio H, Love T, et al. Speech repetition as a window on the neurobiology of auditory-motor integration for speech: A voxel-based lesion symptom mapping study. Neuropsychologia 2015; 71: 18-27.

Roland D, Dick F, Elman JL. Frequency of Basic English Grammatical Structures: A Corpus Analysis. J Mem Lang 2007; 57(3): 348-79.

Rorden C, Karnath H-O, Bonilha L. Improving lesion-symptom mapping. J Cogn Neurosci 2007; 19(7): 1081-8.

Saalmann YB, Kastner S. The cognitive thalamus. Front Syst Neurosci 2015; 9: 39.

Saffran EM, Schwartz MF, Linebarger MC. Semantic influences on thematic role assignment: evidence from normals and aphasics. Brain Lang 1998; 62(2): 255-97.

Salmon E, Van der Linden M, Collette F, Delfiore G, Maquet P, Degueldre C, et al. Regional brain activity during working memory tasks. Brain 1996; 119 (Pt 5): 1617-25.

Saur D, Ronneberger O, Kummerer D, Mader I, Weiller C, Kloppel S. Early functional magnetic resonance imaging activations predict language outcome after stroke. Brain 2010; 133(Pt 4): 1252-64.

Schlosser R, Hunsche S, Gawehn J, Grunert P, Vucurevic G, Gesierich T, et al. Characterization of BOLD-fMRI signal during a verbal fluency paradigm in patients with intracerebral tumors affecting the frontal lobe. Magn Reson Imaging 2002; 20(1): 7-16.

Schmahmann JD, Pandya DN. Disconnection syndromes of basal ganglia, thalamus, and cerebrocerebellar systems. Cortex 2008; 44(8): 1037-66.

Sebastian A, Jung P, Neuhoff J, Wibral M, Fox PT, Lieb K, et al. Dissociable attentional and inhibitory networks of dorsal and ventral areas of the right inferior frontal cortex: a combined task-specific and coordinate-based meta-analytic fMRI study. Brain Struct Funct 2016; 221(3): 1635-51.

Seghier ML, Kherif F, Josse G, Price CJ. Regional and hemispheric determinants of language laterality: implications for preoperative fMRI. Hum Brain Mapp 2011; 32(10): 1602-14.

Seghier ML, Patel E, Prejawa S, Ramsden S, Selmer A, Lim L, et al. The PLORAS Database: A data repository for Predicting Language Outcome and Recovery After Stroke. NeuroImage 2016; 124(Pt B): 1208-12.

Seghier ML, Ramlackhansingh A, Crinion J, Leff AP, Price CJ. Lesion identification using unified segmentation-normalisation models and fuzzy clustering. NeuroImage 2008; 41(4): 1253-66.

Shallice T, Burgess PW. Deficits in strategy application following frontal lobe damage in man. Brain 1991; 114 (Pt 2): 727-41.

Shibahara N. Picture-Name Priming in the Cerebral Hemispheres: Evidence for Phonological Access in the Right Hemisphere. Percept Mot Skills 2004; 99(1): 305-14.

Shinoura N, Suzuki Y, Yamada R, Tabei Y, Saito K, Yagi K. Damage to the right superior longitudinal fasciculus in the inferior parietal lobe plays a role in spatial neglect. Neuropsychologia 2009; 47(12): 2600-3.

Shulman GL, Pope DLW, Astafiev SV, McAvoy MP, Snyder AZ, Corbetta M. Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. J Neurosci 2010; 30(10): 3640-51.

Skeel RL, Crosson B, Nadeau SE, Algina J, Bauer RM, Fennell EB. Basal ganglia dysfunction, working memory, and sentence comprehension in patients with Parkinson's disease. Neuropsychologia 2001; 39(9): 962-71.

Sollmann N, Tanigawa N, Ringel F, Zimmer C, Meyer B, Krieg SM. Language and its right-hemispheric distribution in healthy brains: an investigation by repetitive transcranial magnetic stimulation. NeuroImage 2014; 102 Pt 2: 776-88.

Sörös P, Sokoloff LG, Bose A, McIntosh AR, Graham SJ, Stuss DT. Clustered functional MRI of overt speech production. NeuroImage 2006; 32(1): 376-87.

Sperber C, Karnath HO. Topography of acute stroke in a sample of 439 right brain damaged patients. NeuroImage Clin 2016; 10: 124-8.

Sperber C, Karnath HO. Impact of correction factors in human brain lesion-behavior inference. Hum Brain Mapp 2017; 38(3): 1692-701.

Springer JA, Binder JR, Hammeke TA, Swanson SJ, Frost JA, Bellgowan PSF, et al. Language dominance in neurologically normal and epilepsy subjectsA functional MRI study. Brain 1999; 122(11): 2033-46.

Springer L, Mantey S. The Comprehensive Aphasia Test: A review. Commentary on Howard, Swinburn, and Porter, oPutting the CAT out: What the Comprehensive Aphasia Test has to offero. Aphasiology 2010; 24(1): 75-8.

Staudt M, Grodd W, Niemann G, Wildgruber D, Erb M, Krägeloh–Mann I. Early left periventricular brain lesions induce right hemispheric organization of speech. Neurology 2001; 57(1): 122.

Staudt M, Lidzba K, Grodd W, Wildgruber D, Erb M, Krägeloh-Mann I. Right-Hemispheric Organization of Language Following Early Left-Sided Brain Lesions: Functional MRI Topography. NeuroImage 2002; 16(4): 954-67.

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol 1935; 18: 643-62.

Stuss DT, Levine B, Alexander MP, Hong J, Palumbo C, Hamer L, et al. Wisconsin Card Sorting Test performance in patients with focal frontal and posterior brain damage: effects of lesion location and test structure on separable cognitive processes. Neuropsychologia 2000; 38(4): 388-402.

Swinburn K, Porter G, Howard D. Comprehensive Aphasia Test. Hove: Psychology Press; 2004.

Szczepanski SM, Knight RT. Insights into human behavior from lesions to the prefrontal cortex. Neuron 2014; 83(5): 1002-18.

Tan Y, Martin RC, Van Dyke JA. Semantic and Syntactic Interference in Sentence Comprehension: A Comparison of Working Memory Models. Front Psychol 2017; 8: 198.

Teasell R, Bayona NA, Bitensky J. Plasticity and reorganization of the brain post stroke. Top Stroke Rehabil 2005; 12(3): 11-26.

Tervaniemi M, Hugdahl K. Lateralization of auditory-cortex functions. Brain Res Brain Res Rev 2003; 43(3): 231-46.

Thiebaut de Schotten M, Kinkingnehun S, Delmaire C, Lehericy S, Duffau H, Thivard L, et al. Visualization of disconnection syndromes in humans. Cortex 2008; 44(8): 1097-103.

Thiebaut de Schotten M, Tomaiuolo F, Aiello M, Merola S, Silvetti M, Lecce F, et al. Damage to White Matter Pathways in Subacute and Chronic Spatial Neglect: A Group Study and 2 Single-Case Studies with Complete Virtual "In Vivo" Tractography Dissection. Cereb Cortex 2014; 24(3): 691-706.

Thiel A, Habedank B, Herholz K, Kessler J, Winhuisen L, Haupt WF, et al. From the left to the right: How the brain compensates progressive loss of language function. Brain Lang 2006a; 98(1): 57-65.

Thiel A, Habedank B, Winhuisen L, Herholz K, Kessler J, Haupt WF, et al. Essential language function of the right hemisphere in brain tumor patients. Ann NeuroJournal 2005; 57(1): 128-31.

Thiel A, Herholz K, Koyuncu A, Ghaemi M, Kracht LW, Habedank B, et al. Plasticity of language networks in patients with brain tumors: A positron emission tomography activation study. Ann Neuro 2001; 50(5): 620-9.

Thiel A, Schumacher B, Wienhard K, Gairing S, Kracht LW, Wagner R, et al. Direct Demonstration of Transcallosal Disinhibition in Language Networks. J Cereb Blood Flow Metab 2006b; 26(9): 1122-7.

Thompson-Schill SL, D'Esposito M, Aguirre GK, Farah MJ. Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A reevaluation. Proc Natl Acad Sci USA 1997; 94(26): 14792-7.

Thompson HE, Henshall L, Jefferies E. The role of the right hemisphere in semantic control: A case-series comparison of right and left hemisphere stroke. Neuropsychologia 2016; 85: 44-61.

Thompson HE, Jefferies E. Semantic control and modality: an input processing deficit in aphasia leading to deregulated semantic cognition in a single modality. Neuropsychologia 2013; 51(10): 1998-2015.

Tillema J-M, Byars AW, Jacola LM, Schapiro MB, Schmithorst VJ, Szaflarski JP*, et al.* Cortical reorganization of language functioning following perinatal left MCA stroke. Brain Lang 2008; 105(2): 99-111.

Toga AW, Thompson PM. Mapping brain asymmetry. Nat Rev Neurosci 2003; 4(1): 37-48.

Tombaugh TN. Trail Making Test A and B: Normative data stratified by age and education. Arch Clin Neuropsychol 2004; 19(2): 203-14.

Tompkins CA. Rehabilitation for cognitive-communication disorders in right hemisphere brain damage. Arch Phys Med Rehabil 2012; 93(1 Suppl): S61-9.

Tompkins CA, Blake MT, Wambaugh J, Meigh K. A novel, implicit treatment for language comprehension processes in right hemisphere brain damage: Phase I data. Aphasiology 2011; 25(6-7): 789-99.

Tompkins CA, Lehman MT, Wyatt AD, Schulz R. Functional outcome assessment of adults with right hemisphere brain damage. Semin Speech Lang 1998; 19(3): 303-21.

Tremblay P, Dick AS. Broca and Wernicke are dead, or moving past the classic model of language neurobiology. Brain Lang 2016; 162: 60-71.

Tremblay T, Monetta L, Joanette Y. Phonological processing of words in right- and left-handers. Brain Cogn 2004; 55(3): 427-32.

Tyler LK, Marslen-Wilson W, Stamatakis EA. Dissociating neuro-cognitive component processes: voxel-based correlational methodology. Neuropsychologia 2005; 43(5): 771-8.

Tyler LK, Shafto MA, Randall B, Wright P, Marslen-Wilson WD, Stamatakis EA. Preserving syntactic processing across the adult life span: the modulation of the frontotemporal language system in the context of age-related atrophy. Cereb Cortex 2010; 20(2): 352-64.

Tyler LK, Wright P, Randall B, Marslen-Wilson WD, Stamatakis EA. Reorganization of syntactic processing following left-hemisphere brain damage: does right-hemisphere activity preserve function? Brain 2010; 133(11): 3396-408.

Tyler LK, Marslen-Wilson WD, Randall B, Wright P, Devereux BJ, Zhuang J, et al. Left inferior frontal cortex and syntax: function, structure and behaviour in patients with left hemisphere damage. Brain 2011; 134(Pt 2): 415-31.

Van der Werf YD, Scheltens P, Lindeboom J, Witter MP, Uylings HB, Jolles J. Deficits of memory, executive functioning and attention following infarction in the thalamus; a study of 22 cases with localised lesions. Neuropsychologia 2003; 41(10): 1330-44.

Van Lancker DR, Kempler D. Comprehension of familiar phrases by left- but not by right-hemisphere damaged patients. Brain Lang 1987; 32(2): 265-77.

van Oers CA, Vink M, van Zandvoort MJ, van der Worp HB, de Haan EH, Kappelle LJ, et al. Contribution of the left and right inferior frontal gyrus in recovery from aphasia. A functional MRI study in stroke patients with preserved hemodynamic responsiveness. NeuroImage 2010; 49(1): 885-93.

Vargha-Khadem F, Isaacs E, Muter V. A Review of Cognitive Outcome After Unilateral Lesions Sustained During Childhood. J Child Neurol 1994; 9: 2S67-2S73.

Vigneau M, Beaucousin V, Herve PY, Jobard G, Petit L, Crivello F, et al. What is right-hemisphere contribution to phonological, lexico-semantic, and sentence processing? Insights from a meta-analysis. NeuroImage 2011; 54(1): 577-93.

Viñas-Guasch N, Wu YJ. The role of the putamen in language: a meta-analytic connectivity modeling study. Brain Struct Funct 2017; 222(9): 3991-4004.

Visser M, Embleton KV, Jefferies E, Parker GJ, Ralph MAL. The inferior, anterior temporal lobes and semantic memory clarified: novel evidence from distortion-corrected fMRI. Neuropsychologia 2010; 48(6): 1689-96.

Warburton E, Price CJ, Swinburn K, Wise RJ. Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. J Neurol Neurosurg Psychiatry 1999; 66(2): 155-61.

Warburton E, Wise RJ, Price CJ, Weiller C, Hadar U, Ramsay S, et al. Noun and verb retrieval by normal subjects. Studies with PET. Brain 1996; 119 (Pt 1): 159-79.

Warren JE, Crinion JT, Lambon Ralph MA, Wise RJS. Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 2009; 132(Pt 12): 3428-42.

Watanabe Y, Funahashi S. Thalamic mediodorsal nucleus and working memory. Neurosci Biobehav Rev. 2012; 36(1): 134-42.

Wechsler D. Wechsler Intelligence Scale–Fourth Edition (WAIS-IV): Technical and interpretive manual. San Antonio, TX: Pearson; 2008.

Wernicke C. Lehrbuch der gehirnkrankheiten fur aerzte und studirende. Kassel Theodor Fischer 1881; 2: 229-42.

Westbrook C, Roth CK, Talbot J. MRI in Practice: Wiley; 2011.

Westerhausen R, Kompus K, Hugdahl K. Mapping hemispheric symmetries, relative asymmetries, and absolute asymmetries underlying the auditory laterality effect. NeuroImage 2014; 84: 962-70.

Willems RM, Frank SL, Nijhof AD, Hagoort P, van den Bosch A. Prediction During Natural Language Comprehension. Cereb Cortex 2016; 26(6): 2506-16.

Wingfield A, Grossman M. Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. J Neurophysiol 2006; 96(6): 2830-9.

Wlotko EW, Federmeier KD. Finding the right word: hemispheric asymmetries in the use of sentence context information. Neuropsychologia 2007; 45(13): 3001-14.

Woollams AM, J. Lindley L, Pobric G, Hoffman P. Laterality of anterior temporal lobe repetitive transcranial magnetic stimulation determines the degree of disruption in picture naming. Brain Struct Funct 2017; 222(8): 3749-59.

Worsley KJ, Evans AC, Marrett S, Neelin P. A three-dimensional statistical analysis for CBF activation studies in human brain. J Cereb Blood Flow Metab 1992; 12(6): 900-18.

Wright P, Stamatakis EA, Tyler LK. Differentiating hemispheric contributions to syntax and semantics in patients with left-hemisphere lesions. J Neurosci 2012; 32(24): 8149-57.

Xu J, Kemeny S, Park G, Frattali C, Braun A. Language in context: emergent features of word, sentence, and narrative comprehension. NeuroImage 2005; 25(3): 1002-15.

Ye Z, Zhou X. Executive control in language processing. Neurosci Biobehav Rev 2009; 33(8): 1168-77.

Yoon J, Campanelli L, Goral M, Marton K, Eichorn N, Obler LK. The effect of plausibility on sentence comprehension among older adults and its relation to cognitive functions. Exp Aging Res 2015; 41(3): 272-302.

Zaidel E. Auditory Vocabulary of the Right Hemisphere Following Brain Bisection or Hemidecortication. Cortex 1976; 12(3): 191-211.

Zaidel E. On multiple representations of the lexicon in the brain: the case of two hemispheres In: Studdart-Kennedy M, editor. Psychobiology of Language. Cambridge, MA: MIT Press; 1983. p. 105-25.

Zaidel E, Kasher A, Soroker N, Batori G, Giora R, Graves D. Hemispheric contributions to pragmatics. Brain Cogn 2000; 43(1-3): 438-43.

Zaidel E, Peters AM. Phonological encoding and ideographic reading by the disconnected right hemisphere: two case studies. Brain Lang 1981; 14(2): 205-34.

Zatorre RJ. Perceptual asymmetry on the dichotic fused words test and cerebral speech lateralization determined by the carotid sodium amytal test. Neuropsychologia 1989; 27(10): 1207-19.

Zysset S, Huber O, Ferstl E, von Cramon DY. The anterior frontomedian cortex and evaluative judgment: an fMRI study. NeuroImage 2002; 15(4): 983-91.