THE UNIVERSITY OF QUEENSLAND

AUSTRALIA

Neurophysiological Markers of Language Recovery in Subacute Stroke

Tracy Roxbury

Master of Science (Distinction)

A thesis submitted for the degree of Doctor of Philosophy at

The University of Queensland in 2016

School of Health and Rehabilitation Sciences

Abstract

Most patients with aphasia recover language function to some degree, but there is significant variability in the speed, nature, and extent of language recovery that occurs in the months following a stroke. Currently, there is no effective method available to predict how an individual with aphasia will recover. The most accurate predictors of recovery to date rely on global outcome measures which do not provide relevant information regarding recovery of symptoms that are targeted in therapy. The overall goal of this thesis was to examine whether language-related brain activity predicted recovery of specific symptoms in aphasia. The first aim was to gain a clearer understanding of the neural mechanisms which underpin word processing in healthy individuals. Brain activity associated with spoken word processing was investigated firstly in a group of healthy young adults, then in a healthy older cohort in order to ascertain whether task performance was preserved in ageing and if so, whether a preserved performance was underpinned by age-related changes in the neural mechanisms. The second main aim was to investigate the neural substrates which underpin language processing in the subacute (2-6 weeks) and chronic (6 months) phases of aphasia recovery and to determine whether the timing and extent to which these mechanisms are recruited contributes to a good or poor language outcome. An auditory lexical decision task with a novel pseudoword condition was employed to investigate language recovery mechanisms and was selected to ensure that patients with aphasia in the subacute stage would be able to perform the task with sufficient accuracy. The real word stimuli consisted of concrete and abstract items. The stimuli were presented in an event-related fMRI task to young healthy controls, older healthy controls, and patients with aphasia during the subacute and chronic phases post-stroke. A range of behavioural language measures was administered to all three cohorts and at both time points for patients with aphasia.

In the healthy young group, concrete words elicited increased activity in a widely distributed network of brain regions including bilateral angular gyrus (AG), left posterior cingulate and left dorsolateral prefrontal cortex, compared to abstract words. Meanwhile, no region showed increased activity for abstract compared to concrete words, rather differences were only observed in bilateral AG when abstract words were contrasted with pseudowords. In the healthy older group, region of interest (ROI) results identified that a preserved performance was associated with an altered pattern of left hemisphere activity in the inferior and middle frontal regions, the AG and the fusiform gyrus. Differences between the healthy older and healthy young group were identified in key language regions, with the left inferior frontal gyrus (IFG) showing increased activity for abstract and pseudowords compared to concrete words while increased activity in the left AG was observed in the younger group only.

In patients with aphasia at the subacute stage, there was a strong positive correlation between left posterior cingulate activity for pseudowords and improved spoken word comprehension at six months. Negative correlations were also observed between chronic spoken word comprehension and increased subacute left superior frontal gyrus (SFG) activity for pseudowords and increased right SFG activity for abstract > pseudowords. At the chronic time point, activity in left posterior cingulate for both concrete and abstract words continued to be positively correlated with single word comprehension but activity in right prefrontal regions for words > pseudowords was also positively correlated with improved spoken word comprehension.

The findings from this thesis demonstrate the potential of this paradigm to reliably elicit language-related neural activity associated with spoken word recognition in both healthy individuals and in post-stroke aphasia. Furthermore, this thesis demonstrates how the experimental paradigm can be employed successfully in subacute and chronic aphasia to identify neural mechanisms that underpin language recovery and to enhance our understanding of how involvement of these neural substrates changes over the course of recovery and relates to improved spoken word comprehension. While no distinct pattern emerged between the upregulation of right and left hemisphere mechanisms at specific stages of recovery, the results did show that mechanisms in both hemispheres contribute to improved language function. The positive involvement of left posterior cingulate at both time points suggests a key role in recovery that changes over time. While this region is commonly associated with the default mode network, its involvement in recovery observed here is consistent with alternative proposed roles in retrieval of semantic information and episodic memory operations. The negative relationship between subacute stage left SFG activity and recovery of spoken word comprehension, suggests less capacity for recovery when domain-general regions associated with cognitive control are recruited during lexical decision. This research broadens our understanding of the relationship between brain structure and function and the brain mechanisms which underpin improved language function following aphasic stroke and contributes to the growing body of evidence regarding potential predictors of aphasia recovery.

Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my research higher degree candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

I acknowledge that an electronic copy of my thesis must be lodged with the University Library and, subject to the policy and procedures of The University of Queensland, the thesis be made available for research and study in accordance with the Copyright Act 1968 unless a period of embargo has been approved by the Dean of the Graduate School.

I acknowledge that copyright of all material contained in my thesis resides with the copyright holder(s) of that material. Where appropriate I have obtained copyright permission from the copyright holder to reproduce material in this thesis.

Publications during candidature

Published Manuscripts

Roxbury, T., McMahon, K., & Copland, D.A. (2014). An fMRI study of concreteness effects in spoken word recognition. *Behavioral and Brain Functions* 10**,** 34. doi: 10.1186/1744-9081-10-34.

Roxbury, T., McMahon, K., Coulthard, A., & Copland, D.A. An fMRI Study of Concreteness Effects during Spoken Word Recognition in Aging. Preservation or Attenuation? *Frontiers in Aging Neuroscience*, 7, 240. doi:10.3389/fnagi.2015.00240.

Published Conference Abstracts

Roxbury, T., McMahon, K., Read, S., Henderson, R., Wong, A., Coulthard, A., Farrell, A., Burfein, P., Taubert, S., Buckley, R., McHenery, C., & Copland, D.A. (2013). *Neurophysiological Markers of Language Recovery in Subacute Stroke.* Paper presented at the 22nd Royal Brisbane and Women's Hospital Healthcare Symposium, Brisbane, Australia. October 14-18.

Roxbury, T., McMahon, K., & Copland, D.A. (2013). *An fMRI Study of Concreteness Effects in Auditory Lexical Decision.* Paper presented at the Society for the Neurobiology of Language, San Diego, USA. November 6-8.

Roxbury, T., McMahon, K., Coulthard, A., Buckley, R., McHenery, C., & Copland, D.A. (2013). *An fMRI study of concreteness effects in spoken word recognition.* Paper presented at the Society for Neuroscience, San Diego, USA. November 8-13.

Roxbury, T., McMahon, K., Read, S., Henderson, R., Wong, A., Coulthard, A., Farrell, A., Burfein, P., Taubert, S., Buckley, R., McHenery, C., & Copland, D.A. (2014). *Using fMRI to predict post-stroke aphasia recovery.* Paper presented at the SSA ASM Stroke 2014 Conference, Hamilton Island, Australia. July 30 –August 1.

Publications included in this thesis

Roxbury, T., McMahon, K., & Copland, D.A. (2014). An fMRI study of concreteness effects in spoken word recognition. *Behavioral and Brain Functions*, *23*(1), 102-132 – incorporated as Chapter 2.

Contributor	Statement of contribution
Roxbury, T (Candidate)	Study design (60%) Imaging and behavioural data collection (100%) Data analysis and interpretation (60%) Wrote the manuscript (100%)
McMahon, K	Study design (20%) Data analysis and interpretation (20%) Revising the manuscript (40%) Image acquisition and protocol (100%)
Copland, D	Study design (20%) Data analysis and interpretation (20%) Revising the manuscript (60%)

Roxbury, T., McMahon, K., Coulthard, A., & Copland, D.A. An fMRI study of concreteness effects during spoken word recognition in ageing. Preservation or attenuation? Frontiers in Aging Neuroscience, 7, 240 - incorporated as Chapter 3.

Contributor	Statement of contribution
Roxbury, T (Candidate)	Study design (60%) Imaging and behavioural data collection (100%) Data analysis and interpretation (60%) Wrote the manuscript (100%)
McMahon, K	Study design (20%) Data analysis and interpretation (20%) Revising the manuscript (40%) Image acquisition and protocol (100%)
Coulthard, A	Data analysis and interpretation (5%) Revising the manuscript (5%)
Copland, D	Study design (20%) Data analysis and interpretation (15%) Revising the manuscript (55%)

Contributions by others to the thesis

I would like to acknowledge and thank staff from the departments of Speech Pathology, Neurology and Medical Imaging at the Royal Brisbane and Women's Hospital for their contribution to data collection. In particular, I would like to acknowledge Ray Buckley and Christine McHenery for their expertise in acquiring the imaging data and for assisting me in ensuring that the stroke patients were comfortable and well looked after throughout the imaging session. I would also like to extend my thanks to Professor Coulthard for his expertise in reviewing all the research scans and to Dr Stephen Read for his valuable expertise in interpreting the scans and stroke admission data.

Statement of parts of the thesis submitted to qualify for the award of another degree

None.

Acknowledgements

'Restlessness is discontent and discontent is the first necessity of progress. Show me a thoroughly satisfied man and I will show you a failure' Thomas A. Edison. I first read this quote when I was studying my Masters in Language Pathology and it resonated with me. As a child I had always questioned and challenged, likely irritating many adults around me. This questioning nature continued into my adult life and permeated my careers in both education and health as I was often not satisfied with the status quo. So it was with a question that I first approached Professor David Copland in 2009. I had become increasingly frustrated at being unable to answer patient questions regarding their prognosis for language recovery. The evidence was limited and I was only able to provide vague indicators. It was unsatisfactory and I was not satisfied. I started looking for answers and heard about the innovative work Professor Copland was doing in neuroimaging and aphasia. A meeting was organised and the rest is history.

And so it is with the most sincere gratitude that I thank Professor Copland for listening to my disorganised ramblings in that first meeting with such sincerity and then for encouraging me to try to answer the question with this PhD. Your patience, good humour and academic brilliance has been inspirational and your respect of clinicians in our profession is admirable. When I look back over the past six years, I realise that I could never have predicted the depth of learning I would acquire, and whilst I now have many more questions than I have answers, I realise this is the life of a researcher and I am happy to be surrounded by individuals with the same sense of innate curiosity. And with this in mind, I also give my sincerest thanks to Associate Professor Katie McMahon. Your brilliant mind and love of zeros and ones is something to behold, as has been your infinite patience in guiding me through thoroughly unfamiliar subject areas. I feel very fortunate to have been given two such amazing supervisors; my yin and yang of supervision, both perfectly complimenting the other with me in the middle drinking in the knowledge from both of you. Without you, this PhD would never have been started or completed. Thank you so very much.

My sincerest thanks also to all the people who participated in the project. In particular, I am enormously grateful to the participants with aphasia who so willingly took part. I was humbled by your dedication and commitment to advancing aphasia research even though you were in a critical phase of recovery. The PhD would not have been possible without you or the support of your families.

I would also like to acknowledge my friends here in Brisbane, the NZ and the UK. Your constant friendship, good humour and camaraderie throughout this process has been the most welcome tonic. In particular I would like to thank Emma Benton for the numerous visits you have made to the Southern Hemisphere and for your love, warmth and generosity to the children. Joan, Daniel and Alex, completing a PhD with young children and no immediate family in Australia has at times been challenging and I thank you for stepping in, helping out and loving the children as your own. I would also like to acknowledge my dear friend Joanie whose positivity and resoluteness over the past year has been a reminder to me of what is truly important.

Of course, my most enormous heartfelt thanks go to my husband Matt and my three darling children. Matt, you have been the most loyal and supportive friend. You have never complained about being the solo parent and never once have you made me feel guilty for choosing to do this. On the contrary, your gentle encouragement and wise, pragmatic advice has been invaluable in helping me overcome seemingly insurmountable hurdles. Your belief in me has also been unfailing and I could not have completed this PhD without your generous support and understanding. Miranda, Miles and Dominic, during the time I have been working on the PhD, you yourselves have achieved many milestones, grown, lost and grown more teeth, and celebrated many birthdays. You have been my biggest, most adoring fans, never complaining when I worked late and always most gracious, understanding and forgiving when I returned home tired and low on patience. Your smiles, cuddles and kind words have enabled me to keep a balance and perspective throughout. You are growing into such confident, talented, beautiful young people and I am so very proud of you. My hope in return is that in the future you will recognise this achievement, that you will be proud of me also and that it will inspire you. And so to answer your refreshingly innocent question asked so frequently in the past year or so: “Have you finished your PhD today Mummy?”, “Yes my darlings, I have”.

I would also like to acknowledge and thank my family and in particular my mother and father for their constant, unwavering support and guidance. You always encouraged me to read, question, travel, be happy, and to fulfil my potential. Your advice to always seize any learning opportunity offered has been religiously followed. Throughout the PhD, I have often held you in my mind, particularly in those moments when self-doubt was highest. Mom, whenever I think of you I see your deft, nimble hands, busy with one of the numerous artistic pursuits that you were in the process of mastering or had already mastered. Whatever you chose to learn, you learnt to perfection and your patience and determination is so admirable and has been a true inspiration. To my pops, your strong, innate love and thirst for knowledge, and your zest for life is contagious. The success you have made of your own working career is testament to a brilliant, flexible and creative mind. Whenever I was struggling with motivation in my studies, you would gently persuade me to do a little more and before any important exam, you would always calm my fears by saying: “Just do your best, that's all I ask”. That phrase became ritualistic so that even when I was no longer living at home, I would have to ring you just to hear you say those words. So, with that in mind, I would like to dedicate this thesis to my most beloved parents. I know you are proud and I hope that you can see that in this thesis, I have done as you have always asked; I have truly done my best.

Keywords

aphasia, recovery, concrete, abstract, fMRI, neuroimaging

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 170204 Linguistic Processes 50%

ANZSRC code: 170101 Biological Psychology 50%

Fields of Research (FoR) Classification

FoR code: 1103 Clinical Sciences 10%

FoR code: 1109 Neurosciences 45%

FoR code: 1702 Cognitive Sciences 45%

Table of Contents

Abstract i

Declaration by author iii

Publications during candidature iv

Publications included in this thesis v

Contributions by others to the thesis vi

Statement of parts of the thesis submitted to qualify for the award of another degree vi

Acknowledgements vii

Keywords ix

Australian and New Zealand Standard Research Classifications (ANZSRC) ix

Fields of Research (FoR) Classification ix

Table of Contents x

List of Figures xvi

List of Tables xvii

List of Abbreviations xviii

1 Chapter One 1

Introduction 1

1.1 Theoretical Models of Spoken Word Comprehension 3

1.2 Concreteness Effects in Ageing 8

1.3 Aphasia 9

1.4 Aphasia Recovery 11

1.4.1 Stages of Recovery 11

1.4.2 Traditional Determinants of Recovery 12

1.4.2.1. Initial severity, lesion size and site. 12

1.4.2.2. Aphasia subtype. 13

1.5 Neuroimaging 14

1.5.1 Magnetic Resonance Imaging 14

1.5.2 Functional Magnetic Resonance Imaging 15
1.6 Neural Correlates of Spoken Word Comprehension 16
1.6.1 Neural Correlates of Concrete and Abstract Processing in Healthy Young Adults 18
1.6.2 Neural Correlates of Concrete and Abstract Processing in Healthy Older Adults 21
1.6.3 Neural Correlates of Concrete and Abstract Processing in Aphasia. 23
1.6.4 Neural Mechanisms of Recovery in Aphasia 25
1.6.4.1. Neurophysiological mechanisms. 25
1.6.4.2. Stages of recovery. 26
1.6.4.2.1. Acute stage. 26
1.6.4.2.2. Subacute stage. 28
1.6.4.2.3. Chronic stage 31
1.6.4.3. Longitudinal studies of neural recovery mechanisms. 32
1.7 Aims and Rationale for the Current Study 36
2 Chapter Two 40
An fMRI study of Concreteness Effects in Spoken Word Recognition 40
2.1 Abstract 41
2.2 Introduction 42
2.3 Methods 48
2.3.1 Materials 48
2.3.2 Participants 49
2.3.3 Procedure 50
2.3.4 Data Acquisition 52
2.3.5 Image Processing 52
2.3.6 Data Analysis 52
2.4 Results 54
2.4.1 Behavioural Results 54
2.4.2 Anatomical Region of Interest Analyses 55
2.4.3 Whole Brain Analyses 56
2.4.4 Summary of Results 58

2.5 Discussion 58

2.6 Conclusion 65

3 Chapter Three 66

An fMRI study of Concreteness Effects during Spoken Word Recognition in Ageing. Preservation or Attenuation? 66

3.1 Abstract 67

3.2 Introduction 68

3.3 Methods 73

3.3.1 Materials 73

3.3.2 Participants 74

3.3.3 Procedure 75

3.3.4 Data Acquisition 76

3.3.5 Image Processing 76

3.3.6 Behavioural Analysis 76

3.3.7 Imaging Data Analysis 77

3.4 Results 79

3.4.1 Participant Results 79

3.4.2 Behavioural Results 79

3.4.3 Region of Interest Analyses 80

3.4.4 Whole Brain Analyses 83

3.5 Discussion 84

4 Chapter Four 91

Brain Activity during Spoken Word Recognition in Subacute Aphasia 91

4.1 Introduction 91

4.2 Methods 97

4.2.1 Participants 97

4.2.2 Behavioural Assessment 98

4.2.3 fMRI Task 98

4.2.4 fMRI Procedure 99

4.2.5 Data Acquisition 100
4.2.6 Image Processing 100
4.2.7 In-Scanner Behavioural Analysis 101
4.2.8 Imaging Data Analysis 101
4.3 Results 103
4.3.1 Clinical Data 103
4.3.2 Behavioural Results 105
4.3.3 In-Scanner Behavioural Results 108
4.3.4 Region of Interest Analyses 109
4.3.4.1 ANOVA. 109
4.3.4.2 Mann-Whitney: group differences. 112
4.3.4.3 Correlational analyses. 112
4.3.5 Whole Brain Analyses 113
4.4 Discussion 114
5 Chapter Five 121
Neurophysiological Markers of Language Recovery in Subacute Stroke 121
5.1 Introduction 121
5.2 Methods 126
5.2.1 Participants 126
5.2.2 Behavioural Assessment 127
5.2.3 fMRI Task 127
5.2.4 fMRI Procedure 128
5.2.5 Data Acquisition 129
5.2.6 Image Processing 129
5.2.7 In-Scanner Behavioural Analysis 130
5.2.8 Imaging Data Analysis 130
5.3 Results 133
5.3.1 Clinical Data 133

5.3.2 Behavioural Results 136
5.3.3 In-Scanner Behavioural Results 142
5.3.4 Region of Interest Analyses 143
5.3.4.1 Two conditions (word – pseudoword). 143
5.3.4.1.1 Three group comparison (subacute, chronic, controls). 143
5.3.4.1.2 Two group comparison (subacute, chronic). 144
5.3.4.2 Three conditions (concrete, abstract, pseudoword). 144
5.3.4.2.1 Three group comparison (subacute, chronic, controls). 144
5.3.4.2.2 Two group comparison (subacute, chronic). 145
5.3.5 Region of Interest Correlational Analyses 146
5.3.5.1 Subacute ROI activity with chronic behavioural scores. 146
5.3.3.2 Subacute ROI activity with PMRI scores. 147
5.3.5.3 Chronic ROI activity with chronic behavioural scores. 147
5.3.5.4 Chronic ROI activity with PMRI scores. 148
5.3.6 Whole Brain Analyses 148
5.3.7 Whole Brain Correlational Analyses 150
5.3.7.1. Subacute whole brain activity correlated with chronic behavioural scores 150
5.3.7.2 Subacute whole brain activity correlated with PMRI scores. 151
5.3.7.3 Chronic whole brain activity correlated with chronic behavioural scores 151
5.3.7.4 Chronic whole brain activity correlated with PMRI scores. 152
5.4 Discussion 152
5.4.1 Relationship between Subacute Brain Activity and Language Recovery 153
5.4.2 Relationship between Chronic Brain Activity and Language Recovery 157
6 Chapter Six 163
Conclusion 163
6.1 Summary of Major Findings 163
6.1.1 Concreteness Effects and Spoken Word Recognition in Healthy Young Adults 164
6.1.2 Concreteness Effect and Spoken Word Recognition in Healthy Older Adults 165

6.1.3 Brain Activity during Auditory Lexical Decision Making in Subacute Stroke using fMRI 166

6.1.4 Using fMRI to Predict Post-Stroke Aphasia Recovery 168

6.2 Implications of Major Findings.. 171

6.2.1 Clinical Implications... 171

6.2.2 Mechanisms of Recovery 174

6.3 Limitations and Future Directions 176

6.4 Overall Conclusions.. 180

References.. 183

List of Figures

Figure 1. Schematic of spoken word comprehension stages. 5
Figure 2. Acquisition sequence for auditory lexical decision task. 51
Figure 3. Nine anatomical ROIs. 54
Figure 4. Percent signal change from the regions of interest. 56
Figure 5. Whole brain results. 57
Figure 6. Region of interest analysis. 82
Figure 7. Main effect of age. 84
Figure 8. Lesion overlap image. 103
Figure 9. Group by condition interaction in left IFG. Aphasic group and controls x 2 conditions (word 110
Figure 10. Group by condition interactions in two significant ROIs. Aphasic group and controls x 3 conditions (concrete, abstract and pseudoword). 111
Figure 11. Increases in mean signal with single word and sentence comprehension. 113
Figure 12. Significant clusters for the main effect of group. 114
Figure 13. Mean signal extracted from each ROI showing the directionality of the main effect of group. 114
Figure 14. Subacute lesion overlap image. 133
Figure 15. Chronic lesion overlap image. 134
Figure 16. Group by condition interaction in left PCC. Subacute, chronic, controls x 3 conditions (concrete, abstract and pseudoword). 145
Figure 17. Subacute mean signal with the chronic behavioural score from the CAT word subtest. 147
Figure 18. Chronic mean signal with chronic behavioural score of CAT word and CAT sentence subtests. 148
Figure 19. Main effect of group (subacute, chronic, control). 149
Figure 20. Axial slices for key regions in the main effect of group (subacute, chronic, control). ..150
Figure 21. Axial slices for key regions showing subacute brain activity correlated with PMRI scores. 151
Figure 22. Axial slices for key regions showing chronic whole brain activity correlated with chronic language performance scores. 152

List of Tables

Table 1. Summary statistics for the two stimulus conditions (Mean (SD)) for a range of variables, plus the significance from a *t*-test comparing conditions 49
Table 2. Behavioural results....................55
Table 3. Whole brain regions showing significant BOLD peak activation 57
Table 4. Mean reaction times for young and older adults....................79
Table 5. Region of interest - main effect of condition....................81
Table 6. Factorial results from whole brain analysis for main effects between young and older groups....................83
Table 7. Aphasic patient characteristics....................104
Table 8. Language assessment scores from the CAT and WAB-R 106
Table 9. Language assessment scores from the BNT, PALPA, Pyramids and Palm Trees test and ABA-2....................107
Table 10. Mean percent accuracy for aphasic patients and controls....................108
Table 11. Mean reaction times for aphasic patients and controls 109
Table 12. Regions of interest - main effect of condition (concrete – abstract – pseudoword), and post hoc results comparing conditions in each ROI....................110
Table 13. Factorial results from whole brain analysis for main effect of group between aphasic patients and controls....................113
Table 14. Aphasic patient characteristics....................135
Table 15. Subacute language assessment scores from the CAT and WAB-R....................137
Table 16. Chronic language assessment scores from the CAT and WAB-R....................138
Table 17. Subacute language assessment scores from the BNT, PALPA, Pyramids and Palm Trees test and ABA-2....................139
Table 18. Chronic language assessment scores from the BNT, PALPA, Pyramids and Palm Trees test and ABA-2....................140
Table 19. PMRI language scores from the CAT (word and sentence comprehension subtests and CAT overall score)....................141
Table 20. Mean accuracy values for aphasic patients and controls 142
Table 21. Mean reaction times for aphasic patients and controls....................143
Table 22. Factorial results from whole brain analysis for main effect of group between subacute, chronic aphasics and controls (GM masked) 149
Table 23. Subacute whole brain activity related to chronic language performance scores 150
Table 24. Subacute whole brain activity related to PMRI performance scores....................151
Table 25. Chronic whole brain activity related to chronic language performance scores....................152

List of Abbreviations

Ab	abstract
ABA–2	Apraxia Battery for Adults
ACC	anterior cingulate cortex
AG	angular gyrus
aMTG	anterior middle temporal gyrus
ANOVA	analysis of variance
APA	auditory phonological analysis
AQ	aphasia quotient
aSTG	anterior superior temporal gyrus
aSTS	anterior superior temporal sulcus
BA	Brodmann area
BNT	Boston Naming Test
BOLD	blood oxygen level dependant
CAT	Comprehensive Aphasia Test
CELEX	Centre for Lexical Information
Conc	concrete
DWI	diffusion weighted imaging
EHI	Edinburgh Handedness Inventory
EPI	echo planar imaging
F	female
FDR	false discovery rate
FLAIR	fluid-attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FOV	field of view
Fus	fusiform gyrus
FWE	family wise error
FWHM	full width at half maximum
g	gyrus
GM	grey matter
HAROLD	Hemispheric Asymmetry Reduction in Older Adults
HF	high frequency
HG	Heschl’s gyrus
HI	high imageability
HRF	haemodynamic response function
IFG	inferior frontal gyrus
Img	Imageability
IP	ischemic penumbra

IPC	inferior parietal cortex
ITG	inferior temporal gyrus
LF	low frequency
LI	low imageability
M	mean
M	male
MCA	middle cerebral artery
MFG	middle frontal gyrus
MMSE	Mini Mental State Examination
MNI	Montreal Neurological Institute
MP-RAGE	magnetisation prepared rapid gradient echo
MR	magnetic resonance
MRI	magnetic resonance imaging
MTG	middle temporal gyrus
NART	National Adult Reading Test
NIHSS	National Institute of Health Stroke Scale
Orb	pars orbitalis
P&PT	Pyramids and Palm Trees test
PACS	partial anterior circulation syndrome
Pars tri	pars triangularis
PALPA	Psycholinguistic Assessment of Language Processing in Aphasia
PCA	posterior cerebral artery
PCC	posterior cingulate cortex
PET	positron emission tomography
PFC	prefrontal cortex
PHG	parahippocampal gyrus
PIL	phonological input lexicon
PMRI	percentage maximal recovery or impairment
PND	phonological neighbourhood density
POCS	posterior circulation syndrome
PS	pseudoword
PWI	perfusion weighted imaging
R	raw score
RF	radiofrequency
RW	real word
RT	reaction time
ROI	region of interest
RSFC	resting state functional connectivity

SC	Striatocapsular
SD	standard deviation
SE	standard error
SFG	superior frontal gyrus
SMA	supplementary motor area
SMG	supramarginal gyrus
SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
SS	semantic system
STG	superior temporal gyrus
STS	superior temporal sulci
T	T-score
T1	longitudinal relaxation
T2	transverse relaxation
TE	echo time
TI	inversion time
TR	repetition time
VLSM	voxel-based lesion-symptom mapping
WAB-R	Western Aphasia Battery-Revised

1 Chapter One

Introduction

Recovery from post-stroke aphasia is highly variable and while most patients will go on to recover language function to some extent in the weeks and months following a stroke, the speed, nature and amount of recovery an individual will make is difficult to determine. There are currently no effective methods to predict potential for recovery from aphasia. The most accurate predictors of recovery are reliant on global outcome measures which do not provide relevant information regarding recovery of symptoms that are targeted in therapy. The present thesis will focus on the neural mechanisms which underpin spoken word recognition for concrete and abstract words and examine how these mechanisms drive recovery of particular symptoms in aphasia.

Definitive theories regarding the organisation and representation of semantic conceptual knowledge remain elusive. Comparisons between concrete and abstract word processing have proved useful in examining semantic processing in both healthy individuals and people with aphasia. The concreteness effect is a term used to describe a processing advantage in terms of reaction times and accuracy of responses for concrete (e.g. hospital) compared to abstract words (e.g. knowledge). While concreteness effects are present in the performance of both healthy and language impaired individuals, the effects are often more pronounced in aphasia (Coltheart, Patterson, & Marshall, 1980; Franklin, 1989; Goodglass, Hyde, & Blumstein, 1969; Jefferies, Patterson, Jones, & Lambon Ralph, 2009; Sandberg & Kiran, 2014). However, a reversal of concreteness effects has also been reported (Bonner et al., 2009; Breedin, Saffran, & Coslett, 1994; Kousta, Vigliocco, Vinson, Andrews, & Del Campo, 2011; Papagno, Capasso, Zerboni, & Miceli, 2007; Warrington, 1981) which has led to the suggestion that concrete and abstract processing is underpinned by different neural mechanisms.

Studies investigating the neural correlates of concreteness in healthy adults have found varying results although recent meta-analyses by Binder, Desai, Graves, and Conant (2009) and

Wang, Conder, Blitzer, and Shinkareva (2010) have demonstrated some consensus in the findings. Critically, most of the existing studies on concrete and abstract processing have investigated processing differences in healthy young adults and currently there are very few studies which have focused on concreteness effects in older adults and established whether the effects are preserved or attenuated with age, and whether performance is associated with an altered pattern of neural activation. Since most patients with aphasia will fall into the older age-range, the establishment of a baseline regarding neural activity in healthy older adults would seem essential if accurate comparisons are to be drawn about the language processes which underpin aphasia and language recovery.

Recently, a longitudinal study investigating improved language function in post-stroke aphasia showed that recovery is underpinned by distinct neural mechanisms which are implicated at different time points (Saur et al., 2006). While informative, the task selected to investigate recovery in this study proved difficult for many of the patients with aphasia, particularly in the very early acute stage, and this may have confounded the results. The task selection in studies investigating language processing mechanisms is of critical importance and it is essential that people with aphasia are presented with tasks that they can perform accurately and successfully in order that neural activity patterns that are elicited, primarily reflect the language process under investigation rather than other aspects of cognitive processing relating to task performance (Price & Friston, 2002). Longitudinal studies in aphasia recovery, which include an experimental task that patients in the early stages of post-stroke recovery are able to do, are therefore essential if an accurate understanding of the relationship between brain structure and function is to be obtained, although, it is also preferable that the task presented is not so easy that differences associated with performance at different time points cannot be observed (Fernandez et al., 2004). Critically, an enhanced understanding of the neural mechanisms which underpin aphasia recovery has valuable clinical implications and will not only be able to provide a more accurate predictor of an individual's potential for language recovery but may also have implications for the provision and direction of treatment in post-stroke aphasia.

The following review will consider how advances in neuroimaging techniques are contributing to an increased understanding of possible neural mechanisms that are implicated in concrete and abstract processing, changes associated with ageing, and the language recovery process in aphasia. In section 1.1, I begin by discussing cognitive neuropsychological models of spoken language processing, particularly with regard to concrete and abstract processing, and in section 1.2 the literature in ageing and semantic conceptual processing associated with concreteness effects is reviewed. In sections 1.3 and 1.4, I consider the phenomenon of aphasia and the traditional mechanisms of recovery in aphasia while section 1.5 provides a brief overview of neuroimaging and functional magnetic resonance imaging (fMRI). Section 1.6 reviews the neuroimaging literature as it pertains to spoken word processing (specifically with regard to concrete and abstract processing mechanisms) in healthy young and healthy older adults and in people with aphasia. Imaging research into the neural mechanisms of language recovery in aphasia is then considered. Finally, in section 1.7 the aims and rationale for this study are outlined.

1.1 Theoretical Models of Spoken Word Comprehension

The focus in this study is on spoken word comprehension and as such, this review will discuss two of the prominent cognitive neuropsychological theories regarding spoken word comprehension. In 1981, McClelland and Rumelhart designed a highly interactive model called TRACE which emphasised top-down processing whereby acoustic and phonetic information can be directly supported by contextual information. This model proposes a connectionist approach in which different processing units are connected and are activated simultaneously once the acoustic signal is heard (McClelland & Rumelhart, 1981). Activation is bi-directional and occurs along the connections until the target word is activated. Once selection occurs, inhibitory processes are initiated which prevent further competitors being selected (Harley, 2000).

An alternate theory of spoken word processing was proposed in the cohort model of Marslen-Wilson & Warren, subsequently revised many times (1973, 1975, 1987, 1994) in response to findings from experimental studies. In this model, cohorts of items eliminate themselves until a uniqueness point is reached (Marslen-Wilson, 1987). This is achieved via three interactive stages that all occur in parallel. In the first stage, acoustic representations make direct access to the lexicon and a cohort of items is activated. The second stage is the selection phase and this occurs in parallel to the first stage with a lexical item being selected once enough acoustic information has been provided and competitors to the target word have been discarded. This is the lexeme's *uniqueness point* and once this is reached all other linguistic information about the word becomes available. Lastly, the integration stage occurs and is where semantic and syntactic properties are incorporated (Marslen-Wilson & Warren, 1994; Marslen-Wilson, 1987). The most recent 1994 model is much more autonomous than the original model with top-down contextual effects only occurring at the integration (i.e. post-lexical) stage (Harley, 2000).

Language deficits observed in people with aphasia have continued to provide a rich source of evidence to either support or disprove theoretical language processing accounts. Whitworth, Webster, and Howard (2005) discuss three kinds of evidence that can be obtained from analysing aphasic language. The first, a 'critical variable approach' (Shallice, 1988) is where different variables such as word length, frequency and imageability affect performance on comprehension and production tasks. Lexicality, a term used to describe varying performance on real words and nonwords, may also be considered a critical variable. The second type of evidence can be obtained from analysing the nature of the errors made and hypothesising as to the loci of impairment, for instance, errors of imageability suggest a specific deficit in the semantic system. The third type of evidence can be gained by contrasting the performance on tasks that use common processing components. This can be done by either comparing performance of the same task across modalities or comparing the same task at different processing levels within a modality (Franklin, 1989). Typically, data obtained from people with aphasia is mapped onto processing models to identify the proposed loci of impairment and therapy is then targeted at the specific processing deficit. Below I consider spoken word processing impairments in people with aphasia and discuss how these symptoms can inform processing models.

Frauenfelder and Tyler (1987) proposed that there were three stages of spoken word comprehension with the first being initial contact, the second, lexical decision and the third, spoken word recognition. These three distinct phases are also present in current cognitive neuropsychological models which have been informed by patient data and are illustrated in Figure 1. During the initial auditory phonological analysis, speech sounds will be identified and an impairment at this level may cause 'pure word deafness' (Saffran, Marin, & Yeni-Komshian, 1976); that is a profound difficulty with spoken word comprehension in the presence of intact nonlinguistic, environmental sound recognition.

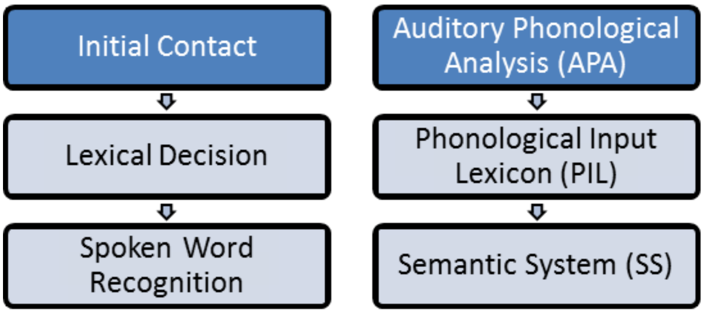

Figure 1. Schematic of spoken word comprehension stages.

The second level incorporates the phonological input lexicon (PIL) and this is where all known auditory word forms are stored. An impairment at this level would cause difficulties with the recognition of real words and the rejection of nonwords and is termed 'word form deafness'. Longer words may be more easily understood as they will have fewer phonological neighbours thus facilitating ease of retrieval (Howard & Franklin, 1988; Luce & Large, 2001). Evidence for an intermediate processing step between the PIL and the semantic system (SS) has also been seen in patients who have 'word meaning deafness'. This impairment occurs when a word is selected as a real word but is not able to be understood and this may be due to a weak drive from the PIL to the SS where the conceptual representations of words are stored. Again, longer words may be better understood here since the distinctiveness of a lexical item increases accessibility to the SS

(Franklin, Turner, Lambon Ralph, Morris, & Bailey, 1996).

The last processing stage to be activated during spoken comprehension is at the semantic system level. This system serves as the store for all word meanings and is activated once a word has been recognised. The semantic system itself can be further divided into progressive stages with more immediate implicit lexical semantics being activated upon initial recognition of a word, while deeper higher order explicit processing occurs when conceptual semantic representations need to be accessed in order to understand words such as is the case with superordinate category judgments (Zahn et al., 2000). Selective deficits of specific word types can also occur at this level and one such example of this is the processing advantage observed in people with aphasia for high imageability, concrete words compared to abstract words (Coltheart et al., 1980).

Processing differences between concrete and abstract words and how the semantic representations associated with these concepts are organised and represented in the brain has been widely investigated. Concrete words such as ‘hospital’ are usually associated with physical objects, have strong mental images and are grounded in sensory-motor experiential knowledge. In contrast, abstract words such as ‘knowledge’ refer to ideas or mental states that are more verbally encoded and are less readily associated with any mental imagery (Paivio, 2007). Imageability refers to the ease in accessing a mental image of a word and while it is generally highly correlated with concreteness, this is not always the case as is exemplified by the word ‘animal’ which whilst being concrete is also of low-imageability (Bedny & Thompson-Schill, 2006). As such, it is generally considered that highly imageable items contain some additional semantic information (Bedny & Thompson-Schill, 2006).

The concreteness effect is a term used to describe the processing advantage for concrete over abstract words. Previous studies have shown that concrete words are processed more accurately and faster than abstract words in healthy adults (Binder, Westbury, McKiernan, Possing, & Medler, 2005; James, 1975; Paivio, 1991, 2007) and in neurological patients with language deficits (Coltheart et al., 1980; Franklin, 1989; Goodglass et al., 1969; Jefferies et al., 2009;

Sandberg & Kiran, 2014). Other studies have reported the reverse behavioural effect, where abstract words have the processing advantage (Bonner et al., 2009; Breedin et al., 1994; Kousta et al., 2011; Papagno et al., 2007; Warrington, 1981) and this had fuelled debate around whether these conceptual representations may be stored independently and can be selectively impaired (Papagno, Fogliata, Catricalà, & Miniussi, 2009).

The two dominant and competing accounts of semantic memory used to explain concreteness effects are dual coding theory (Paivio, 1991) and the context availability theory (Schwanenflugel & Shoben, 1983) (refer to Chapter 2 for a full review). Briefly, dual coding theory proposes that selective processing occurs in a verbal and a nonverbal, perceptual coding system. Concrete and abstract words are both processed in the verbal system but concrete words also able to engage the nonverbal, imagery-based system and this ability to recruit a dual system results in increased efficiency and the concreteness effect (Paivio, 1991). The context availability theory also predicts a processing advantage for concrete words through more efficient processing but it is proposed that this is caused by the amount of available context associated with a word. Concrete words have a rich available context and have access to a greater network of contextual semantic associations compared to abstract words where meaning is derived mainly from verbal associations. This difference in available context therefore contributes to how efficiently a word will be processed and results in the observed concreteness effects (Schwanenflugel & Shoben, 1983).

Whilst the accounts are not necessarily mutually exclusive, differences between the models have concerned the underlying neural mechanisms which underpin concreteness effects. Dual coding theory proposes that abstract words and concrete words are processed in qualitatively distinct systems. While both word types engage the verbal system in the left hemisphere, concrete words also engage the nonverbal, imagery-based system in the right hemisphere resulting in a more bilateral representation (Binder et al., 2005; Paivio, 2007). In contrast, the context availability theory proposes quantitative differences in the verbal left hemisphere only, with concrete and abstract words engaging the same system but to different degrees according to the amount of available context associated with the word. Theories of semantic memory which combine neuroimaging and behavioural data have recently been developed to explain conceptual processing. Embodied abstraction is one such account (Binder & Desai, 2011) and proposes that conceptual knowledge is processed in modality specific and heteromodal convergence zones with the latter being located in temporal and parietal regions. The amount of perceptual and contextual information and the familiarity of a word will affect how it is processed (Binder & Desai, 2011). Thus, concrete words would be expected to elicit increased activity due to their richer set of conceptual features. Applying embodiment theories however to abstract word processing is more problematic (see Chapter 2 for a more detailed discussion). Recent studies have explored the semantic representations associated with abstract concepts (Kousta et al., 2011; Shallice & Cooper, 2013; Vigliocco, Meteyard, Andrews, & Kousta, 2009). Vigliocco et al. (2009) and Kousta et al. (2011) proposed an extended theory of embodiment which includes abstract words. In this framework concrete concepts are embodied through experiential sensorimotor knowledge while abstract words are embodied through both linguistic and the underlying affective and emotional experiential knowledge associated specifically with abstract words (Kousta et al., 2011; Vigliocco et al., 2009).

1.2 Concreteness Effects in Ageing

While deficits in word retrieval in healthy older adults are well documented (Burke & Shafto, 2004; Burke & Shafto, 2008) other language processes such as the knowledge of words (Verhaeghen, 2003) and comprehension of language do not seem to be as susceptible to effects of ageing (Tyler, Wright, Randall, Marslen-Wilson, & Stamatakis, 2010). It might be assumed therefore that concreteness effects and concrete and abstract processing would be preserved in healthy ageing. However, previous studies have reported conflicting findings. An increase in the concreteness effect has been demonstrated, (Rowe & Schnore, 1971; Witte & Freund, 1976) as has an attenuation of the effect (Rissenberg & Glanzer, 1987) but this may be attributed to reduced functionality in an underlying cognitive process, such as memory. Peters and Daum (2008) investigated verbal memory and concreteness effects in a cross-sectional study which included three different age groups (mean 21, 42 and 61 years) and demonstrated both preserved and attenuated effects. While in the three age groups concrete words were easier to recollect than abstract words, the effect was attenuated in the older age group. They attributed this attenuation of concreteness effects to the preserved recollection of abstract words which was present in the older group only (Peters & Daum, 2008). Critically, given that brain structure and function changes over the course of ageing, it is unclear whether any preserved functionality or attenuation of this effect in older adults is associated with the recruitment of different neural mechanisms when processing concrete and abstract words.

Cognitive function and the effects of ageing have been investigated in studies investigating differences in brain activity in young and older adults performing the same task (Cabeza, Anderson, Locantore, & McIntosh, 2002; Shafto & Tyler, 2014; Wingfield & Grossman, 2006) and findings have been considered alongside conceptual accounts of compensation (Reuter-Lorenz & Park, 2010) and dedifferentiation (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Lindenberger & Baltes, 1994; Reinert, 1970). The compensation view holds that in order to counteract age-related deficits and maintain preserved functionality, increased activity in additional brain regions serves as a strategic mechanism as processing becomes shared by multiple components (Cabeza et al., 2002; Cabeza et al., 1997). In comparison, the dedifferentiation view proposes that gradual changes in an ageing brain results in the loss of specialised function in distinct cortical regions and a move towards more generalised functionality resulting in increased, widespread activity in healthy older brains (Li & Lindenberger, 1999). This thesis will examine processing of concrete and abstract words in older adults considering these theories.

1.3 Aphasia

According to the Australian Government Productivity Commission, by 2059-2060 life expectancy for the average Australian is set to reach 89.1 years for men compared to approximately 80.3 years in 2012 and 91.4 years for women compared to around 84.6 years in 2012 (Productivity

Commission, 2013). The change in demographics will create new issues for Australia's public health system and healthcare provision. With an ageing population comes an increase in the medical conditions associated with older age including stroke. Stroke is a leading cause of disability and is currently the second main cause of death after coronary heart disease in Australia (ABS, 2014). It was estimated that in 2015 there would be approximately 50,000 new or recurrent strokes in Australia and a combined total of 440,000 Australians living with the effects of stroke (Deloitte Access Economics, 2014). In addition, around 65% of people living with stroke will also suffer some form of long term disability and in 2012, the fiscal amount associated with stroke care was an estimated $5 billion (Deloitte Access Economics, 2013).

Following a stroke, some people may experience an impairment of language function called 'aphasia'. Aphasia can affect speaking, understanding, reading and writing either selectively or in combination. Approximately one third of all stroke patients will experience some form of aphasia in the acute stages post-stroke with incidence rates ranging from 21% to 38% (Laska, Hellblom, Murray, Kahan, & Von Arbin, 2001; Pedersen, Jorgensen, Nakayama, Raaschou, & Olsen, 1995). Of those patients diagnosed with aphasia, over 60% will continue to have aphasia one year post onset (Pedersen et al., 1995; Pedersen, Vinter, & Olsen, 2004). The impact of aphasia cannot be underestimated. Aphasia can have a significant impact on a person's ability to participate in activities of daily living such as working or living independently (Price, Seghier, & Leff, 2010) and can also have a negative effect on a person's self-image which may lead to profound social isolation (Hillis, 1998).

The most frequently asked question by people with aphasia immediately following a stroke concerns their prognosis in terms of both spontaneous and treatment-induced recovery. Unfortunately, clinicians are ill-equipped to answer this question. One factor that has not been previously considered in depth is the underlying neural mechanisms that support language recovery.

1.4 Aphasia Recovery

As mentioned above, the recovery from aphasia following stroke is not predictable and varies considerably from patient to patient (Kertesz & McCabe, 1977; Lazar & Antoniello, 2008; Pedersen et al., 1995; Pedersen et al., 2004) yet the prognosis of recovery is of paramount importance to the person with aphasia. Most people with aphasia do make some degree of spontaneous recovery (Hillis, 2007; Pedersen et al., 1995) but the course of recovery is variable. Lazar and Antoniello (2008) suggest that the greatest amount of recovery happens in the first three months while Pedersen et al. (2004) suggests that 80% of expressive recovery occurs within the first two weeks and 95% within the first six weeks. However, even if we consider that the majority of spontaneous aphasia recovery occurs in the first three months post-stroke (Hillis, 2007; Szaflarski et al., 2011) the time course and degree of recovery is not predictable even in those patients who present with similar sites of lesion and types of aphasia. Below, I consider the various stages of recovery and some of the traditional factors that have been considered influential in the recovery of aphasia.

1.4.1 Stages of Recovery

Following a stroke, a patient will experience various stages of recovery. These stages are known as acute, subacute and chronic with distinct types of recovery occurring at each phase. The acute phase is experienced within the first 2 weeks following stroke onset and during this stage, language recovery is rapid due to physiological changes in neural plasticity, reduction in oedema and metabolic disturbances (Marsh & Hillis, 2006), as well as reperfusion of the ischaemic penumbra (Hillis et al., 2008; Kiran, 2012). The second stage of recovery is the subacute phase and this lasts until six months post-stroke. Recovery during this period is less rapid and consists of neural reorganisation, specifically, the establishment of alternative networks, synaptic remodelling and axonal sprouting (Lazar & Antoniello, 2008; Marsh & Hillis, 2008). The last stage of recovery is the chronic phase and once this stage is reached, recovery will have slowed considerably. Spontaneous recovery still continues to occur but any differences can be attributed primarily to compensatory reorganisation (Grafman & Litvan, 1999). As such, people with aphasia can learn new ways of accessing intact representations or use an alternative strategy to perform the same task even though neural reorganisation may no longer be occurring. From the above, it is clear that considerable physiological and neural changes are happening immediately post-stroke onset and continue well into the recovery period. Exactly how these neurophysiological changes correlate with language recovery is less clear and below I consider some of the variables that have traditionally been used to predict recovery from aphasia.

1.4.2 Traditional Determinants of Recovery

1.4.2.1. Initial severity, lesion size and site. Currently, one of the most informative determinants of recovery is the initial severity of aphasic symptoms and lesion size (Hillis, 2007; Lazar & Antoniello, 2008; Lazar et al., 2010; Pedersen et al., 1995). Certainly, patients presenting with a moderate to mild aphasia have a better prognosis with more complete recovery (Kreisler et al., 2000; Yang, Zhao, Wang, Chen, & Zhang, 2008) while a large infarct involving multiple language areas has been shown to increase the severity of the aphasia and suggest a less favourable outcome (Enderby, Wood, Wade, & Hewer, 1987; Pedersen et al., 1995). However, this is not always the case as patients presenting with the same level of initial severity can still experience very different recovery trajectories. Lesion size is also considered an unreliable predictor of recovery as multiple small lesions situated in language regions may cause a more severe language impairment than a large lesion in a non-language area (Crinion, Holland, Copland, Thompson, & Hillis, 2013).

The site of the lesion is regarded by some as being an important predictor of aphasia recovery (Crinion et al., 2013) and the resulting negative behavioural influences on language function has provided insights into the functional organization of the brain (Cappa, Perani, Schnur, Tettamanti, & Fazio, 1998) and the widespread distribution of language processing networks (Hickok & Poeppel, 2007). Various studies have identified functional deficits which they attribute to the lesion site. Nonfluency in chronic patients has been attributed to a lesion in the left precentral gyrus (Knopman et al., 1983) while persistent naming disorders in chronic patients have been associated with posterior temporoparietal and insulo-lenticular lesion sites (Knopman et al., 1983). Comprehension disorders have been inextricably linked to the site of the lesion (Cappa, 1998), with Wernicke's area and suprasylvian parietal regions (Selnes, Knopman, Niccum, Rubens, & Larson, 1983), the temporal lobe (Naeser, Helm-Estabrooks, Haas, Auerbach, & Srinivasan, 1987), and the inferior parietal lobe (Kertesz, Lau, & Polk, 1993) variously associated with receptive language deficits. Distinctions between more specific language symptoms were explored recently in a large patient study by Mirman et al. (2015) showing that damage in perisylvian regions was associated with phonological form deficits while damage in extrasylvian regions, including lesions in left anterior temporal lobe and impaired white matter connectivity with the frontal cortex was associated with semantic recognition and production deficits (Mirman et al., 2015).

1.4.2.2. Aphasia subtype. The use of aphasia classifications to predict recovery is considered a less accurate measure of recovery (Cappa, 2008) and has not been predictive beyond being associated with initial severity levels (Pedersen et al., 2004). Apart from demonstrating an evolving aphasia, whereby progression to a milder type of aphasia usually occurs (Laska et al., 2001; Lazar & Antoniello, 2008; Pedersen et al., 2004) there have not been any studies which have shown that one particular type of aphasia has a better recovery than another (Lazar et al., 2010). The use of aphasia type is limited for various reasons and classification of aphasia subtypes are themselves problematic (Lazar et al., 2010). They are made up of a cluster of linguistic symptoms, patients often don't fit precisely within one subtype based on these symptoms, and recovery of these symptoms can occur selectively (El Hachioui et al., 2013). Therefore, assigning a patient to a specific subtype with a particular course of recovery is limiting. Problems can also arise with methods used to assign patients to particular classification subgroups with differences in classification criteria, selection of patients and the timing of assessments confounding the issue of classification. Furthermore, different aphasia subtypes will be associated with different concomitant factors which can affect outcomes. A study by Laska et al. (2001) showed that 25% of all aphasic patients in the acute phase had global aphasia and by the chronic stage, this figure had dropped to only a few percent (Laska et al., 2001). However, this finding may not be attributed to recovery but rather the high rate of morbidity that is associated with global aphasia (Laska et al., 2001). Lazar et al. (2010) suggests that rather than using aphasia subtypes to predict recovery, it is likely to be more beneficial to look at the recovery of language function and identify changes in neurolinguistic abilities that occur over the course of recovery (Lazar et al., 2010).

From the above, it is clear that there may be multiple factors which are associated with language recovery following stroke and that these factors may contribute to recovery of language function at different stages during the course of recovery from aphasia. While factors such as handedness, sex, age and premorbid education levels do not significantly predict recovery outcomes (Lazar & Antoniello, 2008; Lazar et al., 2010), other factors such as initial severity, lesion size, site and type of aphasia have all been posited as potential markers of recovery. One significant factor which has not been previously considered in depth is the underlying brain activity involved in language processing. Below I discuss neuroimaging techniques currently used in aphasia research and discuss their contribution to the current understanding of neural mechanisms of language recovery.

1.5 Neuroimaging

Neuroimaging evidence when combined with behavioural language studies carried out from acute to chronic phases post-stroke can provide insights into structure/function relationships of language and how these change during the course of recovery. A clearer understanding of these processes may provide crucial information on the neural mechanisms that influence recovery and how we can use these mechanisms to predict recovery in aphasia.

1.5.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an imaging technique which can provide *in vivo* structural and functional information in the brain. Below I consider the main principles behind MRI and introduce functional MRI (fMRI).

Magnetic resonance arises from the interaction of nuclei which have a magnetic moment with an applied magnetic field (Matthews, 2001). Protons within the nuclei, have a property defined as a ‘spin’ (Lee, Kannan, & Hillis, 2006) and this can assume either a high-energy (anti-parallel) or a low-energy state (parallel) when placed in a static magnetic field (Matthews, 2001). Exposure to an appropriate radiofrequency (RF) pulse causes the protons to excite to the higher-energy state (Lee et al., 2006; Matthews, 2001). Once excited, the protons induce signal in the coil and return to their resting state (Lee et al., 2006) known as ‘relaxation’. There are two forms of relaxation – T1 or longitudinal relaxation and T2 or transverse relaxation. These relaxation times alter with varying tissue characteristics, and different contrasts in MRI can be achieved by manipulating timing and RF pulses to achieve different weightings (McMahon, Cowin, & Galloway, 2011). T1-weighted scans are able to contrast grey and white matter while T2-weighted scans have bright fluid contrasts, and are effective at identifying oedema and inflammation. The main advantage of MRI is its relatively safety since it uses magnetic fields and RF pulses rather than ionizing radiation (Dronkers & Ludy, 1997).

1.5.2 Functional Magnetic Resonance Imaging

Functional magnetic resonance imaging (fMRI) has caused much excitement in the literature with research driven by attempts to ‘light up’ different regions of the brain in response to specific tasks. The basic principle behind fMRI is that increased brain activity results in localised blood oxygenation changes that can be measured by using an endogenous functional contrast (Hillary & DeLuca, 2007, 31; Lee et al., 2006). As far back as 1936, Pauling and Corryell demonstrated that the magnetic properties of oxygenated haemoglobin are different from deoxygenated haemoglobin with the former being in a diamagnetic state and the latter in a paramagnetic state, which can be measured with MRI sequences sensitive to magnetic susceptibility (Lee et al., 2006). Ogawa, Lee, Kay, and Tank (1990) were the first to detect changes in cerebral blood flow when coupled with neuronal activity. They coined the term Blood Oxygen Level Dependent (BOLD) whereby neural activation causes a haemodynamic response function (HRF), or delayed increase in signal relative to neural activation (Lee et al., 2006).

The potential of fMRI to reveal brain areas involved in language processing and enhance existing functional anatomy maps is enormous. Comparisons between patient and healthy data are able to provide identification of mechanisms that are necessary to perform a particular cognitive function and will enable a critical system of language processing to be developed (Price, Mummery, Moore, Frakowiak, & Friston, 1999). As such, BOLD fMRI is currently the brain activation mapping method of choice for investigating putative brain mechanisms involved in language processing and indeed, a review of fMRI studies by Price (2010) identified 100 such studies in 2009 alone.

However, there are some limitations with the technique which must be considered when using an fMRI experimental design especially with patient populations. Increased movement in the scanner can decrease the ability to detect BOLD changes (Hoeller et al., 2002). In addition, ischaemic infarcts or reduced vascular activity can cause a reduction in the HRF which may affect the BOLD signal detection and create errors in data interpretation. Importantly, delayed HRF has been observed in patients with aphasia (Bonakdarpour, Parrish, & Thompson, 2007) and therefore, it is critical that this issue is considered when designing an experimental paradigm investigating specific cognitive linguistic functions.

From the above, it is clear that the increased advances and refinements in neuroimaging technology that carry minimal patient risk is enabling *in vivo* investigations into cognitive processes that were previously only able to be studied post-mortem. These neuroimaging studies are fundamental for exploring the structure and function relationships in the brain.

1.6 Neural Correlates of Spoken Word Comprehension

Evidence from fMRI language studies both in normal and also brain-damaged populations has enabled the identification of possible brain regions that are involved when a particular task is being performed and has contributed to the understanding of hierarchical processes at work in language processing. In terms of spoken word processing, a more detailed hierarchy has been proposed with activation occurring successively in response to specific acoustic, phonetic and phonological information such as phonetic features, segments, syllable identification and lexical and semantic levels of processing (Davis & Gaskell, 2009; Davis & Johnsrude, 2003; Hickok & Poeppel, 2007; Sharp et al., 2010). Accounts of dual stream processing, which mirror the 'what' and 'where' streams in the visual cortex, have also been suggested. A dual stream account is supported by evidence from animal studies on auditory cortex (Scott & Wise, 2004) as well as data from neuroimaging studies of auditory processing of single words in normal subjects (Hickok, 2009; Hickok & Poeppel, 2007; Saur et al., 2008). Both Hickok and Poeppel (2007) and Saur et al. (2008) identify two streams; a dorsal and ventral stream. The dorsal stream, which is dominant in the left hemisphere, integrates sensory and motor information for articulation and moves through the parietal-temporal junction and frontal lobe. The ventral stream on the other hand is responsible for comprehension of speech and is located in the superior and middle temporal lobe. Whilst the ventral stream is largely organised bilaterally, there may be a weak left hemisphere bias for the comprehension of lexical-semantics (Hickok & Poeppel, 2007).

The dual stream model of Hickok and Poeppel (2007) proposes that the processing of early acoustic information is carried out in the dorsal superior temporal regions bilaterally, including Heschl's gyrus (HG), superior temporal gyri (STG) and planum temporal. From there, more complex acoustic stimuli such as speech are processed further downstream at phonetic and phonological levels in mid-posterior superior temporal sulci (STS) bilaterally, with some studies indicating a more left lateralized STG activation for speech stimuli (Binder et al., 1996; Demonet et al., 1992; Demonet, Thierry, & Cardebat, 2005). At this point, either the ventral route or dorsal route is activated, depending on the processing required. If semantic decoding is required, information is conveyed via the ventral stream and posterior and inferior portions of the temporal lobes are activated. This is the lexical interface and is where phonological information activates associated semantic information (Hickok & Poeppel, 2007). Findings from a recent review by Price

(2010) also indicate bilateral involvement of HG for processing of acoustic signals with speech specific selectivity occurring in the STG and if further semantic processing of single words is required, activation will spread anteriorly, ventrally and posteriorly into the middle and inferior temporal regions (Price, 2010).

From the above, it is clear that neuroimaging is able to provide valuable evidence to inform theoretical models of language processing. Below I consider how concreteness effects and the neural mechanisms which underpin the spoken recognition of concrete and abstract words in healthy and language-impaired individuals can contribute to our understanding of how conceptual semantic representations are organised.

1.6.1 Neural Correlates of Concrete and Abstract Processing in Healthy Young Adults

Increasingly, evidence from neuroimaging studies has been used to support concreteness accounts and identify the brain regions which underpin concrete and abstract processing. While both visual and auditory modalities have been utilized to explore differences between concrete and abstract processing, the majority of studies have employed visual tasks and investigated recognition (Fliessbach, Weis, Klaver, Elger, & Weber, 2006; Mestres-Misse, Munte, & Rodriguez-Fornells, 2009), semantic categorisation (Friederici, Opitz, & von Cramon, 2000; Pexman, Hargreaves, Edwards, Henry, & Goodyear, 2007), semantic similarity decisions (Noppeney & Price, 2004; Sabsevitz, Medler, Seidenberg, & Binder, 2005; Whatmough, Verret, Fung, & Chertkow, 2004), and lexical decision (Binder et al., 2005; Evans, Lambon Ralph, & Woollams, 2012; Fiebach & Friederici, 2004; Kiehl et al., 1999; Perani et al., 1999; Vigliocco et al., 2014). Meanwhile, studies which have used the auditory modality have employed passive listening tasks (Tettamanti et al., 2008; Wise et al., 2000) and mental imagery generation tasks (D'Esposito et al., 1997; Mellet, Tzourio, Denis, & Mazoyer, 1998) although findings from the latter may reflect spoken word recognition rather than neural correlates associated with concrete and abstract word retrieval.

Considered together, the findings from both types of studies have been highly variable with some showing that concrete words were associated with increased left hemisphere (Fiebach &

Friederici, 2004; Jessen et al., 2000; Mellet et al., 1998; Wise et al., 2000) or bilateral activation (Binder et al., 2005; Sabsevitz et al., 2005), while abstract words were associated with increased left (Binder et al., 2005; Noppeney, Price, Duncan, & Koepp, 2005; Sabsevitz et al., 2005), right (Kiehl et al., 1999) or bilateral activation (Friederici et al., 2000; Grossman et al., 2002; Perani et al., 1999; Pexman et al., 2007). The high variability in the results has been attributed not only to possible differences in the methodology and modality of input (Kotz, Cappa, von Cramon, & Friederici, 2002) but also to differences in the baseline contrasts and imaging techniques.

Meta-analyses by Binder et al. (2009) and Wang et al. (2010) have provided some consensus (refer to Chapters 2 and 3 for a more detailed discussion on the findings). The Binder et al. (2009) analysis included 17 studies on concrete (perceptual) and abstract (verbal) processing and found 113 overlapping foci associated with perceptual (concrete) processing and 34 for verbal (abstract) processing. The concrete processing foci included the left and right angular gyrus (AG), left posterior cingulate, left fusiform (occipitotemporal) gyrus, left middle frontal gyrus (MFG) and left superior frontal gyrus (SFG). The 34 foci identified for abstract words were located in left inferior frontal gyrus (IFG), mainly pars orbitalis and left anterior superior temporal sulcus (aSTS) (Binder et al., 2009). The analysis by Wang et al. (2010) was based on 19 studies, ten of which had also been included in the Binder et al. meta-analysis (2009), and arrived at similar conclusions in that concrete words elicited activity in left hemisphere regions including, the fusiform gyrus, posterior cingulate, precuneus and parahippocampus. Left hemisphere activity was also elicited by abstract words but this was focused in the middle temporal gyrus (MTG), STG and IFG (Wang et al., 2010).

Lexical decision tasks are commonly used to explore lexical processing and importantly semantic effects have been reliably observed in priming tasks using lexical decisions (Balota et al., 2007). To date, only a few lexical decision tasks have employed the auditory modality to investigate concreteness effects with the majority utilizing the visual modality (Binder et al., 2005; Fiebach & Friederici, 2004; Kiehl et al., 1999; Perani et al., 1999). However, the visual modality may be associated with some limitations. Firstly, using picture-based stimuli may access visual representation codes which can confound findings. Secondly, written lexical decision tasks may result in shallow processing caused by rapid orthographic analysis (Grainger & Jacobs, 1996) or the orthographic familiarity of the stimuli (Balota, Ferraro, & Connor, 1991; Balota, Paul, & Spieler, 1999). In addition, activity in inferolateral regions has been reported in response to visual lexical decision tasks, possibly reflecting processes associated with grapheme - phoneme conversion rather than semantics (Herbster, Mintun, Nebes, & Becker, 1997; Price, 1998; Rumsey et al., 1997). In contrast to the findings from the visual lexical decision tasks, studies employing the auditory modality have not observed the same pattern of activity in phoneme to grapheme conversion regions (Kotz et al., 2002; Newman & Twieg, 2001), highlighting potential advantages for using spoken word tasks to examine concrete and abstract word processing. Nevertheless, activity elicited in response to auditory tasks has also been variable and inconsistent across studies (Kotz et al., 2002; Newman & Twieg, 2001; Raettig & Kotz, 2008; Shafto, Randall, Stamatakis, Wright, & Tyler, 2012) and one factor that might contribute to this variability is the nonword baseline employed. The types of nonword that may be created can be very different and will depend on the design method used (Bedny & Thompson-Schill, 2006). As a result, different processing mechanisms may be engaged and reflect varying factors such as the point of deviation, phonotactic legality and lexical transparency (Raettig & Kotz, 2008). Thus, if a nonword appears too similar to a real word, semantic representations may be activated. In contrast, if the nonword is too ‘unwordlike’ and phonotactic legality is violated, the processing mechanisms may be very different from that used to process more legal nonwords or real words. Raettig and Kotz (2008) suggest that the use of an opaque pseudoword will ensure that lexical access is prevented, thereby minimising semantic-based activation (Raettig & Kotz, 2008). A more detailed explanation on the design and construction of opaque pseudowords is included in the introduction to Chapter 2.

Based on the above, an auditory lexical decision task with a novel pseudoword condition was employed to examine the neural correlates of concreteness effects and concrete and abstract processing. This experiment forms the basis for Chapter 2.

1.6.2 Neural Correlates of Concrete and Abstract Processing in Healthy Older Adults

The neural mechanisms which underpin concrete and abstract processing in ageing have received less attention than studies investigating the concreteness effects in healthy young adults. Indeed, of the studies included in the Binder et al. (2009) and Wang et al. (2010) meta-analyses only one study investigated concrete and abstract processing in healthy older adults. This PET study by Whatmough et al. (2004) examined concreteness effects in 15 healthy adults (mean age 74.3 yrs) performing a semantic judgement task and found that when the concrete and abstract words were compared to a baseline condition, similar activation in left lateral temporal cortex was elicited. However, when a direct comparison was made between the real word conditions, increased activation was observed in left fusiform gyrus for concrete and right fusiform gyrus for abstract words. Unfortunately, the Whatmough et al. (2004) study did not include a young group for comparison and therefore it is not clear whether age-related neural differences were contributing to the results. Effects of ageing and processing differences associated with concrete and abstract semantic judgement tasks were also examined in an fMRI study by Stebbins et al. (2002). The results identified age-related differences in hemispheric activity with the young group showing greater left hemisphere activity than the older adults (Stebbins et al., 2002).

A more recent study by Shafto et al. (2012) investigated age-related differences in language comprehension in a group of healthy young and older adults whilst performing an auditory lexical decision task. Variables such as phonology were measured by phonological competition and semantics measured by imageability. The results identified both groups as responding faster to words with high imageability, but only the older group showed an increased sensitivity to items of low imageability and this was associated with increased activity in left MTG. These findings suggest that in older adults, a preserved performance on abstract compared to concrete word processing may be associated with an altered pattern of compensatory brain activity such that semantic processing is supported by an upregulation of activity but phonological processing is not (Shafto et al., 2012), but see Geva et al. (2012), where it was argued that compensatory phonological processing was observed in the performance of older adults and associated with an increase in activity in right IFG regions.

Age-related neural differences for semantic versus phonemic fluency were also identified in a study by Meinzer et al. (2012). The findings showed increased right IFG by the older adults accompanied by a reduction in behavioural performance in semantic fluency, suggesting that semantic and phonological processing may differ as a function of age. Thus, while the engagement of prefrontal regions appears to be associated with changes in semantic processing in ageing, other regions seem to be involved in maintaining preserved functionality and it remains unclear whether age-related neural changes reflect compensatory or inefficient processing mechanisms.

Structural changes associated with the normal ageing process are well documented and usually include reductions of grey matter volume (Fjell et al., 2009; Raz et al., 2005) in prefrontal and hippocampal regions (Raz et al., 2005) and decreased white matter integrity (Madden et al., 2009). Given the reported structural changes, it is likely that functional abilities associated with these brain regions will also be affected over the life span and this has been reported for a range of cognitive functions including processing speed (Salthouse, 1996), executive function (West, 1996), working memory (Salthouse & Babcock, 1991), and declarative memory (Murty et al., 2009). In terms of language function, deficits in word retrieval in healthy older adults are well-reported (Burke & Shafto, 2004; Burke & Shafto, 2008) while word knowledge (Verhaeghen, 2003) and language comprehension (Tyler et al., 2010) appear to remain relatively stable in older individuals. A still unresolved issue centres on preserved language function and whether, in view of the significant changes in grey and white matter structures associated with a healthy ageing brain, recruitment of additional neural substrates is a necessary prerequisite to preserve performance.

Neuroimaging studies that have investigated nonlinguistic processes in healthy older and young adults have shown activation differences between the two groups, suggesting a tendency for young adults to show increased focal task-related activity compared to older adults who show a pattern of more widespread activity (Cabeza, 2002). The results from the Cabeza (2002) study also showed hemispheric differences between the two groups in response to the same task. While younger adults tend to elicit activity in the hemisphere which is usually recruited to perform the task, older adults demonstrate the reverse (i.e. greater activity in the non-task dominant hemisphere), with activity most usually observed in prefrontal cortical regions. This shift in lateralisation has been termed the hemispheric asymmetry reduction in older adults or HAROLD (Cabeza, 2002). While a reduction in asymmetrical activation patterns for healthy older adults is well-established, what is less clear is how this reduction in laterality affects function. Questions remain as to whether the upregulation of additional brain regions serves as a compensatory neural response, enabling older individuals to perform a task equally as successfully as their young counterparts or if the increased widespread activity is a result of reduced brain specificity and a decline in neural efficiency (for a review see Park & Reuter-Lorenz, 2009; Park et al., 2003).

As such, based on the behavioural evidence outlined in section 1.2 of this introduction and the neuroimaging evidence discussed above, competing accounts regarding attenuation (as per Peters & Daum, 2008) versus preservation (as per Huang, Meyer, & Federmeier, 2012) of concreteness effects were tested in a group of healthy older adults, and the experiment forms the basis for Chapter 3 of this thesis.

1.6.3 Neural Correlates of Concrete and Abstract Processing in Aphasia.

Comparisons between brain activity elicited by individuals with aphasia and healthy controls performing the same task can provide further insights into the neural mechanisms which underpin abstract and concrete processing (Skipper-Kallal, Mirman, & Olson, 2015). However, it is essential that the imaging protocols employed in studies investigating aphasic language are carefully constructed to ensure reliable and consistent activation is observed (see meta-analysis by Turkeltaub, Messing, Norise, & Hamilton, 2011). Below I consider some of the studies which have investigated concreteness effects in aphasia and consider how they contribute to our understanding of the neural mechanisms which underpin concrete and abstract processing.

While concreteness effects and the processing advantage for concrete over abstract words have been reported in healthy populations (James, 1975; Kroll & Merves, 1986, for a review, refer Pavio, 1991) (see Chapter 2 for a review of concreteness), the effects of concreteness are not only present, but are often exaggerated in people with aphasia (Barry & Gerhand, 2003; Crutch & Warrington, 2005; Martin, Saffran, & Dell, 1996; Newton & Barry, 1997; Sandberg & Kiran, 2014) and also people with semantic dementia (Hoffman, 2015). Other studies have reported a reversal of the effect (Warrington, 1975); that is a processing advantage for abstract over concrete words in patients with semantic dementia (Bonner et al., 2009; Macoir, 2009; Papagno, Capasso, & Miceli, 2009; Yi, Moore, & Grossman, 2007), although these cases are not typical (Hoffman & Lambon Ralph, 2011). Nevertheless, these observations have fuelled the debate regarding whether concrete and abstract processing is underpinned by distinct neural systems which can be selectively impaired following an insult to the brain. While informative, a limitation of the studies investigating concreteness effects in aphasia is that they have largely been behavioural case studies and have also investigated language function in the chronic phase of recovery when significant reorganisation is likely to have already occurred.

To date, there has only been one study that has used fMRI to investigate the neural mechanisms associated with concrete and abstract processing in people with aphasia (Sandberg & Kiran, 2014). In this study, three individuals with chronic aphasia and three healthy age-matched controls were investigated while performing visual, semantic judgement tasks. The results showed that for the aphasic subjects, there was increased activation for abstract compared to concrete words in anterior and posterior brain regions. However, no region elicited increased activity for concrete compared to abstract words. In contrast, activation differences between conditions elicited by the controls were not as robust and the authors suggest that this difference in activation between the two groups may explain the more pronounced effects of concreteness observed in people with aphasia (Sandberg & Kiran, 2014). Whilst not using fMRI in aphasia, Skipper-Kallal et al. (2015) recently demonstrated that patients with lesions involving the temporoparietal cortex had difficulties processing abstract but not concrete words when the words were presented in a related array, providing further insights into effects of aphasia on abstract conceptual processing (Skipper-Kallal et al., 2015).

1.6.4 Neural Mechanisms of Recovery in Aphasia

The development of newer, more refined imaging techniques offers exciting prospects for exploring neural mechanisms of language recovery following stroke. In terms of aphasia and the recovery of language there are two important issues. The first issue concerns the neurophysiological changes that occur following a stroke and cause the language impairment. The second issue relates to the mechanisms of recovery that are responsible for the recovery of the lost language function (Calvert et al., 2000). As discussed above, traditional methods of predicting recovery such as lesion size only account for about a third of the variance (Lazar & Antoniello, 2008) and other factors such as functional neural mechanisms may therefore be contributing to the recovery process. Below I discuss the neural mechanisms of recovery and consider how they might be correlated with functional recovery of language processes.

1.6.4.1. Neurophysiological mechanisms. Following a stroke, a patient may experience loss of function caused by the death of neuronal cells and deafferentation whereby activation of the neural network is interrupted (Muñoz-Cespedes, Rios-Lago, Paul, & Maestu, 2005). From a neurophysiological perspective, mechanisms of recovery will be operating immediately post insult (Muñoz-Cespedes et al., 2005). During the acute stage, recovery occurs rapidly and is mainly caused by restoration of the function of damaged neural tissue, largely brought about by reperfusion of the ischaemic penumbra and reduction of oedema (Lazar & Antoniello, 2008). At the subacute phase, synaptic remodelling and axonal sprouting occurs and recovery at this time slows (Marsh & Hillis, 2006). Finally, once the chronic phase is reached, neural recovery may be complete or have plateaued (Muñoz-Cespedes et al., 2005). While there are clearly distinct neurophysiological mechanisms occurring at different stages, how they contribute to recovery of language function is currently not well understood.

1.6.4.2. Stages of recovery. Most people with aphasia and even those with large perisylvian lesions, go on to make some degree of spontaneous recovery (Thompson & den Ouden, 2008). Following a stroke, neuroplastic changes occur as the brain undergoes reorganisation or repair so that it can compensate for the impaired functionality (Muñoz-Cespedes et al., 2005). Three distinct but clearly overlapping stages of recovery have been proposed with specific underlying neural mechanisms occurring at the different time points (Hillis, 2005; Kiran, 2012; Marsh & Hillis, 2006). Grady and Kapur (1999) suggest that functional recovery can occur following (i) reorganisation within the region, (ii) recruitment of new or alternate network (compensatory mechanism) and (iii) plasticity in regions surrounding the lesion. Breier et al. (2004) describe the three mechanisms as (i) restoration of activity in premorbid areas, (ii) map expansion to perilesional areas within the left hemisphere and (iii) reorganisation of right hemisphere homologues. Below I consider these mechanisms and their influence in the acute, subacute and chronic phases of recovery.

1.6.4.2.1. Acute stage. At the acute stage, there are two mechanisms of recovery. The first is reorganisation and reestablishment of damaged connections and the second is restoration of neural tissue as the damaged area of the brain is reperfused (Marsh & Hillis, 2006). While both mechanisms are important, reperfusion of the dysfunctional area rather than structural reorganisation is probably a more common mechanism of recovery in the first few days of stroke (Marsh & Hillis, 2006) and it is essential to consider its impact on spontaneous aphasia recovery during this period.

Newer methods of imaging however such as diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) have enabled a more detailed understanding of how low blood flow contributes to functional deficits in the acute phase post-stroke. DWI is used to measure the volume of the ischaemic tissue that is permanently infarcted while PWI measures the total volumetric measure of brain tissue that is compromised but salvageable (Lee et al., 2006; Reineck et al., 2005). A diffusion/perfusion mismatch (Lee et al., 2006; Reineck et al., 2005) can be used to define functionally the area known as the ischaemic penumbra (IP). That is, the volume of the penumbra is calculated by subtracting the abnormality seen in DWI from that seen in PWI. The resulting figure is the volume of tissue that, while compromised, has not experienced irreversible infarction (Hillis, Barker, Beauchamp, Gordon, & Wityk, 2000; Hillis et al., 2004). If the IP is reperfused, normal function will resume but if the area remains hypoperfused, permanent cell death will occur (Payabvash et al., 2010). In terms of language function, if the IP is situated in a language area, hypoperfusion can cause language deficits such as aphasia in the acute phase. Studies have shown that once the IP is reperfused, an improvement in language function is seen despite the infarct remaining unchanged (Hillis et al., 2006; Lee et al., 2006).

Language studies which have investigated recovery in the acute stage have largely focused on the contribution of hypoperfusion to aphasia recovery (Hillis, 2005, 2007). DWI and PWI were used by Hillis and Heidler (2002) to examine spoken word comprehension in 110 patients with acute stroke and showed that following successful perfusion of Brodmann area (BA) 22 (Wernicke's area), there was a rapid recovery of language comprehension. In contrast, patients with persisting hypoperfusion in BA 22, continued to show impaired spoken word comprehension (Hillis & Heidler, 2002) demonstrating the important role of reperfusion in early language recovery. Indeed, compromised cerebral perfusion in the acute stages has been considered a more reliable predictor of spontaneous aphasia progression than the size of the lesion (Fridriksson et al., 2002; Hillis et al., 2000). Thus, reperfusion of potentially salvageable tissue appears to be an important early mechanism of recovery in acute aphasia (Cappa, 2008), as compared to neural mechanisms associated with the reorganisation of brain structure and function mechanisms, which may contribute to improved language function but at a later time point. It should be noted that these mechanisms have not been examined as predictors of chronic recovery, but instead have explained changes or between subject differences in behaviour at the acute stage.

1.6.4.2.2. Subacute stage. During the subacute stage, reorganisation and reestablishment of damaged connections continues to occur through restitution and extension of perilesional regions and/or a functional transfer to the right hemisphere homologue (Lazar & Antoniello, 2008; Thompson, 2000a). These two mechanisms have been at the centre of the debate on language recovery for the past 100 years and the emergence of new noninvasive neuroimaging techniques has prompted a renewed interest in determining whether recruitment of residual left hemisphere language regions or contralateral homologues mediates recovery (Muñoz-Cespedes et al., 2005).

The notion that language recovery occurs as a result of recruitment of perilesional tissue is widely accepted (Kertesz, 1988, 1989). Evidence from patient data also supports this 'map extension' (Thompson, 2000a) with reports of renewed language impairments in people with aphasia with previously recovered language function, but who go on to experience a second left hemisphere stroke (Basso, Gardelli, Grassi, & Mariotti, 1989). Neuroimaging studies have also demonstrated activation of perilesional tissue adjacent to the lesioned area in response to language processing (Heiss, Kessler, Thiel, Ghaemi, & Karbe, 1999; Kurland et al., 2004; Warburton, Price, Swinburn, & Wise, 1999). Moreover, if the perilesional area surrounds an active language area it is more likely that it will be able to subsume some of language function previously carried out by the damaged regions (Marsh & Hillis, 2006) perhaps due to functional redundancy (Thompson & den Ouden, 2008). Some researchers have claimed that perilesional restitution is the main substrate for functional language recovery (Breier et al., 2004; Crinion & Price, 2005; Crosson et al., 2007; Meinzer et al., 2008; Sharp et al., 2010; Szaflarski et al., 2011) and is actually indicative of a 'better' recovery (Thompson & den Ouden, 2008). However, it is not clear whether this increased perilesional activation is caused by the left hemisphere assuming new functionality or by reperfusion (Marsh & Hillis, 2006).

The involvement of the right hemisphere in language recovery is also well documented. As far back as 1877, Barlow demonstrated a transference from typical language centres to the right hemisphere (as cited in Crosson et al., 2007). Furthermore, patients with recovered language function following a left hemisphere stroke have been shown to experience a relapse after experiencing new right hemisphere damage (Basso et al., 1989; Thompson & den Ouden, 2008). Similarly, studies demonstrating loss of language function in recovered aphasic patients after anesthetizing the right hemisphere during Wada testing has also provided evidence of right hemisphere involvement in language processing in this patient group (Kinsbourne, 1971). Importantly, the same effect is not seen when the right hemisphere is anesthetized in normal subjects (Marsh & Hillis, 2006). Recent functional neuroimaging research has indicated that right hemisphere involvement is more than a shift of lateralisation and propose that it is actually the homologous regions in the right hemisphere that are implicated in language recovery (Blank, Bird, Turkheimer, & Wise, 2003; Calvert et al., 2000; Cao, Vikingstad, George, Johnson, & Welch, 1999; Crosson et al., 2007; Lazar et al., 2000; Thulborn, Carpenter, & Just, 1999; Weiller et al., 1995).

There seems to be little doubt that the right hemisphere is involved in the recovery of language but its role appears complex and questions surrounding the circumstances, stage and extent of involvement have yet to be answered (van Oers et al., 2010). It is not clear whether right hemisphere involvement actively contributes to recovery of language function or whether it is merely implicated due to transcallosal disinhibition following left cortical damage (Crosson et al., 2007; Price & Crinion, 2005). Furthermore, it is not known whether right hemisphere involvement is actually beneficial (Crosson et al., 2007) or maladaptive (Crosson et al., 2007; Selnes, 1999) and prevents a good recovery through the persistence of residual deficits (Marsh & Hillis, 2006; Martin, 2003). Moreover, since right hemisphere involvement has been documented in healthy controls, activation of these right hemisphere regions may be representative of the large-scale neural network that is usually operational during normal language processing (Crosson et al., 2007; Thompson & Shapiro, 2005) and this must be considered when evaluating the role of this mechanism in language recovery.

Clearly, it would appear that both perilesional restitution and right hemisphere homologues are involved to some degree in the reorganisation and reestablishment of damaged connections in the recovery of language function. A review of fMRI studies investigating mechanisms of recovery in aphasia (Price & Crinion, 2005) concluded that both left and right hemisphere mechanisms do indeed contribute to the recovery of language, although the circumstances under which these mechanisms are involved is not clear (Price & Crinion, 2005), and differences in patterns of neural reorganisation may be attributed to factors such as the type of task investigated, the lesion site and size, and the timing post-stroke. Marsh and Hillis (2006) proposed three possible explanations for differences in reorganisation. In the first instance, the extent of left hemisphere damage and the location may determine which mechanism is recruited, so that perilesional cortex may provide an adequate substrate for a small lesion while a large lesion may be better served by a right hemisphere substrate (Crosson et al., 2007; Vitali et al., 2007). Certainly, right hemisphere recruitment has traditionally been associated with extensive left hemisphere damage (Cao et al., 1999; van Oers et al., 2010). The second explanation is that both left and right hemispheres always support language recovery, possibly through the upregulation of right homologous and left perilesional regions, although the significance of their contribution to the process may be different (Marsh & Hillis, 2006; Noppeney et al., 2005). Lastly, following left hemisphere damage, the contralateral hemisphere may initially be recruited for language function until reintegration can occur in the left hemisphere (Marsh & Hillis, 2006). This last theory has been shown to be predictive of a good recovery (Heiss et al., 1999; Rosen et al., 2000; Saur et al., 2006) while poorer outcomes have been indicated following large left hemisphere lesions and prolonged right hemisphere involvement (Szaflarski, Allendorfer, Banks, Vannest, & Holland, 2013; van Oers et al., 2010).

From the above, it is clear that neural reorganisation is an important mechanism of recovery which starts in the acute stage and continues into the subacute phase albeit at a slower rate. Another neural mechanism of recovery that occurs in the subacute phase is regression of diaschisis (Cappa et al., 1997; Lazar & Antoniello, 2008; Marsh & Hillis, 2006). The term diaschisis refers to a functional impairment that occurs downstream in either an ipsilateral or contralateral area of the brain and is caused by the loss of neural input from the infarcted region (Feeney & Baron, 1986;

Marsh & Hillis, 2006). Once input is received from other, intact areas of the brain, functionality is restored (Marsh & Hillis, 2006). Regression of intrahemispheric and transhemispheric diaschisis during the first six months post-stroke onset has been associated with an improvement in language function and has been considered by some to be the best predictor of language recovery (Cappa et al., 1997) although definitive evidence of this prominent role is lacking.

1.6.4.2.3. Chronic stage. In the chronic stage of recovery, recovery of language function continues and may be achieved by establishing compensatory strategies or learning new ways of performing a task (Holland, Fromm, DeRuyter, & Stein, 1996; Marsh & Hillis, 2006), or by the strengthening and extension of previous networks (Mohr, Difrancesco, Harrington, Evans, & Pulvermüller, 2014). Compensatory masquerade has been proposed as a neuroplastic mechanism whereby a different cognitive process is used to perform a task following impairment to the original cognitive processing mechanism (Grafman, 2000). For example, reading may be accomplished by using a letter by letter reading strategy which whilst being explicit and slower, is nevertheless effective. As such, people with aphasia can learn new ways of accessing intact representations or use an alternative strategy to perform the same task (Lazar & Antoniello, 2008).

Spoken language comprehension in chronic post-stroke aphasia was investigated in an fMRI study by Crinion and Price (2005). Auditory sentence comprehension and speech recognition tasks were presented to 17 aphasic patients. Positive correlations were observed between brain activity in the right superior temporal lobe and auditory sentence comprehension whereas story recognition memory was associated with activity in left IFG and right cerebellum. These findings suggest that right hemisphere regions contribute to auditory sentence comprehension in aphasic recovery. However, since this study investigated people with chronic aphasia, it is possible that the recruitment of right hemisphere homologues reflects a system that had already undergone significant reorganisation.

Whilst beyond the scope of this review, it should be noted that aphasia treatment studies, predominantly conducted in chronic aphasia (for a rare example in acute aphasia see Mattioli et al.

2014), have also provided varying results on the contribution of left and right hemisphere mechanisms to improved language function. Some have shown language improvements associated with left hemisphere regions (Breier, Maher, Novak, & Papanicolaou, 2006; Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Meinzer et al., 2008). Others have shown improvements associated with right hemisphere mechanisms although its involvement does appear to vary so that right activation prior to therapy may predict improved function immediately post-therapy, but may not predict sustained language improvements (Breier et al., 2006; Richter, Miltner, & Straube, 2008). For more detailed information on aphasia treatment studies and fMRI, refer to the reviews of Meinzer et al. (2013), Crosson et al. (2007), Crinion and Leff (2007) and Crinion and Leff (2015).

It is clear from the above, that a variety of neural mechanisms are associated with improved language function over the course of aphasia recovery. However, one of the key limitations with many of existing studies examining aphasia recovery is that language function was only examined at one time point and the exact nature, extent and timing of the neural mechanisms which underpin a successful recovery remain unclear. Importantly, changes to these mechanisms occur relative to time post-stroke onset (Marsh & Hillis, 2006; Thompson & den Ouden, 2008) and therefore longitudinal neuroimaging studies on language recovery in people with aphasia are essential, not only to evaluate what mechanisms contribute to recovery but also to identify when and how these mechanisms are implicated in the process. Below I discuss some of the existing longitudinal studies on aphasia recovery and consider their contribution to the current debate.

1.6.4.3. Longitudinal studies of neural recovery mechanisms. Early longitudinal neuroimaging studies of language recovery used single case studies to investigate possible neural substrates (Fernandez et al., 2004; Léger et al., 2002). Fernandez et al. (2004) used fMRI at one month and again at one year on a patient with a left temporoparietal lesion and resulting conduction aphasia. At the one month period, increased activation was demonstrated in the right homologue and while this increase was still present at the one year stage, a shift towards increased perilesional activity was also noted. However, one of the problems with the Fernandez et al. (2004) study was that the patient was able to complete the speech comprehension task normally at both testing times and as such, no direct correlation between the shift in activation changes from right to left hemisphere could be necessarily attributed to the recovery of language function.

Longitudinal neuroimaging studies on groups of patients have also been carried out to determine the neural mechanisms that are involved at different stages of the recovery process both in cortical (Heiss et al., 1999) and subcortical structures (de Boissezon et al., 2005). The study by Heiss et al. (1999) demonstrated initial right hemisphere recruitment at two weeks post-stroke with a shift to perilesional regions at eight weeks. However, a limitation of this study was that the imaging data was not correlated with language recovery. A more recent neuroimaging study which did investigate language recovery and the contribution of left and right hemisphere mechanisms at two time points was carried out by van Oers et al. (2010). Thirteen patients with aphasia were recruited to the study and underwent a range of language assessments at less than 2 months and one year post-stroke (van Oers et al., 2010). The results indicated that improved overall language performance in the chronic period correlated positively with increased activity in left perisylvian rather than right regions and particularly in left IFG. The authors suggested that these results reflected a role for left IFG in language function in chronic aphasia whereas recruitment of right IFG might be associated with more cognitive, nonlinguistic processing (van Oers et al., 2010). Unfortunately, a significant shortfall with this study was that the functional imaging task was not carried out in the first phase of testing and therefore changes in neural mechanisms associated with the course of recovery were not able to be evaluated.

The neural mechanisms which underpin language recovery were examined in a longitudinal study by Saur et al. (2006). Repeated fMRI examinations and language assessments were administered to14 acute aphasic patients from the acute to chronic time points to determine the mechanisms involved with language reorganisation. The results identified three phases of recovery. During the early, acute phase, left hemisphere language regions were recruited but activity was weak and greatly reduced. In contrast, in the subacute phase, approximately 12 days post-stroke, the entire language network was upregulated and this was accompanied by recruitment of right hemisphere homologues, with peak activation in the right IFG. Finally, in the chronic phase of recovery, more normalised patterns of brain activation were observed, with a decrease in right hemisphere activation and a return to peak activity in the left hemisphere (Saur et al., 2006). Importantly, as this hemispheric shift of brain activity from right to left correlated with improvements in behavioural language measures, Saur et al. (2006) proposed that recruitment of right IFG in the subacute stage might be considered an early mechanism of recovery, while the left hemisphere and specifically the left IFG may play a role in language recovery in the chronic stages (Cappa, 2008; van Oers et al., 2010) and may therefore be considered a later stage mechanism of recovery (Saur et al., 2006).

From the above, it could be suggested that a good recovery from aphasia is associated with a functional transfer in the subacute stage from the right IFG to the left hemisphere in the chronic phase (Saur et al., 2006). However, it is unlikely to be as simple as a right-left transfer since other factors may influence the pattern of recovery and the neural mechanisms recruited. One possible factor concerns the extent of the lesion as the infarct itself may cause a loss of activation or disrupt the language network (Price, Warburton, Moore, Frackowiak, & Friston, 2001). In addition, the infarct may also cause damage to mechanisms that control lateralisation (Crosson et al., 2007) and as such, right hemisphere activation may reflect reduced trans-hemispheric functioning caused by left hemispheric disinhibition, rather than functional recruitment. Consideration also needs to be given to the fact that a weak BOLD signal could cause reduced activation rather than being a result of a functional deficit (Krainik, Hund-Georgiadis, Zysset, & von Cramon, 2005).

Furthermore there were some methodological limitations of the Saur et al. (2006) study which may have contributed to the pattern of results observed and may account for the lack of any correlations between task-related brain activity at any single time point and subsequent language outcome. One significant problem was that some of the aphasic patients were not able to perform the fMRI task due to its complexity (see Chapters 4 and 5 for a more detailed explanation). Thus the interpretation of the imaging data, particularly in the acute phase of testing when accuracy rates were at their lowest (mean accuracy rate in the acute phase was 36%), is problematic as it cannot be determined if the impaired performance is a result of the underlying neural deficit or whether the task-related brain activity actually reflects an impaired performance (Price & Friston, 1999).

A second limitation of the study concerns the sentence level task employed in the study to investigate recovery of spoken language comprehension. Sentence level processing is considered to rely heavily on other cognitive functions, in particular verbal working memory (Caplan, Michaud, & Hufford, 2013). Therefore, the task-related prefrontal activity may actually reflect an increased requirement for attention and cognitive control mechanisms (Geranmayeh, Brownsett, & Wise, 2014) which are reduced in the acute phase, increased in the subacute phase and then return to normal activation patterns in the left hemisphere language areas in the chronic phase once support from the right hemisphere is no longer required (Saur et al., 2006) (this is covered in more depth in the discussion in Chapter 5). As such, while right hemisphere activation and specifically right IFG recruitment might be considered an early neural mechanism of recovery, it could be interpreted as a result of an increased nonlinguistic cognitive process that occurs in response to increased working memory or executive control demands (van Oers et al., 2010).

Thus, it would appear important in studies investigating language recovery that individuals with aphasia are presented with tasks that are not cognitively demanding and that they are able to do with sufficient accuracy. If this is achieved, the task-based activity is likely to reflect the neural substrates associated with the stimuli being shown rather than reflecting processing mechanisms associated with the difficulty of the task or the inaccuracy of responses (Price, Crinion, & Friston, 2006; Price & Friston, 1999). Finally, the predictive mechanisms suggested by Saur et al. (2006) have been suggested in terms of sentence comprehension and it cannot be assumed that the same regions would underpin processing of single words, given the different regions involved in these processes.

In conclusion, while the substrates of language recovery are not well understood, recent neuroimaging studies are beginning to provide further insights into the timing and extent to which certain neural mechanisms underpin improved language function. Perilesional activity has been associated with a good recovery (Heiss et al., 1999) as has bilateral activation (Cardebat et al., 2003; de Boissezon et al., 2005). The benefits of other mechanisms such as right hemisphere homologues are less clear. While recruitment in the subacute stage post-stroke has been associated with an improved language outcome (Saur et al., 2006), it may be that this upregulation is only beneficial if transient and precedes a return to more left hemisphere network in the chronic phase. Furthermore, right hemisphere homologous activity may actually indicate a poorer recovery outcome (Zahn et al., 2004) or reflect maladaptive processes when its involvement is sustained well into the chronic recovery period (Szaflarski et al., 2013; van Oers et al., 2010).

There is no doubt that the neural mechanisms which underpin improved language function are dynamic and are implicated at different times during the recovery process. A successful language recovery may follow a systematic time course so that residual perilesional activity occurs in early post-stroke aphasia, followed by recruitment of right homologues in the subacute phase (Rochon et al., 2010; Saur et al., 2006) or as necessary (Crosson et al., 2007), and a subsequent return to the upregulation of perilesional regions in the left hemisphere in the chronic phase (Saur et al., 2006; van Oers et al., 2010). However, recovery is highly variable and there is clearly a need for more longitudinal fMRI studies which examine how brain structure and function is reorganised over the course of aphasia recovery and contributes to improved language function. An increased understanding of the stages involved in recovery has significant clinical implications both in terms of providing an accurate prognosis for recovery and also in guiding treatment provision. Based on this, a longitudinal study of the neural correlates of recovery, particularly as related to spoken word processing, was carried out in the subacute and chronic stages of aphasia and is reported in Chapters 4 and 5.

1.7 Aims and Rationale for the Current Study

The first aim of this thesis (reported in Chapter 2) was to investigate the neural substrates which underpin spoken word processing and specifically concrete and abstract processing in healthy young adults (Roxbury, McMahon, & Copland, 2014). Previous studies on concrete and abstract processing have focussed on the visual modality while the auditory modality has been left largely unexplored. This study employs an auditory lexical decision to explore processing differences between concrete and abstract and therefore avoids some of the limitations associated with using the visual modality. It was hypothesised that by using a lexical decision task with a robust baseline, differences in brain activity elicited during the task would represent discrete language processing mechanisms associated with semantic or phonological processing. In addition, by making the pseudowords as close to real words as possible and therefore increasing task difficulty, it was also hypothesised that maximal semantic-based activation would be observed in response to the concrete and abstract words (Evans et al., 2012).

The second aim of this thesis was to employ the same paradigm to investigate the effects of healthy ageing on the neural substrates of concrete and abstract processing (Roxbury, McMahon, Coulthard, & Copland, 2016). Chapter 3 tested competing hypotheses regarding whether concreteness effects are attenuated with age (as per Peters & Daum, 2008) or whether they are preserved (as per Huang et al., 2012), and if preserved, whether performance by the older adults was associated with patterns of neural activity not observed in the younger adults.

The major aim of the experiments investigating aphasia recovery was to explore the neural mechanisms underpinning language processing in subacute (2 - 6 weeks) and chronic (6 months) aphasia and to examine whether the extent to which these mechanisms are recruited and the time at which this occurs contributes to an improved language recovery. The intention behind using the auditory lexical decision task was to ensure that all patients with aphasia, even in the early stages of recovery, would be able to perform the task with sufficient accuracy as this has been a limitation with previous studies investigating language processing in subacute aphasia (Saur et al., 2006).In addition, by using an auditory task, aphasic patients with visual deficits did not need to be excluded from the study. Importantly, the use of a lexical decision task enabled evaluation of phonological and semantic processing as these components are reliant on a widely-distributed network and are often disrupted in early post-stroke aphasia (Hillis & Heidler, 2002).

Chapter 4 outlines the experiment in patients with aphasia during the subacute phase of recovery and considers the results alongside those from a group of healthy age-matched controls. The same experimental paradigm as the one employed in the previous two experiments was used to determine whether patterns of brain activity would be similar to that of healthy older adults performing the same task or whether there would be increased contralateral activation as previously reported in patients in subacute aphasia performing a spoken comprehension task (Saur et al., 2006). Based on previous reports that concreteness effects (the processing advantage for concrete over abstract words) are maintained in aphasic language and are often more pronounced, a primary aim was to investigate the neural substrates associated with concrete and abstract processing in subacute aphasia. Consistent with previous studies investigating concreteness effects in aphasia (Sandberg & Kiran, 2014), it was hypothesised that greater activity would be elicited for abstract compared to concrete words in the aphasic group. The second aim of this experiment was to investigate whether there was a relationship between brain activity elicited in response to the fMRI task and measures of spoken language comprehension and confrontation naming taken outside the scanner. Based on the findings of Crinion and Price (2005) it was hypothesised that there would be a positive correlation between right hemisphere activity and spoken word and sentence comprehension.

The experimental procedure described above was repeated in the same group of aphasic patients in the chronic (6 months) phase of recovery and is detailed in Chapter 5. The aim of the experiment was to investigate the neural mechanisms associated with improved language recovery in post-stroke aphasia and specifically set out to determine whether measures of language related fMRI activity at 2-6 weeks post-onset can *predict* aphasia recovery at 6 months. In addition, the experiment aimed to identify whether the brain activity in the subacute and chronic stage can predict aphasia recovery and to determine *how* these measures of brain function relate to a range of clinical language measures. Recovery of specific language functions is considered rather than more global language measures. Based on the findings of Saur et al. (2006) and Crinion and Price (2005), it was predicted that right hemisphere homologous recruitment in the subacute phase, followed by a shift back to more left hemisphere recruitment in the chronic phase would be associated with improved language function at six months.

The research addressed in this thesis has the potential to further our insights into the neural substrates which underpin spoken word recognition in healthy adults and how these mechanisms can be impaired in aphasia. At present there are few neuroimaging studies that have used a longitudinal approach on a group of people with aphasia to determine the neural mechanisms that contribute to functional recovery of language. Outcomes of this thesis therefore provide an enhanced understanding of the timing and extent to which neural mechanisms which underpin language function contribute to a successful recovery from aphasia. The clinical outcomes associated with this research are significant. The development of more reliable neurophysiological markers of language recovery in subacute stroke has the potential to provide people with aphasia in the early post-stroke recovery period with a more informed and accurate prognosis of recovery. In addition, increased knowledge of predictors of language recovery may assist clinicians in determining the most appropriate assessment and therapeutic approach, both in terms of timing and type of intervention, thereby maximising outcomes for the person with aphasia. Furthermore, a greater understanding of the brain mechanisms underlying successful language recovery may initiate the development of new treatment approaches.

2 Chapter Two

An fMRI study of Concreteness Effects in Spoken Word Recognition

---

The following chapter provides an introduction into the neural mechanisms associated with the spoken word recognition of concrete and abstract words in young adults. This chapter has been previously published in a manuscript entitled "An fMRI study of concreteness effects in spoken word recognition" (Roxbury et al., 2014)[1]. The aim of this current chapter was to investigate the neural basis of concreteness effects during spoken word recognition when young adults performed an auditory lexical decision task. It was hypothesised that concrete words would elicit greater activity in bilateral brain regions while activity in response to abstract word processing would be contained to the left hemisphere.

[1] The content of this chapter has been modified from the original publication in terms of the formatting in order that the thesis style can be adhered to. As such, the formatting and numbering of the figures and headings differ to that of the manuscript. In all other respects, the chapter is identical to the published manuscript.
Pages 53 and 59 have been modified in the thesis in response to examiner feedback.

2.1 Abstract

Evidence for the brain mechanisms recruited when processing concrete versus abstract concepts has been largely derived from studies employing visual stimuli. The tasks and baseline contrasts used have also involved varying degrees of lexical processing. This study investigated the neural basis of the concreteness effect during spoken word recognition and employed a lexical decision task with a novel pseudoword condition. The participants were seventeen healthy young adults (9 females). The stimuli consisted of (a) concrete, high imageability nouns, (b) abstract, low imageability nouns and (c) opaque legal pseudowords presented in a pseudorandomised, event-related design. Activation for the concrete, abstract and pseudoword conditions was analysed using anatomical regions of interest derived from previous findings of concrete and abstract word processing.

Behaviourally, lexical decision reaction times for the concrete condition were significantly faster than both abstract and pseudoword conditions and the abstract condition was significantly faster than the pseudoword condition ($p < .05$). The region of interest analysis showed significantly greater activity for concrete versus abstract conditions in the left dorsolateral prefrontal cortex, posterior cingulate and bilaterally in the angular gyrus. There were no significant differences between abstract and concrete conditions in the left superior temporal gyrus or inferior frontal gyrus. These findings confirm the involvement of the bilateral angular gyrus, left posterior cingulate and dorsolateral prefrontal cortex in retrieving concrete versus abstract concepts during spoken word recognition. Significant activity was also elicited by concrete words relative to pseudowords in the left fusiform and left anterior middle temporal gyrus. These findings confirm the involvement of a widely distributed network of brain regions that are activated in response to the spoken recognition of concrete but not abstract words. Our findings are consistent with the proposal that distinct brain regions are engaged as convergence zones and enable the binding of supramodal input.

2.2 Introduction

How conceptual knowledge is represented and organised in the brain is a question that remains a point of contention. Previous language studies have attempted to unravel some of the complexities surrounding the organisation and access of semantic conceptual representations and have investigated processing differences between concrete and abstract words. Concrete words such as ‘hospital’ are grounded in sensory-motor experiential knowledge while abstract words such as ‘knowledge’ refer more to verbally encoded concepts (Paivio, 2007). Imageability is often associated with concreteness and these constructs have been treated synonymously (Reilly & Kean, 2007). However, we acknowledge that they are distinct psycholinguistic concepts (Barber, Otten, Kousta, & Vigliocco, 2013; Kousta et al., 2011) and for the purposes of this study, focus on processing differences associated with concrete versus abstract words in spoken word recognition.

Behavioural evidence from healthy individuals has demonstrated that concrete items are processed faster and more accurately than abstract items (Binder et al., 2005; James, 1975; Paivio, 1991, 2007). This processing advantage or concreteness effect has been reported in people with aphasia (Sandberg & Kiran, 2014), deep dyslexia (Coltheart et al., 1980; Franklin, 1989; Goodglass et al., 1969) and semantic dementia (Jefferies et al., 2009). However, the reverse effect, where abstract words are able to be processed more efficiently than concrete words has also been observed (Bonner et al., 2009; Breedin et al., 1994; Kousta et al., 2011; Papagno et al., 2007; Warrington, 1981). This reversal of behavioural effects has been used to suggest the possible independent storage of these conceptual representations.

Theories of semantic memory have been developed to explain concreteness effects. Two prominent and competing accounts are the dual coding theory (Paivio, 1991) and the context availability theory (Schwanenflugel & Shoben, 1983). Both theories predict a superior processing advantage for concrete words due to the increased efficiency of processing systems associated with concrete words. Dual coding theory proposes that two structurally distinct coding systems, a verbal code and a nonverbal, perceptual code, are selectively engaged in response to different types of stimuli. According to this theory, both abstract and concrete words are processed in the verbal system but concrete words are able to recruit additional representations in a nonverbal, imagery-based system. As a result of this dual representation, concrete words are able to be processed more efficiently, resulting in the processing advantage.

In comparison, the context availability theory (Schwanenflugel & Shoben, 1983) suggests that the efficiency with which a word is able to be processed is due to the amount of available context associated with the target. Available context can be thought of in terms of the additional discourse/contextual information preceding the target word (Schwanenflugel, Harnishfeger, & Stowe, 1988) or the specific semantic knowledge about the target word which is individual to each person (Holcomb, Kounios, Anderson, & West, 1999). Words with richer available context, such as concrete concepts, will be processed more efficiently since they have access to a larger network of contextual semantic associations thus resulting in the observed concreteness effect. Abstract words do not have the same level of context surrounding them as their meaning is largely derived from other verbal codes and as such, they are not able to be processed as efficiently.

Both theories acknowledge that abstract words are associated with a reduced set of semantic associations compared to concrete words either in terms of imagery or available context (Pexman et al., 2007). However, differences between the models are centred around the underlying neural substrates which contribute to concreteness effects. Dual coding theory proposes qualitatively distinct systems which are differentially activated such that abstract words and concrete words are processed in the same verbal system in the language dominant left hemisphere but concrete words are able to utilize the additional nonverbal, imagery-based system in the right hemisphere. As a result, concrete words should have a more bilateral representation (Binder et al., 2005; Paivio, 2007). Context availability theory on the other hand proposes quantitative differences within a single system located in the verbal left hemisphere. Both abstract and concrete words will utilize the same system but activation for concrete items will be more extensive due to their richer context availability.

More recent theories of semantic memory have combined neuroimaging and behavioural data to explain conceptual processing. One such account by Binder and Desai (2011) describes a modified embodiment theory ('embodied abstraction') which proposes that conceptual information is processed by modality-specific and heteromodal convergence zones. The convergence zones are located in temporal and inferior parietal regions situated between sensory, motor and affective systems. Modality-specific representations initially develop in response to repeated perceptual experiences and these modal representations converge with high-level heteromodal convergence zones which serve to bind the representations from different modalities (Binder & Desai, 2011). Concept representations are differentially processed based on how familiar they are and the amount of perceptual and contextual information that is available about the target (Binder & Desai, 2011). Thus, as concrete words have strong sensory-motor representations, they would be expected to elicit increased activation compared to abstract words due to their richer set of conceptual features.

It is clear that embodiment theories can account for the representation of concrete concepts but the case for abstract concepts is less obvious. Recent studies have investigated the semantics associated with abstract words (Kousta et al., 2011; Shallice & Cooper, 2013; Vigliocco et al., 2009). Vigliocco et al. (2009) and Kousta et al. (2011) have proposed an extended theory of embodiment and applied a framework which includes abstract words and meaning. They suggest that semantic conceptual representations of concrete and abstract words are acquired through experiential and linguistic knowledge but to different degrees. They argue that concrete concepts are strongly associated with experiential knowledge based in sensory-motor experiences while abstract words and meanings are strongly grounded in linguistic *as well as* experiential knowledge (Kousta et al., 2011; Vigliocco et al., 2009). However, it is the type of experiential knowledge associated with the two word types that differs. While concrete words are embodied through sensorimotor experiential knowledge, abstract words are also embodied but their embodiment occurs instead through the underlying affective and emotional experiential knowledge associated with abstract words (Kousta et al., 2011; Vigliocco et al., 2014; Vigliocco et al., 2009).

Increasingly, neurophysiological evidence has been used to buttress accounts of concreteness and define putative brain regions associated with concrete and abstract conceptual processing. Both auditory and visual modality paradigms have been employed but visual modality tasks have been the most utilized and have included visual recognition (Fliessbach et al., 2006; Mestres-Misse et al., 2009), visual semantic similarity decisions (Noppeney & Price, 2004; Sabsevitz et al., 2005; Whatmough et al., 2004), visual semantic categorisation tasks (Friederici et al., 2000; Pexman et al., 2007) and visual lexical decision tasks (Binder et al., 2005; Evans et al., 2012; Fiebach & Friederici, 2004; Kiehl et al., 1999; Perani et al., 1999; Vigliocco et al., 2014). Auditory modality studies meanwhile have utilized passive listening (Tettamanti et al., 2008; Wise et al., 2000) and mental imagery generation (D'Esposito et al., 1997; Mellet et al., 1998) but it is unclear how these latter studies relate to spoken word recognition versus the retrieval of concrete versus abstract representations.

In general, findings from both visual and auditory studies investigating concrete and abstract words have been highly variable and far from conclusive. Some studies have reported greater left hemisphere activity associated with concrete word processing (Fiebach & Friederici, 2004; Jessen et al., 2000; Mellet et al., 1998; Wise et al., 2000) while others have shown more of a bilateral pattern of activation for concrete words (Binder et al., 2005; Sabsevitz et al., 2005) and greater left hemisphere activation for abstract words (Binder et al., 2005; Sabsevitz et al., 2005) which has been used to support theories of dual coding. Meanwhile, other studies have not shown activation for concrete words in either hemisphere but instead elicited activity for abstract words only and this varied from the left (Noppeney & Price, 2004) to right (Kiehl et al., 1999) to bilateral hemispheres (Friederici et al., 2000; Grossman et al., 2002; Perani et al., 1999; Pexman et al., 2007). These findings do not support either context availability theory or dual coding theory as neither suggests greater activity for abstract terms should occur. The discrepant findings on concreteness effects have been largely attributed to differences in methodology, modality of input (Kotz et al., 2002), baseline contrasts, and differences in imaging techniques.

Recent meta-analyses by Binder et al. (2009) and Wang et al. (2010) have combined findings from previous studies on concreteness effects with the aim of clarifying some of the inconsistent results. The meta-analysis by Binder et al. (2009) included 17 studies on concrete and abstract processing and identified 113 overlapping foci associated with perceptual (concrete) processing and 34 for verbal (abstract) processing. Regions associated with concrete processing were located in bilateral angular gyrus (AG), left posterior cingulate, left dorsomedial prefrontal cortex and left mid fusiform while left inferior frontal gyrus (IFG), largely pars orbitalis and anterior superior temporal sulcus (aSTS) were associated with abstract processing. The meta-analysis on concrete word processing by Wang et al. (2010) was based on 19 studies, ten of which were also included in the Binder et al. meta-analysis (2009). Concrete words showed more activation in left precuneus, left posterior cingulate, left fusiform and left parahippocampal regions while abstract processing was associated with left IFG, left middle temporal gyrus (MTG) and left superior temporal gyrus (STG).

One type of task commonly used to explore putative cognitive processing mechanisms associated with word recognition and semantic processing is a lexical decision task which is the focus of the present study. Lexical decisions have been shown to produce reliable semantic effects when used in a priming paradigm (Balota et al., 2007) and have been used to explore effects of concreteness. However, to date, the majority of the imaging studies investigating lexicality have focused on the visual modality (Binder et al., 2005; Fiebach & Friederici, 2004; Kiehl et al., 1999; Perani et al., 1999) while lexical decision tasks employing the auditory modality have been largely neglected. Critically, the visual modality has a number of limitations. Visual representation codes associated with picture-based stimuli may have a confounding effect while shallow processing has been associated with rapid orthographic analysis in written lexical decision tasks (Grainger & Jacobs, 1996). Visual lexical-semantic tasks might be able to be performed with only superficial semantic processing due to orthographic familiarity of the stimuli (Balota et al., 1991; Balota et al., 1999) and furthermore, studies that have investigated visual lexical decision tasks have identified increased activation in the inferolateral regions which may be more attributable to grapheme - phoneme conversion routes rather than semantic processing per se (Herbster et al., 1997; Price, 1998; Rumsey et al., 1997).

Findings from auditory modality studies investigating lexicality have in some cases not observed activity in regions associated with phoneme to grapheme conversion (Kotz et al., 2002; Newman & Twieg, 2001), further highlighting the benefits of using the spoken word to explore concrete and abstract processing. However, to date, the reported activation from auditory modality tasks has also not been consistent across studies (Kotz et al., 2002; Newman & Twieg, 2001; Raettig & Kotz, 2008; Shafto et al., 2012). One possible reason for this variability is the type of nonword baseline used to discriminate phonological and semantic based processes. Methods used to create nonwords can vary enormously and result in the formation of very different types of nonwords (Bedny & Thompson-Schill, 2006) which may engage different processing mechanisms (Raettig & Kotz, 2008). Raettig and Kotz (2008) demonstrated that lexical transparency, the point of deviation and phonotactic legality all affect how a nonword will be processed. If a nonword is too like a real word, it may activate semantic representations whereas if it is too ‘unwordlike’ it will be dismissed prior to any phonological level processing. They conclude that opaque pseudowords are the preferred type of nonword stimuli. While opaque pseudowords are able to be processed phonologically as legal real words, lexical access is prevented and consequently any semantic based processing will be minimised (Raettig & Kotz, 2008).

As such, the aim of this study was to investigate the neural basis of the concreteness effect during spoken word recognition and employ a lexical decision task with a novel pseudoword condition. The method used in this study to generate the pseudowords is comparable to the Balota, Cortese, Sergent-Marshall, Spieler, and Yap (2004) study in that the nonwords were created by reordering the real word stimuli. However the stimuli employed in the Balota et al. (2004) study were monosyllabic words of 1 to 3 letters whereas this present study used polysyllabic words which were developed according to the criteria described in Raettig and Kotz (2008) and Valdois et al.

(2006). This method involved rearranging the syllables from the real word conditions while ensuring that the constituent position of each syllable remained constant (Valdois et al., 2006). As a result, the pseudowords were comparable to the real words in terms of phonology, length and legality but opaque enough to prevent elicitation of conceptual semantic representations (Raettig & Kotz, 2008). Consequently, we predicted that the use of a robust baseline would enable observation of discrete brain activation associated with concrete and abstract spoken word processing. In addition, by making the pseudowords as close to real words as possible, discrimination between the word types was made as difficult as possible thereby increasing any associated semantic based activation associated with the real word conditions (Evans et al., 2012). We examined activity in regions of interest (ROIs) selected from the meta-analysis of Binder et al. (2009) to explore whether the reported 'perceptual' and 'verbal' regions could be reliably activated during spoken word recognition of concrete and abstract words using an auditory lexical decision task.

2.3 Methods

2.3.1 Materials

The stimuli consisted of 60 English real words and 60 phonologically legal pseudowords. The 60 real words comprised 30 concrete, high imageability polysyllabic nouns (e.g. wallet, hospital) and 30 abstract, low imageability polysyllabic nouns (e.g. saga, rarity). Stimuli in both real word conditions were controlled for the following variables; (i) spoken word frequency (SpFreq), (ii) written word frequency (WFreq), (iii) phoneme length, (iv) phonological neighbourhood density (PND), (v) concreteness (Concr), (vi) imageability (Img) and (vii) number of syllables (Refer Table 1 for statistical significance and stimuli characteristics). There were no significant differences ($p >$ .05) between the two real word conditions on any of the variables except for (v) concreteness and (vi) imageability. Average durations for the stimuli were analysed using the Kruskal-Wallis test (Kruskal & Wallis, 1952) and were not significantly different across conditions ($p > .05$) with mean durations of 724ms (*SD*: 105ms) for concrete, 772ms (*SD*: 119ms) for abstract and 780ms (*SD*: 93ms) for pseudowords.

Table 1. Summary statistics for the two stimulus conditions (Mean (SD)) for a range of variables, plus the significance from a *t*-test comparing conditions

Condition	SpFreq CELEX[1]	Phonemes MRC[2]	WFreq CELEX[1]	PND ELP[3]	Concr MRC[2]	Img MRC[2]	Syllable MRC[2]
Concrete	30.2 (46.4)	6.1 (1.4)	45.9 (45.3)	1.0 (1.2)	586.9 (27.4)	600.5 (17.2)	2.47 (0.5)
Abstract	39 (31.3)	6.2 (1.4)	52.4 (38.7)	0.77 (0.9)	300.03 (42.2)	328.9 (31.3)	2.47 (0.5)
p	*.397 ns*	*.780 ns*	*.553 ns*	*.345 ns*	*<.0001*	*<.0001*	*1.000 ns*

[1]N-Watch database (Davis, 2005).
[2]MRC psycholinguistic database (Wilson, 1988).
[3]English Lexicon Project (Balota et al., 2007).

Sixty pseudowords, matched for phonemes and syllables were created from the 60 real words. All the real words were segmented according to their syllable boundaries, taken from the MRC database (Wilson, 1988). The syllables for each word were then recombined but kept in their original constituent positions (Valdois et al., 2006) in order to control for syllable frequency. Thus sixty, phonologically legal, opaque pseudowords of 2 and 3 syllables were created (e.g. culief, esiter) in accordance with Raettig and Kotz (2008). Syllable boundaries were checked to ensure legality. Any mix of syllables that resulted in an illegal combination or a word that resembled a real word was not selected for inclusion. All stimuli were digitally recorded with a Rode NTK condenser microphone in a soundproofed room using a trained, female native English speaker who was not made aware of the study purpose.

2.3.2 Participants

Twenty-six healthy young participants aged between 18 and 35 years were recruited to the study. All participants had English as a primary language, were right-handed as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971) and had sufficient vision and hearing to perform the task. None of the participants reported any neurological disease or disorder, mental illness, head trauma, alcoholism or cerebral tumour. Structural scans from all participants were reviewed by a neuroradiologist for abnormalities. As a result, three of the 26 participants were identified as having an incidental finding of clinical significance and were not included in the analysis. Six additional participants were excluded due to subject compliance and technical issues leaving a total of 17 subjects in the analysis (9 female, 8 male; mean age 27, *SD*: 5.1). The study received approval from the Queensland Health Ethics Committee, University of Queensland Medical Research Ethics Committee and site specific approval from the Royal Brisbane and Women's Hospital Ethics Committee. Full written consent was obtained from all participants and each received a $30 reimbursement.

2.3.3 Procedure

The experiment consisted of 120 trials presented in an event-related design with two individual runs completed in the same session. Prior to the scanning session, the task was explained to each participant and examples practised until at least an 80% success rate was achieved. Once inside the scanner, the button press was placed in the participant's left hand and reminders given about the correct orientation for response, with a left button for 'yes' to respond to real words and a right button for 'no' to respond to pseudoword stimuli. The left hand was used to enable comparisons to be made with a future-planned companion study on people with post-stroke aphasia performing the same task. At the start of each stimulus presentation, a small black fixation cross was presented visually in 48 point font for 2.3s, along with the instruction 'Is it a real word?'. Each real word or pseudoword was presented auditorily with the mean length of presentation lasting an average of 764ms (*SD*: 105ms). After hearing each stimulus, subjects had 3.5s to respond. During the response/sound window a black "+" was on the screen plus Yes/No indicating the correct orientation for response. Once a response had been received, a large blue cross (84 point font) appeared on the screen. After 1s, this changed to a black cross (84 point font) which remained visible until the start of the next trial/event as detailed in Figure 2.

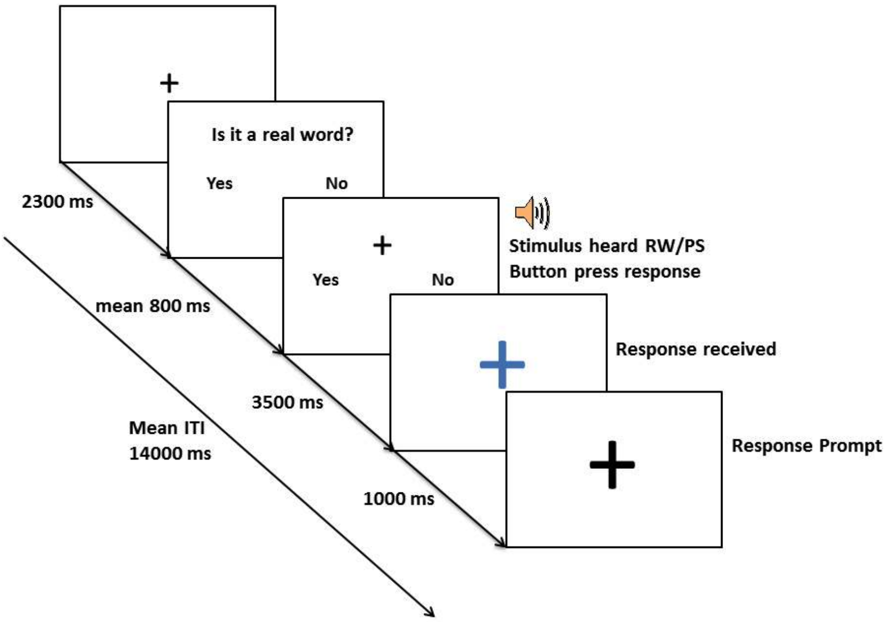

Figure 2. Acquisition sequence for auditory lexical decision task. (RW – real word, PS – pseudoword).

A long inter-trial interval (jittered between 10-18s, mean 14s) was employed to allow for the delayed hemodynamic response function observed with stroke patients (Bonakdarpour et al., 2007; Meinzer, Lahiri, Flaisch, Hannemann, & Eulitz, 2009) and to enable future comparison with a planned companion study on individuals with post-stroke aphasia. Order of presentation within each run was pseudorandomised with no more than four items from any one condition (concrete real words, abstract real words and pseudowords) being presented in succession and never more than four words or pseudowords in a row. Additionally, real words and pseudowords which shared constituent syllables were never presented in consecutive order. Five different pseudorandomised orders were applied to reduce order effects across participants. All stimuli were presented binaurally using MR confon headphones (MR Confon GmbH, Magdeburg, Germany) and responses recorded with an MR compatible button box (Current Designs Inc, Philadelphia PA). Prior to the scan, subjects were reminded to keep their eyes open and to look at the fixation cross in order to prevent eye movement.

2.3.4 Data Acquisition

Structural and functional images were collected on a Siemens Trio (3T; Siemens Erlangen) at the Royal Brisbane and Women's Hospital. The design of the fMRI task was a pseudo-randomised event-related design consisting of two runs of approximately 14.4 minutes administered across one session. Gradient echo EPI images with BOLD sensitivity were acquired during each of the runs, resulting in 390 brain volumes, 36 x 3mm slices, with a 0.3mm gap, FOV 220x220mm, flip angle 90, matrix 64x64, TE 30, TR 2210ms. A high resolution 3D structural T1-weighted MP-RAGE image was also acquired ($(0.9mm)^3$ resolution; TE/TR 2.4/1900ms TI 900ms).

2.3.5 Image Processing

Images were processed and analysed using statistical parametric mapping software (SPM8, Wellcome Department of Cognitive Neurology, London, UK) with MATLAB 2009a (The MathWorks Inc., Natick, MA). To allow for steady state magnetization, five dummy scans were acquired at the start of each run and excluded from analysis. INRIAlign (Freire, Roche, & Mangin, 2002) was used for spatial preprocessing of the image time series and to correct for motion artefacts. Registration of the time series mean EPI image in Run 1 and Run 2 was coregistered with the T1 image which had been acquired in the same scan session. The T1 image was segmented using New Segment (Ashburner & Friston, 2005). A DARTEL template was created from all participants and each subject normalized to it (Ashburner, 2007). These transformations were applied to the realigned EPI time series before an 8mm full-width half-maximum (FWHM) Gaussian kernel was applied to spatially smooth the normalised volumes ($3.0 \times 3.0 \times 3.0mm^3$).

2.3.6 Data Analysis

A general linear model analysis using a hemodynamic response function with derivatives was used for the fixed effects analysis per subject. Conditions in Run 1 and Run 2 were combined in the design matrix. Due to the small numbers of errors (average 2 per subject), incorrect trials were excluded from the time series. Realignment parameters in 6 degrees of freedom were included as regressors of no interest. Covariates were created to model the BOLD signal change associated with the different event trials and contrasts included concrete – abstract, concrete – pseudoword and abstract - pseudoword. The mean corrected reaction time was included in the regression model, similar to Binder et al. (2005), to remove any confounding effects associated with the variability in reaction time from the comparisons of concrete to abstract to pseudowords.

A random effects analysis of the group was carried out on each condition. Differences in BOLD signal between the three conditions of concrete, abstract and pseudoword were evaluated using a regression analyses. The FWHM was calculated from the square root of the residuals (with 3dFWHMx; Analysis of Functional Neuroimages (Cox, 1996)) and used as input to 3dClustSim to calculate a cluster threshold correction for multiple comparisons. Adopting a height threshold of $p < .001$ uncorrected for the whole brain analysis, a FWE (familywise error) rate of $p < .05$ was achieved with a minimum cluster threshold of 45 contiguous voxels. The probabilistic cytoarchitectonic maps from the Anatomy Toolbox (Eickhoff et al., 2007) were used to identify the neuroanatomical location of peak maxima for the specific contrasts.

Region of interest (ROI) analyses were carried out based on a priori hypotheses about hemispheric lateralization differences associated with the processing of concrete and abstract words and findings from the Binder et al. meta-analysis (2009). As a result, a total of nine anatomical ROIs were selected (see Figure 3). Six of these ROIs were associated with concrete processing and were created in the left and right AG, left superior frontal gyrus (SFG), left middle frontal gyrus (MFG), left posterior cingulate and left fusiform. Binder et al. (2009) also reported increased activation for abstract concepts in the left IFG (mainly pars orbitalis) and left aSTS. As such, three further ROIs were created to explore potential activity associated with abstract word processing. ROIs were created in the anterior superior temporal gyrus (aSTG) and anterior middle temporal gyrus (aMTG) to enable investigation of the aSTS and a third ROI was created in the left pars orbitalis.

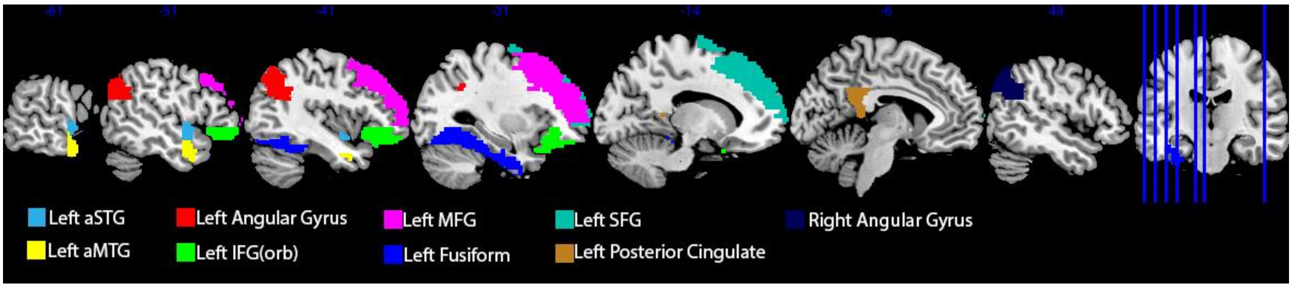

Figure 3. Nine anatomical ROIs. Light blue – aSTG, yellow – aMTG, green – IFG(orb), pink – MFG, turquoise – SFG, blue – Fusiform, red – left AG, dark blue – right AG, gold –posterior cingulate.

ROIs were created by using the IBASPM 116 Human Atlas in WFU PickAtlas (Maldjian, Laurienti, & Burdette, 2004; Maldjian, Laurienti, Kraft, & Burdette, 2003) in SPM8 (Friston, 2007). Anterior ROIs (aSTG and aMTG) were subdivided based on the classification of Indefrey and Levelt (2004) of y<-7. MarsBaR (Brett, Anton, Valabregue, & Poline, 2002), a region of interest toolbox for SPM8, was used to extract the percentage mean signal change for each participant for each ROI. Group statistical analyses were then performed using SPSS Statistics version 21 (IMB; Armonk, New York, USA). A repeated measures analyses of variance (ANOVA) with factors of condition (3) x ROI (9) was performed. Huynh-Feldt corrections (Huynh & Feldt, 1970) were applied when the assumption of sphericity was not met and are reported throughout with the original degrees of freedom. Testing for pairwise differences between conditions (concrete – abstract, concrete – pseudoword, abstract – pseudoword) in all nine ROIs was performed with an adjusted *p* level using Benjamini and Hochberg's correction for multiple comparisons (Benjamini & Hochberg, 1995).

2.4 Results

2.4.1 Behavioural Results

Reaction time data was calculated from stimulus onset. Only correct responses were analysed, with trials less than 100ms removed. There was a significant main effect for condition $F(2, 1999) = 91.582$, $p < .0001$. Participants responded fastest to concrete words followed by abstract words then pseudowords (see Table 2) with a significant difference between each condition (all $p < .001$). There was no statistically significant difference in accuracy between conditions ($p = .386$).

Table 2. Behavioural results

CONDITION	Reaction Time (*SE*) (ms)	% accuracy
Concrete	1187.19 (15.89)	98.6 (0.006)
Abstract	1262.99 (16.00)	97.5 (0.006)
Pseudoword	1433.81 (11.26)	98.1 (0.004)

2.4.2 Anatomical Region of Interest Analyses

Results from the ROI analyses are shown in Figure 4 with the mean percent signal change of BOLD signal for the three conditions in each of the ROIs. There was a main effect of condition for the left AG, $F(1.225, 19.601) = 18.248$, $p < .0001$. Increased BOLD signal was observed for concrete ($p < .0001$) and abstract ($p = .008$) compared to pseudowords and concrete compared to abstract words ($p < .0001$). There was a main effect of condition for the right AG, $F(2, 15) = 21.15$, $p < .0001$ and increased BOLD signal for concrete ($p < .0001$) and abstract ($p = .025$) compared to pseudowords. Concrete words also elicited increased BOLD signal compared to abstract words ($p = .007$).

A main effect of condition was observed for left SFG $F(2, 15) = 8.812$, $p = .003$. There was increased BOLD signal for concrete compared to abstract ($p = .049$) and pseudoword ($p = .004$). There was a main effect of condition for left MFG $F(2, 15) = 9.897$, $p = .002$ and increased BOLD signal for concrete compared to abstract ($p = .008$) and pseudoword ($p < .0001$). There was also a main effect of condition for left posterior cingulate $F(2, 15) = 12.579$, $p = .001$ with increased BOLD signal for concrete compared to abstract ($p = .004$) and pseudoword ($p < .0001$). A main effect of condition in the left fusiform $F(1.346, 21.529) = 4.811$, $p = .03$ was also seen with increased BOLD signal for concrete compared to pseudowords ($p < .0001$).

The left IFG (pars orbitalis), aSTG and aMTG ROIs were included to investigate association with abstract word processing (Binder et al., 2009). Of these only left aMTG showed a main effect for condition $F(2, 15) = 7.49$, $p = .006$, but with increased BOLD signal for concrete compared to pseudowords ($p = .025$).

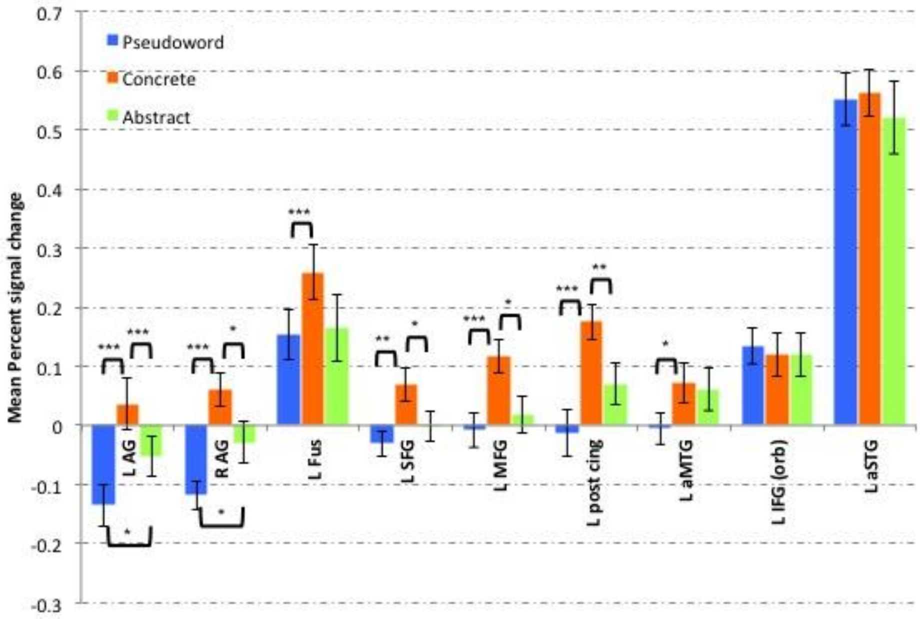

Figure 4. Percent signal change from the regions of interest.
* $p < .05$; ** $p < .005$; *** $p < .0001$.
(Abbreviations: L AG = left angular gyrus; R AG = right angular gyrus; L Fus = left fusiform, L SFG = left superior frontal gyrus; L MFG = left middle frontal gyrus; L post cing = left posterior cingulate; L aMTG = left anterior middle temporal gyrus; L IFG (orb) = left inferior frontal gyrus (pars orbitalis); L aSTG = left anterior superior temporal gyrus).

2.4.3 Whole Brain Analyses

The whole brain results for concrete greater than pseudoword, abstract greater than pseudoword and concrete greater than abstract are shown in Table 3 and Figure 5. No cortical regions were significantly more activated for abstract greater than concrete words. There was a bilateral pattern of activity for both concrete and abstract words when compared to pseudowords. The right precuneus was the sole region that was commonly activated by both concrete greater than pseudoword and abstract greater than pseudoword contrasts and this was more extensive for concrete than abstract words, extending into right AG and occipital regions. In the direct contrast between concrete and abstract, a bilateral pattern of activity was elicited for concrete words.

However, this bilateral activity appeared to be slightly more left-lateralised.

Table 3. Whole brain regions showing significant BOLD peak activation

Contrast	Structure	*x*	*y*	*z*	Volume	*Z*-score
Concrete>Pseudoword	right precuneus	7	-50	47	6101	6.14
	right hippocampus	32	-32	-7	609	4.93
	left MFG	-32	25	54	341	4.49
	Left ITG	-54	-14	-25	105	4.26
Abstract>Pseudoword	left MTG	-54	-58	18	82	4.37
	right SMG	50	-40	32	62	4.04
	right precuneus	14	-50	32	58	3.86
Concrete>Abstract	right mid occipital g	40	-65	29	85	4.89
	left IPC (PGP)[1]	-47	-76	29	141	4.53
	left calcarine g	-7	-58	7	349	4.47
	left fusiform	-22	-36	-18	51	4.47
	right MFG	25	22	40	53	4.16

Peak activations for whole brain analyses for all participants in each condition ($p < .001$ probability threshold and 45 voxel cluster threshold). MFG = middle frontal gyrus, ITG = inferior temporal gyrus, MTG = middle temporal gyrus, SMG = supramarginal gyrus, g = gyrus.

[1] See Caspers et al 2006 (Caspers et al., 2006) for details of this area.

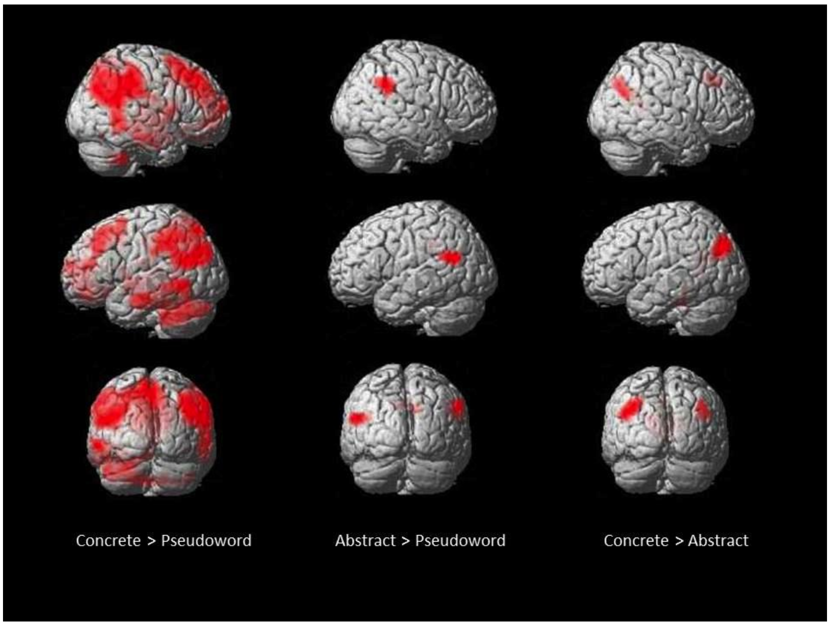

Figure 5. Whole brain results. Significant peak activations for group whole brain analyses in each condition are shown in red on a rendered brain. Surface structures are in darker shades of red. Significance was determined by a $p < .001$ probability threshold and 45 voxel cluster threshold.

2.4.4 Summary of Results

There was a concreteness effect in terms of faster speed of response for concrete words compared to abstract words. Anatomical ROI analyses revealed significant increased signal for concrete words compared to both abstract and pseudowords in left and right AG, left SFG, left MFG, left posterior cingulate. Significant signal differences were also observed in the left fusiform and left aMTG for concrete words but only for the concrete – pseudoword contrast. The AG was the sole brain region which elicited significant differences in activity between all three conditions, with concrete words eliciting greater activation than both abstract and pseudowords. Abstract words also produced greater activity than pseudowords in bilateral AG. Greater activity for abstract words compared to concrete words was not observed in any of the nine ROIs. Whole brain results showed bilateral activity for concrete and abstract words when compared to pseudowords. Bilateral activation was also seen for concrete words when directly compared to abstract words.

2.5 Discussion

The aim of this study was to investigate brain activity associated with recognising spoken concrete and abstract words. We predicted that concreteness effects would be reflected in reaction time data and accuracy of response. We also predicted that the use of an opaque pseudoword condition would provide a robust baseline against which to measure differential brain-related activity elicited directly in response to concrete and abstract spoken word recognition. We anticipated that concrete words would elicit increased brain activity in bilateral brain regions while abstract words would elicit greater activity in left-lateralised language processing networks. The present study revealed bilateral activity for concrete words, however, we did not see a left-lateralised pattern of activity for abstract words. Our results confirm the involvement of the angular gyrus, posterior cingulate and dorsolateral prefrontal cortex in retrieving concrete versus abstract concepts during spoken word recognition, consistent with previous meta-analyses on concrete and abstract processing based primarily on visually presented words (Binder et al., 2009; Wang et al., 2010). Overall, our findings suggest that heteromodal association areas were activated when recognising spoken concrete and abstract words consistent with the view that these regions interface with a critical set of modality-specific representations.

The behavioural results showed that concrete items were responded to significantly faster than both abstract and pseudoword conditions and the abstract condition was significantly faster than the pseudoword condition. The observed increased efficiency for concrete over abstract words is in accordance with the two dominant theoretical accounts used to explain effects of concreteness; dual coding theory (Paivio, 1991) and context availability theory (Schwanenflugel, 1991; Schwanenflugel & Shoben, 1983) which both predict a processing advantage for concrete words. There was no difference in accuracy across the three conditions which was most likely due to a ceiling effect.

Of the nine ROIs selected to investigate concrete and abstract word processing, the right and left AG proved to be the sole brain region that showed significant differences in activation between all three contrasts with concrete words eliciting greater activity than both abstract words and pseudowords and abstract words eliciting stronger activation than pseudowords. Increased activation for concrete items in the right AG has previously been reported in visual word processing studies investigating concrete and abstract words (Binder et al., 2005; Jessen et al., 2000). These findings provide support for dual coding theory which predicts that concrete words will recruit additional image-based codes represented in the right hemisphere. However, our results also showed stronger activation in the left AG for concrete items compared to abstract words which is inconsistent with dual coding theory. Rather, it is more consistent with a single system model of processing such as the context availability theory. This model suggests that concrete words access the same verbal regions as abstract words but to a greater degree due to the larger amount of associated context available to concrete words. As such while the context availability theory does not preclude right hemisphere involvement, the verbal language-based left hemisphere regions are more likely to be recruited. The left AG has been associated with general semantic retrieval processes (Price, 2010) and was the region which was most reliably activated across the 120 studies in the Binder et al. (2009) semantic meta-analysis as well as having the largest number of activation foci for concrete words specifically (Binder et al., 2009).

The ROI analysis also revealed greater activity for concrete versus abstract words in the left posterior cingulate, SFG and MFG. The posterior cingulate has previously been described as a connector hub, structurally linking other cortical and subcortical brain networks (Hagmann et al., 2008). Binder et al. (2009) suggest that this region is implicated in many semantic based tasks as a result of the nature of episodic encoding. Words that have a richer set of concepts and associations such as concrete items will evoke enhanced episodic encoding (Binder et al., 2009) while activation of abstract words will be less strong as they have weaker associations with specific episodic memories.

Significantly greater activity for concrete compared to abstract words in the left MFG and SFG also suggests a critical involvement of these frontal regions in the processing of concrete information. However, the specific role of these regions in semantic conceptual processing is not well understood and their activation in language-based tasks is commonly thought to be in response to more executive type task demands. The MFG and SFG have previously been associated with working memory (Peelle, McMillan, Moore, Grossman, & Wingfield, 2004) and have been implicated in a distributed network monitoring and facilitating comprehension (Hampson, Driesen, Skudlarski, Gore, & Constable, 2006; Scott, Leff, & Wise, 2003). The MFG has been associated specifically with auditory lexical decision tasks (Rissman, Eliassen, & Blumstein, 2003) and controlled cognitive processing (Aron, Monsell, Sahakian, & Robbins, 2004). Whole brain results also indicated an involvement of the right MFG for the concrete greater than abstract contrast and this region has previously been associated with auditory attention and comprehension (Giraud et al., 2004; Rissman et al., 2003) and monitoring (Stuss, 2011).

Previously, executive task-related engagement of frontal regions has been associated with increased effort and a corresponding increased response time, however the findings in this present study do not support this view as our behavioural results demonstrate clear involvement of these regions in concrete word processing without any associated increase in time on task. It is possible these frontal regions are recruited to monitor activation of the word candidate in the associated lexical-semantic network while a decision on lexicality is made (Rissman et al., 2003), however this does not explain why significant activity was observed for concrete words only. An alternative proposal is that these frontal regions are implicated in the creation, integration and manipulation of a strong mental representation as sensory-motor information associated with concrete concepts is activated within the language processing network (Barber, Kousta, Otten, & Vigliocco, 2010; Barber et al., 2013). This interpretation should be treated with caution however, given that our whole brain analyses did not identify increased activity in other regions associated with sensory-motor processing for this contrast.

ROI analyses of both the left fusiform gyrus and aMTG elicited additional activation in the concrete greater than pseudoword contrast. The fusiform has been referred to as a basal temporal language area (Luders et al., 1991) and our findings for concrete words are consistent with a role that this region plays in visual imagery associated with language processing. The fusiform has previously been associated with both lexical decisions (Kiehl et al., 1999) and auditory semantic retrieval processes (Adams & Janata, 2002). Discrete activation in this brain region relating to concrete word processing has also been observed in studies investigating imageability associated with concrete and abstract word processing (D'Esposito et al., 1997; Mellet et al., 1998; Sabsevitz et al., 2005; Wise et al., 2000) and this has been attributed to the greater levels of visual imagery associated with concrete concepts (D'Esposito et al., 1997; Fiebach & Friederici, 2004; Sabsevitz et al., 2005; Wise et al., 2000). Wise et al. (2000) suggest that once a word has been perceived as real, the fusiform serves to encode semantic representations (in terms of episodic and semantic memory) associated with the verbal input and this region may therefore act as a lexical-semantic store (Gold et al., 2006).

The aMTG was examined as an ROI to explore the aSTS, which was reliably activated by abstract words in the Binder et al. meta-analysis . In order to ensure complete coverage of the aSTS, both the aMTG and aSTG were included as ROIs although neither region elicited any increase in activity for abstract words. On the contrary, our results for aMTG showed a significant increase in activity for concrete words when compared to pseudowords. The anterior MTG has previously been associated with the access of conceptual representations as they become increasingly more semantically specific (Price, 2012) and the anterior temporal lobe has been described as an amodal semantic hub, implicated in the integration of conceptual and semantic information (Bonner & Price, 2013; Patterson, Nestor, & Rogers, 2007). Lesions in aMTG have been associated with lexical-semantic deficits and category specific impairments (Lambon Ralph, Lowe, & Rogers, 2007; Warrington & Shallice, 1984). The literature is mixed on the results of aMTG lesions and concreteness effects with Jefferies et al. (2009) showing a processing advantage for concrete over abstract words while other studies have demonstrated a reverse concreteness effect (i.e. greater preservation of abstract words)(Reilly, Peelle, & Grossman, 2007; Yi et al., 2007).

Our results clearly demonstrate that lateral and ventral temporal regions were engaged in lexical-semantic processes but only for the concrete greater than pseudoword contrast. No differences were observed in these regions for either the concrete greater than abstract or abstract greater than pseudoword contrasts. As such, we tentatively propose that these regions may serve as lexical-semantic stores prior to subsequent processing and that the selective activation observed for concrete words when compared to pseudowords may be due to equivalent activation in these regions from processing nonverbal codes associated with abstract words and processing verbal codes associated with opaque pseudowords. To expand on the first point, we suggest that abstract words like concrete words are in fact associated with a set of nonverbal imaginal representations although they are just more weakly represented than the nonverbal representations associated with concrete words. For instance, a word such as *charity* might be associated with nonverbal, imaginal associative knowledge such as a collection tin or a red cross sign (Wise et al., 2000) and will therefore activate a set of nonverbal associations, albeit more weakly than concrete words which have strong imaginal referents attached to them. As a result, potential differences in brain-related activity in these regions related to concrete and abstract conceptual processing will be reduced.

Secondly, no significant differences in activation between abstract and pseudowords were observed in these lateral and ventral regions. Indeed, the lack of activation differences associated with abstract and pseudoword processing was a common finding in this study. Of the nine ROIs, only bilateral AG elicited a difference between abstract and pseudoword processing. We suggest that this finding may be due to the type of pseudowords employed in this study and the verbal codes attached to them. The opaque pseudowords shared features common to both the abstract and concrete words such as phonemes and syllables which enabled them to be processed in the same lexical networks as the real words (Hickok & Poeppel, 2007). However, the opaqueness minimised any word specific knowledge and subsequent semantic based activity (Raettig & Kotz, 2008). As such, the opaque pseudowords activated associated verbal codes as the lexicon was searched for real word matches, resulting in brain activity similar to that evoked during the auditory presentation of abstract words to a degree and reducing any activation differences associated with the spoken word recognition of abstract and pseudowords. However, unlike the abstract words, nonverbal representations were not associated with the pseudowords as the stimuli were meaningless and imaginal codes therefore non-existent. Thus, we suggest that where there were differences between concrete and pseudoword contrasts only, such as in the lateral and temporal regions, these are likely due to the strong nonverbal (conceptual) representations or features associated with concrete words, which are only weakly represented in abstract words and not associated at all with the opaque pseudowords.

In summary, our findings demonstrate that brain activity was reliably elicited during this auditory lexical decision paradigm in most of the regions previously showing activity for concrete word processing using visual word processing paradigms; bilateral AG, left posterior cingulate, SFG, MFG, fusiform and aMTG. In terms of the prominent theories regarding concrete and abstract word processing our findings for the recognition of spoken concrete words provide some support for both a dual representation and single system model. The selective activation of concrete words in three of the six ‘perceptual’ regions; left SFG, MFG and posterior cingulate, identified in the Binder et al. meta-analysis , provides support for dual coding theory which predicts that concrete words are represented in distinct neural systems which are differentially activated in response to more image-based, nonverbal codes. The additional activation for concrete items in the right AG is also consistent with dual coding theory which predicts greater recruitment of nonverbal, right hemisphere for concrete words.

However, we also observed quantitative activation differences for all three conditions in left and right AG suggesting that this brain region serves as a common zone which is differentially activated in response to both abstract and concrete terms compared to pseudowords. These findings provide support for the context availability theory which proposes that in a single system model, common regions will be implicated in real word processing but to differing degrees. Since concrete words have a richer set of contextual representations available to them than abstract words, they will elicit stronger activity than abstract words although activity will occur in common regions.

Importantly, our findings provide support for the embodied abstraction theory proposed by Binder and Desai (2011) which suggests that large parts of the temporal and inferior parietal cortex serve as multimodal convergence zones and are integral in the binding of modality-specific information. Specifically, our results support the view that bilateral AG serves as a convergence zone binding supramodal input from modality-specific and heteromodal systems. Conceptual representations of concrete and abstract words will be differentially processed according to the amount of associated sensory, motor and affective representations with levels of activity in the AG responding to the amount of semantic information associated with the target word. Both concrete and abstract words will elicit greater levels of activity compared to pseudowords due to the greater amount of semantic representations attached to real words. However, concrete words will elicit stronger activity than abstract words as they are associated with stronger conceptual representations.

Lastly, the ROI and whole brain results for abstract word processing in this present study are in agreement with both dual coding and context availability theory in that neither theory proposes that greater activity should be elicited by abstract compared to concrete words. However, our results also show minimal processing differences when abstract words were compared with pseudowords and this lack of activation difference was a pattern which was consistent in all ROIs except bilateral AG. This is an interesting finding and whilst we have provided a tentative explanation for the increased activity observed for concrete but not abstract words when compared to pseudowords, the present study cannot definitively say whether the this pattern of activity can be attributed to the type of stimuli, the task employed or modality of presentation. Future studies investigating spoken word recognition of concrete and abstract words will need to consider possible effects of the verbal and nonverbal, imaginal codes likely associated with abstract conceptual representations.

Whilst this study has provided a number of findings regarding the processing of spoken concrete and abstract words during a lexical decision task, we acknowledge that there are some limitations with the stimuli selection employed. Firstly, we were unable to control for the first phoneme across the conditions and as such, this needs to be considered as a possible confound and the results interpreted accordingly. Secondly, the abstract stimuli selected for use in this study were also of very low imageability and it may be helpful in future studies to attempt to match for imageability across both concrete and abstract conditions although this is challenging.

2.6 Conclusion

Findings from the ROI analyses in this study demonstrate that the recognition of spoken concrete words reliably activates a wide network of brain regions in the AG bilaterally, left posterior cingulate and left dorsolateral prefrontal cortex more than both abstract and pseudowords. Concrete words also activated regions in the left fusiform and left anterior MTG but this activation was only elicited for the concrete greater than pseudoword contrast. Our findings further define possible convergence zones proposed to bind supramodal input from modality-specific and heteromodal systems, and confirm the role of these regions in processes beyond initial modality specific lexical processing.

3 Chapter Three

An fMRI study of Concreteness Effects during Spoken Word Recognition in Ageing. Preservation or Attenuation?

Chapter 3 examined whether the activation patterns observed in Chapter 2 would be replicated in a group of older adults performing the same fMRI task. In particular, we wanted to examine whether the effects of concreteness showed attenuation or preservation in ageing and whether a difference in performance from that of the healthy young adults was accompanied by an altered pattern of neural activity. It was hypothesised that if the older adults demonstrated preserved concreteness effects, this would be accompanied by an age-related upregulation possibly involving the right prefrontal cortex. The content of this chapter has been published in Frontiers for Aging Neuroscience (Roxbury et al., 2016)[2].

[2] This chapter has been modified from the original publication in order that the formatting requirements for the numbering of the headings, figures and tables are consistent with the format of the thesis. No other modifications have been made and the content is identical to the published manuscript.
Pages 70 and 72 have been modified in the thesis in response to examiner feedback.

3.1 Abstract

It is unclear whether healthy ageing influences concreteness effects (i.e. the processing advantage seen for concrete over abstract words) and its associated neural mechanisms. We conducted an fMRI study on young and older healthy adults performing auditory lexical decisions on concrete versus abstract words. We found that spoken comprehension of concrete and abstract words appears relatively preserved for healthy older individuals, including the concreteness effect. This preserved performance was supported by altered activity in left hemisphere regions including the inferior and middle frontal gyri, angular gyrus, and fusiform gyrus. This pattern is consistent with age-related compensatory mechanisms supporting spoken word processing.

3.2 Introduction

Word retrieval deficits are well documented in healthy older individuals (Burke & Shafto, 2004; Burke & Shafto, 2008) while word knowledge (Verhaeghen, 2003) and language comprehension abilities appear less susceptible to ageing effects (Tyler et al., 2010). The present study is focused on how older adults process concrete versus abstract words, where there are conflicting findings of (1) a reduction in concreteness effects (the processing advantage observed with concrete over abstract words) in recall and recollection memory tasks (Peters & Daum, 2008; Rissenberg & Glanzer, 1987) versus (2) a preservation of concreteness effects with lexical tasks (Huang et al., 2012). Given age-related changes in brain structure and function it is also not clear whether recruitment of different neural mechanisms is necessary during concrete versus abstract word processing in order to ensure preserved functionality in older adults.

There is an extensive literature demonstrating that concrete words are more easily recalled in memory tasks (Paivio, 1971) and tend to be responded to more quickly and accurately than abstract words during lexical decision tasks (James, 1975; Kroll & Merves, 1986). Historically, concreteness effects and conceptual differences between concrete and abstract words have been investigated and explained by two prominent theories of cognition: dual coding theory (Paivio, 1971, 1986) and context availability theory (Schwanenflugel & Shoben, 1983). Dual coding theory proposes that the processing advantage for concrete words is due to the dual system representation (verbal and nonverbal) available to concrete but not abstract words (Paivio, 1971, 1986) while context availability attributes the processing efficiency observed with concrete words to an increased amount of available context, associated with concrete but not abstract words due to their richer set of semantic-based representations (Schwanenflugel & Shoben, 1983). However, the results from neuroimaging studies investigating concrete and abstract processing have been inconsistent and a definitive interpretation in support of either of these two dominant theories has thus far proved elusive.

In a meta-analysis of brain imaging studies involving concrete (perceptual) and abstract (verbal) conceptual processing, Binder et al. (2009) found that concrete words were strongly associated with a wide network of regions including the left angular gyrus (AG), the left fusiform (occipitotemporal) gyrus, left superior frontal gyrus (SFG), left middle frontal gyrus (MFG), left posterior cingulate and right AG. Abstract words were associated with left anterior superior temporal sulcus (aSTS) and left inferior frontal gyrus (IFG) (Binder et al., 2009). A meta-analysis by Wang et al. (2010) reached similar conclusions with concrete words eliciting left hemisphere activity in the posterior cingulate, fusiform, precuneus and parahippocampal regions. Abstract word processing also elicited left hemisphere activity but this was in the left IFG, middle temporal gyrus (MTG) and superior temporal gyrus (STG) (Wang et al., 2010).

Findings from imaging studies have been variously used to support dual coding theory (Binder et al., 2005; Sabsevitz et al., 2005), or dual coding and context availability theory (Fiebach & Friederici, 2004). Yet other studies showed no differences in activity for concrete compared to abstract words (Grossman et al., 2002; Kiehl et al., 1999; Noppeney & Price, 2004; Perani et al., 1999), which makes an interpretation in support of either theory problematic. Pexman et al. (2007) investigated concrete and abstract processing during a semantic categorization task and evaluated their findings within the frameworks of dual coding and context availability theory. Their results showed increased widespread activity for abstract words compared to concrete words and this was observed in brain regions normally associated with semantic-based conceptual representations including temporoparietal and frontal cortex. Since, neither dual coding nor context availability theory predict increased activity for abstract words, Pexman et al. (2007) suggested that their findings were instead more compatible with Barsalou’s perceptual symbol systems (Barsalou, 1999). In this strong embodiment theory of semantic representations, abstract words are expected to activate similar semantic-based regions to concrete words but with differences in the focus of the situational content. Thus, concrete words will have a more focused referent while the situational focus for abstract concepts is more distributed due to a more complicated set of referents (Barsalou, 1999; Barsalou & Wiemer-Hastings, 2005).

A modified theory of embodiment, termed *embodied abstraction* is a recent view put forward by Binder and Desai (2011) which proposes that conceptual information is represented in multiple levels in sensory, motor and affective systems and undergoes a process of abstraction from these inputs. They suggest that conceptual information develops in modality-specific representations (located near sensory, motor and emotional networks) and interacts with modality-independent (supramodal) systems, located in the temporal and inferior-parietal lobes. These higher-level cortical regions serve to bind representations from different modalities with various levels of access activated in response to determining variables such as context, familiarity or task demands (Binder & Desai, 2011). According to this view, the comprehension of conceptual information undergoes a process of gradual abstraction such that concrete words, which are associated more with sensory-motor experiential information will require less detailed simulations than abstract words. Other related theories have argued that processing abstract words is associated with greater emotional processing and associated neural mechanisms (Vigliocco et al., 2014).

Results from behavioural studies investigating concreteness and ageing have provided mixed results with some reporting increases in the effects of concreteness with ageing (Rowe & Schnore, 1971; Witte & Freund, 1976) while others have shown an attenuation of the effect (Rissenberg & Glanzer, 1987), possibly attributable to reduced cognitive function in underlying processes, such as memory. A cross-sectional study across three age groups (mean ages 21, 42 and 61 years) investigated concreteness effects and verbal memory (Peters & Daum, 2008). Concrete words were better recollected than abstract words in the three age groups, supporting the expected concreteness effect. However, they observed an attenuation of the effect in the older age group. While recollection of concrete words showed a steady, continuous decline with age, a reduction in the recollection of abstract words only occurred from the young to the middle-aged group. No further reduction was observed for the older group resulting in the attenuated concreteness effects (Peters & Daum, 2008).

To date, there have been very few neuroimaging studies which have directly investigated concrete and abstract processing effects in ageing. Processing differences between young and older adults when making semantic judgments on concrete and abstract words, were investigated in an fMRI study conducted by Stebbins et al. (2002). The findings of this study showed hemispheric differences between the two groups with the young adults eliciting greater activity in the left hemisphere compared to the older adults. In a PET study, Whatmough et al. (2004) also investigated semantic judgments for concrete and abstract words in a group of older adults. They found that left lateral temporal cortex was similarly activated for both word types when compared to a baseline condition. However, a direct comparison between concrete and abstract conditions showed that concrete words elicited activity in left fusiform while for abstract words, the activity was observed in right fusiform regions. However, as Whatmough et al. (2004) did not include a comparison group of young adults, it is unclear whether their results reflected age-related neural differences.

Shafto et al. (2012) employed an auditory lexical decision task in a group of healthy young and older adults to investigate language comprehension function and specifically factors of (i) semantics (as measured by imageability) and phonology (as measured by phonological competition) in ageing (Shafto et al., 2012). While both groups responded more quickly to words with high imageability, only the older adults showed an increased behavioural sensitivity to low imageability words and this was associated with greater activity in the left MTG. The findings of Shafto et al. (2012) suggest that preserved processing of abstract versus concrete words in older adults may be associated with age-related compensatory brain activity but the balance between discrete processing components may change, such that an age-related upregulation for the semantic task serves a compensatory role while the differences that occur in response to phonological processes may not (Shafto et al. (2012) but see Geva et al. (2012)). Meinzer et al. (2012) observed a difference in brain activity between young and older adults for semantic but not phonemic fluency, with older adults showing an upregulation of the right IFG and a reduced behavioural performance compared to the young adults, further suggesting that age-related changes in language processing may vary as a function of semantic versus phonological processing. Meinzer et al. (2012) interpret this finding as reflecting ineffective compensation for left IFG semantic functions. While recruitment of prefrontal structures appears to play a role in age-related changes in semantic processing, other regions also appear to be integral in maintaining preserved language functions and should not be overlooked (Shafto et al., 2012) and it remains unclear as to whether age-related differences that may be associated with the processing of concrete versus abstract words reflect compensatory or inefficient mechanisms.

Conceptual theories of ageing and cognitive performance such as dedifferentiation (Baltes et al., 1980; Lindenberger & Baltes, 1994; Reinert, 1970) and compensation (Reuter-Lorenz & Park, 2010) have been used to explain functional differences between the brain activity elicited by young compared to older adults when performing the same task (Cabeza et al., 2002; Shafto & Tyler, 2014; Wingfield & Grossman, 2006). The dedifferentiation hypothesis proposes that increased, widespread activity in healthy older brains is necessary and occurs as distinct cortical regions lose their specialized functionality (Li & Lindenberger, 1999). The compensation hypothesis meanwhile proposes that increased activity of additional brain regions serves as a strategic mechanism (Cabeza et al., 2002; Cabeza et al., 1997) to enable a preserved functional performance while compensating for neurocognitive decline in the ageing brain (Park et al., 2004; Park et al., 2003; Reuter-Lorenz & Park, 2010).

In the present study, we employed an fMRI task to investigate the spoken word comprehension of concrete and abstract words in young and older adults performing a lexical decision task. We wanted to test competing hypotheses: that concreteness effects are attenuated with age (as per Peters & Daum, 2008) versus the preservation of the effect consistent with the findings of Huang et al. (2012). We also wanted to determine whether a preserved performance by the older adults was associated with age-related differences in neural activity between groups. In view of structural changes in prefrontal regions associated with ageing, we predicted that a preserved performance by older adults would be accompanied by changes in the underlying substrates associated with concrete and abstract processing in healthy young adults and reported previously in Roxbury et al. (2014). We employed an auditory lexical decision task with a novel pseudoword condition to investigate the different processing mechanisms associated with concrete and abstract words in young and older adults considering the key brain regions previously reported as being reliably associated with concrete and abstract processing (Binder et al., 2009; Wang et al., 2010). Given the evidence for upregulation of the contralateral prefrontal cortex (PFC) by healthy older adults during semantic fluency tasks (Meinzer et al., 2012; Meinzer, Wilser, et al., 2009), we also examined age-related differences in the right IFG.

3.3 Methods

3.3.1 Materials

A total of 120 polysyllabic words and pseudowords were included in the stimuli list. Sixty of the 120 were pseudowords while the other sixty were English real words. The real word condition was manipulated to include 30 high imageability, concrete nouns (e.g. wallet, hospital) and 30 low imageability, abstract nouns (e.g. saga, rarity). Real word stimuli were controlled for a number of variables including (i) spoken word frequency, (ii) written word frequency, (iii) phoneme length, (iv) phonological neighbourhood density, (v) concreteness, (vi) imageability and (vii) number of syllables. There was no statistical significance difference ($p > .05$) between abstract and concrete words for any of the variables except concreteness and imageability (for stimuli characteristics and statistical significance, refer to Table 1 in Chapter 2 or in Roxbury et al. (2014). All pseudoword stimuli conformed to English phonological rules. Mean average durations were calculated for the three conditions [concrete, 724ms (*SD* 105ms); abstract, 772ms (*SD* 119ms) and pseudowords, 780ms (*SD* 93ms)] and a Kruskal-Wallis test (Kruskal & Wallis, 1952) revealed no statistical, significant difference ($p > .05$).

The 60 pseudowords were matched for number of phonemes and syllables with the 60 real words, and syllable boundaries determined from the MRC database (Wilson, 1988). In order to control for syllable frequency, the syllables from each real word were re-combined to make the pseudowords whilst ensuring that their original constituent position remained constant (Valdois et al., 2006). As a result, sixty, phonologically legal, opaque polysyllabic pseudowords were created as per Raettig and Kotz (2008), resulting in 120 items as detailed in Roxbury et al. (2014). A native female English speaker recorded all stimuli digitally in a soundproofed room using a Rode NTK condenser.

3.3.2 Participants

Twenty-six healthy young and twenty-four healthy older adults were initially recruited to the study. The young participants have previously been reported in Roxbury et al. (2014). Recruitment for the older participants was achieved through advertising flyers in local community centres and in the University of Queensland newsletters. Written consent was obtained from all participants with each receiving $30 in reimbursement. Following the scanning session, all scans were reviewed by a neuroradiologist for possible structural abnormalities. Incidental findings of clinical significance were noted in six scans (three younger adults and three older adults) and these subjects excluded. A further six young adults and four older adults were also excluded from analysis due to technical and subject compliance issues. As a result, 17 young adults aged between 18 and 35 years (M = 27.35, SD = 5.1; 8 males), and 17 older adults ranging from 64 to 83 years (M = 71, SD = 5.07; 6 males) were included in the present study.

All participants were right hand dominant according to the Edinburgh Handedness Inventory (Oldfield, 1971) and reported using English as a first language. Knowledge of vocabulary was assessed using the National Adult Reading Test (NART) (Nelson & Wilson, 1991). The Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was also administered to the older group as a test to confirm the absence of cognitive impairment. None of the participants from either group reported a history of neurological disease, head trauma, alcoholism, mental illness, or cerebral tumour and all had sufficient vision and hearing to perform the task. Hearing thresholds were also confirmed in the older group using a pure tone audiometry test to rule out significant hearing impairment and all average thresholds were under 40 dB (M = 28.55, SD =

3.41). Ethical approval for this study was received from the University of Queensland Medical Research Ethics Committee and the Queensland Health Human Research Ethics Committee. Site-specific research governance was also obtained from the Royal Brisbane and Women's Hospital Ethics Committee.

3.3.3 Procedure

The lexical decision task was explained to each participant prior to the scanning session and a computer-based practice task administered until a score of over 80% was achieved. The fMRI task consisted of 120 individual stimuli, presented binaurally via MRI confon headphones (MR Confon GmbH, Magdeburg, Germany) across two runs within the same scanning session (refer to Figure 1 in Roxbury et al. (2014) for acquisition sequence). At the start of each trial participants saw a small black fixation cross (48 point font) for 2.3s and a visual prompt 'Is it a real word?'. A word or pseudoword was then heard by the participant with a mean length of auditory presentation lasting an average of 764ms (*SD* = 105ms). Participants had 3.5s to make a response and during this response/sound window, a screen with a black "+" and the correct orientation for Yes/No was displayed. Participants selected their response using an MR compatible button press box (Current Designs Inc, Philadelphia PA). A left button press signalled a positive (yes) response and a right button press signalled a negative (no) response. A large blue cross (84 point font) appeared on the screen to indicate that a response had been selected and remained visible for 1s. After this time, a black cross (84 point font) appeared and stayed on screen until the start of the next trial. Participants were asked to keep their eyes open for the duration of the scanning session and to look at the fixation cross. Participants used their left hand to make their responses on the button response box in order to allow for a future comparison study on patients with aphasia following stroke.

Stimuli were presented in a pseudorandomised, event related design with a maximum of two consecutive trials from any one condition (concrete real words, abstract real words and pseudowords). To reduce order effects, five different pseudorandomised orders were employed. In addition, words and pseudowords which shared constituent syllables were not presented in consecutive order. An inter-trial interval (jittered between 10-18s, mean 14s) followed each auditory stimulus presentation. The long interval was designed to allow for future comparison of this data with that of patients with post-stroke aphasia, who can experience a delay in hemodynamic response function (Bonakdarpour et al., 2007).

3.3.4 Data Acquisition

Participants underwent one scanning session at the Royal Brisbane and Women's Hospital with a Siemens 3 Tesla Trio scanner (Siemens Erlangen). A pseudorandomised event-related design was employed and stimuli delivered in two runs lasting approximately 14.4 minutes in duration. During the two task runs, a total of 390 gradient echo EPI images with BOLD sensitivity were acquired (TR 2210ms; TE 30ms; slice thickness 3mm with 0.3mm gap; 36 axial slices, FOV 220x220mm, flip angle 90, matrix 64x64). At the start of the scanning session, a 3D T1-weighted image was also acquired [MP-RAGE; TR 1900ms; TE 2.4ms; TI 900ms; $(0.9\text{mm})^3$ resolution].

3.3.5 Image Processing

Statistical parametric mapping software (SPM8; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm) was used to process and analyse the images with MATLAB 2009a (The MathWorks Inc., Natick, MA). The first five volumes acquired at the beginning of each run were discarded to ensure that images were only included for analysis once magnetization had reached steady state. EPI images from run 1 and run 2 were realigned using INRIAlign (Freire et al., 2002) to correct for motion artefacts and a mean image created. This mean EPI was then coregistered with the T1 image acquired in the same session and the T1 image segmented and spatially normalized (Ashburner & Friston, 2005). A DARTEL template (Ashburner, 2007) was created for both groups and each subject's T1 and EPI image normalized to the standard Montreal Neurological Institute (MNI) space. The EPI images were then resampled (3.0 x 3.0 x 3.0 mm^3) and spatially smoothed using an 8 mm full-width half-maximum (FWHM) Gaussian smoothing kernel.

3.3.6 Behavioural Analysis

Mean accuracy was calculated per subject. Reaction times were calculated from the beginning of the sound onset and all incorrect trials plus those that were shorter than 100ms were removed prior to analysis. Both mean accuracy and reaction time data were not normally distributed (Shapiro-Wilk test of normality: accuracy $p < .003$; RT $p < .0001$). As group variances could be treated as equal (using a non-parametric Levene's test) a Mann-Whitney test was employed. In addition, to determine whether the concreteness effect existed for each group we compared concrete and abstract processing differences associated with accuracy and reaction time, using a Wilcoxon Signed-Ranks test.

3.3.7 Imaging Data Analysis

A fixed effects analysis was employed for each subject. The general linear model was constructed using a hemodynamic response function with derivatives. This was done to model the increased variability due to ageing (D'Esposito, Deouell, & Gazzaley, 2003). The realignment parameters (6 degrees of freedom) were included as regressors of no interest. In order to exclude BOLD response effects which were due to variability in reaction time (or time on task), a parametric modulation for each of the three conditions (concrete, abstract and pseudoword) was included using the mean corrected reaction time for each trial. Contrasts included concrete – abstract, concrete – pseudoword and abstract – pseudoword. Error trials were modelled separately, and included both incorrect and trials where the reaction time was less than 100ms.

For the whole brain analyses, a group by condition (2 x 3) factorial analysis was completed to determine the main effects. Anatomy Toolbox (Eickhoff et al., 2007) was used to determine the neuroanatomical locations of peak maxima for significant clusters elicited in the different contrasts. To correct for multiple comparisons, a Monte Carlo simulation calculation was performed and cluster thresholds calculated by using the full-width half-maximum of the square root of the residuals (3dFWHMx and 3dClustSim; Analysis of Functional Neuroimages) (Cox, 1996). Using a height threshold of $p < .001$ uncorrected, a family wise error rate of $p < .05$ was achieved with a minimum cluster threshold of 44 contiguous voxels. Regions showing a main effect of condition or group were investigated further to explore directionality and mean percent signal change calculated for each region.

A priori regions of interest (ROIs), determined from Binder et al. (2009) and Cabeza et al. (2002), were created using IBASPM 116 Human Atlas in WFU PickAtlas (Maldjian et al., 2004; Maldjian et al., 2003) in SPM8 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). A total of 10 ROIs were created; six to examine concrete word processing (left AG, right AG, left MFG, left SFG, left posterior cingulate and left fusiform), three for abstract processing, left IFG; pars orbitalis and left aSTS – split into anterior superior temporal gyrus (aSTG) and anterior middle temporal gyrus (aMTG). An additional ROI in right IFG (pars orbitalis) was included, to investigate recruitment of homologous, contralateral brain regions particularly the ventral, inferior frontal cortex by older adults (Cabeza et al., 2002). The anterior, superior and middle temporal cortical regions were subdivided according to the delineation of y<-7 for anterior by Indefrey and Levelt (2004) so that potential activity in the aSTS could be thoroughly examined.

Mean percent signal for each participant in each of the ROIs was extracted using MarsBaR (Brett et al., 2002), a region of interest toolbox for SPM8. SPSS Statistics version 21 (IMB; Armonk, New York, USA) was used for group statistical analyses. Data was checked for normality of distribution and when not normally distributed a Log10 transformation was applied to create normality. Two (young, old) x 3 (concrete, abstract and pseudoword) repeated measures ANOVAs were then conducted to test for mean percent signal change differences between conditions within the 10 ROIs. Where the assumption of sphericity had been violated, degrees of freedom were corrected using Huynh-Feldt estimates of sphericity and are reported throughout along with original degrees of freedom. Post hoc pairwise comparisons (concrete – abstract, concrete – pseudoword, abstract – pseudoword) in the 10 ROIs were evaluated using an adjusted *p* level following correction for multiple comparisons (Benjamini & Hochberg, 1995). Where results indicated a group by condition interaction, an ANOVA was conducted to explore the interactions within a single group between conditions.

3.4 Results

3.4.1 Participant Results

There was no significant difference between cohorts on either the NART score [*p* =.2, young mean 32.18 (*SD* 5.07), older mean 35.18 (*SD* 7.95)] or mean years of education [*p* =.5, young mean 16.5 yrs (*SD* 2.1), older mean 15.5 yrs (*SD* 4)]. Scores from the MMSE (Folstein et al., 1975) confirmed intact cognition of the older group (max = 30, group mean = 28.82, *SD* = 0.95).

3.4.2 Behavioural Results

The mean accuracy for all conditions was high in both groups. Mann-Whitney *U* tests between the groups indicated that accuracy of pseudowords was significantly greater for young adults (*M* = 97.9, *SD* = 2.3) than for older adults (*M* = 95.2, *SD* = 4.1) *U* = 79.5, *Z* = -2.295, *p* = .022, but there was no significant difference between the groups for accuracy in either the concrete (young *M* = 98.6, *SD* = 2.4; older *M* = 97.1, *SD* = 4.4) or abstract conditions (young *M* = 97.5, *SD* = 1.9; older *M* = 93.5, *SD* = 7.5).

The percentage of reaction times removed (incorrect or < 100ms) was 4.6% for older adults and 2% for younger adults. A Mann-Whitney *U* test on mean response times for the young and old groups (see Table 4) indicated that young adults were significantly faster than older adults for all three conditions; pseudoword *U* = 311864, *Z* = -13.746, *p* < .001 two-tailed, concrete *U* = 100275, *Z* = -5.319, *p* < .001 two-tailed, and abstract *U* = 97875, *Z* = -4.807, *p* < .001 two-tailed.

Table 4. Mean reaction times for young and older adults

	Pseudoword	Concrete	Abstract
	Mean (*SD*)	Mean (*SD*)	Mean (*SD*)
Young adults	1434ms (396)	1187ms (274)	1263ms (346)
Older adults	1738ms (588)	1288ms (318)	1356ms (353)

Concreteness effects, or the processing advantage seen for concrete over abstract words in terms of accuracy and reaction time, were tested in both the young and old groups. The older group was significantly more accurate for concrete over abstract words $Z = -2.116$, $p = .034$ but there was no significant difference for the younger group ($p = .303$). The results for reaction times indicate faster processing for concrete over abstract words, with a significant difference for both the young group $Z = -15.316$, $p < .001$ and the older group $Z = -13.241$, $p < .001$ (See Table 4) and confirm that the expected processing advantage for concrete words occurred.

3.4.3 Region of Interest Analyses

Results for the left fusiform ROI indicated that there was a main effect of group $F(1, 16) = 7.523$, $p = .014$, with older adults eliciting increased activity in this region ($M = 0.304$, $SE = 0.062$) compared to young adults ($M = 0.207$, $SE = 0.041$). A main effect of group was also observed in the left AG $F(1, 16) = 38.329$, $p = < .001$, with older adults eliciting increased activity ($M = 0.282$, $SE = 0.028$) compared to young adults ($M = -0.065$, $SE = 0.035$). No other region showed a main effect of group.

A main effect for condition was found for left AG, right AG, left posterior cingulate, left aMTG, left MFG, left SFG, left aSTG, and left IFG. Regions showing significant main effects for condition effects after FDR correction (Benjamini & Hochberg, 1995) are listed in Table 5.

Table 5. Region of interest - main effect of condition

Region	*F* value	Concrete - Pseudoword	Abstract - Pseudoword	Concrete - Abstract
Left AG	$F(2, 15) = 9.643$, $p = .002$	Conc > PS $p < .001$	Ab > PS $p = .017$	Conc > Ab $p = .017$
Right AG	$F(2, 15) = 13.315$, $p < .001$	Conc > PS $p < .001$	Ab > PS $p = .009$	Conc > Ab $p = .030$
Left posterior cingulate	$F(2, 15) = 16.161$, $p < .001$	Conc > PS $p < .001$	Ab > PS $p = .013$	Conc > Ab $p = .002$
Left aMTG	$F(2, 15) = 8.101$, $p = .004$	Conc > PS $p = .009$	Ab > PS $p = .002$	*ns*
Left MFG	$F(2, 15) = 6.04$, $p = .012$	Conc > PS $p = .009$	Ab > PS $p = .03$	*ns*
Left SFG	$F(2, 15) = 11.260$, $p = .001$	Conc > PS $p < .001$	Ab > PS $p = .017$	*ns*
Left aSTG	$F(2, 15) = 18.568$, $p < .001$	Conc > PS $p < .001$	PS > Ab $p = .03$	*ns*
Left IFG	$F(2, 15) = 10.124$, $p = .002$	PS > Conc $p = .047$	*ns*	Ab > Conc $p < .001$

Results from the repeated measures ANOVA for each of the 10 ROIs revealed a significant age x condition interaction in four ROIs; left AG $F(1.431, 22.903) = 9.102$, $p = .003$ (Huynh-Feldt correction), left IFG $F(2, 15) = 8.936$, $p = .003$, left fusiform $F(2, 15) = 6.531$, $p = .009$ and left MFG $F(2, 15) = 6.040$, $p = .011$. Follow-up analyses on the significant interactions were conducted to find the differences in the mean percent change between conditions within each group. The interactions and mean percent BOLD signal change in the four ROIs can be seen in Figure 6. There was a condition effect in the left IFG for the older adults only $F(2, 15) = 17.127$, $p = < .001$. Post hoc pairwise comparisons indicated significant differences for the concrete compared to both the pseudoword ($p = .001$) and abstract ($p < .001$) conditions. Mean percent signal change was greater for the abstract ($M = 0.20$, $SE = 0.05$) and pseudowords ($M = 0.24$, $SE = 0.06$) compared to the concrete words ($M = 0.17$, $SE = 0.04$). Results also indicated a significant difference in activity for condition in the left AG for the young adults only $F(2, 15) = 11.270$, $p = .001$. Pairwise comparisons indicated that the differences between contrasts were significant for all three conditions ($p \leq .001$) with greatest activity for the concrete condition (*M* = 0.02, *SE* = 0.04), followed by abstract words (*M* = -0.06, *SE* = 0.04) and then pseudowords (*M* = -0.14, *SE* = 0.04).

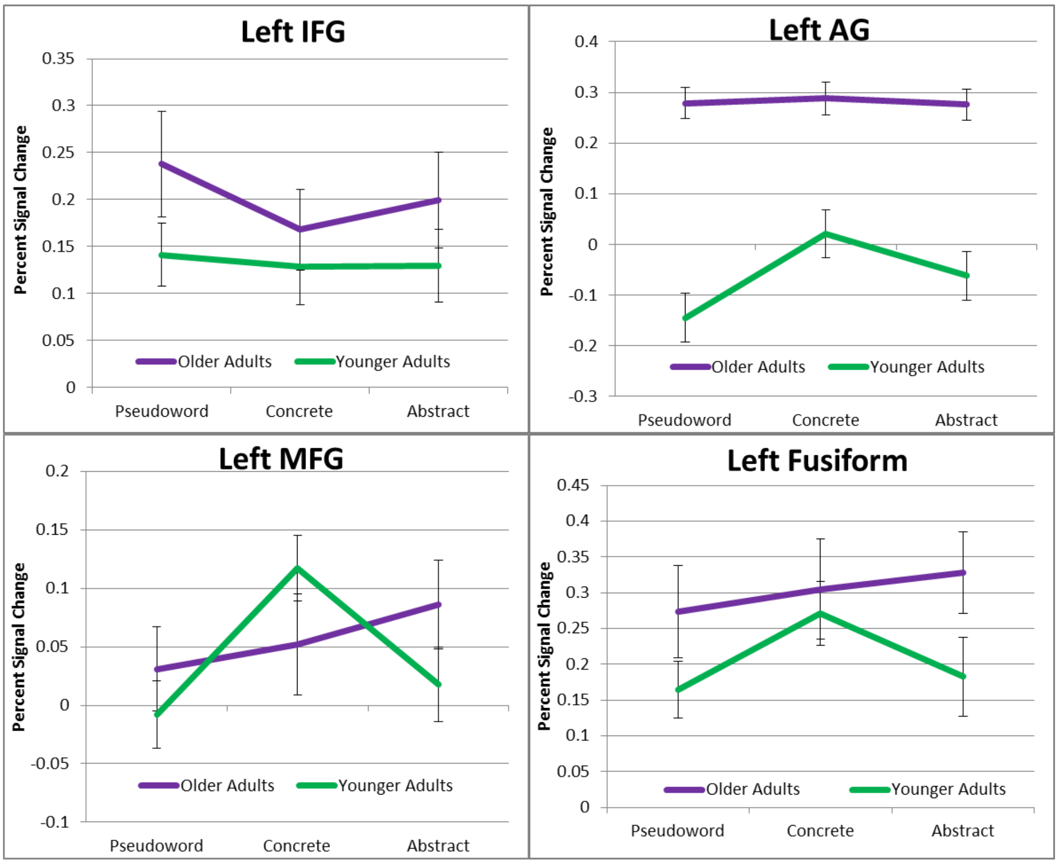

Figure 6. Region of interest analysis. Illustrates ROIs which showed a significant group by condition interaction.

An effect of condition was observed in the left MFG for both the older adults $F(2,15) = 4.268$, $p = .034$ and young adults $F(2, 15) = 9.897$, $p = .002$. Post hoc pairwise comparisons further indicated a significant difference in the older adults for the abstract - pseudoword contrast ($p = .018$) with mean percent signal change elicited being significantly higher for abstract (*M* = 0.09, *SE* = 0.04) compared to pseudowords (*M* = 0.03, *SE* = 0.04). A significant difference was observed in the young group for concrete words when compared to both abstract ($p = .003$) and pseudoword conditions ($p < .001$). Mean percent signal change indicated that greatest activity was elicited for the concrete words (*M* = 0.12, *SE* = 0.03) compared to abstract (*M* = 0.02, *SE* = 0.03) and pseudoword (*M* = -0.01, *SE* = 0.03) conditions. A condition effect was also observed in the left fusiform for both groups [older adults $F(2, 15) = 10.114$, $p = .002$ and young adults $F(2, 15) = 14.952$, $p < .001$]. Pairwise comparisons between conditions indicated significant differences in the older adults for abstract and pseudoword condition ($p = .001$) with abstract words eliciting greater activity (*M* = 0.33, *SE* = 0.06) than pseudowords (*M* = 0.27, *SE* = 0.07). Significant differences for the young group were observed for the concrete – pseudoword ($p < .001$) and abstract –pseudoword condition ($p = .044$). Mean percent signal change was greater for both the concrete (*M* = 0.27, *SE* = 0.04) and abstract conditions (*M* = 0. 18, *SE* = 0.06) when compared to pseudowords (*M* = 0.16, *SE* = 0.04).

3.4.4 Whole Brain Analyses

We also ran exploratory whole brain analyses which revealed a main effect of age in the left precentral, left supplementary motor area (SMA), left IFG (pars triangularis) and right IFG (pars triangularis extending into pars opercularis) for the word greater than pseudoword contrast. A main effect of condition was also observed in the left calcarine gyrus (refer Table 6). There were no significant group by condition interactions for the whole-brain analyses.

Table 6. Factorial results from whole brain analysis for main effects between young and older groups

Main effect	Structure	*x*	*y*	*z*	Volume	*Z*-score
Age	left precentral gyrus	-36	4	32	53	4.65
	right IFG (pars triangularis)	54	18	22	65	4.62
	left SMA	-7	25	47	62	4.62
	left IFG (pars triangularis)	-50	32	18	138	4.45
Condition	left calcarine gyrus	-7	-50	7	76	4.54

$p < .001$ probability threshold and cluster threshold level of 44 voxels.

Brain regions in which a main effect of age was indicated were investigated further to explore directionality of the effect. Differences in activity were calculated using the mean percent signal change extracted for each cluster (see Figure 7) and show that older adults elicited increased activity in all four regions compared to the young adults.

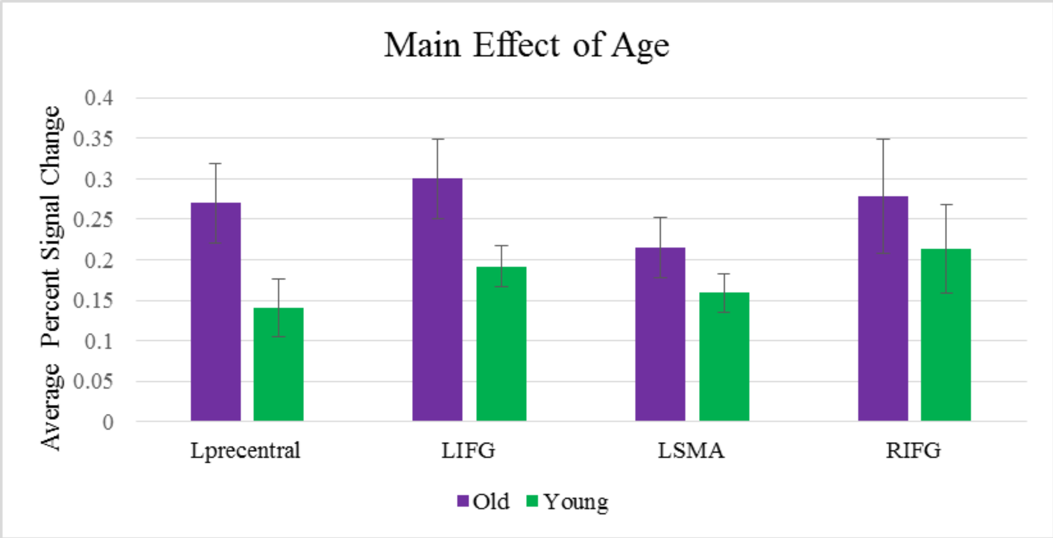

Figure 7. Main effect of age. Activation differences were calculated using the mean percent signal change extracted for each cluster.

Mean percent signal change was also calculated to explore the main effect of condition in the calcarine gyrus. Results indicate that concrete words elicited increased activity (M = 0.06, SD = 0.04) in this region than abstract words (M = 0.07, SD = 0.04) across groups.

3.5 Discussion

We investigated concreteness effects during spoken word comprehension in young versus old adults and tested the competing age-related hypotheses of attenuation (Peters & Daum, 2008) versus preservation (Tyler et al., 2010; see Wingfield and Grossman, 2006 for a review) in concrete and abstract word processing. We also examined whether behavioural performance was associated with age-related changes in neural activity. We found that comprehension of spoken concrete and abstract words and the concreteness effect is indeed preserved in ageing. However, the neural substrates that underpin this preserved performance appear to vary as a function of age and may reflect compensatory age-related upregulation.

The expected processing advantage for concrete over abstract words was observed in both groups for reaction time and for accuracy in the older adults only. The lack of concreteness effect in accuracy for the young cohort was most likely due to a ceiling effect. Results for accuracy between the two groups for concrete and abstract words revealed no significant differences. These findings are consistent with previously reported observations in the healthy ageing literature, which suggests that spoken word comprehension remains relatively preserved throughout life (Burke & Shafto, 2008; Shafto et al., 2012). A significant difference in accuracy did emerge for the pseudoword condition and showed that older adults were less accurate than the young adults when responding to these non-lexical items. With regard to reaction times, our results showed that the older adults were significantly slower than their younger counterparts for all three conditions. This result is in agreement with previous observations of a consistent, general slowing in lexical decision response times as people age (Gold, Andersen, Jicha, & Smith, 2009; Madden, 1992). Whilst both groups responded to pseudowords slower than both concrete and abstract words, the response time observed for the older adults was dramatically slower compared to the young adults. This is consistent with the model of Balota and Chumbley (1984) which proposes that fast lexical decision responses can be facilitated by the familiarity or unfamiliarity of the stimuli. Since, the pseudowords employed in this study were opaque (Raettig & Kotz, 2008), and ageing is associated with an increase in lexical knowledge (Burke & Shafto, 2008), the slower response time observed for the older adults to the pseudowords might be due to a more extensive lexical search which is required before a decision can be made.

In the left IFG ROI, older adults showed increased activity for abstract and pseudowords compared to concrete words, whereas young adults showed no difference between conditions. This recruitment by the older adults of a mechanism not used by the young group for abstract and pseudoword processing, accompanied by a preserved performance suggests an element of age-related compensatory upregulation. Studies investigating differences between semantic and phonological processes and IFG activity have shown that different linguistic processing components can be differentially affected in ageing (Diaz, Johnson, Burke, & Madden, 2014; Geva et al., 2012; Meinzer et al., 2012; Meinzer, Wilser, et al., 2009; Shafto et al., 2012). Previous studies investigating concreteness have shown involvement of left inferior frontal regions when abstract words are directly contrasted with concrete words (Binder et al., 2005; Fiebach & Friederici, 2004;

Mellet et al., 1998; Noppeney & Price, 2004; Perani et al., 1999; Wise et al., 2000) and this may represent strategic retrieval of semantic knowledge (Fliessbach et al., 2006). However, the fact that this region was also activated more for pseudowords compared to concrete words, but not when directly contrasted with abstract words makes it unlikely that upregulation of this region by the older adults reflects semantic-based processes. Rather, we suggest that the current findings are more consistent with previous studies which have indicated a role for left IFG in more phonologically-based, short term working memory processes (Binder et al., 2005; Fiebach & Friederici, 2004; Sabsevitz et al., 2005). This is supported by results from a study investigating differences in word learning strategies in ageing, which demonstrated that when older adults are engaged in word learning tasks, they rely more on phonological processes and less on semantic working memory (Service & Craik, 1993). Our findings are also in agreement with reports that pseudoword processing activates more focal phonological processes compared to real words which activate lexical representations at a higher level (Davis & Gaskell, 2009). Thus, since we observed greater activation for abstract and pseudowords compared to concrete words in left IFG for the older adults only, we propose the involvement of the left IFG may instead reflect an age-related compensatory upregulation of more phonologically-based, rather than semantically-mediated or working memory processes.

Young adults showed increased left AG activity for concrete words compared to abstract words, with both concrete and abstract words also showing greater activity than pseudowords. In contrast, older adults showed no change in AG activity for the different conditions. Involvement of the left AG in semantic-based processing generally is well documented (Price, 2010) and this was also the region identified in the Binder et al. (2009) meta-analysis as being most reliably activated in response to semantic-based tasks. Findings from our previous study investigating concreteness effects in healthy young adults showed that the left AG was the region most robustly activated by concrete compared to abstract words (Roxbury et al., 2014). Recent work has suggested that the AG may act as a supramodal zone, binding and integrating sensory-motor information from modality-specific regions (Binder & Desai, 2011). The findings in the present study are consistent with this view and demonstrate that the young adults are reliably using this region when accessing semantic conceptual knowledge. However, this is not the case for the older adults. While older adults do recruit left AG, and generally elicit greater activity than the young adults, no activation differences between the conditions suggests that older adults are recruiting the left AG for more general lexical processing. As such, we propose that this reduction in specificity may be due to a change in focus by the older adults who attend more to phonological rather than semantic aspects of processing in order to maintain a preserved performance.

In the present study, we observed increased activation for abstract compared to pseudowords in left MFG for the older adults. The MFG has generally been considered to be associated with more executive type functions relating to working memory, inhibition and processing speed (Grady, 2008; Reuter-Lorenz & Park, 2010) and thus the finding of increased activation for abstract words by the older adults might reflect an engagement of executive resources. This increased neural activity for the older adults for abstract word processing is supported by the behavioural findings which showed both slower reaction times and reduced accuracy for the abstract condition suggesting that abstract words required more effortful processing. However, we also observed increased activation in this region for the young group for the concrete words compared to both abstract and pseudowords and this was associated with an intact behavioural performance both in terms of reaction time and accuracy. These findings are not therefore consistent with an executive function explanation for this region. Instead, activity in this region has previously been observed in semantic-based tasks although its precise function in language processing is not yet well understood. Thus the finding of increased activity for concrete words in the young adults could potentially reflect processes involved with the retrieval of semantic knowledge (Binder et al., 2009; Diaz et al., 2014; Peelle, Troiani, Wingfield, & Grossman, 2010), which is greater for concrete concepts due to their richer set of conceptual features.

In the left fusiform gyrus older adults showed a generalized increase in activity overall and elicited greater activity for abstract words compared to pseudowords. In contrast, the young adults reliably recruited this region for the processing of real words (concrete and abstract) compared to pseudowords. The left fusiform gyrus is considered to be a conceptual semantic store and associated with the retrieval of visual attributes (Binder et al., 2009). Since concrete words are associated with stronger visual attributes than abstract words, the expectation is that concrete words will elicit increased activity in this region. However, while some have shown increased activity in this region for concrete compared to abstract words (D'Esposito et al., 1997; Fiebach & Friederici, 2004; Mellet et al., 1998; Whatmough et al., 2004; Wise et al., 2000), others have not (Binder et al., 2005; Friederici et al., 2000; Jessen et al., 2000; Kiehl et al., 1999; Noppeney & Price, 2004; Perani et al., 1999). The findings in this present study differ from those of Whatmough et al. (2004) who observed increased activity for concrete words in the left fusiform gyrus and these differences may be due to the nature of the lexical decision task we employed with does not require deeper conceptual processing. Nevertheless, our finding of increased activity in the young group for both concrete and abstract words compared to the pseudowords suggests that lexical processing was occurring and we tentatively interpret this result as reflecting differences associated with real word imagery and features, compared to pseudowords that have no meaning and therefore no imagery or features attached to them. Meanwhile, the increased activity for the abstract compared to pseudoword condition for the older group might suggest that the older adults were engaged in increased visual imagery for retrieving abstract words in order to maintain a preserved performance.

Results for the whole brain analysis revealed a main effect of age in left IFG (pars triangularis, extending into pars opercularis), right IFG (pars triangularis), left precentral gyrus and left SMA with older adults eliciting increased activity in each of these regions compared to the young adults for words compared to pseudowords. The increase in bilateral PFC activity is consistent with the HAROLD model (Cabeza, 2002) which proposes that when performing the same task, older adults elicit additional activity in the contralateral right PFC regions (Cabeza et al., 2004). However, the HAROLD model also predicts that activity elicited by older adults will be less-lateralized than that observed in young adults. The current results do not support a reduction in laterality in the older group since we also observed increased activity in the left hemisphere in the older compared to young adults. This trend towards a general increase in brain activity in the older compared to the young adults suggests a compensatory upregulation of brain regions, which are required to maintain performance in word processing.

The fMRI data in the present study confirm involvement of a large network of common regions which are activated in response to both concrete and abstract words regardless of age. Of the eight regions which showed condition effects, three ROIs (left AG, right AG and left posterior cingulate) showed greater activation for concrete greater than abstract greater than pseudowords. The results for increased activation for concrete compared to abstract words in left and right AG are consistent with Binder and Desai's (2011) view of embodied abstraction which proposes that bilateral AG acts as a convergence zone with the purpose of binding conceptual representations from modal-specific regions. Differences in processing in this region are associated with the different amounts of conceptual information associated with a word. As such, in this framework, concrete words would be expected to elicit more activity than abstract words due to their stronger semantic representations, largely associated with sensory-motor knowledge (Binder & Desai, 2011).

With regard to the two prominent theories of concreteness and abstract processing, the results for bilateral AG activity cannot be fully explained by either account. Context availability theory does not predict increased right hemisphere activity for abstract or concrete concepts, since quantitative differences between these word types should occur in left hemisphere regions (Schwanenflugel & Shoben, 1983). In terms of dual coding theory, involvement of the nonverbal right hemisphere is predicted by the model for concrete words, due to their richer image-based associations. However, we also observed a significant condition effect in the left IFG with greater activity for abstract compared to concrete words. While this is consistent with dual coding theory, which predicts that abstract words will activate qualitatively distinct systems in the verbal left hemisphere, we also observed greater activity for pseudowords compared to concrete words in this region which is not predicted by the model. Instead, as discussed above, this finding suggests that the older adults recruit left IFG as a compensatory mechanism in order to maintain performance during more phonologically-based processes.

In summary, our results show that, despite a general reduction in response times, spoken language comprehension of concrete and abstract words, and concreteness effects remain relatively preserved in ageing. Interestingly, the pseudoword condition proved most problematic for the healthy older adults and we suggest that may be due to the additional strategic processing required as they search through a more extensive lexicon (Kemper & Sumner, 2001; Verhaeghen, 2003) before deciding to discard an item. The results from the imaging data showed that a large network of brain regions, previously reported as being involved in concrete and abstract processing (Binder et al., 2009; Wang et al., 2010), are similarly activated by both groups in response to concrete and abstract words although the older adults routinely showed increased activation compared to the young adults. Age-related vascular changes need to be considered when comparing activity between young and older adults (D'Esposito et al., 2003). A general reduction in BOLD has been observed previously, meaning a decrease in activation cannot be directly tied to a decrease in neural activity. However, this doesn’t explain the increased activity in older compared to younger adults seen in this study, which is contrary to the expected direction based on possible biological differences, and indicate a larger neuronal activation or BOLD response. Selective regions also showed activation differences between conditions for the two groups. The findings for left IFG and left AG present an interesting dichotomy. These findings suggest that while the spoken recognition of concrete and abstract processing remains preserved in ageing, this preserved performance is accompanied by compensatory upregulation in regions which are differentially recruited by the two groups such that older adults are required to focus more on phonological and less on semantic aspects of processing and this appears essential for preservation of functionality.

4 Chapter Four

Brain Activity during Spoken Word Recognition in Subacute Aphasia

---

The results from Chapter 3 confirmed that the neural mechanisms which underpin the recognition of spoken concrete and abstract words are altered in ageing and as such, the first aim of Chapter 4 was to examine how this brain activity is altered in people with aphasia during the subacute phase of recovery compared to a group of aged-matched healthy controls. The second aim was to determine the relationship between brain activity elicited during the fMRI task and performance on a range of language measures taken outside the scanner. Based on previous aphasia studies, it was hypothesised that increased right hemisphere activity would be elicited in response to the fMRI task during this subacute period (Saur et al., 2006) and that greater activity would be observed for abstract compared to concrete words in the aphasic group compared to the aged-matched controls (Sandberg & Kiran, 2014).

4.1 Introduction

Recovery from post-stroke aphasia is considered to occur in three separate stages, underpinned by distinct neural mechanisms (Kiran, 2012). The acute phase is experienced within the first two weeks following stroke onset and during this phase, language recovery is rapid due to physiological changes in neural plasticity, reduction in oedema and metabolic disturbances as well as reperfusion of the ischaemic penumbra (Marsh & Hillis, 2006). The second stage of recovery is the subacute phase which occurs weeks to months post-stroke. During this period recovery is less rapid and consists primarily of neural reorganisation leading to the formation of new alternative networks and changes in the efficacy of synaptic connections (Lazar & Antoniello, 2008). Recovery in this phase is thought to be associated with the regression of diaschisis (that is the normalisation over time of dysfunctional brain activity in areas remote or distant to the lesion and which correlate with behaviour, see Carrera and Tononi (2014) for a full review), perilesional restitution

(Thompson & den Ouden, 2008; Warburton et al., 1999) or a functional transfer to the right hemisphere homologue (Saur et al., 2006). The chronic phase of recovery is dominated by neural reorganisation and compensatory cognitive strategies which may continue for a number of years (Grafman & Litvan, 1999).

Observations of task-related brain activity can provide insights into the mechanisms of recovery in patients with aphasia when performance is compared to that of healthy controls. Turkeltaub et al. (2011) conducted a meta-analysis on fMRI studies investigating the consistency in brain activity elicited by people with chronic aphasia in response to language tasks. The findings indicated that while controls recruited consistent left hemisphere language areas, aphasic subjects employed both intact language areas, as well as recruiting new areas within the left hemisphere and right hemisphere language homologues (Turkeltaub et al., 2011). These findings demonstrate that critical information on the regions and mechanisms associated with recovery can be derived from carefully constructed imaging protocols which enable a comparison between the performance of controls and aphasic subjects to be made.

Imaging studies investigating recovery and aphasia have provided some intriguing insights into the brain mechanisms that underpin language function in the acute stages post-stroke (Hillis, 2007; Hillis et al., 2005). Hillis and Heidler (2002) investigated spoken word comprehension in 110 patients with acute stroke and used perfusion-weighted imaging (PWI) and diffusion-weighted imaging (DWI) to examine the relationship between severity of hypoperfusion and the level of comprehension impairment. Rapid improvements in spoken word comprehension in acute aphasia was directly associated with successful reperfusion of BA 22 (Wernicke's area) (Hillis & Heidler, 2002; Hillis et al., 2005) whereas, those patients with persisting hypoperfusion in BA 22 also had persisting spoken word comprehension deficits. Hillis and Heidler (2002) concluded that early recovery is attributable to reperfusion rather than early reorganisation of structure/function relationships which they suggest are likely to play more of a role in subsequent stages of recovery (Hillis & Heidler, 2002). However, the exact nature and timing of the neural reorganisation associated with subsequent stages of recovery (including the subacute phase) for spoken word comprehension is still unclear.

A longitudinal fMRI study by Saur et al. (2006) provided a number of insights into the mechanisms of language recovery associated with the different stages of language recovery. A group of 14 acute aphasic subjects were scanned initially within 4 days post-stroke and then again in the subacute phase approximately two weeks later. A third scanning session was conducted in the chronic phase of recovery between 4 to 12 months post. The fMRI task employed was an auditory sentence comprehension task with correct, incorrect and reversed speech sentences and the aphasic patients were required to respond using a two button press to indicate 'correct' versus 'incorrect' sentences. During the acute phase, weak activity was elicited in left IFG. However, in the subacute phase, there was a shift to a more bilateral pattern of activity in the language networks, particularly in right IFG, and this was associated with improved language function. In the chronic phase, there was a return to left hemisphere activation, similar to that of the controls, and this was associated with further improvements in language recovery (Saur et al., 2006). These findings suggest that successful recovery of language function is associated with a dynamic hemispheric reorganisation.

One limitation of the Saur et al. (2006) study concerns the complexity of the task. During pretesting, the sentence-level task proved difficult for some of the aphasic patients and as a result, the task needed to be modified so that a response with a button press was only required when an incorrect sentence was heard. Thus, reversed speech and violated sentences were both categorized as incorrect. Despite simplification of the task, accuracy was still poor in the acute phase (mean 36% correct). This poses problems when interpreting task-related brain activity, as it cannot be ascertained whether the brain activity elicited reflects an impaired performance or whether the impaired performance is caused by the underlying neural deficits (Price & Friston, 1999). A further limitation of the Saur et al. (2006) study relates to the use of a sentence level task as sentence comprehension in aphasia is significantly reliant on other cognitive functions, particularly verbal working memory (Caplan et al., 2013). Since task-related activity observed in aphasia often reflects increased cognitive control and attention (Geranmayeh et al., 2014), there is a need to consider less cognitively demanding language tasks that can provide unique insights into aphasia recovery. Therefore, in order to further investigate the brain mechanisms associated with language processing in acute and subacute phases, it is important that patients are presented with in-scanner tasks that can be performed successfully and with enough accuracy to ensure that the brain activity elicited during the task reflects the neural responses to the stimuli being presented, rather than reflecting other processes which may be related more to task difficulty or inaccurate responses (Price et al., 2006; Price & Friston, 1999).

In order to examine the brain mechanisms associated with spoken word comprehension in subacute aphasia, the present study investigated concrete versus abstract word processing as this has proven an informative method for examining lexical-semantic function in aphasia. Concreteness effects (i.e. the processing advantage observed for concrete (e.g. blanket) over abstract words (e.g. belief) have been reported in healthy populations (James, 1975; Kroll & Merves, 1986, for a review, refer Pavio, 1991) (see Chapter 2 for a review of concreteness). Behaviourally, exaggerated effects of concreteness (whereby concrete words appear to be processed better than abstract words) have been observed in people with aphasia (Barry & Gerhand, 2003; Crutch & Warrington, 2005; Martin et al., 1996; Newton & Barry, 1997; Sandberg & Kiran, 2014) and also people with semantic dementia (Hoffman, 2015). These findings suggest that distinct neural mechanisms are involved in the processing of concrete and abstract concepts and these can be differentially affected by brain lesions. However, the studies which have reported these effects have largely been behavioural case studies and have investigated aphasic subjects in the chronic phases of recovery.

Two recent meta-analyses have provided insights from neuroimaging studies of concrete versus abstract processing in healthy adults (Binder et al., 2009; Wang et al., 2010). A combined total of 26 neuroimaging studies were examined, ten of which fitted the inclusion criteria for both meta-analyses, and the findings showed consistent activation for both concrete and abstract words. While concrete words were associated with stronger activation in a widely distributed network of language regions, including the right hemisphere, activity elicited for abstract words was observed in fewer regions and these were in the left hemisphere only (see Chapter 2 for a full review). These findings are consistent with dual coding theory (Paivio, 1991) which predicts that concrete words are processed in a widely distributed language network and abstract word processing is more contained in the verbal left hemisphere. Importantly, the results from the meta-analyses demonstrate that in healthy young adults, concrete and abstract words consistently elicit different patterns of neural activity in distinct brain regions which suggests that conceptual processing associated with these word types may be underpinned by different mechanisms.

Recently, accounts of semantic memory and theoretical models on the neural organization of conceptual knowledge have been developed by combining findings from behavioural and neuroimaging studies. One such account is the embodied abstraction account of Binder and Desai (2011) which is based on a modified theory of embodiment. The embodied abstraction view suggests that conceptual information undergoes a process of embodiment in different levels in motor, sensory and affective systems with these systems being located near associated modality specific cortical regions. Modal regions interact with non-modality specific, supramodal systems which are located in temporal and inferior parietal cortex. Conceptual knowledge is abstracted gradually from the modal-specific systems and interacts with the supramodal convergence zones with the purpose of binding the representations. Different levels of access are determined by variables such as familiarity or context and thus, according to this view, concrete words will elicit greater activation than abstract words due to the increased amount of associated semantic conceptual information. Vigliocco et al. (2014) have argued that abstract words can be also be accounted for in an embodied view. They propose an extended theory of embodiment and suggest that abstract words achieve embodiment through affective and emotional experiential knowledge rather than in sensory-motor experiences.

A recent study by Sandberg and Kiran (2014) investigated concrete and abstract word processing in three people with chronic aphasia and three healthy aged-matched controls when performing a visual, semantic judgement task (word judgement and synonym judgement). During the word judgement task, there was increased activity for abstract compared to concrete words in a widely distributed bilateral network in anterior and posterior regions. In contrast, no region showed increased activation for the concrete greater than abstract condition in either of the tasks. The neural difference in activation between the two conditions was not as robust for the healthy older controls and the authors suggest that this may reflect the exaggerated behavioural effects of concreteness often observed in people with aphasia (Sandberg & Kiran, 2014).

The present study sought to further investigate the neural basis of concrete versus abstract word processing in aphasia, but unlike Sandberg and Kiran (2014), we focused on subacute aphasia and also examined the relationship between observed brain activity and spoken language comprehension outside the scanner (see Crinion and Price (2005) for a similar approach with sentence comprehension in chronic aphasia). Our first aim was to investigate the neural mechanisms underpinning concrete versus abstract word processing in people with aphasia during the subacute phase of their recovery compared to healthy age-matched controls. As described in Chapter 3, we observed differences between young adults and older adults in select brain regions. In the left IFG, the older adults showed an increase in activity for abstract and pseudoword processing but not for concrete word processing compared to the young adults. Meanwhile in the left AG, the older adults elicited increased activity for all three conditions but with no differences observed between conditions, suggesting indiscriminate use of this region by the older adults compared to the young adults. In the present study, we wanted to examine whether similar patterns of activity are evident in people with subacute aphasia, or whether increased contralateral activity would be elicited (see Saur et al., 2006). Based on Sandberg and Kiran (2014) we also expected greater activity for abstract versus concrete words in the aphasia group compared to controls. Our second aim was to explore the relationship between brain activity elicited with the fMRI task and out of scanner language performance (in spoken language comprehension and confrontation naming). Based on Crinion and

Price (2005) we predicted right hemisphere activity would be positively correlated with spoken word and sentence comprehension.

4.2 Methods

4.2.1 Participants

Twenty aphasic patients were recruited from the Stroke Unit at the Royal Brisbane and Women's Hospital. Inclusion criteria were: (i) single left hemisphere stroke as diagnosed by a clinical structural scan, (ii) the presence of aphasia as indicated in the clinical chart or as confirmed by assessment of the Western Aphasia Battery - Revised (WAB-R; Kertesz, 2007), (iii) able to provide informed consent, (iv) English as primary language, and (v) sufficient hearing and vision to perform the tasks. Exclusion criteria were (i) any other neurological disorder, mental illness, head trauma, alcoholism and cerebral tumour, (ii) any contraindications for MRI, (iii) significant cognitive deficits as identified on the MMSE (Folstein et al., 1975), and (iv) severe comprehension difficulties that would impede following fMRI instructions. Six aphasic patients were unable to complete the scanning protocol due to (i) technical issues (n = 2) (ii) MRI contraindications (n = 1), (iii) site of lesion (n = 2 pons region) or (iv) were transferred to another hospital before their scanning session could be completed (n = 1). A total of 14 aphasic patients (10 males, M = 63.8 yrs, SD = 11.1 yrs) were included.

An aged-matched control group $t(15.243) = -1.839$, $p = .085$ of 15 healthy adults (10 females, M = 69.5 yrs, SD = 3.4 yrs) was recruited through advertising flyers in the University of Queensland newsletters and from local community centres. Inclusion and exclusion criteria were the same as that of the aphasic patients except for the absence of stroke and aphasia. The MMSE (Folstein et al., 1975) was administered to confirm the absence of cognitive impairment.

Detailed written information regarding the research was provided to all participants and carers of the participants with aphasia were asked to be present during the consent procedures. All subjects provided full written consent and control subjects received $30 in reimbursement. The study received approval from the University of Queensland Medical Research Ethics Committee and the Queensland Health Human Research Ethics Committee. Site-specific research governance was also obtained from the Royal Brisbane and Women's Hospital Ethics Committee.

4.2.2 Behavioural Assessment

Preliminary assessments were administered to aphasic patients within a week of the scan date and included: (i) the MMSE (Folstein et al., 1975), (ii) the Edinburgh Handedness Inventory (EHI; Oldfield, 1971), (iii) the WAB-R (Kertesz, 2007) and (iv) the Apraxia Battery for Adults (ABA-2; Dabul, 2000). A more detailed language battery was administered to each participant within 24 to 48 hours of the scanning procedure and comprised of: (i) the Comprehensive Aphasia Test (CAT; Swinburn, Porter, & Howard, 2004) (ii) the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), (iii) the Pyramids and Palm Trees test (Howard & Patterson, 1992) and (iv) subtests 5 (Auditory Lexical Decision), 25 (Visual Lexical decision), 49 (Auditory Synonym Judgements), 8 (Nonword Repetition) and 9 (Real Word Repetition) of the Psycholinguistic Assessment of Language Processing in Aphasia (PALPA; Kay, Lesser, & Coltheart, 1992). Control participants were administered the full assessment battery within one week of their individual scan date.

4.2.3 fMRI Task

The fMRI paradigm consisted of an auditory lexical decision task and employed real word and pseudoword stimuli as previously reported in Chapters 2 and 3. Using an event-related design we presented 120 individual stimuli (30 concrete words, 30 abstract words and 60 pseudowords) in the same session. The stimuli were split into two runs of 14.4 minutes duration and sixty items were administered in each run. Order of stimuli within a session was pseudorandomised to prevent items with the same constituent syllables being presented one after the other and to ensure that no more than two trials from any of the three conditions (concrete, abstract and pseudowords) ever appeared consecutively. Five different lists were created to account for order effects and these were randomised across the aphasic patients. The auditory stimuli were digitally recorded in a soundproofed room with a Rode NTK condenser microphone using a native female English speaker's voice. Audacity, a software editing tool, (http://www.audacity.sourceforge.net) was used to edit each spoken word and pseudoword. Mean durations were 723.7ms (*SD*: 105.0ms) for concrete, 771.93ms (*SD*: 118.7ms) for abstract and 779.8ms (*SD*: 92.6ms) for pseudowords. A Kruskal-Wallis test (Kruskal & Wallis, 1952) revealed no significant difference between conditions ($p > .05$).

4.2.4 fMRI Procedure

All aphasic patients were scanned between 2 – 6 weeks post-stroke onset (*M* = 23.4 days, *SD* = 10.3 days). Before the scanning session, a full explanation of the auditory lexical decision task was provided to all participants and a demonstration provided with a computer-based example of the task using 10 items. The participants practised the task until a success rate of approximately 80 percent had been achieved. Participants used their non-dominant hand to respond to 'Is it a real word', with the middle finger indicating 'yes' and the index finger indicating 'no'. Once inside the scanner, an MR compatible response box (Current Designs Inc, Philadelphia PA) was placed in the participant's non-dominant hand. Stimuli were delivered binaurally with MRI confon headphones (MR Confon GmbH, Magdeburg, Germany) and hearing levels of the audio checked once in the scanner to ensure adequate volume for each individual participant. All participants were reminded to keep as still as possible and to keep their eyes open during the fMRI sequence. Fixation crosses and the written prompt, 'Is it a real word?' were presented on a screen positioned behind the scanner. The screen could be viewed by the participants in a mirror attached to the headcoil. The fMRI acquisition sequence began with the visual presentation of a small black fixation cross (48 point font) and the words 'Is it a real word?'. This screen was visible for 2.3s. After this, a response screen with a fixation cross and Yes/No was displayed simultaneously with an audio presentation of either a word or a pseudoword. The participants were given 3.5s to respond. To indicate that a response had been made, a large blue 84 point font cross appeared on the screen. This cross was visible for 1s after which time a black 84 point font appeared on the screen and remained visible until the beginning of the following trial. A long inter-trial interval (jittered between 10-18s, mean

14s) followed each auditory stimulus presentation in order to allow for the delayed hemodynamic response function previously observed in patients with post-stroke aphasia (Bonakdarpour et al., 2007; Meinzer, Lahiri, et al., 2009).

4.2.5 Data Acquisition

The fMRI data were acquired using a Siemens 3 Tesla Trio scanner (Siemens, Erlangen) at the Royal Brisbane and Women's Hospital. A standard gradient echo-planar imaging pulse sequence (repetition time (TR): 2210ms; echo time (TE): 30ms; flip angle: 90°; field of view (FOV): 220x220mm and acquisition matrix: 64x64) was used, covering whole brain with 36 contiguous axial slices of 3mm thickness with 0.3mm inter-slice interval. A total of 390 volume images with BOLD contrast were collected during the same session in two separate runs, with each run lasting 14.4 mins in duration. During the same scanning session, a high resolution T1-weighted anatomical image (MP-RAGE; TR 1900ms; TE 2.4ms; TI 900ms; $(0.9\text{mm})^3$ resolution) and FLAIR image (TE 87ms, TR 9000ms, TI 2500ms, 36 3mm slices, 0.9x0.9mm in-plane resolution) were acquired for each participant. To minimize potential head movements, vacuum cushions were placed between the headphones and the head coil.

4.2.6 Image Processing

Statistical parametric mapping was performed using SPM8 and 12 software (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm) with MATLAB 2011 (The MathWorks Inc., Natick, MA). The first five (dummy) volumes of each run were discarded to allow for steady-state magnetization effects. All remaining EPI volumes for each participant from run 1 and run 2 were motion corrected and realigned using INRIAlign (Freire et al., 2002) and a mean image created. A T1-weighted image, acquired during the same session, was then coregistered with the mean EPI and segmented (Ashburner & Friston, 2005). Lesion masks were created for every participant using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron), by manually drawing the lesion outline onto each individual's high resolution T1 image, with FLAIR images used as points of reference. A group specific template was created for both groups using the

DARTEL toolbox (Ashburner, 2007) and each subject's T1 and each EPI image were then spatially normalized to the standard Montreal Neurological Institute (MNI) template. Finally, EPI volumes were resampled (3.0 x 3.0 x 3.0 mm^3) and spatially smoothed with an 8 mm full-width at half-maximum (FWHM) isotropic Gaussian kernel.

4.2.7 In-Scanner Behavioural Analysis

Behavioural measures were taken for both accuracy and response times. For accuracy, a mean was calculated per subject, per condition. Response times were calculated from the start of sound onset for each trial. Responses less than 100ms and incorrect trials were removed from analysis. Normality of distribution was tested using Shapiro-Wilk. Non-normal distributions were tested using a Mann-Whitney *U* test, otherwise an independent *t*-test was used for normally distributed data. Concreteness effects for both accuracy and reaction time were also tested using a Wilcoxon Signed-Ranks test for data that was not normally distributed or a paired *t*-test for normally distributed data.

4.2.8 Imaging Data Analysis

An individual analysis per subject was carried out using a fixed-effects model. Using a hemodynamic response function with derivatives, the general linear model was created with realignment parameters (6 degrees of freedom) entered as regressors of no interest. For each condition (concrete, abstract and pseudoword), a parametric regressor for mean corrected reaction time per trial was included thereby ensuring that any BOLD signal responses were not confounded by differences of reaction time or time-on-task. Incorrect responses and trials with reaction times less than 100ms were modelled separately. Four contrasts were created at first level or within-subject analysis; concrete – pseudoword, abstract – pseudoword, concrete – abstract, and word (average response of concrete and abstract) – pseudoword.

We used an ROI approach and developed 10 ROIs based on a priori findings relating to concrete and abstract processing (Binder et al., 2009) and subacute aphasia recovery (Saur et al., 2006). The ROIs were defined using IBASPM 116 Human Atlas and created in WFU PickAtlas

(Maldjian et al., 2004; Maldjian et al., 2003) of SPM8 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). Six regions were selected to examine activity associated with concrete words and included: left AG, right AG, left MFG, left SFG, left posterior cingulate and left fusiform gyrus. Abstract word processing was investigated with ROIs in the left IFG and left aSTS with the latter being subdivided into left aMTG and left aSTG using the delineation of y<-7 for anterior by Indefrey and Levelt (2004) to ensure complete coverage of the left aSTS region. Based on the findings of Saur et al. (2006) the right IFG was included as an additional ROI in order to investigate the potential upregulation of this region in the subacute phase of aphasia recovery.

For the individual a priori ROIs, each participant's mean percentage signal was extracted for each condition using the region of interest toolbox, MarsBaR (Brett et al., 2002) in SPM8. Statistical group analyses were carried out using SPSS Statistics version 21 (IMB; Armonk, New York, USA) to determine differences between the two groups by condition. Normality was calculated for each ROI and for those regions where the data was not normally distributed, logarithm or square root transformations were applied (or inverse of both, as appropriate based on skew). For every ROI where data could be normalized by transformation, we used two-way repeated ANOVAs; 2 (aphasic, control) x 3 (concrete, abstract and pseudoword) to calculate differences in mean signal. In instances where the data could not be normalized, a non-parametric Mann-Whitney *U* test was applied. Assumptions of sphericity were checked and where they had been violated, a Huyhn-Feldt correction was applied. In all other instances, the original degrees of freedom are reported. Where normality of distribution could not be assumed, nonparametric statistical tests were applied.

In those brain regions where a significant effect of group, condition or a group by condition interaction was observed, further correlational analyses were carried out between imaging data and behavioural data using either a Pearson's Correlation Coefficient or Spearman's rank correlation depending on whether the data was normally distributed or not. Out of scanner scores from the BNT and spoken word and spoken sentence comprehension subtests from the CAT were correlated with the mean signal elicited during the fMRI task.

In addition to the ROI analysis, exploratory whole brain analyses were conducted to investigate differences between groups by condition using a 2 (aphasic, control) x 2 (concrete-pseudoword, abstract-pseudoword) factorial analysis. The direction of any significant main effects was then explored using an independent *t*-test for given contrasts. We used the Anatomy Toolbox (Eickhoff et al., 2007) to identify the coordinates of peak maxima for neuroanatomical locations significantly activated in response to the different contrasts. In order to correct for multiple comparisons, a minimum cluster threshold was determined by using Bonferroni correction (FWE $p < .05$) in SPM12 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm).

4.3 Results

4.3.1 Clinical Data

Characteristics of the fourteen aphasic subjects recruited to the study are shown in Table 7. Site of lesion was confirmed using a T1 structural scan taken during the research scanning session and evaluated by a neuroradiologist. Figure 8 shows the lesion overlay for the group of aphasic patients.

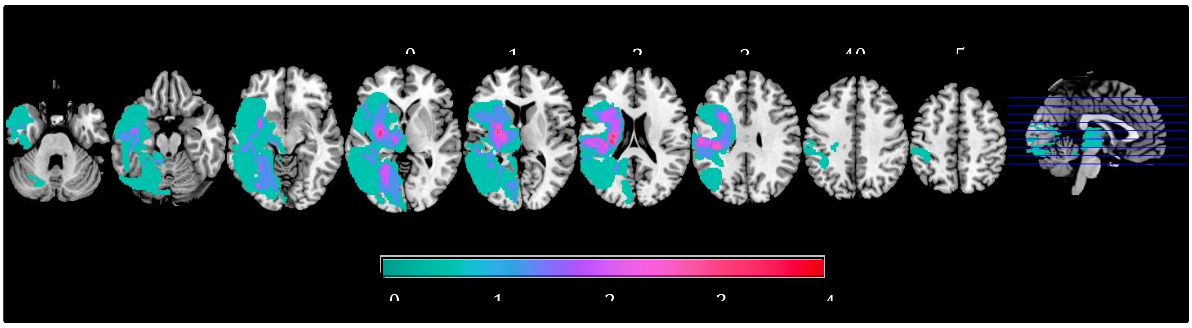

Figure 8. Lesion overlap image. Representative axial slices show the lesion overlap in the 14 aphasic subjects. A lesion map was drawn on the T1-weighted images, using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron), using the FLAIR images for guidance. The colour intensity bar indicates the number of overlapping lesions. The lesion overlap is greatest in left putamen with six of the 14 aphasic patients having an overlap in this region.

Table 7. Aphasic patient characteristics

Patient ID	Age (yrs)	Sex	Handed-ness (EHI)	Education (yrs)	fMRI (days post stroke)	NIHSS at admission	Oxford Stroke Classification	Site of lesion	Thrombolysis (min post-stroke)	Lesion volume (3mm voxels)
P01 ML	49	M	88.8	10	16	5	PACS	L MCA: Temporal + parietal	No	265
P02 NL	68	F	100	11	6	4	POCS	L Cerebellar	No	131
P03 WB	56	M	90	11	18	17	PACS	L MCA: SC + frontal	200	964
P04 DB	84	F	100	8	25	4	PACS	L MCA: Frontal + parietal	No	332
P05 GS	51	M	100	17	23	23	PACS	L MCA: SC + parietal + temporal	150	2036
P06 RT	66	M	100	10	36	6	PACS	L MCA: Frontotemporal + SC	No	3000
P07 CH	70	F	-100	8	23	12	PACS	L Thalamus + SC	No	342
P08 PL	58	M	100	14	41	12	POCS	L PCA: Cerebellar + thalamus	No	1687
P09 DC	76	M	80	16	17	12	PACS	L Thalamus +SC	No	530
P10 PK	52	M	-90	15	13	5	PACS	L MCA: Frontal + temporal	No	289
P11 HH	63	F	50	9	23	1	PACS	L MCA: Temporoparietal + occipital	No	3037
P12 RC	54	M	60	13	42	4	PACS	L MCA: SC	210	63
P13 HH	66	M	70	13	25	3	PACS	L MCA: Frontal	No	176
P14 DH	80	M	100	7	19	2	POCS	L PCA: Occipital + thalamus	No	1456

M = male, F = female; EHI = Edinburgh Handedness Inventory: left-handed = < -40, right-handed > +40; NIHSS = National Institute of Health Stroke Scale: 0 = no deficit, 34 = maximal deficit; PACS = partial anterior circulation syndrome; POCS = posterior circulation syndrome; L = left; MCA = middle cerebral artery; PCA = posterior cerebral artery; SC = striatocapsular.

4.3.2 Behavioural Results

The MMSE (Folstein et al., 1975) scores indicated that the control group did not have cognitive impairment (max = 30, group *M* = 29.0, *SD* = 0.9) while scores for the aphasic group indicating a mild cognitive impairment (group *M* = 21.8, *SD* = 6.0) although it should be noted that performance on a number of MMSE tasks requires verbal responses, so impaired performance may reflect aphasia. Two of the aphasic patients and one control were confirmed as being left-handed according to the EHI (Oldfield, 1971). The two groups differed in number of years of education $t(27) = -2.776$, $p = .010$ (controls *M* = 15.3 yrs, *SD* = 3.9 yrs; aphasics *M* = 11.6 yrs, *SD* = 3.2). Scores from the language assessments are summarised and shown in Table 8 and Table 9. At the time of admission to the hospital, deficits in language had been observed and presence of aphasia was confirmed by an impaired performance in at least one of the language assessments. Using the WAB classification criteria, at the time of recruitment to the study, eight aphasic patients presented with anomic aphasia (4 = mild, 3 = mild to moderate and 1 = moderate severity), two with Broca’s aphasia (very severe) and two with conduction aphasia (moderate to severe). The remaining two aphasic patients presented with mild language disturbance and did not receive a WAB classification.

Table 8. Language assessment scores from the CAT and WAB-R

Language Assessment	Score	P01 ML	P02 NL	P03 WB	P04 DB	P05 GS	P06 RT	P07 CH	P08 PL	P09 DC	P10 PK	P11 HH	P12 RC	P13 HH2	P14 DH	Max
CAT																
Semantic Memory	R	20	19	**15***	20	**16***	**18***	19	**16***	19	19	20	20	19	**15***	20
	T	62	54	**43***	62	**45***	50	54	**45***	54	54	62	62	54	**43***	62
Aud Word Comp	R	29	30	28	28	**17***	**25***	30	**22***	28	30	27	30	30	**22***	30
	T	60	65	58	58	**41***	**51***	65	**46***	58	65	55	65	65	**46***	65
Aud Sent Comp	R	32	31	**25***	**14***	**12***	**17***	30	28	**26***	29	**19***	30	28	**6***	32
	T	72	67	**57***	**46***	**44***	**49***	65	61	58	63	**51***	65	61	**37***	72
Aud Para Comp	R	4	**3***	**2***	4	**3***	**3***	**3***	**2***	**2***	4	4	4	**3***	**2***	4
	T	60	**49***	**43***	60	**49***	**49***	**49***	**43***	**43***	60	60	60	**49***	**43***	60
Written Word Comp	R	30	30	**18***	**25***	**6***	**23***	**28***	**28***	**28***	30	**25***	30	29	**0***	30
	T	65	65	**43***	**50***	**35***	**47***	**55***	**55***	**55***	65	**50***	65	59	**28***	65
Written Sent Comp	R	31	32	**14***	**18***	**12***	**17***	30	**15***	30	**23***	**11***	30	**24***	**0***	32
	T	68	72	**47***	**51***	**46***	**50***	67	**48***	67	**57***	**45***	67	59	**25***	72
Naming	R	79	92	**0***	**0***	**0***	**15***	**61***	**50***	**47***	77	**44***	108	74	**31***	94+
	T	68	74	**35***	**35***	**35***	**46***	**58***	**55***	**54***	67	**53***	75	65	**49***	75
Repetition	R	72	74	**14***	**29***	**4***	**49***	**66***	**64***	67	67	**66***	74	70	**54***	74
	T	66	72	**43***	**46***	**40***	**55***	59	**58***	59	59	59	72	62	**53***	72
Reading	R	**52***	66	**0***	**0***	**0***	**49***	**55***	**40***	64	61	**35***	70	61	n/c	70
	T	**55***	64	**38***	**38***	**38***	**53***	**56***	**50***	62	**55***	**49***	71	59	**38***	71
Writing	R	73	71	**27***	**31***	**9***	**55***	71	**36***	70	70	**61***	75	70	**4***	76
	T	62	60	**46***	**47***	**41***	**52***	60	**48***	59	59	**55***	65	59	**40***	69
WAB-R																
Speech		**16***	20	**1***	**10***	**0***	**11***	**18***	**13***	**15***	20	**11***	20	**18***	**14***	20
Comp		9.85	10	**6***	**7.55***	**5.45***	**6.4***	10	**9.3***	9.7	10	7.7*	10	10	**9***	10
Repetition		9.5	9.8	**3.1***	**5.8***	**0***	**6.5***	9.7	9.6	**8.6***	10	**7.9***	9.8	10	**8.8***	10
Naming		**9.1***	9.7	**0.9***	**2.5***	**0***	**2.9***	**8.7***	**7.1***	**5.9***	9.4	**3.7***	10	9.4	**5.8***	10
WAB AQ		88.9	99	22	51.7	10.9	53.6	92.8	78	78.4	98.8	60.6	99.6	94.8	75.2	100
Classification		Anomic	n/a	Broca's	Conduction	Broca's	Conduction	Anomic	Anomic	Anomic	Anomic	Anomic	n/a	Anomic	Anomic	
Severity		Mild		very severe to severe	moderate to severe	very severe	moderate to severe	mild	mild to moderate	mild to moderate	mild	moderate		mild	mild to moderate	

CAT = Comprehensive Aphasia Test; WAB-R = Western Aphasia Battery-Revised, R = Raw, T = T-score, Aud = Auditory, Comp = Comprehension, Sent = Sentence, Para = Paragraph, AQ = Aphasia Quotient, ***** *indicates impaired performance based on published norms, dis = discontinued, n/c = not collected, n/a = not applicable*.

Table 9. Language assessment scores from the BNT, PALPA, Pyramids and Palm Trees test and ABA-2

Language Assessment	P01ML	P02 NL	P03WB	P04DB	P05 GS	P06 RT	P07CH	P08 PL	P09 DC	P10 PK	P11 HH	P12RC	P13HH2	P14DH	Max
BNT	**47***	54	**1***	**5***	**0***	**6***	**29***	**28***	42	51	**20***	55	56	**6***	60
PALPA 5															
Real word	79	80	73	70	70	63	77	75	74	80	80	79	79	65	80
HI/HF	20	20	20	**18***	**17***	20	20	20	20	20	20	20	20	**17***	20
HI/LF	20	20	**18***	**18***	**16***	**19***	20	20	**18***	20	20	20	20	**19***	20
LI/HF	20	20	20	**18***	20	**15***	20	20	**19***	20	20	20	**19***	**17***	20
LI/LF	19	20	**15***	**16***	**17***	**9***	**17***	**15***	**17***	20	20	19	20	**12***	20
Nonword	79	78	74	**56***	71	72	75	**65***	70	78	**66***	77	74	70	80
PALPA25															
Real word	60	60	56	57	58	51	53	27	60	55	32	57	60	n/c	60
HI/HF	15	15	14	15	15	15	15	**10***	15	15	**10***	14	15	n/c	15
HI/LF	15	15	15	15	14	14	14	**6***	15	15	**9***	15	15	n/c	15
LI/HF	15	15	**14***	15	**14***	**14***	15	**5***	15	**14***	**4***	15	15	n/c	15
LI/LF	15	15	**13***	**12***	15	**8***	**9***	**6***	15	**11***	**9***	**13***	15	n/c	15
Nonword	**58***	59	**48***	**36***	**28***	**54***	60	**45***	59	**53***	**55***	60	**56***	n/c	60
PALPA 9															
HI/HF	20	20	**2***	**11.5***	**1***	20	20	**17***	20	20	19	20	20	**18***	20
HI/LF	19.5	20	**5.5***	**8***	**0***	19.5	19	**12***	20	19	18	20	19	18	20
LI/HF	**18.5***	20	**7***	**4***	**0***	**17***	20	**15.5***	**18***	19.5	**15***	20	20	20	20
LI/LF	**17.5***	20	**5***	**3.5***	**0***	**17***	19	**15***	**17***	20	**16***	20	19	**17.5***	20
PALPA 8	**23**$^{\Delta}$	27	**4**$^{\Delta}$	**4**$^{\Delta}$	Dis	**26**$^{\Delta}$	27	**21**$^{\Delta}$	**24**$^{\Delta}$	29	**20**$^{\Delta}$	28	**24**$^{\Delta}$	**20.5**$^{\Delta}$	30
Control data: M = 29.07; SD = 1.39															
PALPA 49															
HI	30	30	**14**$^{\Delta}$	**14**$^{\Delta}$	**18**$^{\Delta}$	**25**$^{\Delta}$	29	**25**$^{\Delta}$	30	29	**27**$^{\Delta}$	30	29	**27**$^{\Delta}$	30
Control data: M = 29.73; SD = 0.59															
LI	28	30	**16**$^{\Delta}$	**15**$^{\Delta}$	**17**$^{\Delta}$	**17**$^{\Delta}$	**20**$^{\Delta}$	**18**$^{\Delta}$	27	28	**23**$^{\Delta}$	29	27	**16**$^{\Delta}$	30
Control data: M = 28.67; SD = 1.54															
P&PT V1	50	51	47	48	**40***	**38***	48	**39***	47	51	**46***	51	50	n/c	52
ABA-2	N	N	Mod	Mi	Mod-Sev	N	N	N	Mi	N	N	N	N	N	

BNT = Boston Naming Test; WAB-R = Western Aphasia Battery-Revised; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia: PALPA 5 = Auditory Lexical Decision; PALPA 25 = Visual Lexical Decision; PALPA 9 = Real Word Repetition; PALPA 8 = Nonword Repetition; PALPA 49 = Auditory Synonym Judgement; P&PT V1 = Pyramids and Palm Trees(Version 1 – 3 pictures); ABA-2 = Apraxia Battery for Adults – Second Edition; N= None, Mi = Mild, Mod = Moderate, Sev = severe

***** *indicates impaired performance based on published norms,* $^{\Delta}$ *indicates impaired performance based on control results where published norms were not available, dis = discontinued, n/c = not collected.*

4.3.3 In-Scanner Behavioural Results

Mean accuracy was calculated for each condition in the aphasic and control groups (see Table 10). Values indicated that while accuracy for the concrete and pseudowords for both groups was relatively high (> 90%), accuracy for the abstract condition was considerably lower for the aphasic group.

Table 10. Mean percent accuracy for aphasic patients and controls

Condition	Aphasics Mean (*SD*)	Controls Mean (*SD*)
Concrete	92.4 (10.2)	97.6 (3.7)
Abstract	83.1 (14.6)	95.1 (4.8)
Pseudoword	90.2 (9.5)	95.0 (4.3)

The accuracy values were not normally distributed ($p < .044$) and a non-parametric Mann-Whitney *U* test was used. Neither the concrete or the pseudoword conditions showed significant differences between groups ($p > .123$) but the aphasic group were significantly less accurate for abstract words than controls $U = 41.5$, $Z = -2.8$, $p = .004$.

The percentage of reaction times that were removed (response times < 100ms or incorrect) was 9.1% for aphasic patients and 4.4% for controls. Differences between response times for the two groups were investigated using a Mann-Whitney *U* test. Controls were significantly faster than the aphasic subjects for all three conditions; pseudoword $U = 304253$, $Z = -2.120$, $p = .034$ two-tailed, concrete $U = 64111$, $Z = -6.043$, $p < .0001$ two-tailed, and abstract conditions $U = 58232$, $Z = -5.706$, $p < .0001$ two-tailed (see Table 11).

Table 11. Mean reaction times for aphasic patients and controls

Condition	Aphasics Mean (*SD*)	Controls Mean (*SD*)
Concrete	1406ms (446)	1263ms (186)
Abstract	1539ms (531)	1335ms (219)
Pseudoword	1779ms (609)	1736ms (585)

Both accuracy and response times were examined for concreteness effects (i.e. the processing advantage observed for concrete over abstract words) using Wilcoxon Signed-Ranks Tests separately in the two groups. Individuals with aphasia were significantly more accurate for concrete compared to abstract words $Z = -3.084$, $p = .002$ but there was no difference for the controls ($p = .082$). Results for reaction times showed that concreteness effects were maintained in both groups with concrete words being responded to significantly faster than abstract words in the aphasic group $Z = -4.004$, $p < .0001$ and the controls $Z = -4.818$, $p < .0001$.

4.3.4 Region of Interest Analyses

4.3.4.1 ANOVA. Results for the main effects of condition between the concrete, abstract and pseudoword conditions are shown in Table 12. Main effects were observed in left AG, right AG, left SFG, left posterior cingulate and left fusiform gyrus ($p < .05$, FDR corrected).

Left IFG showed an effect of group $F(1, 14) = 5.718$, $p = .031$ with the control group eliciting greater signal ($M = 0.287$, $SE = 0.019$) compared to the aphasic group ($M = 0.133$, $SE = 0.032$). Where a significant effect of group had been observed, the degree of lesion overlap in that region was examined to see if that alone could explain the group effect. Only three aphasic patients had some damage within the left IFG, with 1.52%, 10.82% and 44.43% lesion overlap in this area.

Table 12. Regions of interest - main effect of condition (concrete – abstract – pseudoword), and post hoc results comparing conditions in each ROI

Region	*F* value	Concrete – Pseudoword	Abstract – Pseudoword	Concrete – Abstract
Left AG	*F*(2, 13) = 14.493, *p* = < .001	Conc > PS *p* = .001	Ab > PS *p* < .001	*ns*
Right AG	*F*(2, 13) = 9.728, *p* = .003	Conc > PS *p* < .001	Ab > PS *p* = .007	*ns*
Left SFG	*F*(2, 13) = 6.258, *p* = .012	*Ns*	Ab > PS *p* = .003	*ns*
Left posterior cingulate	*F*(2, 13) = 24.655, *p* < .001	Conc > PS *p* = .001	Ab > PS *p* < .001	*ns*
Left fusiform	*F*(1.471, 20.593) = 4.856, *p* = .027*	Conc > PS *p* = .039	Ab > PS *p* = .006	*ns*

* Huynh-Feldt correction.

In the word (concrete and abstract words combined) versus pseudoword contrast, a significant group by condition interaction was observed in left IFG $F(1, 14) = 10.062$, $p = .007$ (see Figure 9). The control group elicited increased activity compared to the aphasic group for pseudowords (control $M = 0.33$, $SE = 0.03$; aphasic $M = 0.13$, $SE = 0.05$) and words (control $M = 0.26$, $SE = 0.03$; aphasic $M = 0.13$, $SE = 0.06$). A within group paired *t*-test revealed that differences between the conditions was only significant for the control group $t(3.239) = 14$, $p = .006$.

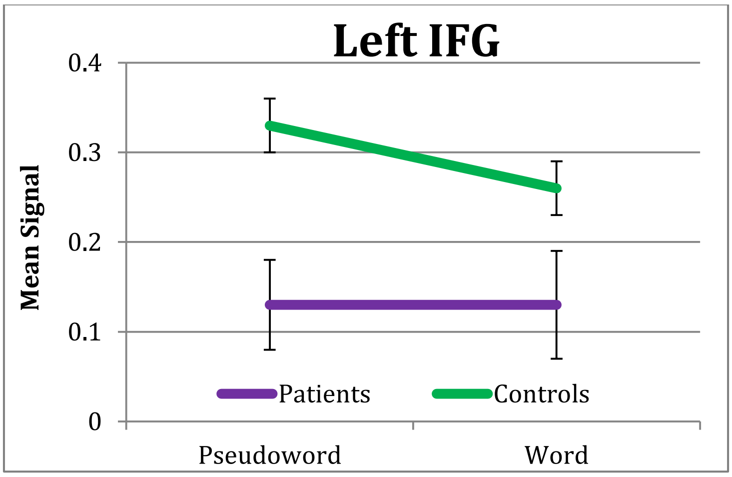

Figure 9. Group by condition interaction in left IFG. Aphasic group and controls x 2 conditions (word and pseudoword).

Within the individual conditions (concrete, abstract and pseudoword), significant group by condition interactions were observed in two of the ROIs; left IFG $F(2, 13) = 6.635$, $p = .010$ and left aMTG $F(2, 13) = 4.666$, $p = .030$ (refer to Figure 10). These interactions were further explored by examining differences in mean signal between conditions separately for each group. An effect of condition was observed in the left IFG for the controls only $F(2, 13) = 8.384$, $p = .005$ and post hoc pairwise comparisons indicated significant differences for all three contrasts ($p < .009$) with greatest activity for the pseudowords ($M = 0.34$, $SE = 0.03$), followed by abstract words ($M = 0.28$, $SE = 0.03$) and then concrete words ($M = 0.25$, $SE = 0.03$). There was a significant difference in activity for condition in the left aMTG for the aphasic group only $F(2, 13) = 5.909$, $p = .015$. Pairwise comparisons indicated that the differences between contrasts were significant for all three conditions ($p < .013$). Mean signal was greatest for concrete words ($M = 0.09$, $SE = 0.03$), followed by pseudowords ($M = 0.05$, $SE = 0.03$) and then abstract words ($M = 0.02$, $SE = 0.03$).

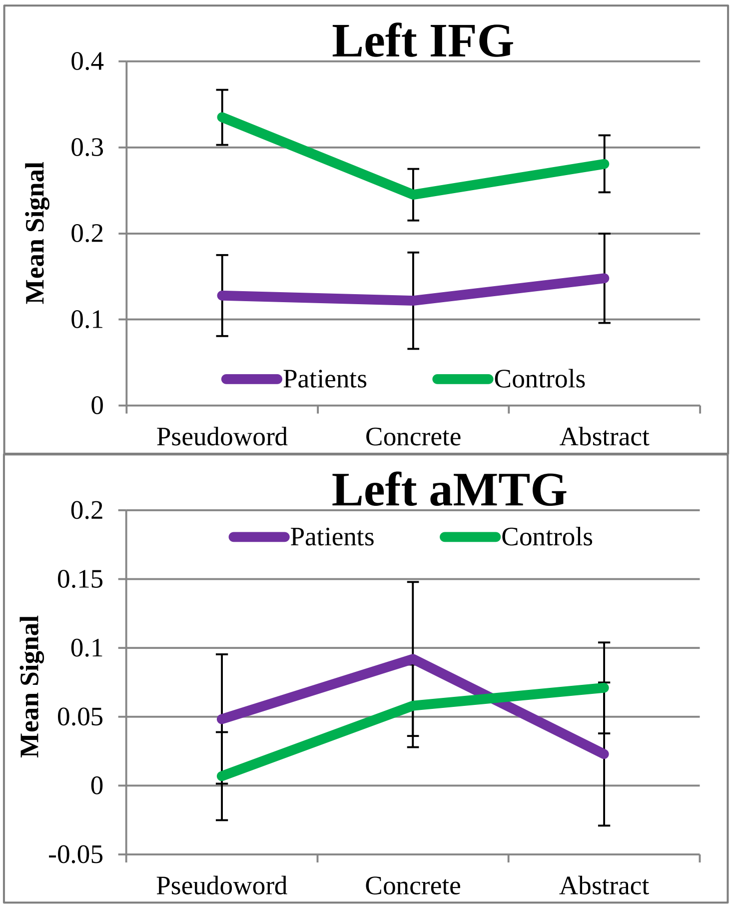

Figure 10. Group by condition interactions in two significant ROIs. Aphasic group and controls x 3 conditions (concrete, abstract and pseudoword).

4.3.4.2 Mann-Whitney: group differences. We also conducted group-wise comparisons for each condition in the right IFG where Mann Whitney tests were required due to non-normal data. Results showed a significant difference between groups for the pseudoword condition only $U = 51$, $Z = -2.357$, $p = 0.18$ two tailed with the control group ($M = 0.289$, $SE = 0.035$) eliciting significantly more activity in this region than the aphasic group ($M = 0.146$, $SE = 0.040$).

4.3.4.3 Correlational analyses. Regions where significant main effects or interactions had been observed were examined further using a correlation analysis to explore subacute brain activity and performance in confrontation naming and spoken comprehension tests. Eight ROIs were therefore included in the analysis: left AG, right AG, left SFG, left posterior cingulate, left fusiform gyrus, left aMTG, left IFG and right IFG. For the word (concrete and abstract words combined) contrast, a significant positive correlation was observed between right AG activity and CAT spoken word comprehension $r_s = .554$, $p = .04$. For the concrete contrast, positive correlations were observed in the right AG with CAT spoken word $r_s = .687$, $p = .007$ and spoken sentence comprehension $r = .590$, $p = .026$. A positive correlation was also observed in the left posterior cingulate for the abstract contrast with the spoken word comprehension task $r_s = .545$, $p = .044$. Significant results are shown in Figure 11. No other significant correlations were observed in subacute aphasic patients. No significant correlations were found for controls. In order to further explore the basis for right AG correlations we also examined left AG lesions. Results showed that only one patient had damage to the left AG with a 42.8% lesion overlap.

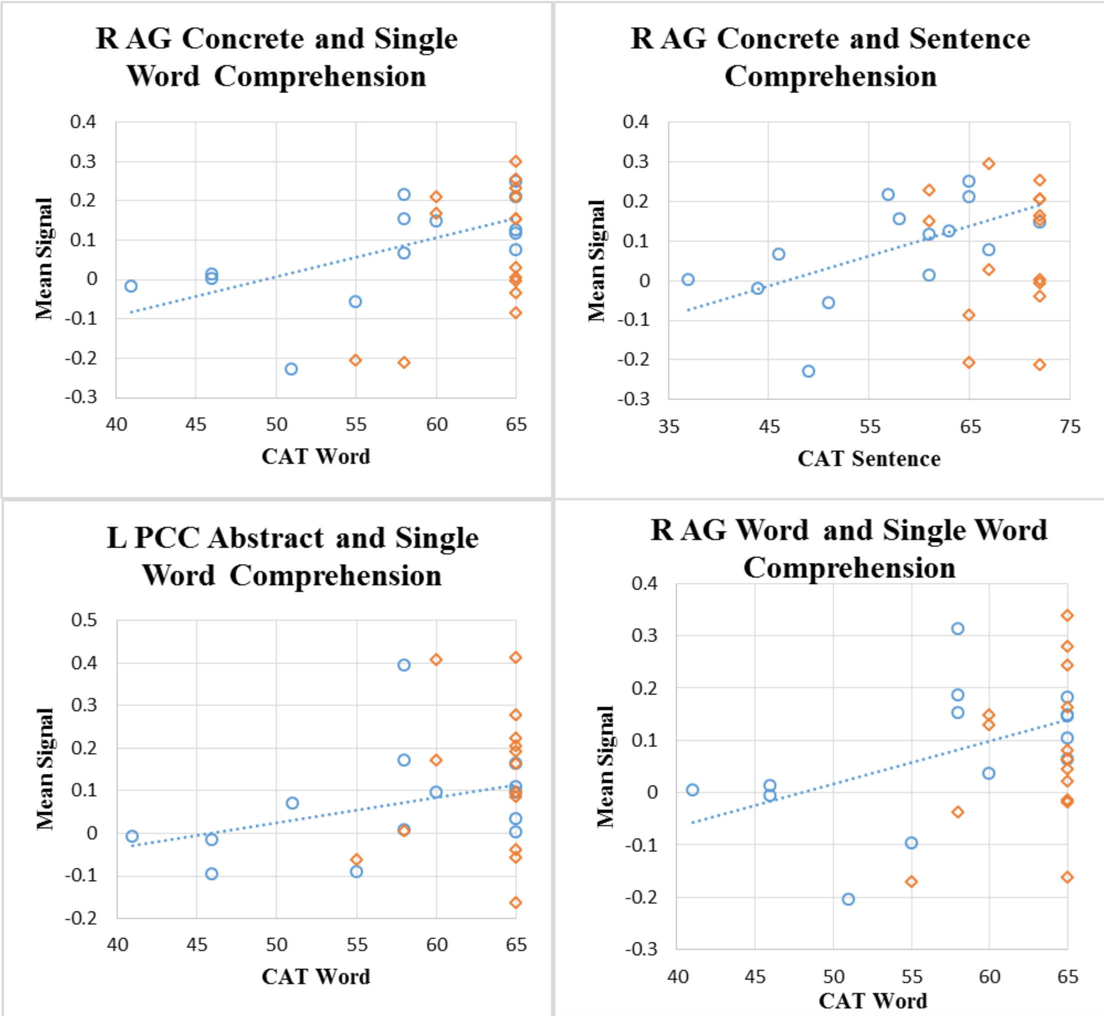

Figure 11. Increases in mean signal with single word and sentence comprehension.
Aphasic patients ○ Controls ◇

4.3.5 Whole Brain Analyses

A main effect of group was observed in left IFG (pars opercularis extending into pars triangularis) and left superior medial gyrus extending into SMA (refer Table 13 and Figure 12). No other main effects of condition or group by condition interactions were observed in the whole brain analyses.

Table 13. Factorial results from whole brain analysis for main effect of group between aphasic patients and controls

Main effect	Peak Maxima	Cluster *p*FWE	Cluster (*k*)	*x*	*y*	*z*	*Z*-score
Group	left IFG (pars opercularis)	< .001	463	-50	11	11	5.36
	left superior medial gyrus	= .007	96	-7	25	43	4.45

$p < .001$ probability threshold and cluster thresholded at FWE $p < .05$

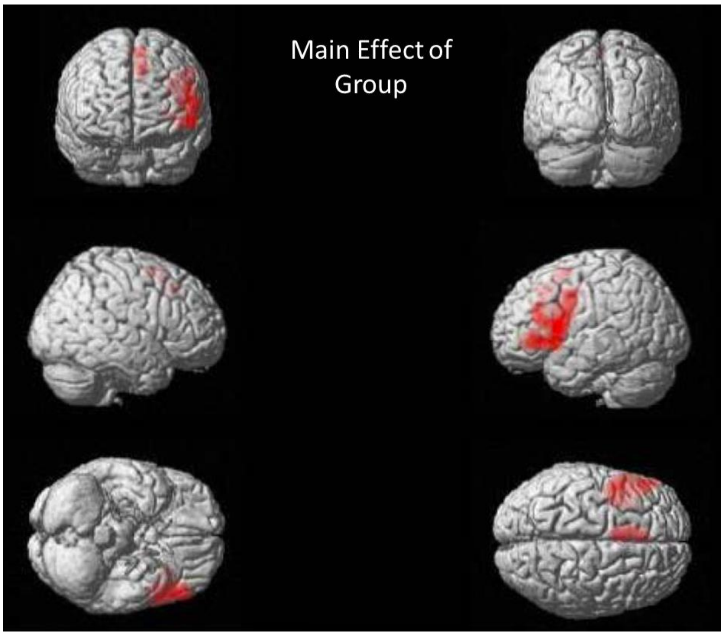

Figure 12. Significant clusters for the main effect of group.

In the brain regions where a main effect was observed, we conducted further tests to explore the direction of activity in each of the regions. Results of the mean signal per group are shown in Figure 13.

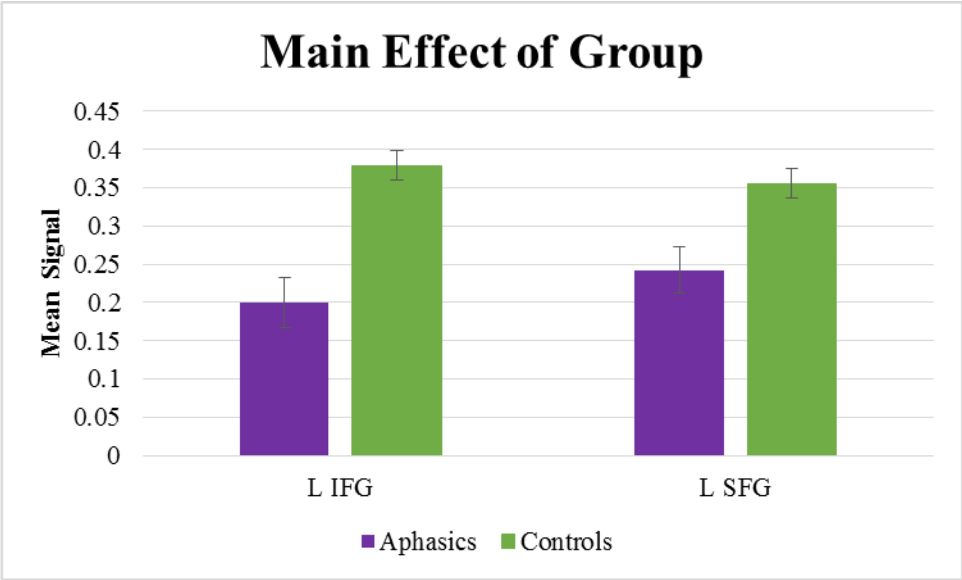

Figure 13. Mean signal extracted from each ROI showing the directionality of the main effect of group.

4.4 Discussion

We investigated neural activity associated with the recognition of spoken concrete and abstract words in a group of aphasic patients in the subacute phase of recovery and compared their performance to a group of healthy aged-matched controls. We also examined the relationship between brain activity elicited during the fMRI task and language performance outside the scanner. We found that activity in right AG elicited during concrete word processing correlated positively with spoken word and sentence comprehension. We also found significant group by condition interactions in left aMTG and left IFG, demonstrating that these regions are recruited differently in spoken word recognition by people with aphasia during the subacute phase of recovery compared to healthy controls performing the same task.

Behavioural results from the in-scanner task revealed a difference in accuracy for abstract word processing between the two groups. Compared to the controls, the aphasic group was significantly less accurate for abstract word recognition. In addition, a significant difference in accuracy was observed between conditions for the aphasic group with abstract word recognition being significantly less accurate than either concrete or pseudoword processing. The reduction in accuracy for abstract words is consistent with findings in the behavioural literature which show worse performance for abstract over concrete words both in the spoken (Franklin, 1989) and written comprehension in aphasia (Barry & Gerhand, 2003; Crutch & Warrington, 2005). Thus, it would appear that reduced accuracy for abstract words, rather than a better performance for concrete words may contribute to exaggerated concreteness effects. No differences were observed in the control group between any of the conditions for accuracy and this is likely due to a ceiling effect. Both groups responded faster to concrete words than abstract words and faster to abstract words than pseudowords, thus confirming the presence of concreteness effects in this task. Comparisons across the two groups indicated that the controls were faster on all three conditions compared to the aphasic subjects. Previous studies have shown that there is a consistent slowing in response times by healthy older adults when performing a lexical decision task (Gold et al., 2009; Madden, 1992) and the additional slowing in response times seen in the aphasic patients suggests that lexical decision processes are further slowed in the subacute phase of post-stroke aphasia.

Significant positives correlations between the concrete contrast and spoken language comprehension at the single word and sentence level were observed in the right AG for the aphasic subjects. The strongest correlation for the aphasic group was observed between the concrete contrast and single word comprehension whereas the correlation between the sentence comprehension was weaker, suggesting that right AG may be less sensitive to sentence level tasks. The association between recruitment of right hemisphere regions and improved language function is in general agreement with previous observations of increased right hemisphere activity in post-stroke aphasia (Crinion & Price, 2005; Saur et al., 2006). Crinion and Price (2005) looked specifically at auditory comprehension recovery in chronic post-stroke aphasia. Right superior temporal lobe activity elicited during an in-scanner auditory comprehension task of meaningful narrative versus meaningless reversed speech was positively correlated with out of scanner performance on auditory sentence comprehension and story recognition tasks. The present study suggests that other right hemisphere regions elicited during single word processing also support auditory comprehension in post-stroke aphasia. The different regions identified in these two studies may in part reflect the imaging tasks employed, with the present finding of comprehension-related activity in the right AG reflecting the more selective semantic processing elicited during the lexical decision task compared to narrative comprehension as in Crinion and Price (2005)(see also below). It is also possible that these differences reflect the fact that Crinion and Price (2005) investigated the chronic phase of recovery, where the right superior temporal recruitment observed may reflect activity in a network that has already undergone significant reorganisation.

Saur et al. (2006) looked specifically at recovery mechanisms associated with recovery in subacute aphasia. They found increased right IFG activity in response to an auditory sentence task, compared to controls. While we did not observe any such differences between the two groups in this present study, we did observe correlations between right AG and spoken word comprehension. A possible explanation for the correlated activity in right AG and not in other right hemisphere regions such as right IFG, could be due to the nature of the task employed in this study. In aphasia, the processing of sentences is considered to be heavily dependent on other cognitive functions such as verbal working memory (Caplan et al., 2013) and associated with left IFG (Binder et al., 2009; Binder et al., 2005). In contrast, activity in the left AG associated with semantic processing has been widely reported (Price, 2010) and indeed, a meta-analysis on semantics by Binder et al. (2009) identified this region as being the most routinely activated in response to semantic-based tasks. The reliable involvement of this region in semantic processing has prompted some to suggest that the AG acts to integrate and bind sensorimotor knowledge received from modality specific regions (Binder & Desai, 2011). Results from a recent study investigating concrete and abstract processing in healthy ageing are reported in Chapter 3 and showed that older adults elicited greater activity than young adults in left AG for both real words and pseudowords and thus appear to reliably recruit this region for lexical processing (Roxbury et al., 2014). The correlation between activity in the right AG and auditory comprehension in the present study indicates that recruitment of the homologous region in the subacute aphasia may serve as a compensatory recovery mechanism which possibly contributes to speech comprehension both at the single word and sentence level during post-stroke aphasia recovery. There was no correlation in this region for the controls (although this likely reflects a ceiling effect in spoken word and sentence comprehension performance). Intriguingly, in the present study, all the aphasic patients except one had an intact left AG and thus in the subacute phase of aphasia recovery, it appears that recruitment of the right homologous AG in response to spoken word recognition occurs despite there being no direct lesion in the corresponding contralateral region.

Additionally, since we employed a simple auditory lexical decision task in this present study, we ensured that a successful performance was achievable for most of the aphasic subjects. Thus, we are confident that the strong positive correlation observed in the right AG for the concrete contrast and single word comprehension, reflects neural activity associated with the accurate processing of spoken word recognition in the subacute recovery phase. This relationship between right AG and auditory comprehension is further highlighted by the fact that the activity elicited during the task and out of scanner performance is specific to comprehension and does not extend to less directly related functions such as confrontation naming.

A moderate positive correlation was also observed in left posterior cingulate with the abstract contrast and single word comprehension in the aphasia group. In healthy individuals, the posterior cingulate is often implicated in semantic-based processing and episodic encoding (Binder et al., 2009). It has also been more specifically associated with concrete word processing (Binder et al., 2009; Wang et al., 2010) and it is suggested that this is due to the richer set of conceptual features in concrete words which evoke strong episodic memories (Binder et al., 2009). However, since specific episodic memories are less strongly linked to abstract words, activity elicited in this region should be reduced for abstract conceptual processing. Thus, the relationship observed between abstract words and single word comprehension in left posterior cingulate by the aphasic patients may reflect the retrieval of additional episodic memories required to assist with the processing of abstract words.

Significant group by condition interactions were observed in left aMTG and left IFG. Further analyses of the interaction in the left aMTG showed that for the aphasic group only, there were differences between all three conditions, with concrete words eliciting greater activity than pseudowords and pseudowords eliciting greater activity than abstract words. It should be noted that this is not consistent with the findings of Sandberg and Kiran (2014). However, this may be due to differences in the patient cohort. While the MTG generally has been considered a critical region in the language comprehension network, with multiple fibre pathways converging beneath this region and cortical association areas directly connected to it (Turken & Dronkers, 2011), the more anterior portions of the temporal lobe have been described as an amodal conceptual hub (Patterson et al., 2007) and considered a critical region for semantic memory, although its precise function remains unclear (Bonner & Price, 2013). Evidence from the aphasia literature has shown that lesions in the anterior temporal region are associated with semantic recognition and production deficits (Mirman et al., 2015) and that auditory comprehension deficits are associated with a disruption in the ventral stream pathway which connects regions in the temporal and prefrontal lobes (Kümmerer et al., 2013). In terms of concrete and abstract processing specifically and focal aMTG lesions, the literature has shown mixed results. While our finding is consistent with a processing advantage observed for concrete over abstract words in patients with semantic dementia (Jefferies et al., 2009), reverse effects (i.e. worse performance on concrete compared to abstract words) have also been reported (Reilly et al., 2007; Yi et al., 2007) although it should be noted that these reversal effects are much less typical (Hoffman, 2015; Hoffman & Lambon Ralph, 2011).

In the left IFG, the controls showed significant differences between all three conditions with greatest activity elicited by pseudowords, followed by the abstract and then concrete words. This finding is consistent with the view that left IFG is involved in controlled processes associated with semantic retrieval and maximally so with stimuli that are associated with weak or ambiguous semantic conceptual representations (Hoffman, 2015). This pattern was not observed in the aphasia group, where there was no difference between conditions. In addition, we observed a main effect of group in left IFG with the controls eliciting significantly greater activity than the aphasic subjects. The differences in recruitment of this region between the two groups is unlikely to be explained by effects of lesion alone as only three aphasic patients had involvement of left IFG and of those, only one had a lesion that involved greater than 11 percent of the region. Furthermore, since the aphasic patients were able to perform the task, we suggest that the differences observed between the two groups and specifically the underactivity (relative to the controls) observed in this region by the aphasic patients may reflect diaschisis, whereby activity in the left IFG is compromised as it is dependent on inputs from distant but connected lesioned regions (Carrera & Tononi, 2014; Price et al., 2001).

In summary, we observed decreased left IFG and increased left aMTG activity during spoken word recognition in the subacute aphasic group compared to controls. Results from the correlation analysis between task-related brain activity and out of scanner language performance on comprehension tasks in subacute stroke provided some intriguing insights, demonstrating that increased right AG activity supported auditory comprehension in the aphasic group, and this relationship was not observed in the control group. Furthermore, the recruitment of the right AG was evident despite only one patient having a lesion involving the left AG suggesting a novel compensatory mechanism that does not occur in response to contralateral lesions. These findings provide further insights into the neurobiology of language recovery in subacute aphasia.

5 Chapter Five

Neurophysiological Markers of Language Recovery in Subacute Stroke

---

Chapter 4 showed that activity in the right AG during concrete word processing was positively correlated with spoken language comprehension in the subacute stage of recovery. The aim of Chapter 5 was to extend on these findings by examining how the neural mechanisms associated with spoken word recognition change over the course of aphasia recovery and to determine whether language-related fMRI activity obtained in subacute aphasia is able to predict language recovery at the chronic time-point. Previous longitudinal aphasia recovery studies have shown that in the subacute phase, brain activity is associated with an upregulation of right hemisphere homologues but that this changes in the chronic phase when a return to more left hemisphere networks is observed (Saur et al., 2006), and based on this study it was hypothesised that a similar pattern of right/left hemisphere shift would be observed.

5.1 Introduction

It has been proposed that language recovery in aphasia is associated with distinct neural mechanisms which are engaged at different time points (Kiran, 2012). In the first few weeks following a stroke, recovery from aphasia can be rapid. This accelerated recovery is due largely to physiological changes which result in reperfusion of the ischaemic penumbra and a reduction in oedema and metabolic disturbance (Marsh & Hillis, 2006). In the subacute phase, which begins at approximately two weeks post-stroke and lasts for weeks, the recovery process slows and the upregulation of intact, undamaged regions occurs as new alternate networks are reorganised and formed (Lazar & Antoniello, 2008). Mechanisms during this recovery phase include recruitment of perilesional tissue (Warburton et al., 1999), an engagement of homologous language regions (Saur et al., 2006; Turkeltaub et al., 2011) or resolution of diaschisis whereby a reduction in dysfunctional brain activity occurs in structurally unaffected regions, that are connected to but distant from the lesion (for a review see Carrera & Tononi, 2014). During the final chronic phase, after the language network has experienced significant reorganisation and language recovery has stabilised, neural reorganisation and compensatory cognitive strategies continue to contribute to recovery and this may continue for many years (Grafman & Litvan, 1999; Muñoz-Cespedes et al., 2005).

Most neuroimaging research investigating the mechanisms of language recovery has focussed on people with aphasia at one point during the recovery process either in the early phase (Hillis & Heidler, 2002; Hillis, Kane, et al., 2001; Hillis et al., 2005; Hillis, Wityk, et al., 2001; Reineck et al., 2005) or the chronic phase (Crinion & Price, 2005; Crinion, Warburton, Lambon-Ralph, Howard, & Wise, 2006; Heath et al., 2012; Heath et al., 2013; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014). The studies which have investigated recovery in the acute stage have largely focused on the contribution of hypoperfusion to aphasia recovery (Hillis & Heidler, 2002; Hillis et al., 2005). The Hillis and Heidler (2002) study employed PWI and DWI to investigate spoken word comprehension in acute aphasia. They found that when BA 22 (Wernicke's area) was successfully reperfused, recovery of spoken word comprehension was rapid. In comparison, patients with persisting hypoperfusion in BA 22 remained impaired in their spoken comprehension abilities, demonstrating that early recovery of receptive language function is largely attributable to reperfusion (Hillis & Heidler, 2002).

In comparison, studies investigating the chronic phase of recovery have identified other mechanisms associated with aphasia recovery. A recent meta-analysis by Turkeltaub et al. (2011) reviewed 12 studies and compared the consistency in brain activity in people with chronic aphasia performing language tasks with that of controls. Chronic aphasic subjects reliably recruited intact language areas, new left hemisphere regions and right hemisphere homologues (Turkeltaub et al., 2011) suggesting that recovery may involve multiple patterns of adaptation which vary depending on the specific location of the lesion and whether residual function in the left hemisphere language networks is still available or not. Crinion and Price (2005) looked specifically at auditory comprehension and examined the relationship between brain activity and language performance in chronic post-stroke aphasia. In this study, aphasic subjects listened to meaningful narrative and meaningless reversed speech. Brain activity elicited during the task was correlated with out of scanner performance on auditory sentence comprehension and story recognition tasks. There was a positive correlation between activity in the right superior temporal lobe and both auditory sentence and narrative speech comprehension suggesting the upregulation of right hemisphere homologues may underpin language comprehension in chronic aphasia. A limitation of these studies however, is that they examine the neural mechanisms associated with aphasia at one time point in the recovery process and cannot therefore provide insights into the exact nature and timing of the neural reorganisation associated with the different stages of aphasia recovery and successful language outcomes.

Longitudinal aphasia recovery studies which have investigated language improvement and changes in brain activity on patient cohorts, while few in number, have provided insights into the dynamic process of language reorganisation. Heiss et al. (1999) investigated aphasic patients at 2 and 8 weeks post-stroke in a PET study and found that successful language recovery was associated with the preservation of left temporal areas. However, the study did not investigate whether there was a correlation between language recovery and brain activity. In another longitudinal PET study, Cardebat et al. (2003) recruited aphasic patients at 2 and 11 months post-stroke and demonstrated that increased activation in perisylvian regions was associated with improved language outcome. de Boissezon et al. (2005) employed the same experimental paradigm as that of Cardebat et al. (2003) in a subgroup of patients with subcortical aphasia and showed that language improvement was associated with increased activity in bilateral temporal regions. However the process of reorganisation, in terms of the timing and extent to which different neural mechanisms are recruited over the course of recovery, was not considered in either of these studies.

Saur et al. (2006) addressed some of these limitations in a longitudinal fMRI study on a group of 14 aphasic patients in the acute (< 4 days post-stroke), subacute (~ 2 weeks post-stroke) and chronic phase (4 to 12 months post onset). An auditory sentence comprehension fMRI task was employed and patients were required to identify whether a sentence was correct from correct, incorrect and reversed speech sentences. In the acute phase, weak activation was observed in the left IFG whereas in the subacute phase, there was a significant increase in bilateral activation caused by an upregulation of the entire language network with peak activation observed in right IFG and this was associated with improved language performance. Finally, at the chronic stage, a return to more normal patterns of left hemisphere activity comparable to that of the controls was observed and this was associated with further language improvements (Saur et al., 2006). Thus, it appears that neural reorganisation associated with improved language function is a dynamic process and distinct aspects of the reorganisation are critical at different points during the recovery period.

Unfortunately, a limitation of the Saur et al. (2006) study was that the aphasic patients had some difficulty responding to the sentence-level task, having an average of 36% accuracy in the acute testing period. This presents a problem in the interpretation of brain activation as it is unclear whether the activity is indicative of an impaired performance or whether it is attributable to the neural deficit itself which underlies the impairment (Price & Friston, 1999). In addition, the type of task employed required sentence comprehension which is known to rely significantly on other cognitive functions and in particular on verbal working memory (Caplan et al., 2013). Geranmayeh et al. (2014) have suggested that much language-related brain activity observed in aphasia studies can be explained by the upregulation of regions more associated with attention and cognitive control and as such, they suggest that language tasks employed for aphasic patients need to be less cognitively demanding in order that mechanisms associated specifically with language processes can be clearly determined. Therefore, in order to establish clear relationships between brain activity and language function it is preferable that aphasic subjects are presented with experimental fMRI tasks that are less reliant on other cognitive processes and can be performed with sufficient accuracy.

Despite these limitations, a follow-up study including an additional seven patients (total 21) who performed a different but related sentence comprehension task showed striking results (Saur et al., 2010). Overall, 86% of stroke patients with aphasia at 2 weeks were correctly predicted as having good or poor language recovery at over 6 months based on fMRI data in addition to language performance and age (with similar results for predicting improvement). While the results are very promising, recovery was only considered via one global binarised language measure of good / bad outcome (combining repetition, reading comprehension, spontaneous speech, functional communication, and in-scanner performance). It has been noted that this approach precludes prediction of specific language symptom recovery (Stinear & Ward, 2013) which would aid therapy planning. The need to predict recovery of specific aphasia symptoms is further highlighted by the observation that different aspects of language recover with different trajectories in aphasia (El Hachioui et al., 2013) and recovery of one function is not necessarily related to recovery of another (Swinburn et al., 2004).

The present study sought to further investigate the neural mechanisms associated with improved language function post-stroke. It addresses the limitations of previous studies by using a simple word processing task and examining the recovery of specific language functions. Our primary aim was to determine whether language related fMRI activity at 2-6 weeks post-onset *predicts* aphasia recovery at 6 months. We employed a simple spoken word recognition fMRI task and scanned people with aphasia in the subacute and chronic phases of recovery. Recovery of language was examined using behavioural measures of spoken word and sentence comprehension and confrontation naming. The fMRI paradigm examined the neural substrates associated with processing concrete and abstract words compared to pseudowords. People with aphasia often demonstrate an exaggerated effect of concreteness (Barry & Gerhand, 2003; Crutch & Warrington, 2005; Martin et al., 1996; Newton & Barry, 1997; Sandberg & Kiran, 2014) and this manipulation allows further examination of recovery of lexical-semantics post-stroke. Based on Saur et al. (2006) and Crinion and Price (2005), we predicted that increased recovery would be associated with recruitment of right hemisphere homologues in the subacute phase followed by a return to increased left hemisphere recruitment in the chronic phase.

5.2 Methods

5.2.1 Participants

Recruitment of patients with left hemisphere stroke and language impairment was conducted at the stroke unit at the Royal Brisbane and Women's Hospital. Inclusion criteria were: (i) first ever left hemisphere stroke confirmed on structural imaging; (ii) evidence of aphasia in the WAB-R (Kertesz, 2007) or in milder impairment, language disturbance reported in the medical chart; (iii) primary language English; (iv) adequate vision and hearing for the tasks; and (v) adequate comprehension to provide informed consent. Exclusion criteria were (i) previous neurological or psychiatric diagnoses; (ii) MRI contraindications; (iii) severe cognitive impairment on the MMSE (Folstein et al., 1975), and (iv) severe comprehension impairment that would impact on performing the fMRI task. Following the screening procedure, a total of 19 aphasic patients provided consent for the study. Five of the 19 were excluded from the study due to (i) technical issues (n = 2); (ii) transference to another hospital facility before the scheduled fMRI scanning date (n = 1); or (iii) lesion site (n = 2 in the pons region). A total of 14 patients with aphasia (10 males, M = 63.9 yrs, SD = 11.1 yrs) were scanned in the subacute stage, 1 – 5 weeks post-stroke (M = 23.3 days, range: 6 – 41 days). At six months, all 14 patients were invited to come back for a repeat follow-up. Twelve patients (8 males, M = 63.0 yrs, SD = 10.8 yrs) returned for the chronic phase testing (M = 202.3 days post-stroke, range = 184 – 237 days). The remaining two aphasic patients declined due to ongoing health issues.

A control group was recruited from advertising in local community centres and via flyers in the University of Queensland newsletters. A total of 15 (10 females, M = 69.5 yrs, SD = 3.4 yrs) healthy aged-matched adults was recruited (age matched against patients at the time of the acute testing $t(12.689) = -1.900$, $p = .080$) and tested at one time point only. The controls all satisfied the same inclusion and exclusion criteria as the patient group with the exception of presence of stroke and aphasia. Cognition was measured using the MMSE (Folstein et al., 1975) to confirm no cognitive impairment was present.

Full written consent was obtained from all participants in the study and a reimbursement of $30 was given to each control participants. Carers of the participants with aphasia also received the detailed written information and were present during the consenting process. Approval for the study was obtained from the University of Queensland Medical Research Ethics Committee, the Queensland Health Human Research Ethics Committee and site-specific research governance from the Royal Brisbane and Women's Hospital Ethics Committee.

5.2.2 Behavioural Assessment

In the subacute stage and a week prior to the scan date, a series of preliminary assessments were administered to the aphasic patients including the: (i) MMSE (Folstein et al., 1975), (ii) EHI (Oldfield, 1971), (iii) WAB-R (Kertesz, 2007) and (iv) ABA-2 (Dabul, 2000). Within 24 to 48 hours of the scan date, each participant underwent further testing using a more comprehensive language battery. This battery comprised of the following: (i) the CAT (Swinburn et al., 2004) (ii) the BNT (Kaplan et al., 1983), (iii) subtests 5 (Auditory Lexical Decision), 25 (Visual Lexical decision), 49 (Auditory Synonym Judgements), 8 (Nonword Repetition) and 9 (Real Word Repetition) from the PALPA; (Kay et al., 1992) and (iv) the Pyramids and Palm Trees test (Howard & Patterson, 1992). At the six month time point and within a week of the second scan date, the entire assessment process was repeated. All control subjects were scanned once and were tested using the full language assessment battery within one week of the scanning session.

5.2.3 fMRI Task

We employed an auditory lexical decision paradigm with real words and pseudowords, the development of which has previously been described in Roxbury et al. (2014) (see Chapter 2). We used an event-related design to present a total of 120 stimuli (30 concrete words, 30 abstract words and 60 pseudowords). The stimuli were pseudorandomised to ensure that there were no more than two trials in succession from any condition and also to prevent constituent syllables appearing in consecutive order. Order effects were minimised by using five different stimuli lists and these were randomised across the aphasic patients and control subjects. The 120 stimuli were split equally into two runs (sixty items per run). The auditory stimuli were digitally recorded using a native female English speaker's voice with a Rode NTK condenser microphone in a sound-proofed room. Audacity, a digital recording and editing software package (http://www.audacity.sourceforge.net) was used to edit the stimuli. Mean durations of the spoken word stimuli were 723.7ms (*SD*: 105.0ms) for concrete words, 771.93ms (*SD*: 118.7ms) for abstract words and 779.8ms (*SD*: 92.6ms) for pseudowords and a Kruskal-Wallis test (Kruskal & Wallis, 1952) indicated no significant difference between conditions ($p > .05$).

5.2.4 fMRI Procedure

Aphasic patients had two fMRI scans (at the subacute and chronic time points), while controls were only scanned once. The fMRI task started with a small black fixation cross (48 point font) with the written words 'Is it a real word?' displayed on the screen. This screen remained visible for 2.3s. Following this, a new response screen appeared with a fixation cross and Yes/No. Participants simultaneously heard the audio of a word or pseudoword and had 3.5s to respond. As soon as a response was made, a large blue cross (84 point font) appeared on the screen and was visible for 1s duration. Following this, a new screen appeared with a large black (84 point font). This stayed visible until the start of the next trial. Between each stimulus presentation there was a long inter-trial interval with a jitter of between 10-18s, mean 14s. This was incorporated into the design to allow for the delayed hemodynamic response function which has previously been reported in post-stroke aphasia (Bonakdarpour et al., 2007).

Before each scanning session, the task was explained to the participants and a computer-based demonstration of the task with 10 practice words and pseudowords was shown and practised until an accuracy rate of approximately 80 percent was reached. Once inside the scanning suite, an MR safe button response box (Current Designs Inc, Philadelphia PA) was placed in the non-dominant hand of each participant and a reminder given as to the correct button press orientation. A headcoil with a mirror attachment was positioned over the participant's head and adjusted until the screen behind the scanner, displaying a fixation cross and the written words 'Is it a real word?', was fully visible. The stimuli were presented binaurally via MRI confon headphones (MR Confon GmbH, Magdeburg, Germany), the hearing levels adjusted to ensure adequate volume for each individual participant, and the response box checked.

5.2.5 Data Acquisition

The fMRI was carried out on a Siemens 3 Tesla Trio scanner (Siemens, Erlangen) at the Royal Brisbane and Women's Hospital. A total of 390 volume images with BOLD sensitivity were acquired during each scanning session (2 runs of 14.4 mins per run) with 36 contiguous axial slices covering the whole brain (3mm thickness with 0.3mm inter-slice interval). A standard gradient echo-planar imaging (EPI) pulse sequence [repetition time (TR) = 2210ms, echo time (TE) = 30ms, flip angle = 90°, field of view = 220x220mm, matrix = 64x64] was used. Within the scanning session, a high-resolution anatomical T1-weighted image (MP-RAGE; TR = 1900ms, TE = 2.4ms, TI = 900ms, $(0.9\text{mm})^3$ resolution) for each participant was acquired. A FLAIR image (TE 87ms, TR 9000ms, TI 2500ms, 36 3mm slices, 0.9x0.9mm in-plane resolution) was also acquired. To ensure that motion artefact due to potential head movement was minimised, vacuum cushions were positioned between the head coil and the headphones.

5.2.6 Image Processing

Image preprocessing and fMRI statistical analysis were performed using SPM software (v8 and 12; Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm) with MATLAB 2011 (The MathWorks Inc., Natick, MA). To allow for T1 equilibration effects, the first five (dummy) volumes acquired from each run were discarded. The remaining volumes from runs 1 and 2 were motion corrected and spatially realigned using INRIAlign (Freire et al., 2002), and a mean EPI image was created for each participant. The mean EPI image was coregistered to a T1-weighted image acquired during the same scanning session, and the transformation was applied to all realigned images. The T1-weighted image was segmented (Ashburner & Friston, 2005). Using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron), lesion masks for both acute and chronic patients were manually drawn on the high resolution T1 images, using the FLAIR images as a reference guide. A DARTEL template of patients was created using the segmentation results and weighting with the lesion information (Brett et al., 2002). Finally, to account for intersubject variability, normalized EPI images were then resampled (3.0 x 3.0 x 3.0 mm^3) and smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM).

5.2.7 In-Scanner Behavioural Analysis

In-scanner behavioural data consisted of mean accuracy rates calculated per subject, per condition and mean response times (for correct trials and responses greater than 100ms only), calculated from the beginning of the sound onset for each trial. SPSS Statistics version 22 (IMB; Armonk, New York, USA) was used to analyse the data and to conduct an independent *t*-test when the assumption of normal distribution was met (using Shapiro-Wilk), or a non-parametric Mann-Whitney *U* test otherwise. Accuracy rates and reaction times were also examined within group to determine concreteness effects. This was tested using a paired *t*-test when data was normally distributed or with a nonparametric Wilcoxon Signed-Ranks test.

5.2.8 Imaging Data Analysis

Imaging data from both runs were combined for each subject and individually analysed using a fixed effects model. The fMRI time series were analysed in an event-related approach in the context of a general linear model with realignment parameters (6 degrees of freedom) entered into the design matrix as regressors of no interest, after convolving each event-related unit impulse with a hemodynamic response function with derivatives. To ensure that the BOLD signal responses were not confounded by differences in time-on-task or reaction times, we included a parametric regressor for each mean corrected reaction time per trial for each condition (concrete, abstract and pseudoword). Trials for reaction times that were less than 100ms and that were incorrect were modelled separately as errors in the general linear model. First level or within-subjects analysis included four contrasts; concrete – pseudoword, abstract – pseudoword, concrete – abstract and word (average response of concrete and abstract) – pseudoword.

We conducted ROI analyses to test activity within a priori regions previously associated with concrete and abstract processing (Binder et al., 2009) and with language comprehension in subacute aphasia (Saur et al., 2006). A total of 10 ROIs were defined using IBASPM 116 Human Atlas and constructed using WFU PickAtlas (Maldjian et al., 2004; Maldjian et al., 2003) within SPM8 (Wellcome Trust Centre for Neuroimaging; http://www.fil.ion.ucl.ac.uk/spm). Activity associated with concrete word processing was investigated in the following six ROIs: left AG, right AG, left MFG, left SFG, left posterior cingulate and left fusiform gyrus. The ROIs associated with abstract words were left IFG and left aSTS. Left aSTS was further subdivided, using the delineation of y<-7 for anterior by Indefrey and Levelt (2004), into left aMTG and left aSTG in order that full coverage of the left aSTS was achieved. Thus, a total of three ROIs were examined for abstract processing. An additional ROI in right IFG was created and included in the analysis based on a priori hypotheses regarding the upregulation of this region as being a critical mechanism in aphasia recovery (Saur et al., 2006).

The region of interest toolbox, MarsBaR (Brett et al., 2002) in SPM8 was used to extract mean signal of event-related responses for each condition from all individual ROIs for each participant. Differences between the two groups (group and condition effects) were analysed using SPSS Statistics version 22 (IMB; Armonk, New York, USA). When the assumption of normal distribution was met (using Shapiro-Wilk), activation differences between each ROI using the mean signal were calculated and entered into a two-way repeated ANOVA. First the data was tested to see if the subacute or chronic phase was significantly different to controls in a 3 x 3 (concrete, abstract, pseudoword) or 3 x 2 (word, pseudoword) design. Then longitudinal differences were tested in either a 2 (subacute, chronic) x 3 or 2 x 2 design. For regions with non-normal distributions, logarithm or square root transformations (or inverse of both, as appropriate based on skew) were applied. Non-parametric tests (Kruskal-Wallis for 3 group comparison; subacute – chronic - control or Wilcoxon Signed Rank for 2 group comparison; subacute – chronic) were used when data could not be transformed to a normal distribution. *F* values were checked and the original degrees of freedom are reported throughout unless there was a violation in the assumption of sphericity in which case they were corrected using Huyhn-Feldt adjustment.

Correlational analyses were conducted to investigate the relationship between brain activity elicited during the fMRI task and out of scanner language performance. The mean signal elicited in each ROI for the three individual contrasts at both the subacute and chronic time-points was correlated with language assessment scores obtained outside the scanner from the spoken word comprehension subtests (word, sentence and combined overall total) of the CAT (Swinburn et al., 2004) using both chronic T-scores and improvement scores as measures. Improvement scores from the language assessments were calculated using the chronic scores minus the subacute score and dividing by the amount of possible maximal recovery (maximum test score – subacute score) or maximal impairment (subacute score – minimum test score) if the chronic score is lower than subacute. These percentage maximal recovery or impairment (PMRI) values were used in the correlational analyses and this approach is based on similar methods that have been used previously to measure language improvement in aphasia (see Lazar, Speizer, Festa, Krakauer, & Marshall, 2008; Saur et al., 2006; Saur et al., 2010)

Separate whole brain analyses were conducted using a factorial ANOVA with the group as the between-subject and conditions as the within-subject factor. Four analyses were carried out, using a 2 (subacute, chronic) x 2 (word, pseudoword), a 2 (subacute, chronic) x 3 (concrete, abstract, pseudoword), a 3 (subacute, chronic, control) x 2 (word, pseudoword) and a 3 (subacute, chronic, control) x 3 (concrete, abstract, pseudoword) factorial. Any main effects of group or condition or group by condition interactions were analysed further using an independent *t*-test to identify the directionality of the effect. Results were generated with grey matter masking, and significance was determined using $p < .01$ incorrectness threshold, with cluster thresholding using Bonferroni correction (FWE $p < .05$) in SPM12. In those regions that were significant, the neuroanatomical location based on the coordinates of the peak maxima was identified using the Anatomy Toolbox (V20) (Eickhoff et al., 2007). Whole brain regression analyses were conducted in the same manner as the ROI analyses for the subacute and chronic groups, using out of scanner behavioural language scores and PMRI measures.

5.3 Results

5.3.1 Clinical Data

Patient characteristics for the twelve subjects included in the study are displayed in Table 14. The T1-weighted structural scan acquired during the research scanning protocol was evaluated by a neuroradiologist to confirm site and size of lesion. The lesion overlay for the group of aphasic subjects in the subacute and chronic phase is shown in Figure 14 and Figure 15 respectively.

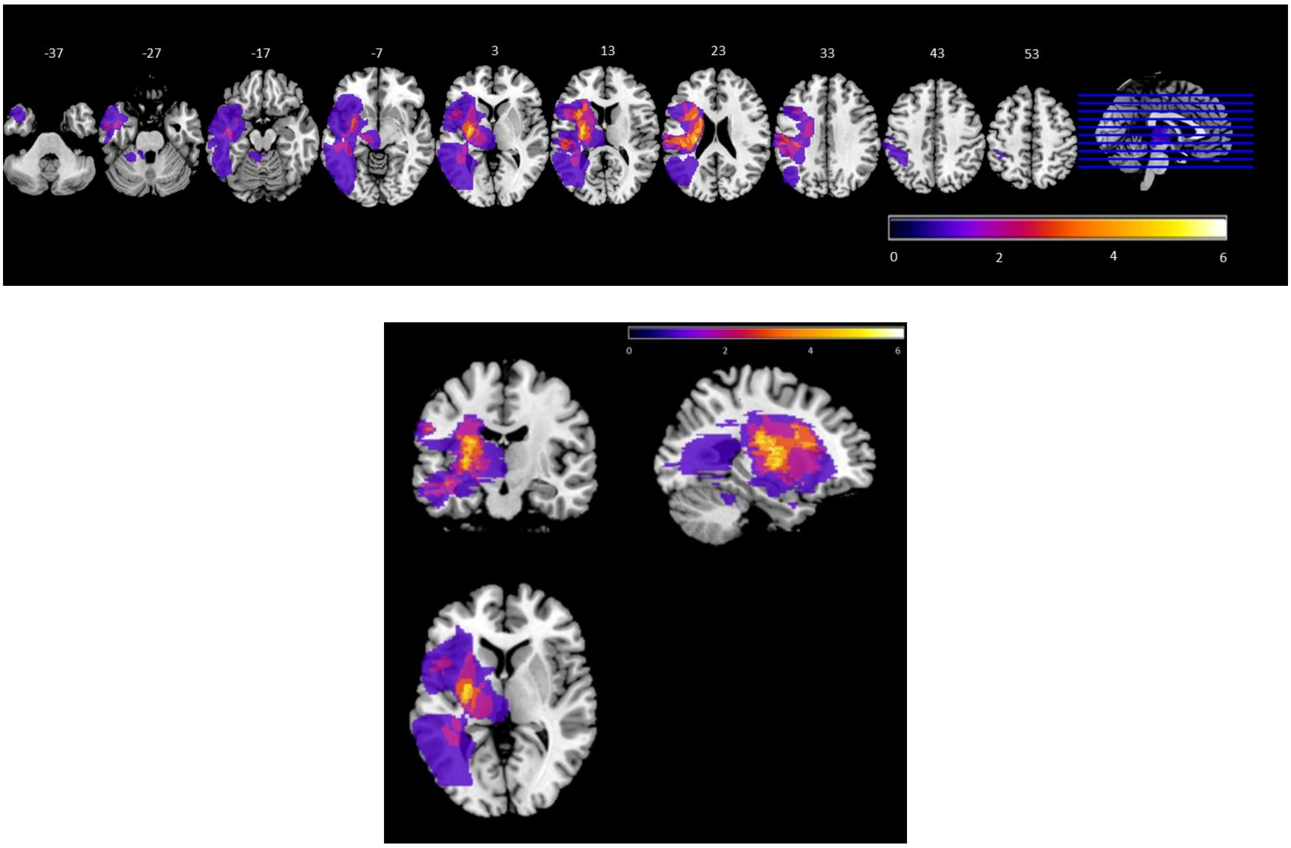

Figure 14. Subacute lesion overlap image. Representative slices show the lesion overlap in the 12 aphasic subjects in the subacute phase of recovery. The number of overlapping regions is shown in the colour intensity bar with the lighter colours indicating greater overlap. The region with the maximal overlap was left putamen with 6 of the 12 aphasic patients showing involvement of this region.

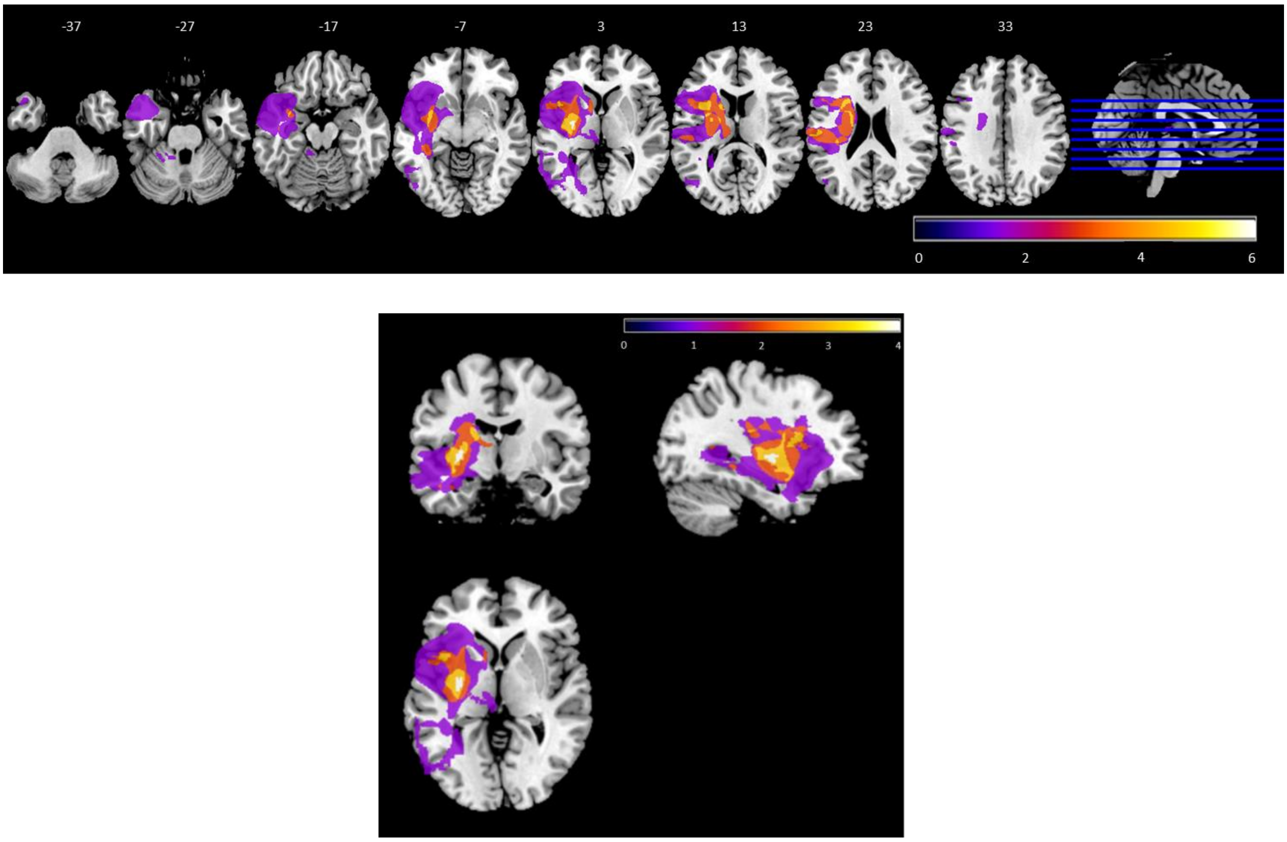

Figure 15. Chronic lesion overlap image. Representative slices show the lesion overlap in the 12 aphasic subjects in the chronic phase of recovery. The number of overlapping regions is shown in the colour intensity bar with the lighter colours indicating greater overlap. The region with maximal overlap in the chronic phase was left putamen with 4 of the 12 aphasic patients showing involvement of this region.

Table 14. Aphasic patient characteristics

Patient ID	Age at scan 1 (years)	Sex	Handedness (EHI)	Education (years)	fMRI 1 (days post stroke)	fMRI 2 (days post stroke)	NIHSS at admission	Oxford Stroke Classification	Site of lesion	Lesion Volume (3mm voxels)	Thrombolysis (min post-stroke)
01 ML	49	M	88.8	10	16	191	5	PACS	L MCA: Temporal + parietal	265	No
02 NL	68	F	100	11	6	195	4	POCS	L Cerebellar	131	No
03 WB	56	M	90	11	18	185	17	PACS	L MCA: SC + frontal	964	200
04 DB	84	F	100	8	25	186	4	PACS	L MCA: Frontal + parietal	332	No
05 GS	51	M	100	17	23	184	23	PACS	L MCA: SC + parietal + temporal	2036	150
06 RT	66	M	100	10	36	204	6	PACS	L MCA: Frontotemporal + SC	3000	No
07 CH	70	F	-100	8	23	191	12	PACS	L Thalamus + SC	342	No
08 DC	76	M	80	16	17	209	12	PACS	L Thalamus + SC	530	No
09 PK	52	M	-90	15	13	212	5	PACS	L MCA: Frontal + temporal	289	No
10 HH	63	F	50	9	23	205	1	PACS	L MCA: Temporoparietal + occipital	3037	No
11 RC	54	M	60	13	42	237	4	PACS	L MCA: SC	63	210
12 HH	66	M	70	13	25	229	3	PACS	L MCA: Frontal	176	No

M = male, F = female; EHI = Edinburgh Handedness Inventory: left-handed = < -40, right-handed > +40; NIHSS = National Institute of Health Stroke Scale: 0 = no deficit, 34 = maximal deficit; PACS = partial anterior circulation syndrome; POCS = posterior circulation syndrome; L = left; MCA = middle cerebral artery; SC = striatocapsular.

5.3.2 Behavioural Results

MMSE scores were obtained for both the control and aphasic group. Group results showed no cognitive impairment in the control group (max = 30, group *M* = 29.0, *SD* = 0.9). The scores for the aphasic group indicated reduced performance (group *M* = 22.42, *SD* = 5.96) in the subacute phase although this performance improved in the chronic phase (group *M* = 25.58, *SD* = 3.85). The EHI (Oldfield, 1971) confirmed left-handedness in two of the aphasic patients and one control. Years of education were significantly different $t(24.987) = -2.616$, $p = .015$ (equal variances not assumed) between the two groups (aphasic group *M* = 11.8 yrs, *SD* = 3.0; controls *M* = 15.3 yrs, *SD* = 3.9 yrs).

Language assessments were administered to the aphasic group at both time points and results are shown in Table 15, Table 16, Table 17, Table 18, and Table 19. Language deficits had been observed in all aphasic patients included in the study at the time of their initial admission into hospital. These deficits were then confirmed by an impaired performance in one of the assessments included in the language battery. At the time of recruitment to the study the WAB-R classification criteria indicated that two of the aphasic patients had very severe Broca’s aphasia and two had moderate to severe conduction aphasia. The majority of the aphasic patients (n = 6) had anomia ranging from mild to moderate in severity (1 = moderate, 1 = mild to moderate and 4 = mild). The final two patients did not receive a WAB-R classification or severity score as they presented with mild language disturbance. It should be noted that BNT results were skewed for this cohort, with an extreme outlier who declined from subacute to chronic stages. This precluded calculation of the PMRI and this distribution was not able to be normalised. As a result the BNT was not included in the correlational analyses.

Table 15. Subacute language assessment scores from the CAT and WAB-R

Language Assessment	Score	P01 ML	P02 NL	P03 WB	P04 DB	P05 GS	P06 RT	P07 CH	P08 DC	P09 PK	P10 HH	P11 RC	P12 HH2	Max
CAT														
Semantic Memory	Raw	20	19	15*	20	16*	18*	19	19	19	20	20	19	20
	T Score	62	54	43*	62	45*	50	54	54	54	62	62	54	62
Aud Word Comp	Raw	29	30	28	28	17*	25*	30	28	30	27	30	30	30
	T Score	60	65	58	58	41*	51*	65	58	65	55	65	65	65
Aud Sent Comp	Raw	32	31	25*	14*	12*	17*	30	26*	29	19*	30	28	32
	T Score	72	67	57*	46*	44*	49*	65	58	63	51*	65	61	72
Aud Para Comp	Raw	4	3*	2*	4	3*	3*	3*	2*	4	4	4	3*	4
	T Score	60	49*	43*	60	49*	49*	49*	43*	60	60	60	49*	60
Written Word Comp	Raw	30	30	18*	25*	6*	23*	28*	28*	30	25*	30	29	30
	T Score	65	65	43*	50*	35*	47*	55*	55*	65	50*	65	59	65
Written Sent Comp	Raw	31	32	14*	18*	12*	17*	30	30	23*	11*	30	24*	32
	T Score	68	72	47*	51*	46*	50*	67	67	57*	45*	67	59	72
Naming	Raw	79	92	0*	0*	0*	15*	61*	47*	77	44*	108	74	94+
	T Score	68	74	35*	35*	35*	46*	58*	54*	67	53*	75	65	75
Repetition	Raw	72	74	14*	29*	4*	49*	66*	67	67	66*	74	70	74
	T Score	66	72	43*	46*	40*	55*	59	59	59	59	72	62	72
Reading	Raw	52*	66	0*	0*	0*	49*	55*	64	61	35*	70	61	70
	T Score	55*	64	38*	38*	38*	53*	56*	62	55*	49*	71	59	71
Writing	Raw	73	71	27*	31*	9*	55*	71	70	70	61*	75	70	76
	T Score	62	60	46*	47*	41*	52*	60	59	59	55*	65	59	69
WAB-R														
Speech		16*	20	1*	10*	0*	11*	18*	15*	20	11*	20	18*	20
Comp		9.85	10	6*	7.55*	5.45*	6.4*	10	9.7	10	7.7*	10	10	10
Repetition		9.5	9.8	3.1*	5.8*	0*	6.5*	9.7	8.6*	10	7.9*	9.8	10	10
Naming		9.1*	9.7	0.9*	2.5*	0*	2.9*	8.7*	5.9*	9.4	3.7*	10	9.4	10
WAB AQ		88.9	99	22	51.7	10.9	53.6	92.8	78.4	98.8	60.6	99.6	94.8	100
Classification		Anomic	n/a	Broca's	Conduction	Broca's	Conduction	Anomic	Anomic	Anomic	Anomic	n/a	Anomic	
Severity		Mild		very severe to severe	moderate to severe	very severe	moderate to severe	mild	mild to moderate	mild	moderate		mild	

CAT = Comprehensive Aphasia Test; WAB-R = Western Aphasia Battery-Revised, R = Raw, T = T-score, Aud = Auditory, Comp = Comprehension, Sent = Sentence, Para = Paragraph, AQ = Aphasia Quotient,
***** *indicates impaired performance based on published norms.*

Table 16. Chronic language assessment scores from the CAT and WAB-R

Language Assessment	Score	P01 ML	P02 NL	P03 WB	P04 DB	P05 GS	P06 RT	P07 CH	P08 DC	P09 PK	P10 HH	P11 RC	P12 HH2	Max
CAT														
Semantic	Raw	18*	20	20	19	18*	19	19	20	18*	20	20	18*	20
Memory	T Score	50*	62	62	54	50*	54	54	62	50*	62	62	50*	62
Aud Word	Raw	29	30	30	21*	24*	30	27	28	30	27	29	30	30
Comp	T Score	60	65	65	45*	49*	65	55	58	65	55	60	65	65
Aud Sent	Raw	31	29	28	22*	23*	26*	30	28	31	25*	29	28	32
Comp	T Score	67	63	61	54*	55*	58*	65	61	67	57*	63	61	72
Aud Para	Raw	4	3*	3*	3*	3*	2*	3*	4	4	3*	4	4	4
Comp	T Score	60	49*	49*	49*	49*	43*	49*	60	60	49*	60	60	60
Written	Raw	30	30	28*	28*	24*	30	29	30	28*	30	30	28*	30
Word Comp	T Score	65	65	55*	55*	49*	65	59	65	55*	65	65	55*	65
Written	Raw	32	30	26	18*	23*	21*	30	30	29	29	30	29	32
Sent Comp	T Score	72	67	61	51*	57*	55*	67	67	65	65	67	65	72
Naming	Raw	86	96	37*	7*	4*	50*	77	67	92	80	105	92	94+
	T Score	72	75	51*	44*	43*	55*	67	59	74	68	75	74	75
Repetition	Raw	70	74	50*	27*	36*	68*	74	66*	74	64*	74	68*	74
	T Score	62	72	52*	45*	47*	60*	72	59*	72	58*	72	60*	72
Reading	Raw	58*	69	39*	10*	22*	60	57*	70	64	47*	70	62	70
	T Score	57*	67	49*	45*	47*	59	57*	71	62	52*	71	60	71
Writing	Raw	74	72	65*	43*	39*	64*	70	73	74	72	76	75	76
	T Score	64	61	57*	49*	48*	56*	59	62	64	61	69	65	69
WAB-R														
Speech		19*	20	13*	11*	7*	18*	20	19*	20	18*	20	20	20
Comp		9.85	10	9.5	8.3*	5.9*	9.7	10	9.5	10	9.6	10	10	10
Repetition		10	10	7.2*	3.7*	6.4*	8.2*	10	9.3	10	9.4	10	10	10
Naming		10	10	6.7*	3.1*	2.2*	7.6*	9.6	8.7*	10	9.5	10	10	10
WAB AQ		97.7	100	72.8	52.2	43	87	99.2	93	100	93	100	100	100
Classification		Anomic	n/a	Broca's	Conduction	Broca's	Anomic	n/a	Anomic	n/a	Anomic	n/a	n/a	
Severity		n/a		Mod	Mod	Severe	Mild		Mild		Mild			

CAT = Comprehensive Aphasia Test; WAB-R = Western Aphasia Battery-Revised, R = Raw, T = T-score, Aud = Auditory, Comp = Comprehension, Sent = Sentence, Para = Paragraph, AQ = Aphasia Quotient,
***** *indicates impaired performance based on published norms.*

Table 17. Subacute language assessment scores from the BNT, PALPA, Pyramids and Palm Trees test and ABA-2

Language Assessment	P01ML	P02NL	P03WB	P04DB	P05GS	P06RT	P07CH	P08DC	P09PK	P10HH	P11RC	P12HH2	Max
BNT	47*	54	1*	5*	0*	6*	29*	42	51	20*	55	56	60
PALPA 5													
Real word	79	80	73	70	70	63	77	74	80	80	79	79	80
HI/HF	20	20	20	18*	17*	20	20	20	20	20	20	20	20
HI/LF	20	20	18*	18*	16*	19*	20	18*	20	20	20	20	20
LI/HF	20	20	20	18*	20	15*	20	19*	20	20	20	19*	20
LI/LF	19	20	15*	16*	17*	9*	17*	17*	20	20	19	20	20
Nonword	79	78	74	56*	71	72	75	70	78	66*	77	74	80
PALPA25													
Real word	60	60	56	57	58	51	53	60	55	32	57	60	60
HI/HF	15	15	14	15	15	15	15	15	15	10*	14	15	15
HI/LF	15	15	15	15	14	14	14	15	15	9*	15	15	15
LI/HF	15	15	14*	15	14*	14*	15	15	14*	4*	15	15	15
LI/LF	15	15	13*	12*	15	8*	9*	15	11*	9*	13*	15	15
Nonword	58*	59	48*	36*	28*	54*	60	59	53*	55*	60	56*	60
PALPA 9													
HI/HF	20	20	2*	11.5*	1*	20	20	20	20	19	20	20	20
HI/LF	19.5	20	5.5*	8*	0*	19.5	19	20	19	18	20	19	20
LI/HF	18.5*	20	7*	4*	0*	17*	20	18*	19.5	15*	20	20	20
LI/LF	17.5*	20	5*	3.5*	0*	17*	19	17*	20	16*	20	19	20
PALPA 8 *Control data:* *M = 29.07; SD = 1.39*	23$^{\Delta}$	27	4$^{\Delta}$	4$^{\Delta}$	dis	26$^{\Delta}$	27	24$^{\Delta}$	29	20$^{\Delta}$	28	24$^{\Delta}$	30
PALPA 49													
HI *Control data:* *M = 29.73; SD = 0.59*	30	30	14$^{\Delta}$	14$^{\Delta}$	18$^{\Delta}$	25$^{\Delta}$	29	30	29	27$^{\Delta}$	30	29	30
LI *Control data:* *M = 28.67; SD = 1.54*	28	30	16$^{\Delta}$	15$^{\Delta}$	17$^{\Delta}$	17$^{\Delta}$	20$^{\Delta}$	27	28	23$^{\Delta}$	29	27	30
P&PT V1	50	51	47	48	40*	38*	48	47	51	46*	51	50	52
ABA-2	N	N	Mod	Mi	Mod	N	N	Mi	N	N	N	N	

BNT = Boston Naming Test; WAB-R = Western Aphasia Battery-Revised; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia: PALPA 5 = Auditory Lexical Decision; HI = High Imageability; HF = High Frequency; LI = Low Imageability; LF = Low Frequency; PALPA 25 = Visual Lexical Decision; PALPA 9 = Real Word Repetition; PALPA 8 = Nonword Repetition; PALPA 49 = Auditory Synonym Judgement; P&PT V1 = Pyramids and Palm Trees(Version 1 – 3 pictures); ABA-2 = Apraxia Battery for Adults – Second Edition; N= None, Mi = Mild, Mod = Moderate.

***** *indicates impaired performance based on published norms,* $^{\Delta}$ *indicates impaired performance based on control results where published norms were not available*.

Table 18. Chronic language assessment scores from the BNT, PALPA, Pyramids and Palm Trees test and ABA-2

Language Assessment	P01ML	P02 NL	P03WB	P04DB	P05 GS	P06 RT	P07CH	P08DC	P09PK	P10HH	P11RC	P12HH2	Max
BNT	48*	54	7*	2*	0*	16*	43	52	53	39*	55	57	60
PALPA 5													
Real word	79	80	74	67	79	68	74	79	80	78	79	77	80
HI/HF	20	20	20	18*	20*	20	20	20	20	20	20	20	20
HI/LF	20	20	18*	19*	20	20	20	20	20	19*	20	19*	20
LI/HF	20	20	20	17*	20	17*	19*	20	20	19*	20	20	20
LI/LF	19	20	16*	13*	19*	11*	15*	19*	20	20	19	18*	20
Nonword	78	77	74	56*	75	73	68	74	77	67*	79	76	80
PALPA25													
Real word	60	59	57	59	58	54	57	59	55	56	60	58	60
HI/HF	15	15	15	14	15	15	15	15	15	14	15	15	15
HI/LF	15	15	14	15	15	14	15	14	15	14	15	13*	15
LI/HF	15	15	15	15	13*	15	15	15	15	14*	15	15	15
LI/LF	15	14	13*	15	15	10*	12*	15	10*	14	15	15	15
Nonword	60	59	57*	42*	47*	60	60	59	60	58*	60	60	60
PALPA 9													
HI/HF	19	20	18*	16*	7.5*	20	20	20	20	20	20	20	20
HI/LF	19	20	12*	7.5*	7*	20	20	18	20	18	20	20	20
LI/HF	19	20	14.5	3*	4*	20	19	20	20	19	20	20	20
LI/LF	17.5*	20	14*	8.5*	6*	18*	20	20	20	19	20	20	20
PALPA 8 *Control data:* *M = 29.07; SD = 1.39*	22$^{\Delta}$	30	10$^{\Delta}$	4$^{\Delta}$	6$^{\Delta}$	27	28	27	29	21$^{\Delta}$	29	24.5$^{\Delta}$	30
PALPA 49													
HI *Control data:* *M = 29.73; SD = 0.59*	28.5$^{\Delta}$	30	28.5$^{\Delta}$	24$^{\Delta}$	29	26$^{\Delta}$	29	30	29	30	30	30	30
LI *Control data:* *M = 28.67; SD = 1.54*	27	28.5	24$^{\Delta}$	19$^{\Delta}$	23$^{\Delta}$	20$^{\Delta}$	25$^{\Delta}$	30	26	29	29	28	30
P&PT V1	52	51	47	46*	47	44*	49	50	52	51	50	52	52
ABA-2	N	N	Mi to mod	Mi to mod	Mod	Mild	N	N	N	N	N	N	

BNT = Boston Naming Test; WAB-R = Western Aphasia Battery-Revised; PALPA = Psycholinguistic Assessment of Language Processing in Aphasia: PALPA 5 = Auditory Lexical Decision; HI = High Imageability; HF = High Frequency; LI = Low Imageability; LF = Low Frequency; PALPA 25 = Visual Lexical Decision; PALPA 9 = Real Word Repetition; PALPA 8 = Nonword Repetition; PALPA 49 = Auditory Synonym Judgement; P&PT V1 = Pyramids and Palm Trees(Version 1 – 3 pictures); ABA-2 = Apraxia Battery for Adults – Second Edition; N= None, Mi = Mild, Mod = Moderate.

***** *indicates impaired performance based on published norms,* $^{\Delta}$ *indicates impaired performance based on control results where published norms are not available.*

Table 19. PMRI language scores from the CAT (word and sentence comprehension subtests and CAT overall score)

Language Assessment	P01ML	P02 NL	P03WB	P04DB	P05 GS	P06 RT	P07CH	P08DC	P09PK	P10HH	P11RC	P12HH2
CAT												
Aud Word Comp	0.00	0.00	100.00	-22.41	33.33	100.00	-15.38	0.00	0.00	0.00	-7.69	0.00
Aud Sent Comp	-6.94	-5.97	26.67	30.77	39.29	39.13	0.00	21.43	44.44	28.57	-3.08	0.00
*CAT Overall**	10.87	-0.74	39.53	11.83	27.64	32.06	30.26	30.38	55.56	37.82	5.56	27.54

CAT overall score calculated from the average T-scores of the following subtests: Comprehension of spoken language, comprehension of written language, repetition, naming, reading and writing.

5.3.3 In-Scanner Behavioural Results

For the accuracy analyses, mean values were calculated for the control group and the aphasic group at both time points (subacute and chronic). The results are shown in Table 20 and show that accuracy for both concrete and pseudowords was greater than 90 percent for the controls and both aphasic groups.

Table 20. Mean accuracy values for aphasic patients and controls

Condition	Subacute Aphasics Mean (*SD*)	Chronic Aphasics Mean (*SD*)	Controls Mean (*SD*)
Concrete	94.7 (6.7)	91.1 (7.3)	97.6 (3.7)
Abstract	86.4 (11.4)	89.2 (9.5)	95.1 (4.8)
Pseudoword	92.5 (7.1)	94.2 (5.7)	95.0 (4.3)

Accuracy was not normally distributed (Shipiro-Wilk $p < .023$) except for the concrete condition within the chronic aphasic group ($p = .131$). A Kruskal-Wallis test revealed no statistical difference in accuracy between the three groups for the concrete and pseudoword conditions ($p > .076$) although the reduced accuracy for the abstract condition was close to reaching significance ($p = .051$).

Values for incorrect responses or for responses longer than 100ms were removed from analysis (subacute aphasics = 7.9%, chronic aphasics = 7.8%, controls = 4.4%). The reaction times did not have a normal distribution (Shapiro-Wilk $p < .05$) and a non-parametric Kruskal-Wallis test was used. There was a statistically significant difference between the three groups for reaction times for the concrete $H(2) = 25.717$, $p < .0001$ and abstract $H(2) = 23.260$, $p < .0001$ conditions with the controls being significantly faster compared to the chronic aphasics and then the subacute aphasic performance (see Table 21).

Table 21. Mean reaction times for aphasic patients and controls

Condition	Subacute Aphasics Mean (*SD*)	Chronic Aphasics Mean (*SD*)	Controls Mean (*SD*)
Concrete	1397ms (266)	1388ms (282)	1263ms (186)
Abstract	1501ms (306)	1443ms (259)	1335ms (219)
Pseudoword	1715ms (493)	1669ms (449)	1736ms (585)

Behavioural differences between subacute and chronic time-points were directly assessed with a Wilcoxon Signed Ranks test. There was no significant difference between time-points for accuracy ($p > .265$) but there was a significant difference in reaction times ($p < .0001$ for all conditions), with the aphasic patients responding faster in the chronic compared to subacute time point (see Table 21).

Concreteness effects (the performance advantage for concrete over abstract words) were also assessed at each time point using a Wilcoxon Signed Ranks test. Accuracy was significantly greater for concrete compared to abstract items in the subacute testing phase ($p = .005$), but not in the chronic phase ($p = .372$). At both time-points, reaction times were significantly faster for concrete words ($p = .001$ for subacute and $p = .003$ for chronic).

5.3.4 Region of Interest Analyses

5.3.4.1 Two conditions (word – pseudoword).

5.3.4.1.1 Three group comparison (subacute, chronic, controls). Only left posterior cingulate cortex and left aSTG regions could be transformed to a normal distribution for an ANOVA to be applied. The ANOVA examining differences between the three groups for word and pseudoword conditions revealed a main effect of condition in left posterior cingulate $F(1, 14) = 7.440$, $p = .016$ and left aSTG $F(1, 14) = 7.447$, $p = .016$. Mean values for left posterior cingulate indicated greater activity for word ($M = 0.080$, $SE = 0.029$) compared to pseudoword ($M = -0.007$, $SE = 0.029$), whereas for left aSTG mean values were greater for pseudoword ($M = 0.409$, $SE = 0.047$) compared to word ($M = 0.305$, $SE = 0.055$). There were no significant main effects of group or group by condition interactions for these two ROIs.

Of the remaining eight ROIs tested with a Kruskal-Wallis, the left IFG was the sole region to show a significant group difference for the pseudoword condition only $H(2) = 8.366$, $p = .015$. Mean values indicated that the control group elicited greater activity in this region ($M = 0.335$, $SE = .032$), compared to the aphasic group at both the chronic ($M = 0.167$, $SE = .094$) and subacute ($M = 0.121$, $SE = .059$) time points.

5.3.4.1.2 Two group comparison (subacute, chronic). In the direct comparison between aphasic performance at the subacute and chronic time points (2x2 ANOVA), only the left aSTG retained the main effect of condition $F(1, 14) = 6.465$, $p = .023$ and values for mean signal showed greater activity for pseudowords ($M = 0.337$, $SE = 0.066$) compared to words ($M = 0.191$, $SE = 0.075$). There was no other main effect of group or interaction in left aSTG.

For regions where the data could not be transformed to a normal distribution, the subacute to chronic group differences were tested by a Wilcoxon Signed Ranks test. None of those ROIs (left AG, right AG, left fusiform, left SFG, left MFG, left aMTG, left or right IFG) showed a significant difference between groups for any of the conditions.

5.3.4.2 Three conditions (concrete, abstract, pseudoword).

5.3.4.2.1 Three group comparison (subacute, chronic, controls). Left posterior cingulate cortex and left aSTG activity was normally distributed and an ANOVA (3 x 3) was applied. The results revealed a main effect of condition in both ROIs; left posterior cingulate $F(2, 13) = 9.779$, $p = .003$ and left aSTG $F(1.2, 17) = 5.3$, $p = .029$ (Huynh-Feldt corrected). Mean signal in left posterior cingulate was greater for abstract ($M = 0.081$, $SE = 0.031$) compared to concrete ($M = 0.078$, $SE = 0.030$) and then pseudowords ($M = -0.007$, $SE = 0.029$). In the left aSTG, activity was greatest for the pseudoword condition ($M = 0.409$, $SE = 0.047$) compared to both abstract ($M = 0.351$, $SE = 0.059$) and concrete ($M = 0.350$, $SE = 0.055$) conditions. There was no main effect of group in either of the ROIs.

A significant group by condition interaction was observed in left posterior cingulate $F(4, 11) = 3.540$, $p = .043$) for the concrete – abstract – pseudoword comparison. The mean BOLD signal in left posterior cingulate is shown in Figure 16. Follow-up analyses were carried out to determine the nature of the interaction. There was a significant difference for both the subacute and control groups between the concrete and pseudoword conditions (subacute aphasics; p =.013 and controls; p = .018) and abstract and pseudoword condition (subacute aphasics; p = .001 and controls; p = .010). There was no significant difference between conditions for the chronic aphasic group. Mean signal values in the subacute group were greater for the abstract (M = 0.09, SE = 0.04) and concrete (M = 0.06, SE = 0.03) compared to pseudowords (M = -0.06, SE = 0.03), whereas the mean signal values in the control group were greater for the concrete (M = 0.14, SE = 0.05) and abstract words (M = 0.13, SE = 0.04) compared to the pseudowords (M = 0.03, SE = 0.05).

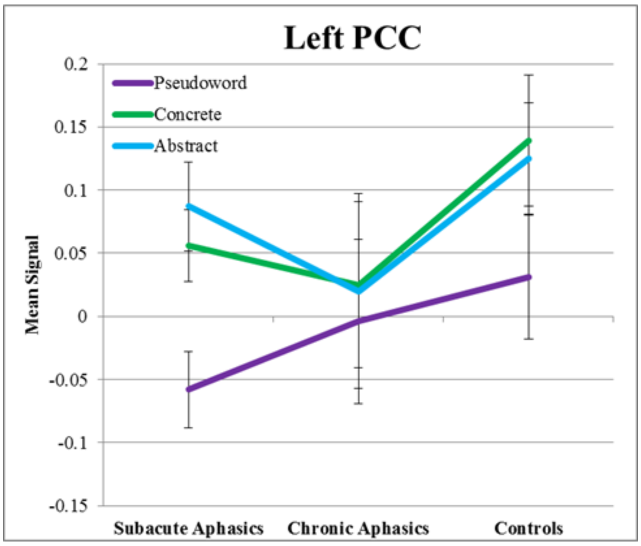

Figure 16. Group by condition interaction in left PCC. Subacute, chronic, controls x 3 conditions (concrete, abstract and pseudoword).

There were no significant group differences in the other eight ROIs, tested by non-parametric Kruskal-Wallis, for either concrete or abstract conditions. (Pseudoword conditions are reported above).

5.3.4.2.2 Two group comparison (subacute, chronic). In the direct comparison between activity elicited by the aphasic groups at the different time points (2 (subacute and chronic) x 3 ANOVA), a main effect of condition was only observed in left posterior cingulate $F(2, 10) = 5.107$, p = .030. Mean values indicated that both concrete (p = .042) and abstract (p = .010) words showed significantly greater activity than pseudowords (concrete: $M = 0.056$, $SE = .029$, abstract: $M = .087$, $SE = .035$ and pseudoword: $M = -.058$, $SE = .030$). A group by condition interaction was observed in left posterior cingulate $F(2, 10) = 4.627$, $p = .038$. There was a significant difference in mean signal for both concrete ($p = .013$) and abstract ($p = .001$) words when compared to pseudowords for the subacute aphasic group only. Mean values are reported above in the 3 x 3 group by condition interaction results.

No subacute-chronic differences were found for any of the other ROIs (left and right AG, left fusiform, left SFG, left MFG, left aMTG, left aSTG, left or right IFG), tested with a Wilcoxon Signed Ranks test, for concrete or abstract conditions.

5.3.5 Region of Interest Correlational Analyses

Correlational analyses were used to explore whether any relationship existed between brain activity elicited during (i) the acute and (ii) the chronic testing phase in specific areas and behavioural scores from confrontation naming and spoken language comprehension assessments (both chronic and PMRI scores).

5.3.5.1 Subacute ROI activity with chronic behavioural scores. There was a positive correlation between subacute activity for pseudowords in the left posterior cingulate cortex $r = .648$, $p = .023$ and CAT word performance at the chronic stage, and a negative correlation between pseudoword activity in the left SFG $r = -.673$, $p = .016$ and chronic CAT word performance. Significant correlations are shown in Figure 17. No other significant correlations were observed.

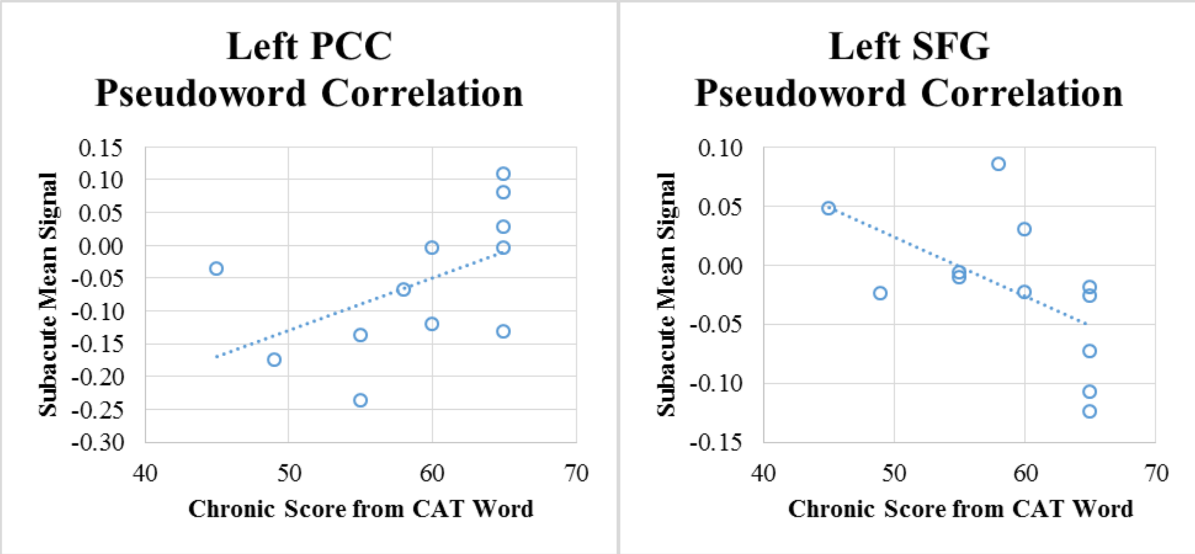

Figure 17. Subacute mean signal with the chronic behavioural score from the CAT word subtest.

5.3.3.2 Subacute ROI activity with PMRI scores. There were no significant correlations between subacute activity and PMRI scores.

5.3.5.3 Chronic ROI activity with chronic behavioural scores. A positive correlation was observed between chronic mean signal in left posterior cingulate cortex for the concrete condition and the chronic CAT word subtest r = .600, p = .039 and for the abstract condition and the chronic CAT sentence subtest r = .579, p = .049. Correlations in left aSTG were observed for all three conditions and the CAT sentence subtest (pseudoword: r = .662, p = .019, concrete: r = .608, p = .036, abstract: r = .780, p = .003) and CAT overall score (pseudoword: r = .623, p = .03, concrete: r = .664, p = .018, abstract: r = .768, p = .004). Negative correlations were observed between left IFG activity for abstract words and the CAT sentence subtest r = .683, p = .014 and CAT overall r = .670, p = .017. Significant correlations are shown in Figure 18. No other correlations between brain activity and behavioural scores in the chronic aphasic group or in the control group were significant.

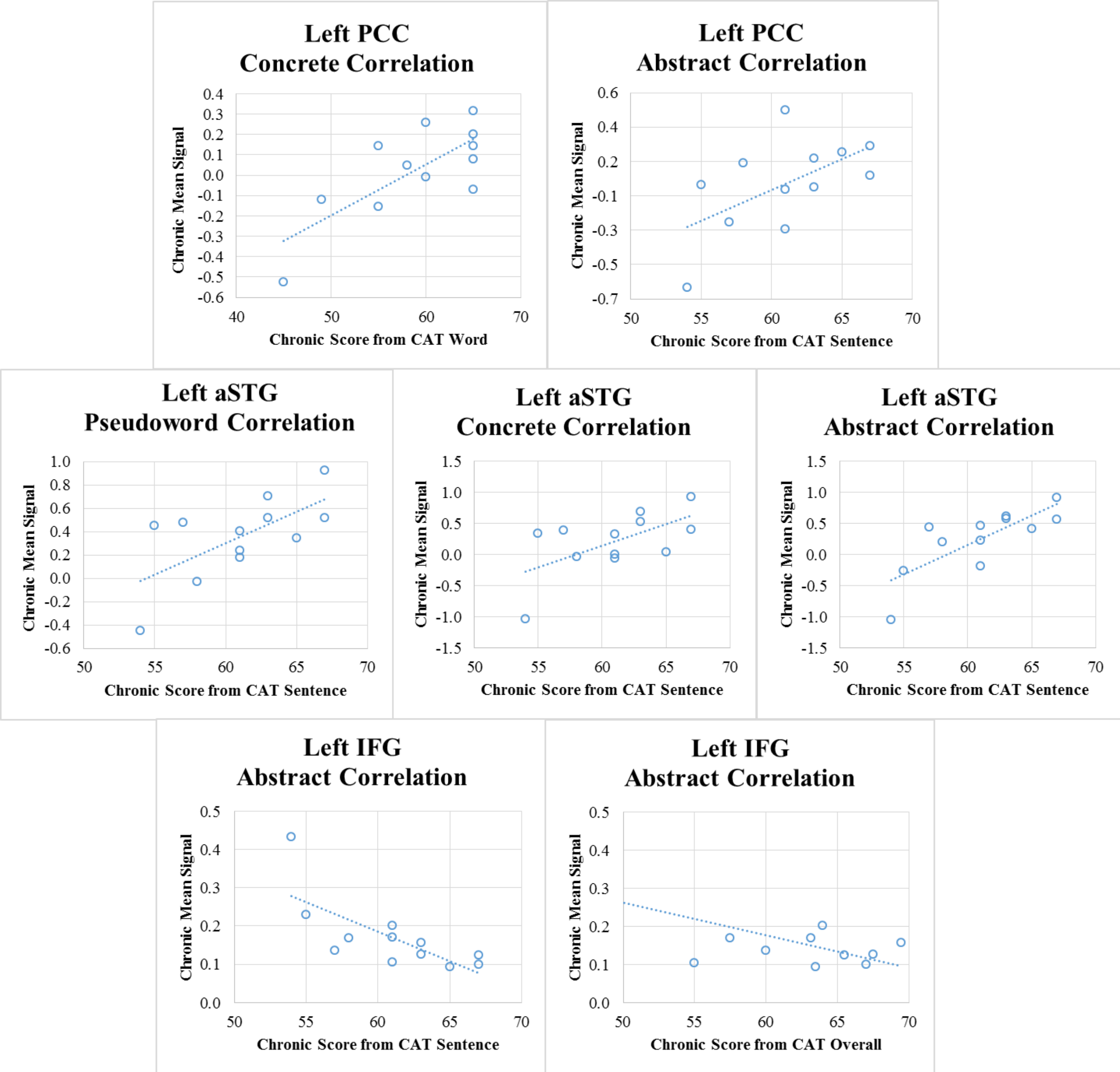

Figure 18. Chronic mean signal with chronic behavioural score of CAT word and CAT sentence subtests.

5.3.5.4 Chronic ROI activity with PMRI scores. No correlations were significant in the chronic aphasic group and no significant correlations were observed in the control group.

5.3.6 Whole Brain Analyses

Exploratory whole brain analyses revealed a significant main effect of group for the 3 (subacute, chronic, control) x 2 (word, pseudoword) in left IFG (pars triangularis) (extending into pars orbitalis and pars opercularis), left parahippocampal gyrus (PHG) (extending into left fusiform gyrus and left thalamus (temporal)), right MFG (extending into right SFG) and right MTG (extending into right middle occipital gyrus) (see Table 22). Figure 19 shows the main effect of group and Figure 20 displays the axial slices illustrating the main effect of group (subacute, chronic, control). There were no significant results in the 2 (subacute, chronic) x 2 (word, pseudoword) ANOVA.

Table 22. Factorial results from whole brain analysis for main effect of group between subacute, chronic aphasics and controls (GM masked)

Main effect	Peak Maxima	Cluster *p*FWE	Cluster (*k*)	*x*	*y*	*z*	*Z*-score
Group	Left IFG (pars tri)	< .001	305	-36	7	29	5.20
	Left PHG	.001	153	-29	-43	-7	4.48
	Right MFG	.036	62	22	25	47	3.92
	Right MTG	.036	62	40	-65	18	4.07

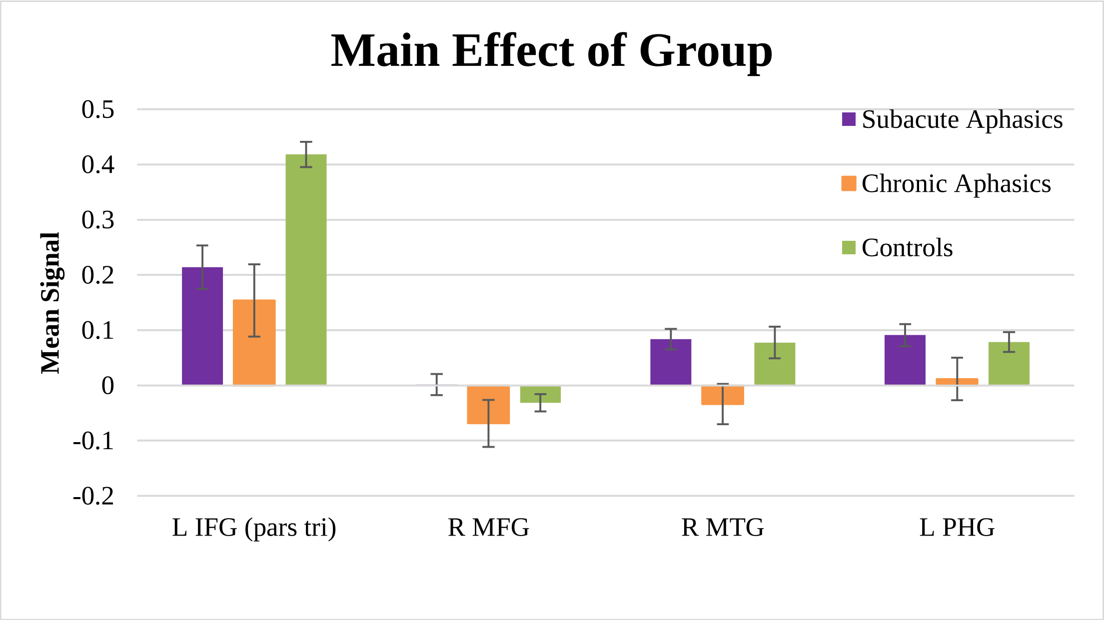

Figure 19. Main effect of group (subacute, chronic, control).

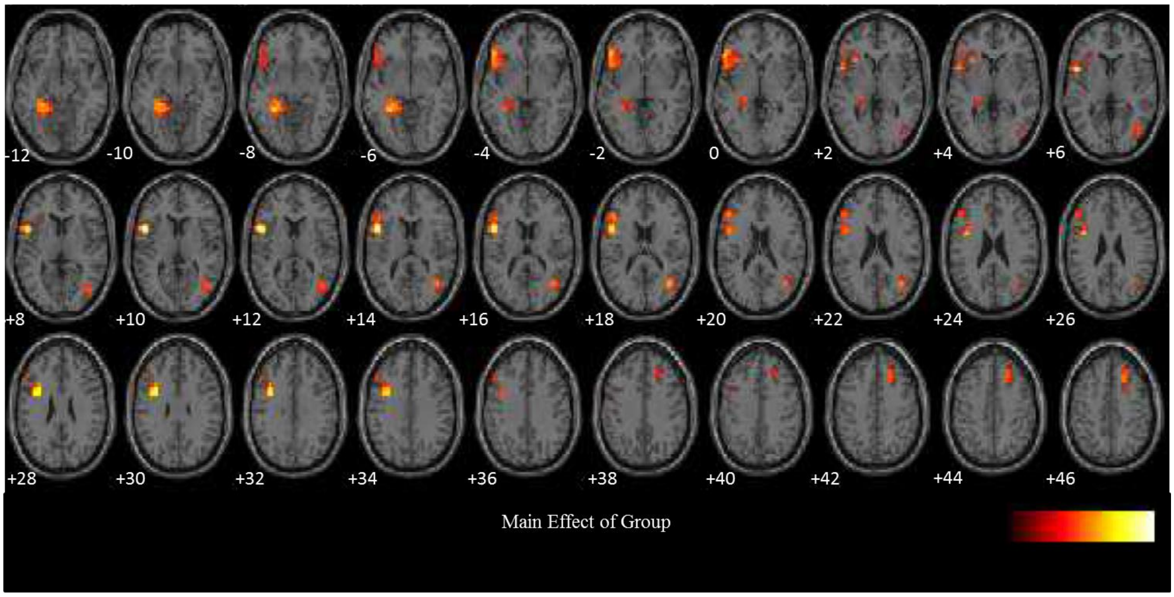

Figure 20. Axial slices for key regions in the main effect of group (subacute, chronic, control).

5.3.7 Whole Brain Correlational Analyses

5.3.7.1. Subacute whole brain activity correlated with chronic behavioural scores.

Results from the subacute whole brain regression analysis with chronic language performance scores are shown in Table 23. The chronic overall CAT score was positively correlated with concrete > abstract activity in the left insula (extending into left IFG; pars triangularis and pars opercularis) and the right MFG. A negative correlation was observed for the CAT word score and right SFG (extending into right MFG) activity for the abstract > pseudoword contrast.

Table 23. Subacute whole brain activity related to chronic language performance scores

	Contrast	Peak Maxima	*p*FWE	Cluster (*k*)	*x*	*y*	*z*	*Z*-score
Positive								
CAT Overall	Conc > Ab	Left insula	.012	59	-32	-4	14	3.83
Negative								
CAT Word	Ab > Pseudoword	Right SFG	.047	41	22	18	54	3.92

p = FWE-corr for cluster threshold

5.3.7.2 Subacute whole brain activity correlated with PMRI scores. Results from the subacute whole brain regression analysis with PMRI language scores are shown in Table 24. Negative associations with PMRI scores from the sentence level assessment in the CAT were observed for concrete > abstract words in the left postcentral gyrus (extending into left precentral and left primary somatosensory and motor cortex). Axial slices for key regions showing subacute brain activity correlated with PMRI scores are shown in Figure 21.

Table 24. Subacute whole brain activity related to PMRI performance scores

	Contrast	Peak Maxima	*p*FWE	Cluster (*k*)	*x*	*y*	*z*	*Z*-score
Negative								
CAT Sentence	Conc > Ab	Left postcentral gyrus	.024	52	-43	-29	50	4.68

p = FWE-corr for cluster threshold.

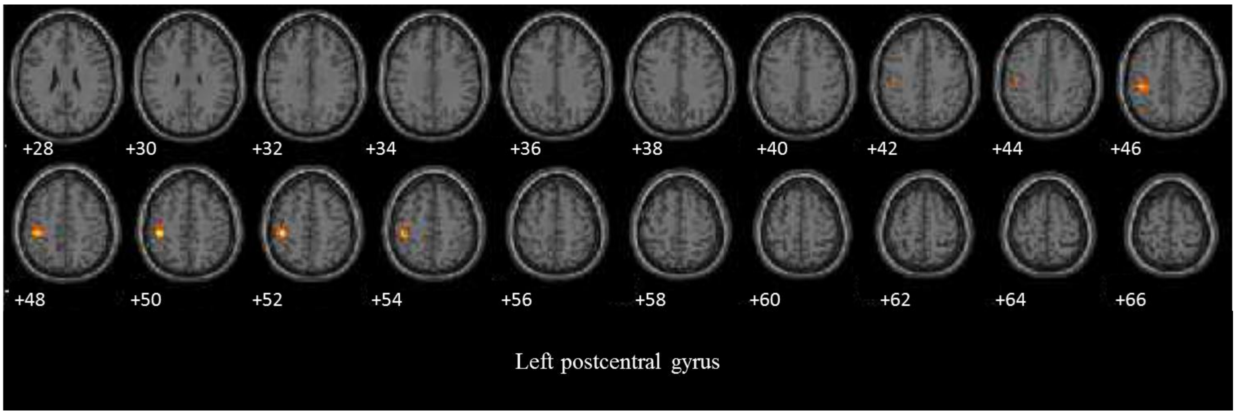

Figure 21. Axial slices for key regions showing subacute brain activity correlated with PMRI scores.

5.3.7.3 Chronic whole brain activity correlated with chronic behavioural scores. Results from the chronic whole brain regression analysis with chronic language performance scores are shown in Table 25 and the axial slices are shown in Figure 22. Chronic CAT word scores were positively correlated with activity for the word > pseudoword contrast in (1) right anterior cingulate cortex (ACC), extending into right mid orbital gyrus, right rectal gyrus and left mid orbital gyrus and (2) right olfactory cortex, extending into right insula and right caudate.

Table 25. Chronic whole brain activity related to chronic language performance scores

	Contrast	Peak Maxima	*p*FWE	Cluster (*k*)	*x*	*y*	*z*	*Z*-score
Positive								
CAT Word	Word > Pseudoword	Right ACC	.030	86	14	43	7	4.14
		Right olfactory cortex	.022	94	7	18	-4	3.70

p = FWE-corr for cluster threshold

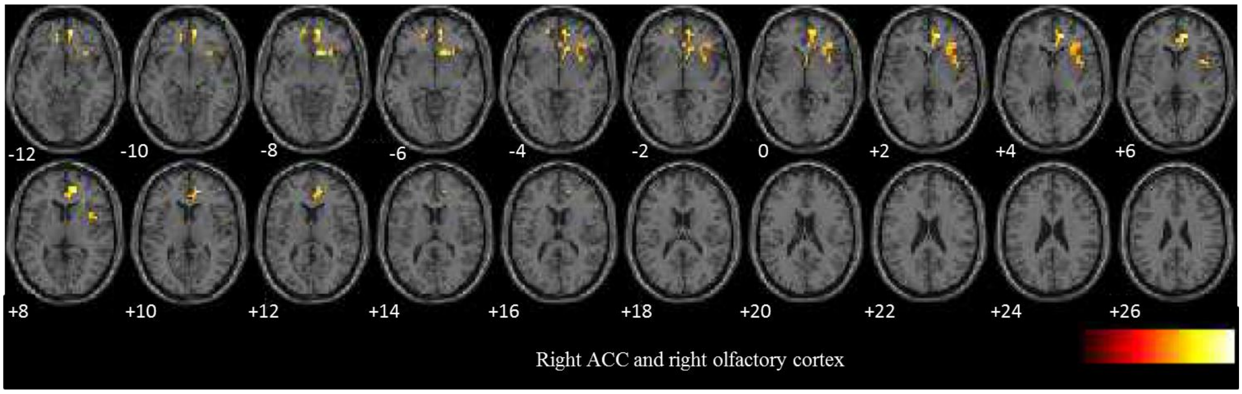

Figure 22. Axial slices for key regions showing chronic whole brain activity correlated with chronic language performance scores.

5.3.7.4 Chronic whole brain activity correlated with PMRI scores. No results were significant for the chronic whole brain regression analysis with PMRI language scores.

5.4 Discussion

We investigated the neural mechanisms underpinning spoken word recognition in a group of aphasic patients in the subacute and chronic stages of stroke recovery and examined whether task-related neural activity in subacute aphasia predicted recovery at the chronic stage. In subacute aphasia, language comprehension recovery was associated with increased activity in left posterior cingulate and left insula/inferior frontal regions while a poorer recovery was associated with increased activity in bilateral dorsolateral regions. In chronic aphasia, improved spoken sentence comprehension was associated with increased brain activity in the left posterior cingulate cortex and left aSTG while improved spoken word comprehension was associated with right anterior cingulate and right olfactory cortex extending into the insula and caudate. In contrast, a poorer outcome on spoken sentence comprehension and overall language performance on the CAT was associated with increased activity in left IFG.

Results for the whole brain analysis revealed a main effect of group in left IFG (pars triangularis) extending into pars orbitalis and pars opercularis, left PHG (extending into left fusiform and the left thalamus), right MFG and right STG with the chronic aphasic group eliciting decreased activity in all four regions compared to both the subacute aphasic group and controls. The left IFG region showed the greatest difference between both aphasic groups and the controls and given that this region was intact in the majority of patients, we suggest that reduced activity of the aphasic patients relative to the controls may reflect diaschisis whereby activity in the left IFG is compromised as it is dependent on inputs from distant but connected lesioned regions (Carrera & Tononi, 2014; Price et al., 2001). The lack of any regions showing increased activity in the aphasia group compared to controls also suggests that upregulation or adoption of novel regions was not a recovery mechanism evident in this cohort.

5.4.1 Relationship between Subacute Brain Activity and Language Recovery

A positive correlation was observed between subacute activity for pseudowords in the left posterior cingulate ROI and spoken word comprehension in the chronic phase. The posterior cingulate is a richly connected brain region which links subcortical and cortical brain networks (Hagmann et al., 2008; Leech & Sharp, 2014) and has been associated with internally directed thought processes (Buckner, Andrews-Hanna, & Schacter, 2008), and is involved in memory recollection and planning for the future (Addis, Wong, & Schacter, 2007; Mason et al., 2007). The involvement of the posterior cingulate in language remains unclear, although it is commonly engaged during semantic processing (Binder et al., 2009). The posterior cingulate also has a central role in the default mode network and connectivity within this network has been associated with treatment-induced aphasia recovery (Marcotte, Perlbarg, Marrelec, Benali, & Ansaldo, 2013). The pseudowords employed in the experimental paradigm were designed to be as close to real words as phonologically possible whilst not requiring semantic activation (although it is acknowledged that semantic activation can occur during such lexical decisions). Thus, the increased activity seen in the subacute aphasic group in response to pseudowords may reflect an increased requirement to draw on internally directed declarative memories to assist in making a decision regarding the lexical status of the pseudoword.

The posterior cingulate also plays an integral role in facilitating or monitoring attentional control (Hahn, Ross, & Stein, 2007; Hampson et al., 2006; Leech, Braga, & Sharp, 2012), integrating information processed in brain networks that are functionally distinct. Thus, if the posterior cingulate serves as a cortical hub, the correlation between increased subacute activity and improved word comprehension may reflect the regulation of attentional control in response to high-level integrative processes in this region.

Comparisons between the control and aphasic group may provide insights into whether the reported involvement of the left posterior cingulate in recovery is attained through normal mechanisms or reflects novel mechanisms. We observed that left posterior cingulate activity differed between the subacute aphasic group and controls as a function of condition. For the subacute group, the abstract word condition elicited greatest activity while in the control group, greatest activity was observed for the concrete condition. The finding in controls is consistent with previous studies showing increased posterior cingulate activation for concrete words (Binder et al., 2005; Ferreira, Gobel, Hymers, & Ellis, 2015; Sabsevitz et al., 2005) and is likely due to the richer set of conceptual representations associated with concrete words. It is unclear why this region would be engaged differentially for abstract words in the subacute aphasic group versus concrete words in the controls, but this may in part be explained by increased attentional engagement (as described above) required in the subacute group during retrieval of abstract words.

A positive correlation was observed between the overall chronic CAT score and subacute activity in the left insula extending into left IFG at whole brain level for concrete > abstract words. While the representation of concrete concepts is considered to involve a widely distributed, predominantly left hemisphere language network (Binder et al., 2009; Wang et al., 2010), this network does not appear to include either the left insula or left IFG, suggesting an alternative role. The left insula is directly connected to Broca's region and has typically been considered to have an involvement in the motoric aspects of speech production and specifically articulatory planning (Ardila, Bernal, & Rosselli, 2014; Dronkers, 1996) and control (Oh, Duerden, & Pang, 2014). However, its central location and connections with regions associated with a more diverse range of language functions including comprehension and lexico-semantic associations (Ardila et al., 2014) suggest that this region has an integral role in language processing (Price, 2010) and may mediate higher-order cognitive functions associated with language function (Oh et al., 2014).

While the left IFG has been associated with controlled lexical-semantic selection and a range of other relevant language processes including strategic semantic retrieval and phonological processing (Binder et al., 2009; Price, 2012), it frequently shows increased activity for words compared to pseudowords (see Davis & Gaskell, 2009 meta-analysis). In a meta-analysis that included 12 studies on aphasia recovery, Turkeltaub et al. (2011) identified activation in left anterior insula and pars orbitalis regions by aphasic patients which was not observed in controls. The upregulation of activity in key regions that were unique to the aphasic subjects was interpreted as a recovery mechanism activated to compensate for reduced functionality of the lesioned areas (Turkeltaub et al., 2011). In the current study, this activity does not appear to represent an upregulation unique to the subacute aphasic group, given that there was no overall increase compared to controls. Nevertheless, the degree of left insula/IFG activity in an individual was related to overall recovery capacity. This finding is in general agreement with the observation that left frontal activity in the subacute stage is associated with improved word comprehension (Heiss et al., 1999) and predictive of global language improvement (Saur et al., 2010).

Bilateral SFG activity at the subacute stage was also related to aphasia recovery, consistent with findings of increased subacute activity in frontal regions in previous longitudinal studies on aphasia recovery (Fernandez et al., 2004; Saur et al., 2006; Saur et al., 2010). However, in the present study, we observed a negative correlation between left SFG subacute activity for pseudowords and single word comprehension at the chronic stage. Activation in this region in response to language-based tasks is typically attributed to executive or other cognitive demands. In particular, the SFG has been associated with working memory (Peelle et al., 2004) and is considered to be part of a distributed network which monitors and facilitates comprehension (Hampson et al., 2006; Scott et al., 2003). Thus, the engagement of left SFG for pseudoword processing in the subacute aphasic group may reflect a possible involvement of this region during lexical decision making, in the monitoring of possible word candidates in the associated lexical-semantic network, required before the pseudoword can be discarded as a nonlexical item. Thus, those aphasic patients who require greater engagement of this region to make an accurate lexical decision in the subacute stage have a reduced capacity for language recovery at the chronic time point.

A negative correlation was also observed between increased right SFG activity for the abstract > pseudoword contrast at whole-brain level in the subacute phase and decreased spoken word comprehension in the chronic phase. The right SFG has been associated with a range of cognitive functions including control of emotions (Falquez et al., 2014) and dealing with conflicting stimuli (Zmigrod, Zmigrod, & Hommel, 2016), while as discussed above, the left SFG has typically been associated with executive functions, working memory and inhibition. Dominant theories of concrete and abstract word processing propose that abstract words, which are reliant on verbally encoded concepts, are processed largely in the left hemisphere (for a full review see Chapter 2). Thus, the engagement of the right SFG for abstract compared to pseudowords in subacute aphasia could support the processing of lexical items when a reduced set of conceptual representations are available in left hemisphere networks. Other accounts of concrete and abstract processing suggest that representations of abstract words are associated with strong affective and emotional experiential knowledge (Kousta et al., 2011; Vigliocco et al., 2014; Vigliocco et al., 2009) and therefore an alternative interpretation for right SFG activity during abstract word processing might be that it is engaging emotional representations to assist with lexical retrieval.

Longitudinal studies on language recovery have shown the relevance of bilateral prefrontal activity to language recovery. Fernandez et al. (2004) demonstrated that at the one month phase of recovery, increased activation in bilateral prefrontal regions was associated with both semantic and phonological tasks but more so with the latter. At the chronic phase of testing (1 year post-stroke), the activation of the prefrontal cortex had decreased and this was accompanied by improved recovery of language function, suggesting that the activation of prefrontal cortical regions may be associated with greater attentional control due to increased task demands (Fernandez et al., 2004). A decrease in bilateral frontal activation has also been reported in treatment induced recovery from aphasia (Léger et al., 2002). The findings in the present study for increased subacute activation in bilateral SFG associated with poorer language recovery outcomes suggests that the recruitment of this region does not necessarily reflect successful functional recruitment. Instead, recruitment of bilateral prefrontal regions in subacute aphasia seems to reflect a requirement for increased support of cognitive control during this early phase (Turkeltaub et al., 2011). In the chronic phase of recovery, we did not observe the same relationship between bilateral SFG and out of scanner performance, suggesting a reduced requirement of cognitive control with recovery.

5.4.2 Relationship between Chronic Brain Activity and Language Recovery

We observed the involvement of several different regions when examining chronic stage brain activity associated with language performance at six months post-stroke. Results for the ROI correlations showed increased activity in left hemisphere language regions which was associated with improved language function and this finding is consistent with the general view that an important mechanism of aphasia recovery is the restoration or restitution of the left hemisphere language network (Crosson et al., 2007; Heiss & Thiel, 2006; Kiran, 2012; Price & Crinion, 2005).

Positive correlations were observed between chronic activity for all three conditions (concrete, abstract and pseudowords) in left aSTG and chronic sentence comprehension performance. Left anterior STG is thought to play a critical role in responding to the acoustic complexity of speech (Price, 2012) and auditory phonological word form (Friederici, 2012), and has also been associated with syntactic processing (Friederici, 2011) or combinatorial processes (Hickok & Poeppel, 2007). In aphasia, focal lesions in the anterior temporal region have been associated with semantic recognition and production impairments (Mirman et al., 2015) while disruption of the ventral stream (a pathway connecting regions in auditory cortex with the anterior temporal lobe and prefrontal cortex) results in auditory comprehension deficits (Kümmerer et al., 2013) and a reduction in accuracy in the conduite d'approche (i.e. multiple repeated attempts to retrieve a target) for real words (Ueno & Lambon Ralph, 2013).

Findings from a longitudinal PET study on aphasia recovery by Heiss et al. (1999) which examined different subgroups of aphasic patients at 2 and 8 weeks post-stroke, demonstrated that patients with subcortical and frontal lesions, showed an upregulation of left STG which was not seen in the patient group with temporal lesions. The authors interpreted this finding as suggesting that efficient recovery of language function is only achievable if the left temporal regions are preserved and are able to be reintegrated as part of the functional language network (Heiss et al., 1999). The current finding of involvement of this region in response to both the word and pseudoword conditions and the positive correlation with improved sentence processing suggests that in chronic aphasia, engagement of the left aSTG during spoken word processing provides a mechanism also supporting sentence comprehension.

The role of left posterior cingulate cortex was also highlighted at the chronic stage, where left posterior cingulate activity during both concrete and abstract word processing was positively correlated with spoken word comprehension and sentence comprehension, respectively. As discussed above, this region has been associated with the control of internally directed thought and attentional processes. Thus, the positive correlations observed at both the subacute and chronic time points suggest that the engagement of the left posterior cingulate may contribute to the successful recovery of language comprehension, although its function over the course of recovery changes such that in subacute aphasia it supports pseudoword processing but in chronic aphasia, it is engaged to support real word processing.

Negative correlations were observed for the chronic left IFG ROI activity between the abstract condition and chronic sentence comprehension and overall CAT scores. The left IFG has, amongst other assumed roles, been associated with phonologically-based, short term working memory processes (Binder et al., 2005; Fiebach & Friederici, 2004; Sabsevitz et al., 2005). It was also one of the main regions reliably activated by abstract words in both the Binder et al. (2009) and Wang et al. (2010) meta-analyses investigating processing differences between concrete and abstract words in healthy individuals and its engagement may therefore reflect strategic semantic retrieval processes (Fliessbach et al., 2006). In terms of longitudinal aphasia studies, a reduced reliance on frontal regions as the need for cognitive control diminishes, accompanied by a return to perisylvian language areas has been associated with a more successful language recovery (Saur et al., 2006).

Our findings are consistent with this view in that we observed a poorer language outcome associated with increased left IFG. However, this correlation was only negative for abstract words and therefore it may be due to unique processing requirements associated with this word type. Abstract words are considered to be processed largely in left hemisphere regions and are thought to have a more ambiguous or weaker set of semantic conceptual representations compared to their concrete counterparts (Hoffmann, 2008). Therefore, the current finding of increased activity in left IFG for abstract word processing in chronic aphasia may reflect an ongoing requirement to engage this area for controlled semantic retrieval when selection demands are increased or retrieval is not successful. As a significant number of language subtests which contribute to the overall CAT score require semantic retrieval to some degree, an increase in the engagement of left IFG in chronic aphasia to assist with semantic retrieval may contribute to a poorer language recovery outcome in general, although it should be noted that other studies have reported increased left IFG activity in chronic aphasia as correlating positively with successful language recovery (Fridriksson, Richardson, Fillmore, & Cai, 2012; Kiran, 2012; Turkeltaub et al., 2011; van Oers et al., 2010). The present findings also highlight the different mechanisms driving recovery at subacute and chronic stages, given the positive association between insula/IFG activity in the subacute phase and chronic overall CAT score discussed earlier.

Results for the chronic whole brain activity and chronic behavioural scores showed right hemisphere recruitment was associated with improved outcome. There was a positive correlation between spoken word comprehension and word greater than pseudoword activity in the right anterior cingulate and right olfactory cortex extending into right insula and right caudate regions. Dorsal anterior cingulate and the adjacent medial SFG region form part of a domain-general cortical system termed the cingulo-opercular network (Dosenbach et al., 2007; Power & Petersen, 2013). While this region is reliably activated in response to more nonlinguistic cognitive tasks (Kennerley, Walton, Behrens, Buckley, & Rushworth, 2006; Lovstad et al., 2012; Torta & Cauda, 2011), activity has also been observed in response to language tasks (Blank et al., 2003; Price, 2012; Warburton et al., 1999). In aphasic patients, the engagement of right frontal regions associated with improved language outcome has been observed from the acute to the subacute phase (Saur et al., 2006), in the subacute (Saur et al., 2010) and chronic (Blank et al., 2003) phases, and also in treatment induced recovery (Crosson et al., 2009).

More recently, the interplay between domain-general cognitive systems and domain-specific language networks that are disrupted in aphasia has been investigated (see Geranmayeh et al., 2014 for a full review), demonstrating that the ability to activate domain general cognitive control networks has a direct influence on the potential outcome for aphasia recovery following treatment (Brownsett et al., 2013). Thus, recruitment of the domain-general right hemisphere regions in early post-stroke aphasia recovery can either be interpreted as a response to an increased requirement for cognitive control of language processes due to compromised functioning of the left hemisphere regions (Saur et al., 2006; Saur et al., 2010) or it may reflect an engagement of a domain-general network in response to impaired task performance and an increased requirement for greater top-down cognitive control (Geranmayeh et al., 2014).

One explanation for the findings showing increased chronic brain activation for words greater than pseudowords in the present study is that domain-general systems are recruited to assist with lexical decision-making processes and reflect an increased requirement for cognitive control which is still required in the chronic phase in order to support compromised language function due to disrupted left hemisphere language networks. However, a role for this region in controlled linguistic processing is consistent with findings from a study by Gold et al. (2006) investigating lexical semantic processes which showed that during a lexical decision bilateral anterior cingulate activation was associated with a strategic semantic inhibition task. The present findings suggest that those aphasic patients who are able to successfully activate these right hemisphere domain-general regions to support controlled language processing, show a more improved language comprehension recovery.

In conclusion, it appears that the neural mechanisms which underpin improved aphasia recovery are dynamic and are differentially recruited at the subacute and chronic stages post-stroke. The role of left hemisphere language regions in aphasia recovery appears critical at both time points. During the subacute phase, improved language function is associated with the engagement of the left posterior cingulate and left insula/inferior frontal regions. In the chronic phase, the left posterior cingulate continues to be associated with a good recovery but restitution of left aSTG function also appears important. The contribution of right hemisphere mechanisms over the course of recovery is less clear. While in the subacute phase, the right prefrontal cortex activity is predictive of poorer language outcome, activation patterns change in the chronic phase such that involvement of key prefrontal regions appears to be associated with improved language outcome. The negative correlations between subacute activity in right SFG and language improvement suggests that the engagement of this region reflects a temporary maladaptive mechanism of recovery or increased cognitive demands, while the right prefrontal cortical regions in the chronic phase appears to play a more complementary role, supporting the processing of more difficult linguistic input. However, the restitution of perisylvian language regions also appears critical and thus a combination of both right and left hemisphere mechanisms intrinsically contribute to improved language outcome in chronic aphasia. These findings provide critical insights into the neural mechanisms underpinning successful language improvement at different stages in the recovery process and highlight the possible use of functional imaging in predictive models of language processing in the clinical setting in the future, both in terms of eventually informing patient outcomes and also enabling the relative effectiveness of treatment programmes and timing of rehabilitation to be measured, thus promoting recovery and ensuring best possible outcomes for individuals with aphasia.

6 Chapter Six

Conclusion

The overall aims of this thesis were two-fold. The first broad aim was to investigate the neural basis of spoken word recognition in healthy individuals with a particular focus on concrete and abstract processing mechanisms. The second overall aim was to identify the neural substrates associated with aphasia recovery from the subacute to chronic phase, in order to address the critical long-term clinical goal of providing people with aphasia with an informed prognosis of likely outcomes in terms of language recovery. Brain activity elicited in response to a spoken word recognition fMRI task was first examined in young and older healthy adults. Patients with post-stroke aphasia were scanned employing the same fMRI paradigm at both the subacute (2 to 6 weeks post-stroke) and chronic (6 months post-stroke) phases of aphasia recovery. Section 6.1 summarises the main findings from the four experiments while section 6.2 considers some of the implications associated with the results. Section 6.3 discusses the limitations of this study and possible future directions that can be explored to extend the findings further. Lastly, section 6.4 considers the final conclusions that can be drawn from this thesis.

6.1 Summary of Major Findings

An auditory processing paradigm was the preferred modality employed to investigate language recovery mechanisms and a simple task was selected to ensure that aphasic patients would be able to perform the task, even in the early stages of aphasia recovery. A lexical decision task with a novel pseudoword condition was selected to explore the neural mechanisms which underpin word form and meaning. Concrete and abstract words were selected as the real word stimuli in order to provide an in depth examination of the semantic system and to address previous reports that people with aphasia show pronounced concreteness effects (i.e. the superior processing advantage for concrete compared to abstract words). Variables associated with these real words were controlled so that task-related activity reflected unique differences between semantic conceptual representations. The pseudowords were designed to be as close to real words as possible in terms of following English phonological rules but were specifically made ‘opaque’ (Raettig & Kotz, 2008) in order to limit semantic-based activity. Furthermore, it was anticipated that making the pseudowords more wordlike, differences attributed to effects of imageability and concreteness would be increased (Evans et al., 2012).

6.1.1 Concreteness Effects and Spoken Word Recognition in Healthy Young Adults

Much of the previous evidence regarding the brain mechanisms recruited during concrete versus abstract word processing has been drawn from studies using visual stimuli. In addition, the investigations into concrete and abstract word processing have used various tasks and baselines, resulting in varying degrees of linguistic processing (refer to Chapter 2 for more details). As such, the aim of Chapter 2 was to examine the neural underpinnings associated with concreteness effects and the recognition of spoken concrete and abstract words in a group of healthy young adults. As predicted, the behavioural results confirmed the presence of concreteness effects for reaction time; that is concrete words were responded to significantly faster than both abstract words and pseudowords and abstract words were responded to faster than pseudowords.

The imaging results confirmed that concrete words elicited more activity compared to abstract words in widely distributed brain regions including bilateral AG, left posterior cingulate and left dorsolateral prefrontal cortex. Concrete words also elicited more activity in the left fusiform gyrus and left aMTG when contrasted with the pseudoword baseline. These qualitative and quantitative findings support both dual coding theory (Paivio, 1971, 1991) and context availability theory (Schwanenflugel et al., 1988; Schwanenflugel & Shoben, 1983) respectively but the lack of left hemisphere activity for abstract greater than concrete words was not consistent with either theory. The engagement of bilateral AG was also considered alongside newer theories of embodied abstraction and interpreted as reflecting a multimodal convergence zone role which interfaces and binds conceptual information from modality specific, heteromodal regions (Binder & Desai, 2011). According to this account, concrete and abstract words will elicit greater activation in convergence zones compared to pseudowords due to the greater amount of conceptual knowledge associated with real words but not pseudowords. Concrete words however should elicit greater activation than abstract words as they are associated with a richer set of semantic conceptual representations, consistent with the findings in the present study.

6.1.2 Concreteness Effect and Spoken Word Recognition in Healthy Older Adults

Much of the existing literature on concreteness effects and the neural mechanisms associated with concrete and abstract processing is derived from studies on younger adults. As such, it is not clear whether concreteness effects and the associated neural mechanisms change as a function of age. This is potentially problematic when using the existing studies on healthy language processing to inform and interpret findings in aphasia as most individuals with aphasia are likely to fall within the older age range.

The older cohort showed concreteness effects in reaction time responses as per the young healthy adults, and an additional processing advantage was observed for accuracy of response. The behavioural results were also consistent with previous observations that spoken word recognition and the concreteness effect appear relatively preserved in ageing (Burke & Shafto, 2008; Shafto et al., 2012). The ROI analyses showed that the preserved performance in the older adults was supported by an altered pattern of neural activity in the left hemisphere, and included inferior and middle frontal regions, the AG and the fusiform gyrus. In particular, the left IFG and left AG were recruited selectively by the older and younger groups respectively. The left IFG showed increased activity in the older group but not in the younger group, for abstract and pseudowords compared to concrete words. This region has previously been associated with phonological and working memory processes (Binder et al., 2005; Fiebach & Friederici, 2004; Sabsevitz et al., 2005) and thus the recruitment of this region in response to abstract and pseudoword processing by only the older adults, coupled with a preserved performance, may reflect an age-associated compensatory mechanism involving increased phonological processing.

In contrast, the left AG showed increased activity in only the younger group. Differences were significant between all three conditions with greatest activity for the concrete words, followed by abstract words and then pseudowords. This result suggests that the younger adults reliably recruit this region when accessing semantic conceptual information and provides further support for the embodied abstraction proposal discussed above (Binder & Desai, 2011) and the role of the AG as a convergence zone. In contrast, the selective pattern of activation in left AG was not observed in the older adults. Instead, the older adults appeared to recruit this region similarly for all three conditions which suggests that in older adults, left AG may play a more general lexical processing role. Interpreted together, the finding for reduction in specificity in left AG, accompanied by an upregulation of left IFG, suggests that in order to maintain a preserved performance, older adults may attend more to phonological than semantic information during lexical decisions. The above findings highlight the need to examine age-related changes in the brain mechanisms underlying language processing in order to provide an accurate comparison for considering aphasia, rather than relying on knowledge derived from young healthy adults.

6.1.3 Brain Activity during Auditory Lexical Decision Making in Subacute Stroke using fMRI

Neuroimaging studies investigating early mechanisms of aphasia recovery have provided interesting insights into brain mechanisms which underpin recovery of language function in the acute stage (Hillis, 2007; Hillis & Heidler, 2002; Hillis et al., 2005). However, the mechanisms which continue to contribute to a successful language outcome in the subsequent stages in post-stroke aphasia are less clear. An influential study by Saur et al. (2006) investigated the neural mechanisms associated with aphasia recovery in the acute, subacute and chronic phases post-stroke. However, limitations with this study concern the complexity of the task and the sentence level task employed, as the reported task-related activity may reflect an involvement of more cognitive strategies rather than language recovery function per se. When investigating language disorders, it is vital that the in-scanner tasks employed can be performed successfully and accurately by people with aphasia in order to ensure that any task-related brain activity reflects the language processes being examined rather than activity associated more with the difficulty of a task or inaccuracy of response (Price et al., 2006; Price & Friston, 1999), although there is also an issue if the task presented is too easy, as differences between time points may not be observed, and sensitivity to language recovery may be reduced (Fernandez et al., 2004). The type of task employed is therefore of critical importance in early post-stroke aphasia studies when any associated language deficits are likely to be at their most severe. Thus, the selection of a spoken word lexical decision task in the present study was the preferred experimental modality, thereby minimising task complexity and increasing the likelihood of task accuracy.

The behavioural results for the in-scanner task showed that both age-matched older adults and subacute aphasic patients responded fastest to concrete words, followed by abstract words and then pseudowords, confirming the presence of concreteness effects. The subacute patients processed abstract words significantly less accurately compared to the age-matched control group. In addition, the subacute group appeared to have significantly greater difficulty in accurately responding to abstract words compared to their processing of both concrete and pseudowords. This suggests that in subacute aphasia it may be the increased difficulty with abstract word processing rather than a reduced performance in concrete words that contributes to the exaggerated concreteness effects observed in aphasia.

Results from the region of interest analyses showed a strong correlation in right AG between concrete word processing and spoken language comprehension for the aphasic subjects in the subacute stage of recovery. Given task-based accuracy was high, it can be assumed that the engagement of right AG reflected activity associated with the spoken recognition of concrete words. This right hemisphere involvement is broadly similar to that of Saur et al. (2006) and Crinion and Price (2005), however, neither study found activity that was specific to right AG and this might reflect the fact that these studies investigated sentence level rather than single word processing tasks. The reliable activation of left AG in response to semantic-based tasks (Binder et al., 2009; Price, 2010) has prompted some to propose that this region may serve as a supramodal zone, binding and integrating sensorimotor representations from modality-specific brain regions (Binder

& Desai, 2011). In the present study, only one patient had a lesion which involved left AG and thus, this selective engagement by the aphasic group suggests that in subacute aphasia, the right AG may be upregulated to support language processing despite there being no predominance of lesions in the contralateral homologue.

The differential effect of condition in the left aMTG observed in the aphasic group only is consistent with previous observations of patients with semantic dementia who show superior processing for concrete over abstract words in this region (Jefferies et al., 2009). An effect of condition was also identified in left IFG between the two groups with the controls showing greater activity for the pseudowords, followed by the abstract and then concrete words. Group differences were also observed in this region with the control group eliciting significantly greater activity than the aphasic group. Thus, since left IFG was minimally impacted in the aphasic group (refer to Chapter 4 for details) and task accuracy above 83% for all conditions was achieved, the differences observed between the two groups and specifically the underactivity in left IFG may reflect diaschisis or distance effects which are present during this subacute period of aphasia recovery (Kiran, 2012).

6.1.4 Using fMRI to Predict Post-Stroke Aphasia Recovery

The neural substrates typically associated with aphasia recovery include both left and right hemisphere mechanisms (see Chapter 1) and these appear to influence language function at different time points during aphasia recovery. In subacute aphasia, it has been proposed that a laterality shift occurs and language recovery is supported by an upregulation of homotopic regions in the right hemisphere, recruited due to compromised functionality in the contralateral regions (Saur et al., 2006; Saur et al., 2010). In the chronic phase of recovery, once much reorganisation has occurred, a good language recovery is associated with a return to left hemisphere language networks (Saur et al., 2006) and persistent involvement of right hemisphere homologues may hinder recovery and instead reflect dysfunctional processing mechanisms (Szaflarski et al., 2013) or transcallosal disinhibition (Naeser et al., 2005). Thus the aim of Chapter 5 was to address the lack of knowledge regarding brain mechanisms which underpin aphasia from the subacute to chronic phases post-stroke in order to provide much needed specificity in determining predictors associated with language recovery.

Subacute activity in left posterior cingulate and left insula/inferior frontal regions predicted improved language function in the chronic phase. Left IFG is a core component of the language network, while left posterior cingulate is often associated with semantic processing and is highly connected with other regions including the medial temporal lobes and ventromedial prefrontal cortex (Leech & Sharp, 2014). Thus, their engagement in response to language functioning may suggest a compensatory role in early aphasia recovery. These results are consistent with the perilesional recovery hypothesis which suggests that left hemisphere regions surrounding the lesion are upregulated to support compromised language function following damage to language nodes (Saur et al., 2006; Zahn et al., 2004). Although it should be noted there is no clear definition of what constitutes “perilesional” and this mechanism may in some cases reflect involvement of other intact ipsilesional regions distant from the damaged region, given the varied locations of lesions in this cohort.

In contrast, other regions activated in the subacute phase showed negative correlations and this activation combined with poorer language function in the chronic phase suggests a possibly maladaptive or unsuccessful recovery mechanism which may indicate the engagement of controlled processes in those patients with reduced potential for recovery. Specifically, a negative correlation was found between the left SFG ROI activity for pseudowords and spoken word comprehension. The specific function SFG plays in language tasks is not clear and while it may reflect semantic retrieval processes (Binder et al., 2009), it has also been associated with more executive type functions including cognitive control (Hampson et al., 2006; Peelle et al., 2004; Scott et al., 2003). In the present study, the activation in left SFG was for pseudowords only and in right SFG was for abstract words greater than pseudowords and thus the activity is unlikely to reflect purely semantic retrieval processes. Rather, the engagement of bilateral SFG may reflect a requirement for more cognitive-linguistic control due to the compromised function in the disrupted left hemisphere language regions. However, since these domain-general regions typically form part of a more distributed cognitive system, their engagement in subacute aphasia, coupled with a poorer performance on spoken word comprehension in chronic aphasia, likely reflects an inefficient compensatory processing mechanism.

Correlations between outcome and chronic brain activity revealed that the recruitment of alternate neural substrates in both left and right hemispheres underpinned an improved language outcome. In the left hemisphere, positive correlations were observed between left posterior cingulate for concrete words and spoken word processing and between abstract words and spoken sentence comprehension confirming its role at both subacute and chronic phases of recovery. Another positive correlation was identified between left aSTG for all three contrasts and sentence comprehension, consistent with a role in syntactic and semantic combinatorial processes (Friederici, 2011; Hickok & Poeppel, 2007; Rogalsky & Hickok, 2009).

The findings in this chapter demonstrate the potential of this paradigm to reliably elicit language-related neural activity in subacute and chronic aphasia and indicate how distinct patterns of left and right hemisphere activity change over the course of recovery and may be predictors of improved spoken word comprehension and overall language function. The positive engagement of left posterior cingulate at both time points suggests that this region contributes to improved language comprehension abilities although its function appears to change over the course of recovery. The role that prefrontal regions play in recovery is less clear. In the subacute stage increased bilateral SFG activity was associated with poorer recovery of spoken word comprehension, while in chronic aphasia, increased activity in right anterior cingulate cortex correlated with improved language comprehension. These data highlight the potential role of more domain-general systems in post-stroke aphasia but suggest this involvement does not always indicate a successful outcome and may be dependent on the stage of recovery.

6.2 Implications of Major Findings

The major findings of this thesis discussed above add to a growing body of evidence regarding the neural mechanisms which underpin language function and provide a better understanding of how these mechanisms contribute to improved language function in subacute and chronic aphasia recovery. In particular, the findings in this thesis demonstrate the potential prognostic capability of this paradigm to predict specific language outcomes at 6 months.

6.2.1 Clinical Implications

The clinical applications of this project are significant. In the first instance, once a more accurate understanding of the neural mechanisms which underpin language recovery is reached, MRI and fMRI may be used clinically as a predictive tool to determine a person's potential to recover from aphasia following stroke (Crosson et al. 2007; Muñoz-Cespedes et al. 2005). With advances in technology, scanning times may be shortened and it is conceivable that a combination of complementary imaging methodologies could be used in the clinical setting and imaging sequences added to routine clinical scanning procedures to inform prognosis and treatment directions. Whilst this suggestion might appear overly optimistic or unrealistic, task-based fMRI investigations are currently being employed clinically for the purpose of language mapping in adults with brain tumours (Peck et al., 2009; Sair et al., 2016).

In addition, imaging modalities where patients are not required to perform a task, such as resting state functional connectivity (RSFC) and diffusion imaging, may have a critical role in predicting outcomes and will be able to capture all patients with aphasia regardless of whether they can perform the task or not. Prediction models such as the PLORAS system (Price et al., 2010) are being further refined and are aiming to predict recovery of language function based on heterogeneous lesion sites and behavioural data from large longitudinal patient population studies, and data from this thesis will contribute to the Price et al. (2010) model. Prediction of system-specific recovery using a support vector machine in post-stroke aphasia has also been shown to have the potential to identify whether a patient will have a good or poor prognosis for recovery

(Saur et al., 2010) and this can then inform rehabilitation programmes. However, this system has not been applied to individual symptoms that are targeted in rehabilitation and does not focus on patients in the subacute 2-6 weeks stage post-stroke which is a critical period when patients and family are in need of information regarding recovery. Other predictive models such as the PREP algorithm (Stinear, Barber, Petoe, Anwar, & Byblow, 2012) have been used successfully in the prognosis of motor function in stroke patients, based on the notion that imaging may be required to provide accurate predictors of recovery in a subset of patients, while recovery in others may be predicted based on behavioural measures. In the future, it may be possible to include information on language assessments in stroke recovery algorithms to further improve prediction. This prognostic information may then be used by clinicians to determine patients who are likely to benefit from rehabilitation. Importantly, for those patients who are not predicted to have a favourable recovery, alternative, appropriate rehabilitation could be offered. Depending on individual factors, it may be beneficial for some people with aphasia to receive more intensive and frequent therapy while for others, it may be of more benefit to focus on a more functional, compensatory therapeutic approach thereby ensuring maximal quality of life outcomes.

A second long-term clinical application of this study concerns the provision of aphasia therapy. Understanding predictors of aphasia may provide the basis for new treatment approaches both in terms of timing and type of intervention and may help identify those patients who are likely to benefit from therapeutic input (Lazar et al., 2008). A crucial question is whether spontaneous recovery can be complemented by language therapy and if so, at what point of recovery is it most beneficial to provide maximal therapeutic intervention. At present it is not known how, or even whether, treatment of aphasia in the acute stages of recovery influences the progressive dynamics of language reorganisation in the brain. While Godecke et al. (2014) suggest that early intervention in acute stroke is associated with an improved outcome, other studies have raised questions about early intervention by showing no significant improvement in those receiving therapy compared to a control group (Bowen et al., 2012).

Studies identifying the brain mechanisms driving treatment-induced recovery have been primarily focused on the chronic phase (Fridriksson, 2010; Fridriksson et al., 2010) and there are likely to be several factors that influence recovery outcomes such as the type of therapy (Heath et al., 2012; van Hees, McMahon, Angwin, de Zubicaray, & Copland, 2014) and frequency of delivery (Bhogal, Teasell, & Speechley, 2003; Dignam et al., 2015). What is well-established is that in the first few weeks post-stroke, rapid neurophysiological spontaneous recovery is occurring (Lazar & Antoniello, 2008; Marsh & Hillis, 2006). Since a significant amount of language improvement occurs within the first three months of recovery (Berthier, 2005; Lazar et al., 2010; Robey, 1998), a more effective utilization of a clinician's time in very early post-stroke recovery may be to carry out informal language assessments, provide alternative or compensatory methods of communication to ensure the patient is able to communicate as functionally as possible, and offer support and education to the family as appropriate. Then, during the subacute phase once much neurobiological restitution has occurred and language recovery has slowed, it may be timely and more appropriate to conduct comprehensive standardised speech and language assessments to enable the clinician to make a more reliable diagnosis and prognosis regarding language recovery and to begin a therapy programme which accurately targets any persisting underlying language deficits.

Clearly, the influence of timing and type of therapeutic intervention needs to be more clearly understood. In the long term, accurate predictors of recovery will enable the relative effectiveness of treatment programmes and timing of rehabilitation to be measured. Once this is achieved targeted, realistic rehabilitation goals can be set and cost effective provision of therapy can be offered to ensure maximal outcomes whilst also ensuring that resource allocation is at its most efficient. Furthermore, the identification of the brain mechanisms driving recovery could provide new targets for neurobiological treatments such as non-invasive brain stimulation or pharmacotherapy.

6.2.2 Mechanisms of Recovery

While it is clear that both left and right hemisphere mechanisms are associated with improved language function in aphasia, the extent and timing of the involvement of these mechanisms and critically, whether their engagement assists or hinders language recovery remains an interesting point of contention. The findings in this thesis contribute to this debate and provide evidence that both left and right hemisphere mechanisms are associated with aphasia recovery, but this involvement varies from the subacute to chronic time points and differentially impacts on improved language function.

In the subacute stage of recovery, neurophysiological changes are still occurring although less rapidly than in the acute stage and thus neural mechanisms at this stage reflect a system that is still undergoing reorganisation. The subacute results in this thesis showed that activity in discrete left hemisphere regions correlated positively with improved language function in the chronic phase. Specifically subacute brain activity in the left posterior cingulate predicted improved spoken word comprehension while subacute activity in the left insular/IFG predicted improved overall language function in the chronic phase of recovery. The left posterior cingulate is frequently activated in semantic-based tasks and is strongly connected with other language regions including the ventromedial prefrontal and medial temporal regions (Leech & Sharp, 2014) while left IFG is considered a key component of the language network and associated with a range of language functions (Binder et al., 2009; Price, 2012). Thus the finding of increased recruitment in the early aphasia recovery period in these ipsilateral regions may reflect compensatory perilesional recruitment, whereby undamaged areas of the left hemisphere language network surrounding the lesion are engaged to support the compromised language functioning (Saur et al., 2006; Thompson, 2000b). It should also be acknowledged that involvement of the left posterior cingulate cortex in conceptual processing tends to occur in stimulus-independent or freewheeling mental activity (Leech & Sharp, 2014).

However, subacute brain activity also correlated negatively with language recovery in left

SFG, left postcentral gyrus regions and in right SFG and therefore the involvement of left hemisphere mechanisms does not always appear beneficial and may predict a poorer outcome. The engagement of these domain-general systems may be caused by the level of damage in domain-specific language systems. Patients with lesions that severely disrupt left hemisphere language systems may recruit these regions to assist with language processing in early aphasia recovery, but since the function of these regions is associated with cognitive control, its involvement is unlikely to be as efficient as the upregulation of regions in more domain-specific language systems.

In the chronic stage of recovery, much of the neurophysiological changes associated with spontaneous recovery have ceased and the system may be considered to have undergone significant reorganisation. The findings in this thesis show that while left hemisphere regions continue to be associated with improved language outcome, right hemisphere mechanisms also appear to play a critical role in recovery in chronic aphasia. The left hemisphere regions that correlated with an improved outcome included the left posterior cingulate and left aSTG and confirm that the ability to recruit regions in the left hemisphere of both domain-general and domain-specific language areas has a critical role in ongoing aphasia recovery. The role of right hemisphere domain-general systems in the chronic phase appears to indicate improved outcome and may reflect a compensatory masquerade (Grafman & Litvan, 1999), that is the carrying out of the same function using a different strategy and associated neural mechanisms, and in this case, an engagement of regions associated with cognitive control recruited to support cognitive-linguistic processes, which are usually dependent on left hemisphere regions but are compromised following disruption to the network.

Findings from this thesis support the view that a combination of neural mechanisms underpin aphasia recovery (Crinion & Leff, 2007; Price & Crinion, 2005; Thompson & den Ouden, 2008) and are implicated at different time points in subacute and chronic aphasia. The role of the left hemisphere appears important at both time points and specifically the engagement of perilesional tissue in domain-general and domain-specific language systems appears to play a significant role in recovery from aphasia. The role of the right hemisphere in language recovery is more unclear and whether its involvement constitutes a compensatory upregulation to support compromised function of the left hemisphere networks or whether its involvement is disadvantageous and associated more with dysfunctional processes and a loss of transcallosal inhibition, is yet to be fully determined.

6.3 Limitations and Future Directions

This thesis successfully used a simple auditory lexical decision task with a novel pseudoword condition, to determine neural underpinnings of spoken word recognition and to identify mechanisms of recovery associated with improved language function in patients in the subacute and chronic stages of post-stroke aphasia. However, some comments regarding the study limitations are necessary as they will benefit future studies. A first limitation concerns the selection of stimuli. As is typical of such studies, the abstract words were of very low imageability and although challenging, future studies may benefit from attempting to match the levels of imageability in both concrete and abstract conditions. A second limitation concerns the inclusion and exclusion criteria which were very stringent in order to ensure that only patients with aphasia who were able to provide informed consent and perform the fMRI task were included in the study. As a result, all patients with severe language comprehension deficits and a more global aphasia presentation were automatically excluded. Thus the small sample size combined with a cohort which did not include more severe aphasia subtypes was not truly representative of the aphasic population. This may have impacted on the results in that the neural mechanisms which were considered to underpin aphasia recovery, may in fact be more representative of a mild-moderate aphasia presentation. For example, remaining intact left hemisphere regions in those patients with milder aphasic symptoms may have inhibited the functional upregulation of the homologous regions as right hemisphere adaption is thought to occur more commonly when the inhibition from the contralateral region is removed (Grafman & Litvan, 1999). Thus, by including more patients with severe aphasia, the upregulation of right hemisphere mechanisms may have been more prevalent. Future studies will undoubtedly benefit from recruiting a larger cohort of patients with a more heterogeneous range of lesions, language deficits and associated recovery trajectories, recruitment issues notwithstanding.

An additional shortfall with the study was that the provision of therapy was not able to be controlled for and thus it is not clear how it may have contributed to recovery. Most patients received usual care while an inpatient in hospital, and while no patient underwent an intensive therapy program, some continued to receive therapy input once they had been discharged from hospital before the chronic stage assessment. Other patients who had a more mild presentation received minimal therapy although some of their symptoms were still persisting in the chronic phase. Thus the effects of therapy from the subacute to chronic period of recovery could not considered and this may have been a factor which influenced the results (Lazar et al., 2010). Future studies will benefit from controlling the type, amount, frequency and timing of therapy intervention to examine whether the recovery mechanisms and functional outcome can be influenced by treatment. Finally, as the current study focussed on single word and sentence outcome measures, future studies will also benefit from moving towards using more ecologically valid, connected speech as an outcome measure to determine the effects of both spontaneous and treatment-induced recovery.

Another limitation of the present study is that additional neuroimaging modalities were not used to inform the interpretation of the results regarding the neural substrates which underpin aphasia recovery. The relative safety and non-invasive nature of MRI has enabled more investigation into brain structure and function relationships and is fundamental for exploring the neural mechanisms involved in language processing. However, there are inherent limitations in using one imaging modality in isolation. Future studies investigating aphasia recovery may benefit from using a combination of complementary MRI techniques.

Diffusion imaging is able to determine the integrity and connectivity of the white matter fibres which can be damaged following stroke and can be combined with other imaging technologies to provide novel insights into language processing mechanisms. Diffusion tensor imaging (DTI) has been used to complement structural language studies in healthy brains (Richardson & Price, 2009) and has also been able to demonstrate that, despite normal MRI morphometry on standard structural scans, language dysfunction may be associated with reduced integrity of white matter structures connecting the anterior and posterior language regions (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008). DTI has also proved a useful imaging technique in exploring longitudinal changes in major fibre trajectories and anatomical predictors associated with aphasia recovery from diffusion tractography (Forkel et al., 2014; van Hees, McMahon, et al., 2014a). In addition, by combining DTI with fMRI, information regarding the language networks and the specific function associated with distinct pathways is able to be examined (Glasser & Rilling, 2008; Saur et al., 2008). Thus, the use of DTI with complementary methodologies in future studies investigating aphasia recovery, may provide novel insights into how white matter integrity influences and predicts functional outcome in aphasia recovery. Measures of structural connectivity may also be combined with measures of functional connectivity within and between relevant language and cognitive networks, particularly given the regions we identified as being correlated with recovery (Geranmayeh et al., 2014).

Another important imaging methodology to consider in future studies investigating aphasia recovery is resting state fMRI to enable analysis of functional connectivity between anatomically distinct brain regions when the brain is ‘at rest’; that is when the brain is not engaged in an overt task. Previous studies have shown that during rest, the brain is not silent, rather there is continual processing of information and ongoing functional connectivity between brain regions (Biswal, Kylen, & Hyde, 1997). RSFC analyses have been used to investigate behavioural differences in a variety of patient populations including Alzheimer’s disease (Supekar, Menon, Rubin, Musen, & Greicius, 2008), schizophrenia (Jafri, Pearlson, Stevens, & Calhoun, 2008) and aphasia (van Hees, McMahon, et al., 2014b) and a recent study investigating longitudinal changes in recovery from traumatic brain injury showed that increased functional connectivity in networks involving the medial temporal and insular regions occurs at 3 to 6 months (Hillary et al., 2011). In addition, the utility of combining resting state data with task-based fMRI data to explore connectivity in key language subregions has also been demonstrated (Jackson, Hoffman, & Pobric, 2016). Critically, because RSFC can be performed without any overt response from the patient, it offers an advantageous imaging technique to characterise network changes in both spontaneous and treatment induced improvements in early post-stroke aphasia and may provide additional insights in future studies investigating longitudinal changes in aphasia recovery.

A further imaging methodology that may provide novel information on predictive neural mechanisms associated with aphasia recovery is voxel-based lesion-symptom mapping (VLSM; Bates et al., 2003). VLSM enables the relationship between the extent of the lesion and language symptoms in aphasia to be examined (Bates et al., 2003; Lee et al., 2006) and provides lesion maps which can be overlaid and within-group analyses carried out. Across-group comparisons can also be made using data from the lesion group and normal subjects, and areas that are identified consistently across a group can then be considered 'necessary' for performance of that particular function (Vandenberghe & Gillebert, 2009) and can inform the neural basis of language (Mirman et al., 2015). In addition, VLSM can be combined with other imaging modalities to provide a more comprehensive understanding of language processing mechanisms. Functional MRI can be used to complement lesion studies such that anatomical maps can be overlaid with lesion maps and fMRI activation maps to identify regions that are critical to the performance of a language task (Price & Friston, 2002; Vandenberghe & Gillebert, 2009). In addition, the complementary use of voxelwise lesion-behaviour mapping (Rorden, Karnath, & Bonilha, 2007) and DTI has been used to examine how damage to ventral and dorsal language pathways affects language comprehension in acute aphasia (Kümmerer et al., 2013) and future longitudinal studies investigating aphasia recovery would benefit from examining how the relationship between structure and function changes over the course of aphasia recovery.

The use of an imaging modality to measure perfusion levels may also be beneficial to future studies investigating longitudinal changes in aphasia recovery. Techniques such as Arterial Spin

Labelling (ASL) measure blood perfusion levels and can identify hypoperfused regions not always identifiable with a structural scan. In acute aphasia, the degree of hypoperfusion is currently considered a more reliable predictor of neurological deficit than the size of the lesion (Hillis et al., 2000) and has been shown to have an influence on language function in the acute stages post-stroke (Hillis et al., 2000; Hillis et al., 2004). However, studies have also demonstrated that cerebral perfusion is still present in chronic stroke patients (Brumm et al., 2010), correlates with the severity of aphasia even at one month post-stroke and is actually a more reliable predictor of aphasia severity than lesion size (Fridriksson et al., 2002). Thus, while the present study did not include patients in the acute recovery stage, it may be beneficial in future studies investigating longitudinal changes associated with aphasia recovery to incorporate ASL since it is a non-invasive technique and can be acquired in conjunction with a structural MRI scan, making it a feasible clinical/research tool.

6.4 Overall Conclusions

Findings from the studies on healthy young and older adults confirmed that concreteness effects were present in both groups and demonstrated that spoken word recognition of concrete and abstract words remains preserved in ageing. The imaging results for both groups also confirmed a range of common regions were activated in response to concrete and abstract words regardless of age. Of these regions, activity in bilateral AG and left posterior cingulate was reliably elicited in response to concrete greater than abstract greater than pseudoword processing. The healthy young adult findings cannot be fully reconciled by either of the two dominant accounts used to explain concrete and abstract processing as dual coding theory would not predict increased left hemisphere activity for concrete compared to abstract words, while context availability theory would not predict increased right hemisphere activity for either concrete or abstract words. Instead, engagement of the bilateral AG was more consistent with contemporary theories of embodiment which propose that the AG acts as a convergence zone. The contrasting findings in healthy older adults were interpreted as reflecting different aspects of age-related compensatory upregulation such that the older adults focus more on phonological and less on semantic aspects of processing in order to maintain a preserved performance.

The findings for the aphasic patients demonstrate the potential of the experimental paradigm to reliably elicit language-related neural activity in both subacute and chronic aphasia and provide an indication as to how distinct patterns of brain activity change over the course of recovery and may relate to improved spoken word comprehension. While no definitive conclusions can be drawn regarding the timing and extent to which the distinct mechanisms underpin a successful recovery, the results do provide support for the view that aphasia recovery is associated with a dynamic set of left and right hemisphere mechanisms which are differentially recruited during subacute and chronic aphasia. The results of this project have demonstrated that the role of the left hemisphere appears critical at both time points and specifically the engagement of regions in domain-general and domain-specific language systems appears to predict improved recovery. In particular, the positive recruitment of left posterior cingulate cortex at both subacute and chronic phases suggests that this region contributes to language comprehension improvements in aphasia recovery, although its function differs depending on the time post-stroke. The role the right hemisphere plays in language recovery is less clear, particularly with regard to the involvement of prefrontal structures. These results contribute to the debate on the role of left and right hemisphere mechanisms in recovery and highlight the potential role of more domain-general systems in post-stroke aphasia.

Currently there is no accurate way to predict an individual's potential for aphasia recovery and there are many factors that may contribute to both spontaneous and treatment-induced improvements (Jarso et al., 2013). While it is acknowledged that the sample size in the present study is small, the findings from this thesis demonstrate the predictive strength of utilizing a paradigm that people with aphasia are able to perform successfully and accurately in the early stages post-stroke. This paradigm has the potential to be used alongside other imaging modalities in future longitudinal studies to enable a more detailed understanding of the complex relationship between brain structure and function in aphasia and the neural mechanisms associated with aphasia recovery. In the future, this information may be combined with clinical data to predict an individual's potential for overall and therapy-induced recovery. Such an approach would transform current practices in aphasia rehabilitation. Not only does this ensure a better quality of life for the person with aphasia but it also has considerable implications for the provision of speech pathology services in the acute-subacute hospital setting, where resources are often limited and targeted, effective therapy optimum.

References

Adams, R. B., & Janata, P. (2002). A comparison of neural circuits underlying auditory and visual object categorization. *Neuroimage, 16*(2), 361-377. doi: 10.1006/nimg.2002.1088

Addis, D. R., Wong, A. T., & Schacter, D. L. (2007). Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration. *Neuropsychologia, 45*(7), 1363-1377. doi: 10.1016/j.neuropsychologia.2006.10.016

Ardila, A., Bernal, B., & Rosselli, M. (2014). Participation of the insula in language revisited: A meta-analytic connectivity study. *Journal of Neurolinguistics, 29*, 31-41. doi: http://dx.doi.org/10.1016/j.jneuroling.2014.02.001

Aron, A. R., Monsell, S., Sahakian, B. J., & Robbins, T. W. (2004). A componential analysis of task-switching deficits associated with lesions of left and right frontal cortex. *Brain, 127*(7), 1561-1573. doi: 10.1093/brain/awh169

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *Neuroimage, 38*(1), 95-113. doi: 10.1016/j.neuroimage.2007.07.007

Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *Neuroimage, 26*(3), 839-851.

Australian Bureau of Statistics. (2014). Causes of Death, Australia 2012. *ABS cat. no. 3303.0.*

Balota, D. A., & Chumbley, J. I. (1984). Are lexical decisions a good measure of lexical access? The role of word frequency in the neglected decision stage. *J Exp Psychol Hum Percept Perform, 10*(3), 340-357.

Balota, D. A., Cortese, M. J., Sergent-Marshall, S. D., Spieler, D. H., & Yap, M. (2004). Visual word recognition of single-syllable words. *J Exp Psychol Gen, 133*(2), 283-316. doi: 10.1037/0096-3445.133.2.283

Balota, D. A., Ferraro, R. F., & Connor, L. T. (1991). On the early influence of meaning in word recognition: A review of the literature. In I. P. Schwanenflugel (Ed.), *The Psychology of Word Meaning* (pp. 187-222). Hillsdale, NJ: Lawrence Erlbaum Associates.

Balota, D. A., Paul, S. T., & Spieler, D. H. (1999). Attentional control of lexical processing pathways during word recognition and reading. In S. Garrod & M. Pickering (Eds.), *Language processing* (pp. 15-57). Hove: Psychology Press.

Balota, D. A., Yap, M. J., Cortese, M. J., Hutchison, K. A., Kessler, B., Loftis, B., . . . Treiman, R. (2007). The English Lexicon Project. *Behav Res Methods, 39*(3), 445-459.

Baltes, P. B., Cornelius, S. W., Spiro, A., Nesselroade, J. R., & Willis, S. L. (1980). Integration versus differentiation of fluid/crytallized intelligence in old age. *Developmental Psychology, 16*(6), 625-635. doi: 10.1037/0012-1649.16.6.625

Barber, H. A., Kousta, S.-T., Otten, L. J., & Vigliocco, G. (2010). Event-related potentials to event-related words: Grammatical class and semantic attributes in the representation of knowledge. *Brain Research, 1332*(0), 65-74. doi: http://dx.doi.org/10.1016/j.brainres.2010.03.014

Barber, H. A., Otten, L. J., Kousta, S. T., & Vigliocco, G. (2013). Concreteness in word processing: ERP and behavioral effects in a lexical decision task. *Brain & Language, 125*(1), 47-53. doi: 10.1016/j.bandl.2013.01.005

Barry, C., & Gerhand, S. (2003). Both concreteness and age-of-acquisition affect reading accuracy but only concreteness affects comprehension in a deep dyslexic patient. *Brain & Language, 84*(1), 84-104.

Barsalou, L. W. (1999). Perceptual symbol systems. *Behav Brain Sci, 22*(4), 577-609; discussion 610-560.

Barsalou, L. W., & Wiemer-Hastings, K. (2005). Situating abstract concepts. In D. Pecher & R. Zwaan (Eds.), *Grounding cognition: The role of perception and action in memory, language and thinking* (pp. 129-163). New York: Cambridge University Press.

Basso, A., Gardelli, M., Grassi, M. P., & Mariotti, M. (1989). The role of the right hemisphere in recovery from aphasia. Two case studies. *Cortex, 25*(4), 555-566.
Bates, E., Wilson, S. M., Saygin, A. P., Dick, F., Sereno, M. I., Knight, R. T., & Dronkers, N. F. (2003). Voxel-based lesion-symptom mapping. *Nat Neurosci, 6*(5), 448-450.
Bedny, M., & Thompson-Schill, S. (2006). Neuroanatomically separable effects of imageability and grammatical class during single-word comprehension. *Brain and Language, 98*(2), 127-139. doi: 10.1016/j.bandl.2006.04.008
Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological), 57*(1), 289-300. doi: 10.2307/2346101
Berthier, M. L. (2005). Poststroke aphasia : epidemiology, pathophysiology and treatment. *Drugs Aging, 22*(2), 163-182.
Bhogal, S. K., Teasell, R., & Speechley, M. (2003). Intensity of aphasia therapy, impact on recovery. *Stroke, 34*(4), 987-993.
Binder, J. R., & Desai, R. H. (2011). The neurobiology of semantic memory. *Trends Cogn Sci, 15*(11), 527-536. doi: 10.1016/j.tics.2011.10.001
Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cereb Cortex, 19*(12), 2767-2796. doi: 10.1093/cercor/bhp055
Binder, J. R., Swanson, S. J., Hammeke, T. A., Morris, G. L., Mueller, W. M., Fischer, M., . . . Haughton, V. M. (1996). Determination of language dominance using functional MRI: a comparison with the Wada test. *Neurology, 46*(4), 978-984.
Binder, J. R., Westbury, C. F., McKiernan, K. A., Possing, E. T., & Medler, D. A. (2005). Distinct brain systems for processing concrete and abstract concepts. *J Cogn Neurosci, 17*(6), 905-917.
Biswal, B. B., Kylen, J. V., & Hyde, J. S. (1997). Simultaneous assessment of flow and BOLD signals in resting-state functional connectivity maps. *NMR in Biomedicine, 10*(4-5), 165-170. doi: 10.1002/(SICI)1099-1492(199706/08)10:4/5<165::AID-NBM454>3.0.CO;2-7
Blank, S., Bird, H., Turkheimer, F., & Wise, R. (2003). Speech production after stroke: the role of the right pars opercularis. *Annals of Neurology, 54*. doi: 10.1002/ana.10656
Bonakdarpour, B., Parrish, T. B., & Thompson, C. K. (2007). Hemodynamic response function in patients with stroke-induced aphasia: implications for fMRI data analysis. *Neuroimage, 36*(2), 322-331. doi: 10.1016/j.neuroimage.2007.02.035
Bonner, M. F., & Price, A. R. (2013). Where Is the Anterior Temporal Lobe and What Does It Do? *The Journal of Neuroscience, 33*(10), 4213-4215. doi: 10.1523/jneurosci.0041-13.2013
Bonner, M. F., Vesely, L., Price, C., Anderson, C., Richmond, L., Farag, C., . . . Grossman, M. (2009). Reversal of the concreteness effect in semantic dementia. *Cogn Neuropsychol, 26*(6), 568-579. doi: 10.1080/02643290903512305
Bowen, A., Hesketh, A., Patchick, E., Young, A., Davies, L., Vail, A., . . . Tyrrell, P. (2012). Clinical effectiveness, cost-effectiveness and service users' perceptions of early, well-resourced communication therapy following a stroke: a randomised controlled trial (the ACT NoW Study). *Health Technol Assess, 16*(26), 1-160. doi: 10.3310/hta16260
Breedin, S. D., Saffran, E. M., & Coslett, H. B. (1994). Reversal of the concreteness effect in a patient with semantic dementia. *Cognitive Neuropsychology, 11*(6), 617 - 660. doi: 10.1080/02643299408251987
Breier, J. I., Castillo, E. M., Boake, C., Billingsley, R., Maher, L. M., Francisco, G., & Papanicolaou, A. C. (2004). Spatiotemporal patterns of language-specific brain activity in patients with chronic aphasia after stroke using magnetoencephalography. *Neuroimage, 23*(4), 1308-1316.
Breier, J. I., Hasan, K. M., Zhang, W., Men, D., & Papanicolaou, A. C. (2008). Language dysfunction after stroke and damage to white matter tracts evaluated using diffusion tensor imaging. *Ajnr: American Journal of Neuroradiology, 29*(3), 483-487.

Breier, J. I., Maher, L. M., Novak, B., & Papanicolaou, A. C. (2006). Functional imaging before and after constraint-induced language therapy for aphasia using magnetoencephalography. *Neurocase, 12*(6), 322-331. doi: T25VT60177P81555 [pii] 10.1080/13554790601126054

Brett, M., Anton, J., Valabregue, R., & Poline, J. (2002). *Region of interest analysis using an SPM toolbox [abstract]*. . Paper presented at the 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan.

Brownsett, S. L. E., Warren, J. E., Geranmayeh, F., Woodhead, Z., Leech, R., & Wise, R. J. S. (2013). Cognitive control and its impact on recovery from aphasic stroke. *Brain*.

Brumm, K. P., Perthen, J. E., Liu, T. T., Haist, F., Ayalon, L., & Love, T. (2010). An Arterial Spin Labeling Investigation of Cerebral Blood Flow Deficits in Chronic Stroke Survivors. *Neuroimage, 51*(3), 995-1005. doi: 10.1016/j.neuroimage.2010.03.008

Buckner, R. L., Andrews-Hanna, J. R., & Schacter, D. L. (2008). The brain's default network: anatomy, function, and relevance to disease. *Ann N Y Acad Sci, 1124*, 1-38. doi: 10.1196/annals.1440.011

Burke, D. M., & Shafto, M. A. (2004). Aging and Language Production. *Curr Dir Psychol Sci, 13*(1), 21-24. doi: 10.1111/j.0963-7214.2004.01301006.x

Burke, D. M., & Shafto, M. A. (2008). Language and aging. In F. I. M. Craik & T. A. Salthouse (Eds.), *The handbook of aging and cognition* (pp. 373-443). New York: Psychology Press.

Cabeza, R. (2002). Hemispheric asymmetry reduction in older adults: the HAROLD model. *Psychol Aging, 17*(1), 85-100.

Cabeza, R., Anderson, N. D., Locantore, J. K., & McIntosh, A. R. (2002). Aging gracefully: compensatory brain activity in high-performing older adults. *Neuroimage, 17*(3), 1394-1402.

Cabeza, R., Daselaar, S. M., Dolcos, F., Prince, S. E., Budde, M., & Nyberg, L. (2004). Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval. *Cereb Cortex, 14*(4), 364-375.

Cabeza, R., Mangels, J., Nyberg, L., Habib, R., Houle, S., McIntosh, A. R., & Tulving, E. (1997). Brain Regions Differentially Involved in Remembering What and When: a PET Study. *Neuron, 19*(4), 863-870. doi: http://dx.doi.org/10.1016/S0896-6273(00)80967-8

Calvert, G. A., Brammer, M. J., Morris, R. G., Williams, S. C., King, N., & Matthews, P. M. (2000). Using fMRI to study recovery from acquired dysphasia. *Brain & Language, 71*(3), 391-399. doi: 10.1006/brln.1999.2272

Cao, Y., Vikingstad, E. M., George, K. P., Johnson, A. F., & Welch, K. M. (1999). Cortical language activation in stroke patients recovering from aphasia with functional MRI. *Stroke, 30*(11), 2331-2340.

Caplan, D., Michaud, J., & Hufford, R. (2013). Short-term memory, working memory, and syntactic comprehension in aphasia. *Cogn Neuropsychol, 30*(2), 77-109. doi: 10.1080/02643294.2013.803958

Cappa, S. F. (1998). Spontaneous Recovery from Aphasia. In B. W. Stemmer, H (Ed.), *Handbook of Neurolinguistics* (pp. 536- 544). California: Academic Press.

Cappa, S. F. (2008). Spontaneous Recovery of Aphasia. In B. W. Stemmer, H (Ed.), *Handbook of the Neuroscience of Language*. London: Academic Press.

Cappa, S. F., Perani, D., Grassi, F., Bressi, F., Alberoni, M., Franceschi, M., . . . Fazio, M. (1997). A PET Follow-up Study of Recovery after Stroke in Acute Aphasics. *Brain and Language, 56*(1), 55-67. doi: http://dx.doi.org/10.1006/brln.1997.1737

Cappa, S. F., Perani, D., Schnur, T., Tettamanti, M., & Fazio, F. (1998). The effects of semantic category and knowledge type on lexical-semantic access: a PET study. *Neuroimage, 8*(4), 350-359.

Cardebat, D., Demonet, J. F., De Boissezon, X., Marie, N., Marie, R. M., Lambert, J., . . . Puel, M. (2003). Behavioral and neurofunctional changes over time in healthy and aphasic subjects: a PET Language Activation Study. *Stroke, 34*(12), 2900-2906.

Carrera, E., & Tononi, G. (2014). Diaschisis: past, present, future. *Brain, 137*(Pt 9), 2408-2422. doi: 10.1093/brain/awu101

Caspers, S., Geyer, S., Schleicher, A., Mohlberg, H., Amunts, K., & Zilles, K. (2006). The human inferior parietal cortex: cytoarchitectonic parcellation and interindividual variability. *Neuroimage, 33*(2), 430-448. doi: 10.1016/j.neuroimage.2006.06.054

Coltheart, M., Patterson, K., & Marshall, J. (Eds.). (1980). *Deep dyslexia*. London: Routledge & Kegan Paul.

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and biomedical research, an international journal, 29*(3), 162-173.

Crinion, J., Holland, A., Copland, D., Thompson, C. K., & Hillis, A. (2013). Quantifying Brain Lesions in Neuroimaging Research Examining Language Recovery after Stroke. *Neuroimage, 73*, 208-214. doi: 10.1016/j.neuroimage.2012.07.044

Crinion, J., & Leff, A. (2007). Recovery and treatment of aphasia after stroke: functional imaging studies. *Current Opinion in Neurology, 20*(6), 667-673.

Crinion, J., & Leff, A. P. (2015). Using functional imaging to understand therapeutic effects in poststroke aphasia. *Current Opinion in Neurology, 28*(4), 330-337. doi: 10.1097/wco.0000000000000217

Crinion, J., & Price, C. J. (2005). Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. *Brain, 128*(Pt 12), 2858-2871.

Crinion, J., Warburton, E., Lambon-Ralph, M., Howard, D., & Wise, R. (2006). Listening to narrative speech after aphasic stroke: the role of the left anterior temporal lobe. *Cereb Cortex, 16*(8), 1116-1125.

Crosson, B., McGregor, K., Gopinath, K., Conway, T., Benjamin, M., Chang, Y., . . . Sherod, M. (2007). Functional MRI of language in aphasia: a review of the literature and the methodological challenges. *Neuropsychol Rev, 17*. doi: 10.1007/s11065-007-9024-z

Crosson, B., Moore, A., McGregor, K., Chang, Y., Benjamin, M., Gopinath, K., . . . Briggs, R. (2009). Regional changes in word-production laterality after a naming treatment designed to produce a rightward shift in frontal activity. *Brain & Language, 111*. doi: 10.1016/j.bandl.2009.08.001

Crutch, S. J., & Warrington, E. K. (2005). Abstract and concrete concepts have structurally different representational frameworks. *Brain, 128*(Pt 3), 615-627. doi: 10.1093/brain/awh349

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: a challenge for neuroimaging. *Nat Rev Neurosci, 4*(11), 863-872.

D'Esposito, M., Detre, J. A., Aguirre, G. K., Stallcup, M., Alsop, D. C., Tippet, L. J., & Farah, M. J. (1997). A functional MRI study of mental image generation. *Neuropsychologia, 35*(5), 725-730.

Dabul, B. L. (2000). *Apraxia Battery for Adults - 2 (ABA-2)* (Second Edition ed.). Austin, Tex: Pro-Ed.

Davis, C. J. (2005). N-watch: a program for deriving neighborhood size and other psycholinguistic statistics. *Behav Res Methods, 37*(1), 65-70.

Davis, M. H., & Gaskell, M. G. (2009). A complementary systems account of word learning: neural and behavioural evidence. *Philos Trans R Soc Lond B Biol Sci, 364*(1536), 3773-3800.

Davis, M. H., & Johnsrude, I. S. (2003). Hierarchical processing in spoken language comprehension. *Journal of Neuroscience, 23*(8), 3423-3431.

de Boissezon, X., Demonet, J. F., Puel, M., Marie, N., Raboyeau, G., Albucher, J. F., . . . Cardebat, D. (2005). Subcortical aphasia: a longitudinal PET study. *Stroke, 36*(7), 1467-1473.

Deloitte Access Economics. (2013). The economic impact of stroke in Australia. Melbourne: National Stroke Foundation.

Deloitte Access Economics. (2014). Stroke in Australia: No postcode untouched. Melbourne: National Stroke Foundation.

Demonet, J. F., Chollet, F., Ramsay, S., Cardebat, D., Nespoulous, J. L., Wise, R., . . . Frackowiak, R. (1992). The anatomy of phonological and semantic processing in normal subjects. *Brain, 115 (Pt 6)*, 1753-1768.
Demonet, J. F., Thierry, G., & Cardebat, D. (2005). Renewal of the neurophysiology of language: functional neuroimaging. *Physiol Rev, 85*(1), 49-95.
Diaz, M. T., Johnson, M. A., Burke, D. M., & Madden, D. J. (2014). Age-related differences in the neural bases of phonological and semantic processes. *J Cogn Neurosci, 26*(12), 2798-2811. doi: 10.1162/jocn_a_00665
Dignam, J., Copland, D., McKinnon, E., Burfein, P., O'Brien, K., Farrell, A., & Rodriguez, A. D. (2015). Intensive Versus Distributed Aphasia Therapy: A Nonrandomized, Parallel-Group, Dosage-Controlled Study. *Stroke, 46*(8), 2206-2211. doi: 10.1161/strokeaha.115.009522
Dosenbach, N. U., Fair, D. A., Miezin, F. M., Cohen, A. L., Wenger, K. K., Dosenbach, R. A., . . . Petersen, S. E. (2007). Distinct brain networks for adaptive and stable task control in humans. *Proc Natl Acad Sci U S A, 104*(26), 11073-11078. doi: 10.1073/pnas.0704320104
Dronkers, N. F. (1996). A new brain region for coordinating speech articulation. *Nature, 384*(6605), 159-161. doi: 10.1038/384159a0
Dronkers, N. F., & Ludy, C. (1997). Lesion analysis in clinical research. In B. W. Stemmer, H (Ed.), *Handbook of Neurolinguistics* (pp. 173 - 187). San Diego: Singular Press.
Eickhoff, S. B., Paus, T., Caspers, S., Grosbras, M. H., Evans, A. C., Zilles, K., & Amunts, K. (2007). Assignment of functional activations to probabilistic cytoarchitectonic areas revisited. *Neuroimage, 36*(3), 511-521. doi: 10.1016/j.neuroimage.2007.03.060
El Hachioui, H., Lingsma, H. F., van de Sandt-Koenderman, M. E., Dippel, D. W., Koudstaal, P. J., & Visch-Brink, E. G. (2013). Recovery of aphasia after stroke: a 1-year follow-up study. *Journal of Neurology, 260*(1), 166-171. doi: 10.1007/s00415-012-6607-2
Enderby, P., Wood, V. A., Wade, D. T., & Hewer, R. L. (1987). Aphasia after stroke: a detailed study of recovery in the first 3 months. *Int Rehabil Med, 8*(4), 162-165.
Evans, G. A., Lambon Ralph, M. A., & Woollams, A. M. (2012). What's in a word? A parametric study of semantic influences on visual word recognition. *Psychon Bull Rev, 19*(2), 325-331. doi: 10.3758/s13423-011-0213-7
Falquez, R., Couto, B., Ibanez, A., Freitag, M. T., Berger, M., Arens, E. A., . . . Barnow, S. (2014). Detaching from the negative by reappraisal: the role of right superior frontal gyrus (BA9/32). *Frontiers in Behavioral Neuroscience, 8*, 165. doi: 10.3389/fnbeh.2014.00165
Feeney, D. M., & Baron, J. C. (1986). Diaschisis. *Stroke, 17*(5), 817-830.
Fernandez, B., Cardebat, D., Demonet, J., Joseph, P., Mazaux, J., Barat, M., & Allard, M. (2004). Functional MRI follow-up study of language processes in healthy subjects and during recovery in a case of aphasia. *Stroke, 35*. doi: 10.1161/01.STR.0000139323.76769.b0
Ferreira, R. A., Gobel, S. M., Hymers, M., & Ellis, A. W. (2015). The neural correlates of semantic richness: evidence from an fMRI study of word learning. *Brain & Language, 143*, 69-80. doi: 10.1016/j.bandl.2015.02.005
Fiebach, C. J., & Friederici, A. D. (2004). Processing concrete words: fMRI evidence against a specific right-hemisphere involvement. *Neuropsychologia, 42*(1), 62-70. doi: 10.1016/s0028-3932(03)00145-3
Fjell, A. M., Walhovd, K. B., Fennema-Notestine, C., McEvoy, L. K., Hagler, D. J., Holland, D., . . . Dale, A. M. (2009). One-year brain atrophy evident in healthy aging. *The Journal of Neuroscience, 29*(48), 15223-15231.
Fliessbach, K., Weis, S., Klaver, P., Elger, C. E., & Weber, B. (2006). The effect of word concreteness on recognition memory. *Neuroimage, 32*(3), 1413-1421. doi: 10.1016/j.neuroimage.2006.06.007
Folstein, M. F., Folstein, S. E., & McHugh, P. R. (1975). "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res, 12*(3), 189-198.
Forkel, S. J., Thiebaut de Schotten, M., Dell'Acqua, F., Kalra, L., Murphy, D. G., Williams, S. C., & Catani, M. (2014). Anatomical predictors of aphasia recovery: a tractography study of

bilateral perisylvian language networks. *Brain, 137*(Pt 7), 2027-2039. doi: 10.1093/brain/awu113
Franklin, S. (1989). Dissociations in Auditory Word Comprehension - Evidence from 9 Fluent Aphasic Patients. *Aphasiology, 3*(3), 189-207. doi: 10.1080/02687038908248991
Franklin, S., Turner, J. E., Lambon Ralph, M. A., Morris, J., & Bailey, P. (1996). A distinctive case of word meaning deafness? *Cognitive Neuropsychology, 13*, 1139 - 1162.
Frauenfelder, U. H., & Tyler, L. K. (1987). The process of spoken word recognition: an introduction. *Cognition, 25*(1-2), 1-20.
Freire, L., Roche, A., & Mangin, J. F. (2002). What is the best similarity measure for motion correction in fMRI time series? *IEEE transactions on medical imaging, 21*(5), 470-484.
Fridriksson, J. (2010). Preservation and modulation of specific left hemisphere regions is vital for treated recovery from anomia in stroke. *Journal of Neuroscience, 30*(35), 11558-11564. doi: 10.1523/jneurosci.2227-10.2010
Fridriksson, J., Bonilha, L., Baker, J. M., Moser, D., & Rorden, C. (2010). Activity in Preserved Left Hemisphere Regions Predicts Anomia Severity in Aphasia. *Cerebral Cortex, 20*(5), 1013-1019. doi: 10.1093/cercor/bhp160
Fridriksson, J., Holland, A. L., Coull, B. M., Plante, E., Trouard, T. P., & Beeson, P. (2002). Aphasia severity: Association with cerebral perfusion and diffusion. *Aphasiology, 16*(9), 859-871. doi: 10.1080/02687030244000347
Fridriksson, J., Richardson, J. D., Fillmore, P., & Cai, B. (2012). Left Hemisphere Plasticity and Aphasia Recovery. *Neuroimage, 60*(2), 854-863. doi: 10.1016/j.neuroimage.2011.12.057
Friederici, A. D. (2011). The brain basis of language processing: from structure to function. *Physiol Rev, 91*(4), 1357-1392. doi: 10.1152/physrev.00006.2011
Friederici, A. D. (2012). The cortical language circuit: from auditory perception to sentence comprehension. *Trends Cogn Sci, 16*(5), 262-268. doi: 10.1016/j.tics.2012.04.001
Friederici, A. D., Opitz, B., & von Cramon, D. Y. (2000). Segregating semantic and syntactic aspects of processing in the human brain: an fMRI investigation of different word types. *Cerebral Cortex, 10*(7), 698-705. doi: 10.1093/cercor/10.7.698
Friston, K. (2007). Statistical parametric mapping. *Statistical Parametric Mapping: The Analysis of Functional Brain Images*, 10-31. doi: 10.1016/B978-012372560-8/50002-4
Geranmayeh, F., Brownsett, S. L. E., & Wise, R. J. S. (2014). Task-induced brain activity in aphasic stroke patients: what is driving recovery? *Brain*.
Geva, S., Jones, P. S., Crinion, J., Price, C., Baron, J.-C., & Warburton, E. A. (2012). The Effect of Aging on the Neural Correlates of Phonological Word Retrieval. *Journal of Cognitive Neuroscience, 24*(11), 2135-2146. doi: 10.1162/jocn_a_00278
Giraud, A. L., Kell, C., Thierfelder, C., Sterzer, P., Russ, M. O., Preibisch, C., & Kleinschmidt, A. (2004). Contributions of sensory input, auditory search and verbal comprehension to cortical activity during speech processing. *Cereb Cortex, 14*(3), 247-255.
Glasser, M. F., & Rilling, J. K. (2008). DTI tractography of the human brain's language pathways. *Cereb Cortex, 18*(11), 2471-2482.
Godecke, E., Ciccone, N. A., Granger, A. S., Rai, T., West, D., Cream, A., . . . Hankey, G. J. (2014). A comparison of aphasia therapy outcomes before and after a Very Early Rehabilitation programme following stroke. *Int J Lang Commun Disord, 49*(2), 149-161. doi: 10.1111/1460-6984.12074
Gold, B. T., Andersen, A. H., Jicha, G. A., & Smith, C. D. (2009). Aging Influences the Neural Correlates of Lexical Decision but Not Automatic Semantic Priming. *Cerebral Cortex, 19*(11), 2671-2679. doi: 10.1093/cercor/bhp018
Gold, B. T., Balota, D. A., Jones, S. J., Powell, D. K., Smith, C. D., & Andersen, A. H. (2006). Dissociation of automatic and strategic lexical-semantics: functional magnetic resonance imaging evidence for differing roles of multiple frontotemporal regions. *Journal of Neuroscience, 26*(24), 6523-6532. doi: 10.1523/jneurosci.0808-06.2006

Goodglass, H., Hyde, M. R., & Blumstein, S. (1969). Frequency, picturability and availability of nouns in aphasia. *Cortex, 5*(2), 104-119. doi: 10.1016/S0010-9452(69)80022-5
Grady, C. L. (2008). Cognitive neuroscience of aging. *Ann N Y Acad Sci, 1124*, 127-144. doi: 10.1196/annals.1440.009
Grady, C. L., & Kapur, S. (1999). The use of neuroimaging in neurorehabilitative research. In D. T. Stuss, G. Winocur & I. H. Robertson (Eds.), *Cognitive neurorehabilitation* (pp. 47–58). New York, NY, US: Cambridge University Press.
Grafman, J. (2000). Conceptualizing functional neuroplasticity. *J Commun Disord, 33*(4), 345-355.
Grafman, J., & Litvan, I. (1999). Evidence for Four Forms of Neuroplasticity. In J. Grafman & Y. Christen (Eds.), *Neuronal Plasticity: Building a Bridge from the Laboratory to the Clinic* (pp. 131-139). Berlin, Heidelberg: Springer Berlin Heidelberg.
Grainger, J., & Jacobs, A. M. (1996). Orthographic processing in visual word recognition: a multiple read-out model. *Psychol Rev, 103*(3), 518-565.
Grossman, M., Koenig, P., DeVita, C., Glosser, G., Alsop, D., Detre, J., & Gee, J. (2002). The neural basis for category-specific knowledge: An fMRI study. *Neuroimage, 15*(4), 936-948. doi: 10.1006/nimg.2001.1028
Hagmann, P., Cammoun, L., Gigandet, X., Meuli, R., Honey, C. J., Wedeen, V. J., & Sporns, O. (2008). Mapping the structural core of human cerebral cortex. *PLoS Biol, 6*(7), e159. doi: 10.1371/journal.pbio.0060159
Hahn, B., Ross, T. J., & Stein, E. A. (2007). Cingulate activation increases dynamically with response speed under stimulus unpredictability. *Cereb Cortex, 17*(7), 1664-1671. doi: 10.1093/cercor/bhl075
Hampson, M., Driesen, N. R., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Brain connectivity related to working memory performance. *Journal of Neuroscience, 26*(51), 13338-13343. doi: 10.1523/jneurosci.3408-06.2006
Harley, T. (2000). *The psychology of language. From data to theory.* . Hove: Psychology Press.
Heath, S., McMahon, K. L., Nickels, L., Angwin, A., MacDonald, A. D., van Hees, S., . . . Copland, D. A. (2012). Neural mechanisms underlying the facilitation of naming in aphasia using a semantic task: an fMRI study. *BMC Neuroscience, 13*(1), 1-19. doi: 10.1186/1471-2202-13-98
Heath, S., McMahon, K. L., Nickels, L., Angwin, A., MacDonald, A. D., van Hees, S., . . . Copland, D. A. (2013). Facilitation of naming in aphasia with auditory repetition: an investigation of neurocognitive mechanisms. *Neuropsychologia, 51*(8), 1534-1548. doi: 10.1016/j.neuropsychologia.2013.05.008
Heiss, W. D., Kessler, J., Thiel, A., Ghaemi, M., & Karbe, H. (1999). Differential capacity of left and right hemispheric areas for compensation of poststroke aphasia. *Annals of Neurology, 45*(4), 430-438.
Heiss, W. D., & Thiel, A. (2006). A proposed regional hierarchy in recovery of post-stroke aphasia. *Brain & Language, 98*(1), 118-123. doi: 10.1016/j.bandl.2006.02.002
Herbster, A. N., Mintun, M. A., Nebes, R. D., & Becker, J. T. (1997). Regional cerebral blood flow during word and nonword reading. *Hum Brain Mapp, 5*(2), 84-92.
Hickok, G. (2009). The functional neuroanatomy of language. *Physics of Life Reviews, 6*(3), 121-143. doi: 10.1016/j.plrev.2009.06.001
Hickok, G., & Poeppel, D. (2007). The cortical organization of speech processing. *Nat Rev Neurosci, 8*(5), 393-402. doi: 10.1038/nrn2113
Hillary, F. G., & DeLuca, J. (Eds.). (2007, 31). *Functional Neuroimaging in Clinical Populations*. New York: The Guilford Press.
Hillary, F. G., Slocomb, J., Hills, E. C., Fitzpatrick, N. M., Medaglia, J. D., Wang, J., . . . Wylie, G. R. (2011). Changes in resting connectivity during recovery from severe traumatic brain injury. *International Journal of Psychophysiology, 82*(1), 115-123. doi: 10.1016/j.ijpsycho.2011.03.011

Hillis, A. E. (1998). Treatment of naming disorders: new issues regarding old therapies. *Journal of the International Neuropsychological Society, 4*(6), 648-660.
Hillis, A. E. (2005). Can shift to the right be a good thing? *Annals of Neurology, 58*(3), 346-348.
Hillis, A. E. (2007). Magnetic resonance perfusion imaging in the study of language. *Brain & Language, 102*(2), 165-175. doi: 10.1016/j.bandl.2006.04.016
Hillis, A. E., Barker, P., Beauchamp, N., Gordon, B., & Wityk, R. (2000). MR perfusion imaging reveals regions of hypoperfusion associated with aphasia and neglect. *Neurology, 55*(6), 782-788.
Hillis, A. E., Barker, P., Wityk, R., Aldrich, E., Restrepo, L., Breese, E., & Work, M. (2004). Variability in subcortical aphasia is due to variable sites of cortical hypoperfusion. *Brain & Language, 89*(3), 524-530.
Hillis, A. E., Gold, L., Kannan, V., Cloutman, L., Kleinman, J., Newhart, M., . . . Gottesman, R. (2008). Site of the ischemic penumbra as a predictor of potential for recovery of functions. *Neurology, 71*(3), 184-189.
Hillis, A. E., & Heidler, J. (2002). Mechanisms of early aphasia recovery. *Aphasiology, 16*(9), 885-895. doi: 10.1080/0268703
Hillis, A. E., Kane, A., Tuffiash, E., Ulatowski, J., Barker, P., Beauchamp, N., & Wityk, R. (2001). Reperfusion of specific brain regions by raising blood pressure restores selective language functions in subacute stroke. *Brain & Language, 79*(3), 495-510. doi: 10.1006/brln.2001.2563
Hillis, A. E., Kleinman, J., Newhart, M., Heidler-Gary, J., Gottesman, R., Barker, P., . . . Chaudhry, P. (2006). Restoring cerebral blood flow reveals neural regions critical for naming. *Journal of Neuroscience, 26*(31), 8069-8073.
Hillis, A. E., Vimal, S., Newhart, M., Aldrich, E., Heidler, J., & Ken, L. (2005). Reperfusion of selective areas is associated with improved naming in acute stroke. *Brain and Language, 95*(1), 100-101. doi: http://dx.doi.org/10.1016/j.bandl.2005.07.055
Hillis, A. E., Wityk, R., Tuffiash, E., Beauchamp, N., Jacobs, M., Barker, P., & Selnes, O. (2001). Hypoperfusion of Wernicke's area predicts severity of semantic deficit in acute stroke. *Annals of Neurology, 50*(5), 561-566.
Hoeller, M., Krings, T., Reinges, M. H., Hans, F. J., Gilsbach, J. M., & Thron, A. (2002). Movement artefacts and MR BOLD signal increase during different paradigms for mapping the sensorimotor cortex. *Acta Neurochir (Wien), 144*(3), 279-284; discussion 284. doi: 10.1007/s007010200036
Hoffman, P. (2015). The meaning of 'life' and other abstract words: Insights from neuropsychology. *J Neuropsychol*. doi: 10.1111/jnp.12065
Hoffman, P., & Lambon Ralph, M. A. (2011). Reverse Concreteness Effects Are Not a Typical Feature of Semantic Dementia: Evidence for the Hub-and-Spoke Model of Conceptual Representation. *Cerebral Cortex, 21*(9), 2103-2112. doi: 10.1093/cercor/bhq288
Hoffmann, M. (2008). Isolated right temporal lobe stroke patients present with Geschwind Gastaut syndrome, frontal network syndrome and delusional misidentification syndromes. *Behavioural Neurology, 20*(3), 83-89.
Holcomb, P. J., Kounios, J., Anderson, J. E., & West, W. C. (1999). Dual-coding, context-availability, and concreteness effects in sentence comprehension: an electrophysiological investigation. *Journal of experimental psychology. Learning, memory, and cognition, 25*(3), 721-742.
Holland, A. L., Fromm, D. S., DeRuyter, F., & Stein, M. (1996). Treatment efficacy: aphasia. *J Speech Hear Res, 39*(5), S27-36.
Howard, D., & Franklin, S. (1988). *Missing the meaning?* Cambridge, MA: MIT Press.
Howard, D., & Patterson, K. (1992). *The pyramids and palm trees test: a test of semantic accesss from words and pictures*. Bury St Edmunds: Thames Valley Test Company.
Huang, H.-W., Meyer, A. M., & Federmeier, K. D. (2012). A “concrete view” of aging: Event related potentials reveal age-related changes in basic integrative processes in language.

Neuropsychologia, 50(1), 26-35. doi: http://dx.doi.org/10.1016/j.neuropsychologia.2011.10.018
Huynh, H., & Feldt, L. S. (1970). Conditions Under Which Mean Square Ratios in Repeated Measurements Designs Have Exact F-Distributions. *Journal of the American Statistical Association, 65*(332), 1582-1589. doi: 10.2307/2284340
Indefrey, P., & Levelt, W. J. (2004). The spatial and temporal signatures of word production components. *Cognition, 92*(1-2), 101-144. doi: 10.1016/j.cognition.2002.06.001
Jackson, R. L., Hoffman, P., & Pobric, G. (2016). The Semantic Network at Work and Rest: Differential Connectivity of Anterior Temporal Lobe Subregions. *36*(5), 1490-1501. doi: 10.1523/jneurosci.2999-15.2016
Jafri, M. J., Pearlson, G. D., Stevens, M., & Calhoun, V. D. (2008). A method for functional network connectivity among spatially independent resting-state components in schizophrenia. *Neuroimage, 39*(4), 1666-1681. doi: 10.1016/j.neuroimage.2007.11.001
James, C. T. (1975). The role of semantic information in lexical decisions. *Journal of Experimental Psychology: Human Perception and Performance, 1*(2), 130-136. doi: 10.1037/0096-1523.1.2.130
Jarso, S., Li, M., Faria, A., Davis, C., Leigh, R., Sebastian, R., . . . Hillis, A. E. (2013). Distinct mechanisms and timing of language recovery after stroke. *Cogn Neuropsychol, 30*(7-8), 454-475. doi: 10.1080/02643294.2013.875467
Jefferies, E., Patterson, K., Jones, R. W., & Lambon Ralph, M. A. (2009). Comprehension of concrete and abstract words in semantic dementia. *Neuropsychology, 23*(4), 492-499. doi: 10.1037/a0015452
Jessen, F., Heun, R., Erb, M., Granath, D. O., Klose, U., Papassotiropoulos, A., & Grodd, W. (2000). The concreteness effect: evidence for dual coding and context availability. *Brain & Language, 74*(1), 103-112. doi: 10.1006/brln.2000.2340
Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *Boston Naming Test.* Philadelphia: Lea & Febiger.
Kay, J., Lesser, R., & Coltheart, M. (1992). *PALPA: Psycholinguistic Assessments of Language Processing in Aphasia.* London: Lawrence Erlbaum Associates.
Kemper, S., & Sumner, A. (2001). The structure of verbal abilities in young and older adults. *Psychol Aging, 16*(2), 312-322.
Kennerley, S. W., Walton, M. E., Behrens, T. E. J., Buckley, M. J., & Rushworth, M. F. S. (2006). Optimal decision making and the anterior cingulate cortex. *Nat Neurosci, 9*(7), 940-947. doi: http://www.nature.com/neuro/journal/v9/n7/suppinfo/nn1724_S1.html
Kertesz, A. (1988). What do we learn from recovery from aphasia? *Adv Neurol, 47*, 277-292.
Kertesz, A. (1989). Hemispheric dominance: its development and relation to speech disorders. *Folia Phoniatr (Basel), 41*(2-3), 61-88.
Kertesz, A. (2007). *The Western aphasia battery.* San Antonio: PsychCorp.
Kertesz, A., Lau, W. K., & Polk, M. (1993). The structural determinants of recovery in Wernicke's aphasia. *Brain & Language, 44*(2), 153-164. doi: 10.1006/brln.1993.1010
Kertesz, A., & McCabe, P. (1977). Recovery patterns and prognosis in aphasia. *Brain, 100 (Pt 1)*, 1-18.
Kiehl, K. A., Liddle, P. F., Smith, A. M., Mendrek, A., Forster, B. B., & Hare, R. D. (1999). Neural pathways involved in the processing of concrete and abstract words. *Hum Brain Mapp, 7*(4), 225-233.
Kinsbourne, M. (1971). The minor cerebral hemisphere as a source of aphasic speech. *Archives of Neurology, 25*(4), 302-306.
Kiran, S. (2012). What Is the Nature of Poststroke Language Recovery and Reorganization? *ISRN Neurology, 2012*, 786872. doi: 10.5402/2012/786872
Knopman, D. S., Selnes, O. A., Niccum, N., Rubens, A. B., Yock, D., & Larson, D. (1983). A longitudinal study of speech fluency in aphasia: CT correlates of recovery and persistent nonfluency. *Neurology, 33*(9), 1170-1178.

Kotz, S. A., Cappa, S. F., von Cramon, D. Y., & Friederici, A. D. (2002). Modulation of the lexical-semantic network by auditory semantic priming: an event-related functional MRI study. *Neuroimage, 17*(4), 1761-1772.

Kousta, S. T., Vigliocco, G., Vinson, D. P., Andrews, M., & Del Campo, E. (2011). The representation of abstract words: why emotion matters. *J Exp Psychol Gen, 140*(1), 14-34. doi: 10.1037/a0021446

Krainik, A., Hund-Georgiadis, M., Zysset, S., & von Cramon, D. Y. (2005). Regional impairment of cerebrovascular reactivity and BOLD signal in adults after stroke. *Stroke, 36*(6), 1146-1152.

Kreisler, A., Godefroy, O., Delmaire, C., Debachy, B., Leclercq, M., Pruvo, J. P., & Leys, D. (2000). The anatomy of aphasia revisited. *Neurology, 54*(5), 1117-1123.

Kroll, J. F., & Merves, J. S. (1986). Lexical access for concrete and abstract words. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 12*(1), 92-107. doi: 10.1037/0278-7393.12.1.92

Kruskal, W. H., & Wallis, W. A. (1952). Use of Ranks in One-Criterion Variance Analysis. *Journal of the American Statistical Association, 47*(260), 583-621. doi: 10.1080/01621459.1952.10483441

Kümmerer, D., Hartwigsen, G., Kellmeyer, P., Glauche, V., Mader, I., Klöppel, S., . . . Saur, D. (2013). Damage to ventral and dorsal language pathways in acute aphasia. *Brain, 136*(2), 619-629.

Kurland, J., Naeser, M. A., Baker, E. H., Doron, K., Martin, P. I., Seekins, H. E., . . . Yurgelun-Todd, D. (2004). Test-retest reliability of fMRI during nonverbal semantic decisions in moderate-severe nonfluent aphasia patients. *Behav Neurol, 15*(3-4), 87-97.

Lambon Ralph, M. A., Lowe, C., & Rogers, T. T. (2007). Neural basis of category-specific semantic deficits for living things: evidence from semantic dementia, HSVE and a neural network model. *Brain, 130*(4), 1127-1137. doi: 10.1093/brain/awm025

Laska, A. C., Hellblom, A., Murray, V., Kahan, T., & Von Arbin, M. (2001). Aphasia in acute stroke and relation to outcome. *Journal of Internal Medicine, 249*(5), 413-422.

Lazar, R. M., & Antoniello, D. (2008). Variability in recovery from aphasia. *Current Neurology and Neuroscience Reports, 8*(6), 497-502.

Lazar, R. M., Marshall, R. S., Pile-Spellman, J., Duong, H. C., Mohr, J. P., Young, W. L., . . . DeLaPaz, R. L. (2000). Interhemispheric transfer of language in patients with left frontal cerebral arteriovenous malformation. *Neuropsychologia, 38*(10), 1325-1332.

Lazar, R. M., Minzer, B., Antoniello, D., Festa, J. R., Krakauer, J. W., & Marshall, R. S. (2010). Improvement in aphasia scores after stroke is well predicted by initial severity. *Stroke, 41*(7), 1485-1488.

Lazar, R. M., Speizer, A. E., Festa, J. R., Krakauer, J. W., & Marshall, R. S. (2008). Variability in language recovery after first-time stroke. *Journal of Neurology, Neurosurgery & Psychiatry, 79*(5), 530-534.

Lee, A., Kannan, V., & Hillis, A. E. (2006). The Contribution of Neuroimaging to the Study of Language and Aphasia. *Neuropsychology Review, 16*(4), 171-183.

Leech, R., Braga, R., & Sharp, D. J. (2012). Echoes of the brain within the posterior cingulate cortex. *Journal of Neuroscience, 32*(1), 215-222. doi: 10.1523/jneurosci.3689-11.2012

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain, 137*(Pt 1), 12-32. doi: 10.1093/brain/awt162

Léger, A., Démonet, J., Ruff, S., Aithamon, B., Touyeras, B., Puel, M., . . . Cardebat, D. (2002). Neural substrates of spoken language rehabilitation in an aphasic patient: an fMRI study. *Neuroimage, 17*. doi: 10.1006/nimg.2002.1238

Li, S.-C., & Lindenberger, U. (1999). Cross-level unification: A computational exploration of the link between deterioration of neurotransmitter systems and dedifferentiation of cognitive abilities in old age. In L. G. N. H. J. Markowitsch (Ed.), *Cognitive neuroscience of memory* (pp. 103-146). Ashland, OH, US: Hogrefe & Huber Publishers.

Lindenberger, U., & Baltes, P. B. (1994). Sensory functioning and intelligence in old age: a strong connection. *Psychol Aging, 9*(3), 339-355.
Lovstad, M., Funderud, I., Meling, T., Kramer, U. M., Voytek, B., Due-Tonnessen, P., . . . Solbakk, A. K. (2012). Anterior cingulate cortex and cognitive control: neuropsychological and electrophysiological findings in two patients with lesions to dorsomedial prefrontal cortex. *Brain Cogn, 80*(2), 237-249. doi: 10.1016/j.bandc.2012.07.008
Luce, P. A., & Large, N. R. (2001). Phonotactics, density, and entropy in spoken word recognition. *Language and Cognitive Processes, 16*(5), 565 - 581.
Luders, H., Lesser, R. P., Hahn, J., Dinner, D. S., Morris, H. H., Wyllie, E., & Godoy, J. (1991). Basal temporal language area. *Brain, 114 (Pt 2)*, 743-754.
Macoir, J. (2009). Is a plum a memory problem? Longitudinal study of the reversal of concreteness effect in a patient with semantic dementia. *Neuropsychologia, 47*(2), 518-535. doi: 10.1016/j.neuropsychologia.2008.10.006
Madden, D. J. (1992). Four to Ten Milliseconds Per Year: Age-Related Slowing of Visual Word Identification. *Journal of Gerontology, 47*(2), P59-P68. doi: 10.1093/geronj/47.2.P59
Madden, D. J., Spaniol, J., Costello, M. C., Bucur, B., White, L. E., Cabeza, R., . . . Huettel, S. A. (2009). Cerebral White Matter Integrity Mediates Adult Age Differences in Cognitive Performance. *Journal of Cognitive Neuroscience, 21*(2), 289-302. doi: 10.1162/jocn.2009.21047
Maldjian, J. A., Laurienti, P. J., & Burdette, J. H. (2004). Precentral gyrus discrepancy in electronic versions of the Talairach atlas. *Neuroimage, 21*(1), 450-455.
Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage, 19*(3), 1233-1239.
Marcotte, K., Perlbarg, V., Marrelec, G., Benali, H., & Ansaldo, A. I. (2013). Default-mode network functional connectivity in aphasia: Therapy-induced neuroplasticity. *Brain and Language, 124*(1), 45-55. doi: http://dx.doi.org/10.1016/j.bandl.2012.11.004
Marsh, E., & Hillis, A. E. (2006). Recovery from aphasia following brain injury: the role of reorganization. *Prog Brain Res, 157*, 143-156.
Marsh, E., & Hillis, A. E. (2008). Dissociation between egocentric and allocentric visuospatial and tactile neglect in acute stroke. *Cortex, 44*(9), 1215-1220.
Marslen-Wilson, W., & Warren, P. (1994). Levels of perceptual representation and process in lexical access: words, phonemes, and features. *Psychol Rev, 101*(4), 653-675.
Marslen-Wilson, W. D. (1987). Functional parallelism in spoken word-recognition. *Cognition, 25*(1-2), 71-102.
Martin, N., Saffran, E. M., & Dell, G. S. (1996). Recovery in deep dysphasia: evidence for a relation between auditory - verbal STM capacity and lexical errors in repetition. *Brain & Language, 52*(1), 83-113. doi: 10.1006/brln.1996.0005
Martin, R. C. (2003). Language processing: functional organization and neuroanatomical basis. *Annu Rev Psychol, 54*, 55-89.
Mason, M. F., Norton, M. I., Van Horn, J. D., Wegner, D. M., Grafton, S. T., & Macrae, C. N. (2007). Wandering Minds: The Default Network and Stimulus-Independent Thought. *Science (New York, N.Y.), 315*(5810), 393-395. doi: 10.1126/science.1131295
Matthews, P. (2001). An introduction to functional magnetic resonance imaging of the brain. In P. Jezzard, P. Matthews & S. Smith (Eds.), *Functional MRI. An Introduction to the Methods*. Oxford: Oxford University Press.
Mattioli, F., Ambrosi, C., Mascaro, L., Scarpazza, C., Pasquali, P., Frugoni, M., . . . Gasparotti, R. (2014). Early Aphasia Rehabilitation Is Associated With Functional Reactivation of the Left Inferior Frontal Gyrus: A Pilot Study. *Stroke, 45*(2), 545-552. doi: 10.1161/strokeaha.113.003192

McClelland, J. L., & Rumelhart, D. (1981). An interactive activation model of context effects in letter perception: Part 1. An account of the basic findings. *Psychological Review, 88*, 375 - 407.
McMahon, K. L., Cowin, G., & Galloway, G. (2011). Magnetic Resonance Imaging: The Underlying Principles. *Journal of Orthopaedic & Sports Physical Therapy, 41*(11), 806-819. doi: doi:10.2519/jospt.2011.3576
Meinzer, M., Beeson, P. M., Cappa, S., Crinion, J., Kiran, S., Saur, D., . . . Thompson, C. K. (2013). Neuroimaging in aphasia treatment research: Consensus and practical guidelines for data analysis. *Neuroimage, 73*, 215-224. doi: 10.1016/j.neuroimage.2012.02.058
Meinzer, M., Flaisch, T., Breitenstein, C., Wienbruch, C., Elbert, T., & Rockstroh, B. (2008). Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage, 39*(4), 2038-2046.
Meinzer, M., Lahiri, A., Flaisch, T., Hannemann, R., & Eulitz, C. (2009). Opaque for the reader but transparent for the brain: neural signatures of morphological complexity. *Neuropsychologia, 47*(8-9), 1964-1971. doi: 10.1016/j.neuropsychologia.2009.03.008
Meinzer, M., Seeds, L., Flaisch, T., Harnish, S., Cohen, M. L., McGregor, K., . . . Crosson, B. (2012). Impact of changed positive and negative task-related brain activity on word-retrieval in aging. *Neurobiol Aging, 33*(4), 656-669. doi: 10.1016/j.neurobiolaging.2010.06.020
Meinzer, M., Wilser, L., Flaisch, T., Eulitz, C., Rockstroh, B., Conway, T., . . . Crosson, B. (2009). Neural signatures of semantic and phonemic fluency in young and old adults. *Journal of Cognitive Neuroscience, 21*(10), 2007-2018. doi: 10.1162/jocn.2009.21219
Mellet, E., Tzourio, N., Denis, M., & Mazoyer, B. (1998). Cortical anatomy of mental imagery of concrete nouns based on their dictionary definition. *Neuroreport, 9*(5), 803-808.
Mestres-Misse, A., Munte, T. F., & Rodriguez-Fornells, A. (2009). Functional neuroanatomy of contextual acquisition of concrete and abstract words. *J Cogn Neurosci, 21*(11), 2154-2171. doi: 10.1162/jocn.2008.21171
Mirman, D., Chen, Q., Zhang, Y., Wang, Z., Faseyitan, O. K., Coslett, H. B., & Schwartz, M. F. (2015). Neural organization of spoken language revealed by lesion-symptom mapping. *Nat Commun, 6*. doi: 10.1038/ncomms7762
Mohr, B., Difrancesco, S., Harrington, K., Evans, S., & Pulvermüller, F. (2014). Changes of right-hemispheric activation after constraint-induced, intensive language action therapy in chronic aphasia: fMRI evidence from auditory semantic processing. *Frontiers in Human Neuroscience, 8*, 919. doi: 10.3389/fnhum.2014.00919
Muñoz-Cespedes, J., Rios-Lago, M., Paul, N., & Maestu, F. (2005). Functional Neuroimaging Studies of Cognitive Recovery After Acquired Brain Damage in Adults. *Neuropsychology Review, 15*(4), 169-183.
Murty, V. P., Sambataro, F., Das, S., Tan, H.-Y., Callicott, J. H., Goldberg, T. E., . . . Mattay, V. S. (2009). Age-related Alterations in Simple Declarative Memory and the Effect of Negative Stimulus Valence. *Journal of Cognitive Neuroscience, 21*(10), 1920-1933. doi: 10.1162/jocn.2009.21130
Naeser, M. A., Helm-Estabrooks, N., Haas, G., Auerbach, S., & Srinivasan, M. (1987). Relationship between lesion extent in 'Wernicke's area' on computed tomographic scan and predicting recovery of comprehension in Wernicke's aphasia. *Archives of Neurology, 44*(1), 73-82.
Naeser, M. A., Martin, P. I., Nicholas, M., Baker, E. H., Seekins, H., Kobayashi, M., . . . Pascual-Leone, A. (2005). Improved picture naming in chronic aphasia after TMS to part of right Broca's area: an open-protocol study. *Brain & Language, 93*(1), 95-105. doi: 10.1016/j.bandl.2004.08.004
Nelson, H. E., & Wilson, J. (1991). *National Adult Reading Test (NART)*. Windsor, UK: NFER-Nelson.
Newman, S. D., & Twieg, D. (2001). Differences in auditory processing of words and pseudowords: an fMRI study. *Hum Brain Mapp, 14*(1), 39-47.

Newton, P. K., & Barry, C. (1997). Concreteness Effects in Word Production but Not Word Comprehension in Deep Dyslexia. *Cognitive Neuropsychology, 14*(4), 481-509. doi: 10.1080/026432997381457

Noppeney, U., & Price, C. J. (2004). Retrieval of abstract semantics. *Neuroimage, 22*(1), 164-170.

Noppeney, U., Price, C. J., Duncan, J. S., & Koepp, M. J. (2005). Reading skills after left anterior temporal lobe resection: an fMRI study. *Brain, 128*(Pt 6), 1377-1385.

Ogawa, S., Lee, T., Kay, A., & Tank, D. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences of the United States of America*(87), 9868-9872.

Oh, A., Duerden, E. G., & Pang, E. W. (2014). The role of the insula in speech and language processing. *Brain & Language, 135*, 96-103. doi: 10.1016/j.bandl.2014.06.003

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*(1), 97-113.

Paivio, A. (1971). *Imagery and verbal processes.* . New York: Holt, Rinehart & Winston.

Paivio, A. (1986). *Mental representations: A dual-coding approach*. New York: Oxford University Press.

Paivio, A. (1991). Dual coding theory: Retrospect and current status. *Canadian Journal of Psychology/Revue canadienne de psychologie, 45*(3), 255-287. doi: 10.1037/h0084295

Paivio, A. (2007). *Mind and Its Evolution: A Dual Coding Theoretical Debate*. Mahwah, New Jersey: Lawrence Erlbaum Associates Inc., Publishers.

Papagno, C., Capasso, R., & Miceli, G. (2009). Reversed concreteness effect for nouns in a subject with semantic dementia. *Neuropsychologia, 47*(4), 1138-1148.

Papagno, C., Capasso, R., Zerboni, H., & Miceli, G. (2007). A reverse concreteness effect in a subject with semantic dementia. *Brain and Language, 103*(1–2), 90-91. doi: 10.1016/j.bandl.2007.07.059

Papagno, C., Fogliata, A., Catricalà, E., & Miniussi, C. (2009). The lexical processing of abstract and concrete nouns. *Brain Research, 1263*, 78-86.

Park, D. C., Polk, T. A., Park, R., Minear, M., Savage, A., & Smith, M. R. (2004). Aging reduces neural specialization in ventral visual cortex. *Proc Natl Acad Sci U S A, 101*(35), 13091-13095. doi: 10.1073/pnas.0405148101

Park, D. C., & Reuter-Lorenz, P. (2009). The adaptive brain: aging and neurocognitive scaffolding. *Annu Rev Psychol, 60*, 173-196. doi: 10.1146/annurev.psych.59.103006.093656

Park, D. C., Welsh, R. C., Marshuetz, C., Gutchess, A. H., Mikels, J., Polk, T. A., . . . Taylor, S. F. (2003). Working memory for complex scenes: age differences in frontal and hippocampal activations. *J Cogn Neurosci, 15*(8), 1122-1134. doi: 10.1162/089892903322598094

Patterson, K., Nestor, P. J., & Rogers, T. T. (2007). Where do you know what you know? The representation of semantic knowledge in the human brain. *Nat Rev Neurosci, 8*(12), 976-987. doi: 10.1038/nrn2277

Payabvash, S., Kamalian, S., Fung, S., Wang, Y., Passanese, J., Souza, L. C., . . . Lev, M. H. (2010). Predicting language improvement in acute stroke patients presenting with aphasia: a multivariate logistic model using location-weighted atlas-based analysis of admission CT perfusion scans. *Ajnr: American Journal of Neuroradiology, 31*(9), 1661-1668.

Peck, K. K., Bradbury, M., Petrovich, N., Hou, B. L., Ishill, N., Brennan, C., . . . Holodny, A. I. (2009). Presurgical evaluation of language using functional magnetic resonance imaging in brain tumor patients with previous surgery. *Neurosurgery, 64*(4), 644-652; discussion 652-643. doi: 10.1227/01.neu.0000339122.01957.0a

Pedersen, P., Jorgensen, H. S., Nakayama, H., Raaschou, H. O., & Olsen, T. S. (1995). Aphasia in acute stroke: incidence, determinants, and recovery. *Annals of Neurology, 38*(4), 659-666. doi: 10.1002/ana.410380416

Pedersen, P., Vinter, & Olsen. (2004). Aphasia after Stroke: Type, Severity and Prognosis. *Cerebrovascular Diseases, 17*(1), 35-43.

Peelle, J. E., McMillan, C., Moore, P., Grossman, M., & Wingfield, A. (2004). Dissociable patterns of brain activity during comprehension of rapid and syntactically complex speech: evidence from fMRI. *Brain & Language, 91*(3), 315-325. doi: 10.1016/j.bandl.2004.05.007

Peelle, J. E., Troiani, V., Wingfield, A., & Grossman, M. (2010). Neural Processing during Older Adults' Comprehension of Spoken Sentences: Age Differences in Resource Allocation and Connectivity. *Cerebral Cortex (New York, NY), 20*(4), 773-782. doi: 10.1093/cercor/bhp142

Perani, D., Cappa, S. F., Schnur, T., Tettamanti, M., Collina, S., Rosa, M. M., & Fazio1, F. (1999). The neural correlates of verb and noun processing: A PET study. *Brain, 122*(12), 2337-2344. doi: 10.1093/brain/122.12.2337

Peters, J., & Daum, I. (2008). Differential effects of normal aging on recollection of concrete and abstract words. *Neuropsychology, 22*(2), 255-261. doi: 10.1037/0894-4105.22.2.255

Pexman, P. M., Hargreaves, I. S., Edwards, J. D., Henry, L. C., & Goodyear, B. G. (2007). Neural correlates of concreteness in semantic categorization. *J Cogn Neurosci, 19*(8), 1407-1419. doi: 10.1162/jocn.2007.19.8.1407

Power, J. D., & Petersen, S. E. (2013). Control-related systems in the human brain. *Curr Opin Neurobiol, 23*(2), 223-228. doi: 10.1016/j.conb.2012.12.009

Price, C. J. (1998). The functional anatomy of word comprehension and production. *Trends in Cognitive Sciences, 2*(8), 281-288. doi: 10.1016/S1364-6613(98)01201-7

Price, C. J. (2010). The anatomy of language: a review of 100 fMRI studies published in 2009. *Ann N Y Acad Sci, 1191*(1), 62-88. doi: 10.1111/j.1749-6632.2010.05444.x.

Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *Neuroimage, 62*(2), 816-847. doi: 10.1016/j.neuroimage.2012.04.062

Price, C. J., & Crinion, J. (2005). The latest on functional imaging studies of aphasic stroke. *Current Opinion in Neurology, 18*(4), 429-434.

Price, C. J., Crinion, J., & Friston, K. J. (2006). Design and analysis of fMRI studies with neurologically impaired patients. *J Magn Reson Imaging, 23*(6), 816-826. doi: 10.1002/jmri.20580

Price, C. J., & Friston, K. J. (1999). Scanning patients with tasks they can perform. *Human Brain Mapping, 8*(2-3), 102-108. doi: 10.1002/(SICI)1097-0193(1999)8:2/3<102::AID-HBM6>3.0.CO;2-J

Price, C. J., & Friston, K. J. (2002). Functional imaging studies of neuropsychological patients: applications and limitations. *Neurocase, 8*(5), 345-354.

Price, C. J., Mummery, C. J., Moore, C. J., Frakowiak, R. S., & Friston, K. J. (1999). Delineating necessary and sufficient neural systems with functional imaging studies of neuropsychological patients. *J Cogn Neurosci, 11*(4), 371-382.

Price, C. J., Seghier, M. L., & Leff, A. P. (2010). Predicting language outcome and recovery after stroke: the PLORAS system. *Nat Rev Neurol, 6*(4), 202-210.

Price, C. J., Warburton, E. A., Moore, C. J., Frackowiak, R. S., & Friston, K. J. (2001). Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. *J Cogn Neurosci, 13*(4), 419-429.

Productivity Commission. (2013). An Ageing Australia: Preparing for the Future *Commission Research Paper*. Canberra.

Raettig, T., & Kotz, S. A. (2008). Auditory processing of different types of pseudo-words: an event-related fMRI study. *Neuroimage, 39*(3), 1420-1428. doi: 10.1016/j.neuroimage.2007.09.030

Raz, N., Lindenberger, U., Rodrigue, K. M., Kennedy, K. M., Head, D., Williamson, A., . . . Acker, J. D. (2005). Regional brain changes in aging healthy adults: general trends, individual differences and modifiers. *Cereb Cortex, 15*(11), 1676-1689. doi: 10.1093/cercor/bhi044

Reilly, J., & Kean, J. (2007). Formal distinctiveness of high- and low-imageability nouns: analyses and theoretical implications. *Cogn Sci, 31*(1), 157-168. doi: 10.1080/03640210709336988

Reilly, J., Peelle, J. E., & Grossman, M. (2007). A unitary semantics account of reverse concreteness effects in semantic dementia. *Brain and Language, 103*(1-2), 86-87. doi: 10.1016/j.bandl.2007.07.057
Reineck, L. A., Agarwal, S., Hillis, A. E., Reineck, L. A., Agarwal, S., & Hillis, A. E. (2005). "Diffusion-clinical mismatch" is associated with potential for early recovery of aphasia. *Neurology, 64*(5), 828-833.
Reinert, G. (1970). Comparative factor analytic studies of intelligence through the human life-span. In L. Goulet & P. Baltes (Eds.), *Life-span developmental psychology: Research and theory* (pp. 468–485). New York: Academic Press.
Reuter-Lorenz, P. A., & Park, D. C. (2010). Human Neuroscience and the Aging Mind: A New Look at Old Problems. *The Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65B*(4), 405-415. doi: 10.1093/geronb/gbq035
Richardson, F. M., & Price, C. J. (2009). Structural MRI studies of language function in the undamaged brain. *Brain Struct Funct, 213*(6), 511-523.
Richter, M., Miltner, W. H. R., & Straube, T. (2008). Association between therapy outcome and right-hemispheric activation in chronic aphasia. *Brain, 131*(5), 1391-1401. doi: 10.1093/brain/awn043
Rissenberg, M., & Glanzer, M. (1987). Free Recall and Word Finding Ability in Normal Aging and Senile Dementia of the Alzheimer's Type: the Effect of Item Concreteness. *Journal of Gerontology, 42*(3), 318-322. doi: 10.1093/geronj/42.3.318
Rissman, J., Eliassen, J. C., & Blumstein, S. E. (2003). An event-related FMRI investigation of implicit semantic priming. *J Cogn Neurosci, 15*(8), 1160-1175. doi: 10.1162/089892903322598120
Robey, R. R. (1998). A meta-analysis of clinical outcomes in the treatment of aphasia. *Journal of Speech Language & Hearing Research, 41*(1), 172-187.
Rochon, E., Leonard, C., Burianova, H., Laird, L., Soros, P., Graham, S., & Grady, C. (2010). Neural changes after phonological treatment for anomia: An fMRI study. *Brain & Language, 114*. doi: 10.1016/j.bandl.2010.05.005
Rogalsky, C., & Hickok, G. (2009). Selective attention to semantic and syntactic features modulates sentence processing networks in anterior temporal cortex. *Cereb Cortex, 19*(4), 786-796. doi: bhn126 [pii] 10.1093/cercor/bhn126
Rorden, C., Karnath, H.-O., & Bonilha, L. (2007). Improving Lesion-Symptom Mapping. *Journal of Cognitive Neuroscience, 19*(7), 1081-1088. doi: 10.1162/jocn.2007.19.7.1081
Rosen, H., Petersen, S., Linenweber, M., Snyder, A., White, D., Chapman, L., . . . Corbetta, M. (2000). Neural correlates of recovery from aphasia after damage to left inferior frontal cortex. *Neurology, 55*. doi: 10.1212/wnl.55.12.1883
Rowe, E. J., & Schnore, M. M. (1971). Item Concreteness and Reported Strategies in Paired-Associate Learning as a Function of Age. *Journal of Gerontology, 26*(4), 470-475. doi: 10.1093/geronj/26.4.470
Roxbury, T., McMahon, K., & Copland, D. A. (2014). An fMRI study of concreteness effects in spoken word recognition. *Behavioral and Brain Functions, 10*(1), 34. doi: 10.1186/1744-9081-10-34
Roxbury, T., McMahon, K., Coulthard, A., & Copland, D. A. (2016). An fMRI study of concreteness effects during spoken word recognition in aging. Preservation or attenuation? *Frontiers in Aging Neuroscience, 7*. doi: 10.3389/fnagi.2015.00240
Rumsey, J. M., Nace, K., Donohue, B., Wise, D., Maisog, J. M., & Andreason, P. (1997). A positron emission tomographic study of impaired word recognition and phonological processing in dyslexic men. *Archives of Neurology, 54*(5), 562-573. doi: 10.1001/archneur.1997.00550170042013
Sabsevitz, D. S., Medler, D. A., Seidenberg, M., & Binder, J. R. (2005). Modulation of the semantic system by word imageability. *Neuroimage, 27*(1), 188-200. doi: 10.1016/j.neuroimage.2005.04.012

Saffran, E. M., Marin, O. S., & Yeni-Komshian, G. H. (1976). An analysis of speech perception in word deafness. *Brain & Language, 3*(2), 209-228.
Sair, H. I., Yahyavi-Firouz-Abadi, N., Calhoun, V. D., Airan, R. D., Agarwal, S., Intrapiromkul, J., . . . Pillai, J. J. (2016). Presurgical brain mapping of the language network in patients with brain tumors using resting-state fMRI: Comparison with task fMRI. *Hum Brain Mapp, 37*(3), 913-923. doi: 10.1002/hbm.23075
Salthouse, T. A. (1996). The processing-speed theory of adult age differences in cognition. *Psychol Rev, 103*(3), 403-428.
Salthouse, T. A., & Babcock, R. L. (1991). Decomposing adult age differences in working memory. *Developmental Psychology, 27*(5), 763-776. doi: 10.1037//0012-1649.27.5.763
Sandberg, C., & Kiran, S. (2014). Analysis of Abstract and Concrete Word Processing in Persons with Aphasia and Age-Matched Neurologically Healthy Adults Using fMRI. *Neurocase, 20*(4), 361-388. doi: 10.1080/13554794.2013.770881
Saur, D., Kreher, B. W., Schnell, S., Kummerer, D., Kellmeyer, P., Vry, M. S., . . . Weiller, C. (2008). Ventral and dorsal pathways for language. *Proc Natl Acad Sci U S A, 105*(46), 18035-18040.
Saur, D., Lange, R., Baumgaertner, A., Schraknepper, V., Willmes, K., Rijntjes, M., & Weiller, C. (2006). Dynamics of language reorganization after stroke. *Brain, 129*(Pt 6), 1371-1384. doi: 10.1093/brain/awl090
Saur, D., Ronneberger, O., Kummerer, D., Mader, I., Weiller, C., & Kloppel, S. (2010). Early functional magnetic resonance imaging activations predict language outcome after stroke. *Brain, 133*(Pt 4), 1252-1264.
Schwanenflugel, P. J. (1991). *Why are abstract concepts hard to understand?* Hillsdale NJ: Erlbaum.
Schwanenflugel, P. J., Harnishfeger, K. K., & Stowe, R. W. (1988). Context availability and lexical decisions for abstract and concrete words. *Journal of Memory and Language, 27*(5), 499-520. doi: 10.1016/0749-596X(88)90022-8
Schwanenflugel, P. J., & Shoben, E. J. (1983). Differential Context Effects in the Comprehension of Abstract and Concrete Verbal Materials. *Journal of Experimental Psychology-Learning Memory and Cognition, 9*(1), 82-102. doi: 10.1037/0278-7393.9.1.82
Scott, S. K., Leff, A. P., & Wise, R. J. (2003). Going beyond the information given: a neural system supporting semantic interpretation. *Neuroimage, 19*(3), 870-876. doi: 10.1016/S1053-8119(03)00083-1
Scott, S. K., & Wise, R. J. (2004). The functional neuroanatomy of prelexical processing in speech perception. *Cognition, 92*(1-2), 13-45. doi]
Selnes, O. A. (1999). Recovery from aphasia: activating the "right" hemisphere. *Annals of Neurology, 45*(4), 419-420.
Selnes, O. A., Knopman, D. S., Niccum, N., Rubens, A. B., & Larson, D. (1983). Computed tomographic scan correlates of auditory comprehension deficits in aphasia: a prospective recovery study. *Annals of Neurology, 13*(5), 558-566.
Service, E., & Craik, F. I. M. (1993). Differences between young and older adults in learning a foreign vocabulary. *Journal of Memory and Language, 32*, 608-623.
Shafto, M. A., Randall, B., Stamatakis, E. A., Wright, P., & Tyler, L. K. (2012). Age-related neural reorganization during spoken word recognition: the interaction of form and meaning. *Journal of Cognitive Neuroscience, 24*(6), 1434-1446. doi: 10.1162/jocn_a_00218
Shafto, M. A., & Tyler, L. K. (2014). Language in the aging brain: The network dynamics of cognitive decline and preservation. *Science, 346*(6209), 583-587. doi: 10.1126/science.1254404
Shallice, T. (1988). *From neuropsychology to mental structure*. Cambridge: Cambridge University Press.
Shallice, T., & Cooper, R. P. (2013). Is there a semantic system for abstract words? *Frontiers in Human Neuroscience, 7*. doi: 10.3389/fnhum.2013.00175

Sharp, D. J., Awad, M., Warren, J. E., Wise, R. J., Vigliocco, G., & Scott, S. K. (2010). The neural response to changing semantic and perceptual complexity during language processing. *Hum Brain Mapp, 31*(3), 365-377.

Skipper-Kallal, L. M., Mirman, D., & Olson, I. R. (2015). Converging evidence from fMRI and aphasia that the left temporoparietal cortex has an essential role in representing abstract semantic knowledge. *Cortex, 69*, 104-120. doi: 10.1016/j.cortex.2015.04.021

Stebbins, G. T., Carrillo, M. C., Dorfman, J., Dirksen, C., Desmond, J. E., Turner, D. A., . . . Gabrieli, J. D. (2002). Aging effects on memory encoding in the frontal lobes. *Psychol Aging, 17*(1), 44-55.

Stinear, C. M., Barber, P. A., Petoe, M., Anwar, S., & Byblow, W. D. (2012). The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain, 135*(Pt 8), 2527-2535. doi: 10.1093/brain/aws146

Stinear, C. M., & Ward, N. S. (2013). How useful is imaging in predicting outcomes in stroke rehabilitation? *Int J Stroke, 8*(1), 33-37. doi: 10.1111/j.1747-4949.2012.00970.x

Stuss, D. T. (2011). Functions of the frontal lobes: relation to executive functions. *Journal of the International Neuropsychological Society, 17*(5), 759-765. doi: 10.1017/s1355617711000695

Supekar, K., Menon, V., Rubin, D., Musen, M., & Greicius, M. D. (2008). Network Analysis of Intrinsic Functional Brain Connectivity in Alzheimer's Disease. *PLoS Comput Biol, 4*(6), e1000100. doi: 10.1371/journal.pcbi.1000100

Swinburn, K., Porter, G., & Howard, D. (2004). *Comprehensive Aphasia Test*. New York: Psychology Press.

Szaflarski, J. P., Allendorfer, J. B., Banks, C., Vannest, J., & Holland, S. K. (2013). Recovered vs. not-recovered from post-stroke aphasia: the contributions from the dominant and non-dominant hemispheres. *Restor Neurol Neurosci, 31*(4), 347-360. doi: 10.3233/rnn-120267

Szaflarski, J. P., Eaton, K., Ball, A. L., Banks, C., Vannest, J., Allendorfer, J. B., . . . Holland, S. K. (2011). Poststroke aphasia recovery assessed with functional magnetic resonance imaging and a picture identification task. *Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 20*(4), 336-345.

Tettamanti, M., Manenti, R., Della Rosa, P. A., Falini, A., Perani, D., Cappa, S. F., & Moro, A. (2008). Negation in the brain: Modulating action representations. *Neuroimage, 43*(2), 358-367. doi: 10.1016/j.neuroimage.2008.08.004

Thompson, C. K. (2000a). The neurobiology of language recovery in aphasia. *Brain & Language, 71*(1), 245-248. doi: 10.1006/brln.1999.2260

Thompson, C. K. (2000b). NEUROPLASTICITY: EVIDENCE FROM APHASIA. *Journal of Communication Disorders, 33*(4), 357-366.

Thompson, C. K., & den Ouden, D. (2008). Neuroimaging and recovery of language in aphasia. *Current Neurology & Neuroscience Reports, 8*. doi: 10.1007/s11910-008-0076-0

Thompson, C. K., & Shapiro, L. P. (2005). Treating agrammatic aphasia within a linguistic framework: Treatment of Underlying Forms. *Aphasiology, 19*(10-11), 1021-1036.

Thulborn, K. R., Carpenter, P. A., & Just, M. A. (1999). Plasticity of language-related brain function during recovery from stroke. *Stroke, 30*(4), 749-754.

Torta, D. M., & Cauda, F. (2011). Different functions in the cingulate cortex, a meta-analytic connectivity modeling study. *Neuroimage, 56*(4), 2157-2172. doi: 10.1016/j.neuroimage.2011.03.066

Turkeltaub, P. E., Messing, S., Norise, C., & Hamilton, R. H. (2011). Are networks for residual language function and recovery consistent across aphasic patients? *Neurology, 76*(20), 1726-1734. doi: 10.1212/WNL.0b013e31821a44c1

Turken, A. U., & Dronkers, N. F. (2011). The neural architecture of the language comprehension network: converging evidence from lesion and connectivity analyses. *Front Syst Neurosci, 5*, 1. doi: 10.3389/fnsys.2011.00001

Tyler, L., Wright, P., Randall, B., Marslen-Wilson, W. D., & Stamatakis, E. A. (2010). Reorganization of syntactic processing following left-hemisphere brain damage: does right-hemisphere activity preserve function? *Brain, 133*(11), 3396-3408. doi: 10.1093/brain/awq262
Ueno, T., & Lambon Ralph, M. A. (2013). The roles of the “ventral” semantic and “dorsal” pathways in conduite d'approche: a neuroanatomically-constrained computational modeling investigation. *Frontiers in Human Neuroscience, 7*, 422. doi: 10.3389/fnhum.2013.00422
Valdois, S., Carbonnel, S., Juphard, A., Baciu, M., Ans, B., Peyrin, C., & Segebarth, C. (2006). Polysyllabic pseudo-word processing in reading and lexical decision: converging evidence from behavioral data, connectionist simulations and functional MRI. *Brain Res, 1085*(1), 149-162. doi: 10.1016/j.brainres.2006.02.049
van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., & Copland, D. A. (2014). Neural activity associated with semantic versus phonological anomia treatments in aphasia. *Brain & Language, 129*, 47-57. doi: 10.1016/j.bandl.2013.12.004
van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., Read, S., & Copland, D. A. (2014a). Changes in white matter connectivity following therapy for anomia post stroke. *Neurorehabilitation & Neural Repair, 28*(4), 325-334. doi: 10.1177/1545968313508654
van Hees, S., McMahon, K., Angwin, A., de Zubicaray, G., Read, S., & Copland, D. A. (2014b). A functional MRI study of the relationship between naming treatment outcomes and resting state functional connectivity in post-stroke aphasia. *Human Brain Mapping, 35*(8), 3919-3931. doi: 10.1002/hbm.22448
van Oers, C., Vink, M., van Zandvoort, M., van der Worp, H., de Haan, E., Kappelle, L., . . . Dijkhuizen, R. (2010). 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, 49*(1), 885-893.
Vandenberghe, R., & Gillebert, C. R. (2009). Parcellation of parietal cortex: convergence between lesion-symptom mapping and mapping of the intact functioning brain. *Behav Brain Res, 199*(2), 171-182.
Verhaeghen, P. (2003). Aging and vocabulary scores: a meta-analysis. *Psychol Aging, 18*(2), 332-339.
Vigliocco, G., Kousta, S. T., Della Rosa, P. A., Vinson, D. P., Tettamanti, M., Devlin, J. T., & Cappa, S. F. (2014). The neural representation of abstract words: the role of emotion. *Cereb Cortex, 24*(7), 1767-1777. doi: 10.1093/cercor/bht025
Vigliocco, G., Meteyard, L., Andrews, M., & Kousta, S. (2009). Toward a theory of semantic representation. *Language and Cognition, 1*(02), 219-247. doi: doi:10.1515/LANGCOG.2009.011
Vitali, P., Abutalebi, J., Tettamanti, M., Danna, M., Ansaldo, A.-I., Perani, D., . . . Cappa, S. F. (2007). Training-induced brain remapping in chronic aphasia: a pilot study. *Neurorehabilitation & Neural Repair, 21*(2), 152-160.
Wang, J., Conder, J. A., Blitzer, D. N., & Shinkareva, S. V. (2010). Neural representation of abstract and concrete concepts: a meta-analysis of neuroimaging studies. *Hum Brain Mapp, 31*(10), 1459-1468. doi: 10.1002/hbm.20950
Warburton, E., Price, C. J., Swinburn, K., & Wise, R. J. (1999). Mechanisms of recovery from aphasia: evidence from positron emission tomography studies. *Journal of Neurology, Neurosurgery & Psychiatry, 66*(2), 155-161.
Warrington, E. K. (1975). The selective impairment of semantic memory. *Q J Exp Psychol, 27*(4), 635-657. doi: 10.1080/14640747508400525
Warrington, E. K. (1981). Concrete word dyslexia. *British Journal of Psychology, 72*(2), 175-196. doi: 10.1111/j.2044-8295.1981.tb02175.x
Warrington, E. K., & Shallice, T. (1984). Category Specific Semantic Impairments *Brain, 107*(3), 829-853. doi: 10.1093/brain/107.3.829

Weiller, C., Isensee, C., Rijntjes, M., Huber, W., Muller, S., Bier, D., . . . Diener, H. C. (1995). Recovery from Wernicke's aphasia: a positron emission tomographic study. *Annals of Neurology, 37*(6), 723-732. doi: 10.1002/ana.410370605
West, R. L. (1996). An application of prefrontal cortex function theory to cognitive aging. *Psychological Bulletin, 120*(2), 272-292.
Whatmough, C., Verret, L., Fung, D., & Chertkow, H. (2004). Common and contrasting areas of activation for abstract and concrete concepts: An (H2OPET)-O-15 study. *Journal of Cognitive Neuroscience, 16*(7), 1211-1226. doi: 10.1162/0898929041920540
Whitworth, A., Webster, J., & Howard, D. (2005). *A cognitive neuropsychological approach to assessment and intervention in aphasia*. Hove: Psychology Press.
Wilson, M. (1988). MRC psycholinguistic database: Machine-usable dictionary, version 2.00. *Behavior Research Methods, Instruments, & Computers, 20*(1), 6-10. doi: 10.3758/bf03202594
Wingfield, A., & Grossman, M. (2006). Language and the aging brain: patterns of neural compensation revealed by functional brain imaging. *J Neurophysiol, 96*(6), 2830-2839. doi: 10.1152/jn.00628.2006
Wise, R. J. S., Howard, D., Mummery, C. J., Fletcher, P., Leff, A., Buchel, C., & Scott, S. K. (2000). Noun imageability and the temporal lobes. *Neuropsychologia, 38*(7), 985-994. doi: 10.1016/s0028-3932(99)00152-9
Witte, K. L., & Freund, J. S. (1976). Paired-associate learning in young and old adults as related to stimulus concreteness and presentation method. *J Gerontol, 31*(2), 183-192.
Yang, Z. H., Zhao, X. Q., Wang, C. X., Chen, H. Y., & Zhang, Y. M. (2008). Neuroanatomic correlation of the post-stroke aphasias studied with imaging. *Neurological Research, 30*(4), 356-360.
Yi, H. A., Moore, P., & Grossman, M. (2007). Reversal of the concreteness effect for verbs in patients with semantic dementia. *Neuropsychology, 21*(1), 9-19. doi: 10.1037/0894-4105.21.1.9
Zahn, R., Drews, E., Specht, K., Kemeny, S., Reith, W., Willmes, K., . . . Huber, W. (2004). Recovery of semantic word processing in global aphasia: a functional MRI study. *Brain Res Cogn Brain Res, 18*(3), 322-336.
Zahn, R., Huber, W., Drews, E., Erberich, S., Krings, T., Willmes, K., & Schwarz, M. (2000). Hemispheric lateralization at different levels of human auditory word processing: a functional magnetic resonance imaging study. *Neuroscience Letters, 287*(3), 195-198.
Zmigrod, S., Zmigrod, L., & Hommel, B. (2016). Transcranial direct current stimulation (tDCS) over the right dorsolateral prefrontal cortex affects stimulus conflict but not response conflict. *Neuroscience, 322*, 320-325. doi: 10.1016/j.neuroscience.2016.02.046