Understanding the neurobiological basis of reading disorders in aphasia and predicting patients' responses to reading therapy

Oscar Mauricio Aguilar Mejia

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Department of Brain repair and Rehabilitation - University College London

This thesis is submitted for the degree of

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Declaration of authorship

‘I, Oscar Mauricio Aguilar Mejia confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

Signed declaration

Abstract (298 words)

This thesis investigated cognitive abilities and brain regions associated with reading impairments in chronic aphasic patients with central alexia (CA). Moreover, analyses on cognitive abilities and brain lesion-site were conducted to determine whether these may predict patients' outcomes in response to a computerised reading therapy called iReadMore.

First, a review of the literature was undertaken. This included reading models and reading impairments in aphasia, neuroanatomical basis of reading, executive function in aphasia, computerised-based aphasia treatments, transcranial direct current stimulation in language therapies, and individual factors that influence aphasia recovery and patients' response to therapy. Second, iReadMore was described and its therapeutic effect on a group of patients (n=23) was reported. Then, behavioural and neuroimaging methods implemented in this thesis were described.

The first experimental chapter explored the cognitive profile of CA patients. Moreover, it included principal component analysis and voxel-based-morphometry conducted to study which brain regions are associated with reading patterns underlying patients' remaining abilities. Here results showed that preserved white matter deep to the lingual gyrus was related to semantic abilities in reading. This region has not been related before.

The second experimental chapter aimed to identify what patients' demographic information, cognitive abilities and brain lesions explain their response to iReadMore. In this study, it is demonstrated for the first time, that lesion-site is determinant in patients' response to therapy and also that therapy response in new patients is predictable.

The final chapter investigated structural brain changes in response to iReadMore. Here a quantitative MRI protocol was implemented to study biomarkers associated with reading improvement. Results showed that iron content increases in two regions infrequently associated with reading, the left superior frontal gyrus and the supplementary motor area bilateral, when patients respond positively to the therapy. Finally, a general discussion and suggestions of new studies were provided.

Statement of publications

The results presented in this thesis have been submitted for publication.

1) The data presented in chapter two have been submitted to Brain. It is currently under review:

Randomized trial of iReadMore word reading training and brain stimulation in central alexia. Woodhead, Z., Kerry, S., Aguilar, O., Ong, YH., Hogan, J., Pappa, K., Leff, AP. & Crinion

The data collection and analyses for the iReadMore trial were done collaboratively with Sheila Kerry and Dr Zoe Woodhead. The data presented in this thesis is a subset of the trial data.

2) The data presented in chapter three (section 3.1.4. and 3.1.5.) have been submitted to Cortex and it is currently under review:

Dorsal and ventral visual stream contributions to preserved reading ability in patients with central alexia. Aguilar, O., Kerry, S., Crinion, J., Callaghan, M., Woodhead, Z. & Leff, AP.

3) The results presented in chapter four (section 4.1.1. and 4.1.2.) are being prepared for submission:

Lesion site dependent treatment responses after stroke. Aguilar, O., Kerry, S., Ong, YH, Callaghan, M., Crinion, J., Woodhead, Z., Price CJ, Leff, AP & Hope, T.

The data analysis was done collaboratively with Dr Tom Hope

4) The results presented in chapter five are being prepared for submission.

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To the memory of my lovely aunty Angela (“La Nena”). Thank you for being the person you were. Thank you for your love and caring. “Siempre he creído que los logros personales son el fruto del esfuerzo de muchos. Por eso siempre te agradeceré todo el amor que incondicionalmente nos diste”.

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Abbreviations

AG	Angular gyrus
AIC	Akaike information criterion
ALI	Automatic Lesion Identification toolbox
ALM	Automatic linear modelling
a-tDCS	Anodal stimulation
ATG	Anterior temporal gyrus
aTL	Anterior temporal pole
B0	External magnetic field
CA	Central alexia
CAT	Comprehensive Aphasia Test
CDP	Communication Disability Profile
CSF	Cerebrospinal fluid
c-tDCS	Cathodal stimulation
DTI	Diffusion tensor imaging
DV	Dependent variable
FLASH	Fast low angle shot
fMRI	Functional MRI
FWHM	Full width at half maximum for a Gaussian
GLM	General linear model
GM	Gray matter
IFG	Inferior frontal gyrus
ILF	Inferior longitudinal fasciculus
ITG	Inferior temporal gyrus
KMO	Kaiser-Meyer Olkin Measure

LTP	Long-term potentiation
MCA	Middle cerebral artery
MNI	Montreal Neurological Institute
MRI	Magnetic resonance imaging
MPM	Multiparameter mapping
MT	Magnetization transfer
MTG	Middle temporal gyrus
N-CV	Nested cross-validation
Neale	Neale Analysis of Reading Ability test
NMDA	N-methyl-aspartate receptors
NV-SART	Non-verbal version of the Sustained Attention to Response Task
O-P	Orthography-to-phonology
O-S-P	Orthography via semantics to phonology
PCA	Principal component analysis
PMT	Porteus Maze Test
PPT	Pyramids and palm trees test
PD*	Effective proton density
PDw	Proton density-weighting
qMRI	Quantitative MRI imaging
RCFT	Rey Complex Figure Test
RF	Radiofrequency
RH	Right hemisphere
RT	Reaction time
R1	Longitudinal relaxation rate
R2*	Effective transverse relaxation rate

SFG	Superior frontal gyrus
SLF	Superior longitudinal fasciculus
SLT	Speech and language therapy
SMA	Supplementary motor area
SMG	Supramarginal gyrus
SPM	Statistical Parametrical Mapping
s-tDCS	Sham stimulation
STG	Superior temporal gyrus
SWR	Single-word reading test
tDCS	Transcranial direct current stimulation
TAB	Two-armed bandit Task
TEA	Test of Everyday Attention
TH	Tower of Hanoi
T1w	T1-weighting
T2w	T2-weighting
VBM	Voxel-based morphometry
VBQ	Voxel-based quantification
VLSM	Voxel-based lesion symptom mapping
v-IFG	Ventral inferior frontal gyrus
v-OT	Ventral occipital-temporal cortex
VSSTM	Visual-spatial short-term memory task
VWFA	Visual word form area
WM	White matter
WPM	Words per minute
WCST	Wisconsin Card Sorting test

Table of Contents

List of figures

List of tables

INTRODUCTION

Aphasia is a language disorder caused by damage of brain regions that support linguistic abilities. Stroke in the territory of the left middle cerebral artery (MCA) is the most common cause of aphasia. It produces devastating impairments in communication abilities such as speech, verbal comprehension, reading and writing. Aphasia significantly impacts patients' activities of daily living and is thus one of the most challenging psychosocial sequela of stroke (Lam & Wodchis, 2010). According of the Stroke Association the number of stroke survivors living in the UK is above 1.2 million, and 33% of these people (i.e. 396,000 approximately) live with aphasia ("State of the nation: Stroke statistics January 2016," 2016).

Generally, after hospital discharge post-stroke aphasic patients are assessed in outpatient speech and language therapy (SLT) services to establish which linguistic abilities are impaired. Then, patients receive treatment that in the UK includes on average between 10-20 sessions (Code & Heron, 2003; Katz et al., 2000; Zheng, Lynch, & Taylor, 2016). The adequate number of SLT sessions (dose) and the intensity (frequency) is still matter of debate. Different studies have shown that aphasic patients require intensive therapy (at least 9 hours per week up to 100 hours) to reach therapeutic recovery of their language abilities (Bhogal, Teasell, & Speechley, 2003; Dignam, Rodriguez, & Copland, 2016; Zheng et al., 2016). Contrary, other studies have shown that less intensive and spaced therapy (2 hours per week up to 50 hours) is enough to accomplish therapeutic outcomes (Dignam et al., 2015; Marshall, 2008; Sage, Snell, & Ralph, 2011). Independently

of the intensity, both views show that the satisfactory number of SLT sessions is higher than the average provided by many health care services.

In recent years, computer-based therapies have arisen as an alternative to support treatments in aphasic patients. There has been an increasing interest in creating novel and effective computerised therapies aiming towards re-learning (restitution) of language skills (Archibald, Orange, & Jamieson, 2009; Ong et al., 2012; Woodhead et al., 2017; Woodhead et al., 2013). However, this has also introduced interesting challenges: the use of computer software to support patients' recovery is increasing, but little is known about which neuropsychological abilities are required for successful engagement with and a positive response to this type of therapy (Zheng et al., 2016). A recent Cochrane review has shown that SLT is effective (Brady, Kelly, Godwin, Enderby, & Campbell, 2016), but aphasic patients are rather heterogeneous and their response to SLT is highly variable independently of the therapy target, delivery method (face to face or computer-based treatment), and dose (Bowen et al., 2012; Brady et al., 2016). There is little knowledge of the individual (demographic and behavioural profile) and neurological (brain-based) variables that influence patients' response to therapy. This variability leads to a poor understanding of the relationship between aphasic impairments and therapy-driven recovery. Ideally, the therapists would have enough knowledge about which cognitive abilities and impairments predict the effectiveness of their therapy in order to tailor the type of therapy to give to each patient. This would maximise the patients' likelihood of successful recovery: before SLT some patients may require general cognitive behavioural treatment to increase the effectiveness of further SLT targeting linguistic domains.

Currently, there is an increasing interest in understanding the influence of cognitive specific and cognitive general domains on therapy-driven recovery. In the case of chronic aphasia, evidence suggests that cognitive/non-linguistic abilities significantly influence the effectiveness of SLT (Brownsett et al., 2014; Cahana-Amitay & Albert, 2015; Crinion & Leff, 2015; Kuzmina & Weekes, 2016; Lambon Ralph, Snell, Fillingham, Conroy, & Sage, 2010; Nicholas, Sinotte, & Helm-Estabrooks, 2005; Penn, Frankel, Watermeyer, & Russell, 2010). Studying preserved and impaired cognitive abilities in chronic stroke patients may help us understand and predict which patients are likely to respond positively or negatively to therapy.

Better understanding of patients' characteristics that impact therapeutic outcomes is essential if we are to create more personalised therapies. This programme of research was motivated by the necessity to increase our understanding about these key characteristics that influence patients' therapeutic outcomes in chronic aphasia, particularly in central alexia (CA). CA is defined as any reading impairments associated with an aphasic disorder (Leff & Starrfelt, 2014). I investigated the effect of both brain lesion-site and preserved/impaired cognitive abilities as predictors of patients' outcomes in response to a computer-based therapy (iReadMore) designed specifically for aphasic patients with CA.

Outline of this thesis

This thesis is organised into six chapters. Chapter one provides a detailed overview of the relevant literature in the field. In it I discuss: reading models, the neuroanatomical basis of reading, reading impairments associated with aphasia (CA), executive functions and language ability in aphasia, computer-based aphasia treatments, transcranial direct current stimulation (tDCS) in SLT, and factors that influence patients' recovery/response to therapy.

Chapter two is a methods chapter that starts with a description of the computer-based therapy (iReadMore) used in this study. Here I report the variability in the therapeutic effect on the aphasic patients that the rest of my thesis aims to understand. Although the use of transcranial direct current stimulation (tDCS) in reading therapy was not the main purpose of this research, I also describe the tDCS protocol implemented in the iReadMore trial. I then discuss the main methods used in this thesis: 1) behavioural protocol: linguistic and non-linguistic tasks tested at baseline; 2) behavioural analyses: principal component analysis (PCA), automatic linear modelling (ALM), and nested cross-validation (N-CV); and 3) MRI sequence and MRI analyses: multiparameter mapping protocol (MPM), voxel-based morphometry (VBM), and voxel-based quantification (VBQ).

In chapter three I present the pre-treatment data (demographics and behavioural) and explore the cognitive profile of CA patients, comparing their linguistic and non-linguistic abilities to age-matched controls. Moreover, I present PCA of reading abilities in our patients and their association with brain regions (VBM analysis).

In chapter four I investigate which cognitive variables and lesioned brain regions predict patients' response to iReadMore. Here the analysis uses baseline (pre-therapy) cross-sectional data to try and explain future responses to therapy. Additionally, I test whether in-sample predictions using this data generalise to new patients (an out-of-sample analysis).

In chapter five I report a longitudinal analysis (brain imaging data from both before and after therapy) and explore changes in brain micro- and macrostructure that may have been induced by the therapy. This analysis uses a novel quantitative neuroimaging method called Multiparameter Mapping (MPM) (Callaghan et al., 2014), applied to tracking therapy effects on patient's brains for the first time. I discuss the pros and cons of this approach to imaging brain plasticity after stroke.

Finally, in chapter six I provide a short, general discussion and conclusion, and suggest new studies based on my current findings.

Ethical approval

The ethics approval for the central alexia study obtained from the London Queen Square Research Ethics Committee is 14/LO/0043 and it is registered with the UCL data protection office with reference Z6364106/2013/11/11. The trial protocol was pre-registered on www.clinicaltrials.gov (NCT02062619).

1. BACKGROUND

1.1. Reading as cognitive process

Reading is a cognitive ability that involves visual processing and interpretation of orthographic stimulus at letter, word, sentence, and text level. Reading can be performed either silently or aloud, but independently of the form it demands interaction among orthographic, phonological and semantic processes. Contrary to other cognitive functions - such as memory, attention or language - reading is ontologically late-acquired, but also highly experience-dependent (environmental exposure to the written words) (Carreiras et al., 2009; Dehaene et al., 2010).

Oral word reading involves several processes that are implemented sequentially or in parallel: 1) visual orthographic analysis to identify letters and their positions in a word; 2) access to an orthographic lexicon to recognise groups of letters as a word; 3) access to a semantic system to activate the meaning of the written word; and, 4) phonological assembly to convert words into a phonological output for reading aloud (Whitworth, Webster, & Howard, 2014).

Studies of reading acquisition in children, as well as in expert or impaired readers, have been useful in the development of computational models of reading (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001; Perry, Ziegler, & Zorzi, 2007; Plaut, 2008; Plaut, McClelland, Seidenberg, & Patterson, 1996). These models attempt to integrate cognitive processes involved in reading. In general, these models propose that:

a) Reading is performed through interaction among “units” in the orthographic, phonological and semantic domains. Each unit plays a unique role in the reading system. Moreover, units’ activation depends on both the input into the system and the strength of connections between them (within and between domains), which are learned through experience. However, depending on the performed task, units can work together or compete in a cognitive process.
b) Two separate routes can be used for word reading: a sublexical and a lexical/semantic route. The sublexical route follows orthography-to-phonology (O-P) mappings. The other route involves maps from orthography, via semantics to phonology (O-S-P).

The present study was based on the “Triangle model” proposed by Plaut et al. (1996) (See Figure 1). This model proposes that the phonological/sublexical route connects straightforward O-P decoding, allowing regular words, pseudowords, and irregular words to be read. Moreover. It proposes a semantic/lexical route that supports reading of irregular words. This route connects O-P, but is mediated by a semantic unit which provides lexical information that facilitates reading of irregular words and comprehension of written words (it is sometimes referred to as the indirect route because semantics help support the path from O-P). The model suggests that both routes are activated during reading, but the relative importance of each route depends on the type of word, and possibly individual differences in reading style. In summary, this model proposes that word reading is a process supported by connections to both phonological and semantic pathways.

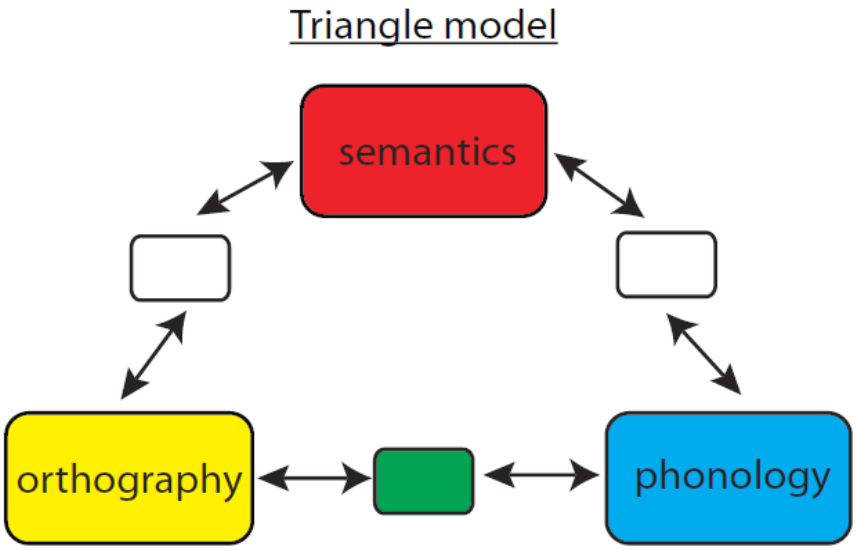

Figure 1. Illustration of the triangle model (Plaut, 2008). Taken from Taylor, Rastle & Davis (2012).

1.1.1. Neuroanatomical basis of reading

In the last thirty years, since the arrival of modern neuroimaging methods, there have been an increasing number of studies investigating the cerebral localization of the cognitive processes and pathways involved in reading (Price, 2012). Evidence for the neuroanatomical basis of reading come from two main lines of investigation: imaging studies on patients with reading impairments (Brambati, Ogar, Neuhaus, Miller, & Gorno-Tempini, 2009; Ripamonti et al., 2014), and functional MRI (fMRI) studies in normal readers (Price, 2012; Taylor, Rastle, & Davis, 2013).

The neuroanatomy of reading can be divided into peripheral (visual) and central (linguistic) systems. Peripheral regions are involved in visual and orthographic abstraction of written words (early visual analysis), and are often discussed in

contrast with recognition of faces, symbols or visual objects. Central regions (late visual analysis) are involved in mapping from abstract orthographic representations to central phonological and semantic representations (i.e. spelling, pseudoword reading, lexical/semantic associations, reading comprehension, and lexical output).

Findings suggest that visual analysis of written words is strongly localized to the left occipitotemporal cortex. Previous research (Cohen et al., 2000; Dehaene, Le Clec, Poline, Le Bihan, & Cohen, 2002) has established that the left ventral occipitotemporal cortex including medial fusiform gyrus produces a higher neural response to written words (i.e. recognition of letter strings) in comparison with other visual forms (i.e. checkerboards). This finding led to denominate this region as the visual word form area (VWFA). However, the exact function(s) associated with this region is still matter of fierce debate (Hellyer, Woodhead, Leech, & Wise, 2011; Kherif, Josse, & Price, 2011; Price & Devlin, 2003, 2011). Further studies have found that anterior and posterior regions of the ventral occipitotemporal cortex respond differentially depending on the stimulus (Szwed et al., 2011). The anterior region activation is associated with recognition of real words, while posterior segment activation is higher for pseudowords.

Central aspects of word recognition comprise processes related to orthographic, semantic and phonological components in reading. Studies have shown a dissociation of two neuroanatomical streams that map onto the dual-route proposed in cognitive models (Dehaene et al., 2010; Jobard, Crivello, & Tzourio-Mazoyer, 2003). The first stream corresponds to a dorsal pathway for sublexical reading. It encompasses left posterior temporal, inferior parietal and premotor

regions (red in Figure 2) as well as dorsal white matter (WM) tracts. fMRI studies have found that pseudoword reading (a task that relies heavily on the sublexical route) integrates activity of the left ventral posterior occipito-temporal cortex (Vigneau, Jobard, Mazoyer, & Tzourio-Mazoyer, 2005; Woodhead, Brownsett, Dhanjal, Beckmann, & Wise, 2011), left posterior superior temporal gyrus (Graves, Desai, Humphries, Seidenberg, & Binder, 2010), supramarginal (Oberhuber et al., 2016) and angular gyrus, anterior insula, precentral gyrus, and left ventral inferior frontal gyrus (Joseph, Noble, & Eden, 2001; Taylor et al., 2013). Moreover, diffusion tensor imaging (DTI) studies have related pseudoword reading to integrity of the left superior longitudinal fasciculus (SLF) and the left arcuate fasciculus (Christodoulou et al., 2017; Rauschecker et al., 2009; Vandermosten et al., 2011; Zhang et al., 2014).

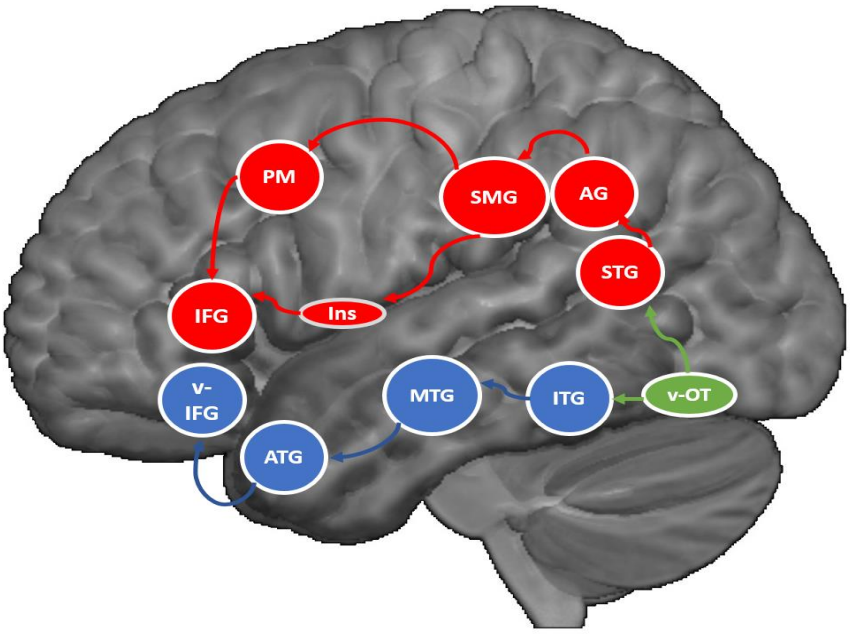

Figure 2. Neuroanatomical streams of reading. This figure only includes grey matter regions. Dorsal stream (in red) is involved in sublexical reading. Ventral stream (in blue) is involved in lexical-semantic reading. v-OT= ventral occipital-temporal cortex; STG= superior temporal gyrus; AG= angular gyrus; SMG= supramarginal; Ins= anterior insula; PM= premotor cortex; IFG= inferior frontal gyrus; ITG= inferior temporal gyrus; MTG= middle temporal gyrus; ATG= anterior temporal gyrus; v-IFG= ventral inferior frontal gyrus.

The other stream corresponds to the ventral pathway for lexical-semantic reading (i.e. irregular and regular words). Similarly to the dorsal stream it encompasses posterior to anterior activity, but via temporal grey matter (GM) regions (blue in Figure 2) and ventral WM tracts. The ventral stream is left-dominant and integrates regions supporting semantic associations, such as the ventral anterior occipito-temporal cortex, superior anterior temporal gyrus, middle and inferior temporal lobe (Rice, Lambon Ralph, & Hoffman, 2015), and inferior frontal gyrus (Hoffman, Lambon Ralph, & Woollams, 2015). Furthermore, DTI studies have linked lexical-semantic reading to integrity of the left inferior longitudinal fasciculus (ILF) (Graves et al., 2014), left inferior fronto-occipital fasciculus, and left uncinate fasciculus (Agosta et al., 2010b; Zhang et al., 2014).

1.2. Acquired reading impairments

Acquired reading impairments refer to reading difficulties caused by brain damage, usually stroke or neurodegenerative disorders. This definition is used to differentiate from neurodevelopmental dyslexia which affects the acquisition of reading skills, frequently associated with other learning disabilities (Peterson & Pennington, 2015). Acquired reading impairments are broadly separated into peripheral and central alexia. The most canonical of the peripheral alexias is pure alexia (Leff & Starrfelt, 2014; Warrington & Shallice, 1980). Patients with pure alexia display a word length effect on their reading performance, and sometimes an overt letter-by-letter reading strategy (Habekost, Petersen, Behrmann, & Starrfelt, 2014; Patterson & Kay, 1982; Starrfelt, Gerlach, Habekost, & Leff, 2013). In pure alexia the preservation of central language skills is evidenced by

preserved writing abilities, and is also known as alexia without agraphia (Jules Dejerine, 1892).

Central alexia (CA) refers to any reading impairment in previously literate individuals who have acquired aphasia. The term CA is generally understood as a broad syndrome disturbing later stages in reading processing, such as meaning or conversion of visual representations (letters or syllables) into sounds (Leff & Starrfelt, 2014). In CA, writing is also impaired, thus it is also known as alexia with agraphia (Jules Dejerine, 1891).

1.2.1. Central alexia subtypes

The most accepted classification of CA deficits, also referred to by convention as dyslexias, comprises three subtypes: phonological, surface, and deep dyslexia. Based on the previously described triangle model of reading (Plaut, 2008), dyslexia subtypes can be explained in terms of damage to phonology, orthography or semantic units, or disconnections between domains.

Phonological dyslexia consists of difficulties reading words, particularly pseudowords and is ascribed to impairment of the direct/sub-lexical route, disconnecting O-P (which is governed by grapheme to phoneme rules) (Beauvois & Derouesne, 1979). In some cases, patients read real words relatively well by relying on their lexical knowledge of written words. This compensation causes a phenomenon known as “lexicalisation” where subjects read pseudowords as real

words (Crisp & Lambon Ralph, 2006). Ocassionally, patients present difficulties reading real words, mostly low-imageability words, function words and morphologically complex words. Moreover, they may exhibit visual, semantic and morphological errors (Whitworth et al., 2014).

Surface dyslexia refers to impaired reading of irregular words caused by damage to the lexical/indirect route. As a result, patients show difficulties in recognising and integrating words as units, and the conversion from the written to the spoken word relies on the non-lexical/direct route and their knowledge of the grapheme-to-phoneme rules. Patients therefore apply the standard O-P rules inappropriately when reading irregular words, but their reading of regular words and pseudowords is relatively well preserved (Binder et al., 2016). These patients may present specific reading errors such as regularisation of irregular words, morphological errors (i.e. substitution, deletion, or addition of letters) and visual errors (i.e. misperception of letters) (Marshall & Newcombe, 1973; Whitworth et al., 2014).

Finally, deep dyslexia is associated with damage to both the direct and indirect routes. Damage to both pathways explains why patients can exhibit symptoms common to both of the other forms of dyslexia along with semantic errors (unique to deep dyslexic patients) (Jefferies, Sage, & Ralph, 2007; Marshall & Newcombe, 1973; Snowden, Kindell, Thompson, Richardson, & Neary, 2012). Semantic errors are the replacement of words for other semantically related (e.g. “sofa” for “chair”). Moreover, patients show morphological and visual errors, along with difficulties reading pseudowords (Whitworth et al., 2014).

1.2.2. Neuroanatomical bases of acquired reading impairments

The neural basis of acquired reading impairments follows a posterior to anterior axis which matches the division between peripheral and central alexia. There is consensus that damage to the posterior areas of the ventral occipitotemporal cortex causes peripheral alexias such as pure alexia in which impairments are related to feature analysis of visual stimulus (Leff & Starrfelt, 2014; Starrfelt et al., 2013; Woodhead et al., 2013).

Regarding central alexia, extensive evidence has accrued showing that the neuroanatomical underpinning of reading impairments is associated to damage to brain regions (both GM and WM) supplied by the middle cerebral artery (i.e. frontal, parietal, and temporal lobes). In the case of anatomical lesion models, research in patients with stroke or dementia has provided a better understanding of brain regions and their role supporting reading skills. Voxel-based morphometry (VBM) and voxel-based lesion symptom mapping (VLSM) studies have shown that, beyond visual areas, reading skills are mediated by a set of largely left-lateralized brain regions around the territory of the MCA. Ripamonti et al. (2014) found that phonological dyslexia in chronic stroke is related to lesions in the left precentral gyrus, insula, and pars opercularis of the inferior frontal gyrus (IFG) whilst surface dyslexia is associated with damage to the left superior, middle and inferior temporal gyri, insula and middle occipital gyrus. Similarly, Binder et al. (2016) found that regularization of irregular words in surface dyslexia is associated to damage in the left posterior middle temporal gyrus.

Brambati et al. (2009) studied the anatomical correlates of reading impairments in patients with primary progressive aphasia. They found a correlation between

pseudoword reading ability and sparing of the left angular gyrus (AG) and posterior middle and superior temporal lobe (areas associated with the dorsal visual stream); while reading irregular words correlated with sparing of the left temporal pole, anterior middle and superior temporal gyrus, and anterior fusiform gyrus (parts of the ventral visual stream).

Deep dyslexia has been associated with extensive damage along perisylvian regions, but mainly in the temporal lobes (Coltheart, 2000; Crisp & Lambon Ralph, 2006; Jefferies et al., 2007; Lambon Ralph & Graham, 2000).

In summary, these findings suggest that phonological dyslexia and sublexical O-P reading are reliant on dorsal parts of the MCA territory (inferior parietal lobe, posterior lateral temporal lobe and dorsal inferior frontal cortex), whereas surface dyslexia and lexical reading (O-P mediated by semantic) are reliant on ventral MCA areas (ventral temporal lobe and middle-to-anterior lateral temporal lobe). Moreover, deep dyslexia that involves both sublexical and lexical reading is reliant on extensive regions encompassing perisylvian regions along the MCA territory.

1.3. Executive functions and language ability in aphasia

A growing body of literature is investigating the influence of domain-general cognitive and executive functions on language ability in aphasia. This has focused on three aspects: 1) investigating which executive functions are impaired in aphasic patients; 2) investigating whether executive functions are associated

with patients' response to therapy; and, 3) investigating whether sparing of non-linguistic extra-sylvian networks are involved in language recovery.

On the subject of the executive impairment in aphasia (1), data from different studies have showed that aphasic patients are impaired in some but not all executive tasks in comparison to healthy subjects. For instance, Purdy (2002) assessed patients' abilities (n=15) in planning behaviour directed to a goal. He used the Porteus Maze Test (PMT), Tower of London and Tower of Hanoi (TH). Moreover, he assessed categorisation and cognitive flexibility with the Wisconsin Card Sorting test (WCST). Patients had poor performance on completing the WCST and the TH (accuracy), they were also less efficient (i.e. more movements) in the PMT, TH, and WCST, and slower in all tasks.

In other study, Jefferies and Lambon Ralph (2006) presented a series of case-studies comparing aphasic with semantic dementia patients. They were tested with linguistic tasks, plus digit span (to test working memory), the Coloured Progressive Matrices of Raven test (for reasoning), the WCST (for categorisation and cognitive flexibility), the Brixton Spatial anticipation test (for anticipation, solving problems, and cognitive flexibility), and the Elevator Counting subtest (for sustained attention) of the Test of Everyday Attention (TEA). Aphasic patients were impaired in all tasks except the Coloured Progressive Matrices test. Moreover, performance in these tasks correlated with semantic abilities that were also impaired.

In another study, Murray (2012) tested 39 aphasic patients with the whole TEA which includes sustained, selective, and divided attention tasks in auditory and visual modalities. Patients exhibited poor performance in all attention types. More recently, Kuzmina and Weekes (2016) investigated cognitive control in a group

of aphasic patients (n= 31) using verbal (the Stroop task and an auditory control task) and non-verbal tasks (the Flanker task and a rule finding task). Patients were presented with fluent and non-fluent aphasia. Results showed that all aphasic patients were impaired in verbal cognitive control tasks. Moreover, non-verbal cognitive control correlated with speech comprehension tasks, while verbal cognitive control correlated with naming tasks. In terms of aphasia type and verbal tasks, patients with non-fluent aphasia performed worse than fluent aphasic patients.

In summary, there seems to be a significant presence of executive deficits in aphasic patients. Patients tend to be impaired in tasks demanding solving problems, cognitive control, working memory, planning, cognitive flexibility, and selective and sustained attention. The severity of these deficits was heterogeneous among patients and correlated with their remaining linguistic abilities.

A related issue is the role of executive function on response to therapy in aphasic patients. It seems plausible that some of the variability in aphasia recovery and response to SLT depend on integrity of general-domain abilities. For instance, during therapy patients would need abilities such as working memory to manipulate information, cognitive control if task difficulty changes, mental flexibility to switch among tasks, monitoring if instructions and feedback are received, or sustained attention to focus continuously on specific aspects of the training. In a study conducted by Nicholas et al. (2005), a small group of non-fluent aphasic patients received training for six months with a computerised therapy. They were tested at baseline with the Boston Diagnostic Aphasia

Examination and five non-linguistic/executive subtests of the Cognitive Linguistic Quick Test. Results showed that patients with preserved executive abilities at baseline had a better response to therapy. Conroy, Sage, and Lambon Ralph (2009) presented a case-series study (n=7) of aphasic patients that received a specific naming therapy. Participants were tested before therapy started with language, memory and executive functions tasks. Specifically, memory and executive tasks included the Camden Memory Test, the Pyramids and palm trees (PPT), the Rey Complex Figure Test (RCFT), WCST, and two subtest of the TEA. Analyses showed that as well as some linguistic tasks, the immediate and delayed copy of the RCFT (which test visual memory and planning) significantly predicted therapy gain in the group of patients. More recently, Lambon Ralph et al. (2010) used PCA to investigate dimensions that predict aphasic patients' responses to a naming therapy based on phonemic and orthographic cues. Baseline assessment included linguistic and executive function tasks. Executive tasks were the PPT, TEA, WCST, and RCFT. Results showed two components that were labelled 'cognitive' and 'phonological'. Specifically, the cognitive component encompassed the executive function tasks. Most importantly, both components significantly predicted therapeutic gain in the group of patients.

The bottom line is that the available research supports the idea that executive function is relevant to aphasia recovery and response to therapy. At the group level, aphasic patients usually have damage along peri-sylvian regions. Research on aphasia recovery has studied the contribution of undamaged regions to the process of language recovery. The literature indicates that both linguistic and extra-sylvian non-linguistic neural networks interact in language tasks and participate in language recovery. For instance, Brownsett et al. (2014) conducted

an fMRI study to investigate whether domain-general cognitive networks participate in language tasks when difficulty increases. They specifically studied the ‘salience network’ that supports attentional abilities and encompasses the anterior cingulate and the superior frontal gyrus. They trained 16 chronic aphasic patients with comprehension difficulties. Then, participants were tested into the scanner to identify brain regions involved in sentence comprehension. Additionally, they scanned 17 healthy participants who completed a language comprehension task characterised by increasing difficulty through introducing noise when participants were listening to sentences. The experiment was designed to recreate a situation that demand cognitive control analogous to that which patients with comprehension difficulties may experience. Results showed that both patients listening to sentences and controls listening to noisy sentences activated the salience network. Moreover, activity in the salience network significantly correlated with comprehension ability in the patient group. They argued that this result supports the hypothesis that general executive functions have in the potential to support recovery from aphasic stroke and might therefore be a therapeutic target.

Similarly, Geranmayeh, Brownsett, and Wise (2014) reviewed the evidence from functional neuroimaging studies regarding domain-general networks and their activation when aphasic patients perform tasks. They reviewed studies on the default mode network (activated during resting), the fronto-parietal control network (involved in executive attention), and the cingulo-opercular network (involved in cognitive control). The authors argued that studies have endorsed language functions in these regions because most experiments in aphasia are centred on language domain-specific tasks. However, they proposed that

contrary to compensatory mechanism of language recovery, contribution of these networks reflects the necessity of domain-general brain activity due to task difficulty that aphasic patients experience when performing linguistic tasks. In other words, they suggested that activation of these networks might be interpreted as implication of executive abilities, specifically cognitive control and attention, which are needed to complete linguistic tasks when language-related regions are lesioned.

Finally, Humphreys and Lambon Ralph (2015) conducted a meta-analysis of 386 fMRI studies (including aphasia literature) to explore the role of the parietal lobe in verbal and non-verbal cognitive domains. They tried to determine whether these cognitive domains are merged or separated in specific parietal areas. The cognitive domains were attention, episodic memory, executive semantic processing, numerical calculation, phonology, sentence-level processing, tool-related tasks, and the default mode network. Results showed a functional division between dorsal and ventral regions. Dorsal parietal regions were associated with verbal and non-linguistic tasks demanding executive abilities whereas ventral parietal regions were associated with tasks demanding automatic processing.

In summary, the review of the literature indicates that aphasic patients have impairments in executive functions such as solving problems, cognitive control, working memory and planning. However, their difficulties are variable and there is no enough evidence in favour of a causal relationship between cognitive/executive functions and verbal functions in aphasia. Moreover, some studies have found that severity of executive impairments might predict therapy-

driven recovery in aphasia. Particularly, abilities in tasks demanding solving problems or planning as well as tasks grouped through PCA components have shown power to predict response to therapy in aphasia. Finally, neuroimaging studies have shown that extra-sylvian regions participate in language recovery; however, it is not clear whether these regions assume language functions or if executive functions support language recovery after stroke.

1.4. Computer-based therapy in aphasia

Computers have become useful instruments in daily life. People from all ages interact with computers for work, entertainment, communication and as a source of information. The development of the internet and powerful personal computers, smartphones, and tablets have increased people's access to apps with multiple utilities and almost unlimited potential. Nowadays, computer-based therapy is a well-accepted means to deliver some aspects of treatment to patients with mental illness (Hoifodt et al., 2013; Olthuis, Watt, Bailey, Hayden, & Stewart, 2016; Sandoval et al., 2017), cognitive impairments (Cerasa et al., 2013; Gooding et al., 2016; Iwata et al., 2017) and communicative disorders (aphasia) (Zheng et al., 2016).

In recent years, different studies have shown that long-term doses of the SLT are required for recovery (Dignam et al., 2015). However, public health systems struggle to provide enough face to face therapy that patients would require to reach clinical and functional criteria of language recovery. Therapy costs are high and patients' commuting from home to health centres is expensive, time

consuming and difficult, especially as many aphasic patients also have movement impairments. Computer-based therapies are a potential solution for several of these problems in therapy delivery. In the last two decades, there has been a proliferation of computer-based therapies for aphasia targeting speech production (Adrian, Gonzalez, Buiza, & Sage, 2011; Laganaro, Di Pietro, & Schnider, 2006; Stark & Warburton, 2016) verbal comprehension (Archibald et al., 2009; Thompson, Choy, Holland, & Cole, 2010), writing (Behrns, Hartelius, & Wengelin, 2009), and reading (Cherney, 2010; Dietz, Ball, & Griffith, 2011; Woodhead et al., 2013).

Detailed examination of the effectiveness of computer therapies in aphasia by Zheng et al. (2016) showed that computer-based interventions might be as good as face to face therapy; also these treatments can be individually tailored to patients' remaining abilities and needs; and most importantly, that patients' recovery of linguistic abilities is significantly higher than aphasic people with no treatment. However, they also highlighted significant limitations: 1) poor consensus regarding therapeutic outcomes; 2) most available studies are single cases or include small groups of patients; and, 3) little generalisation of therapy gain to activities of daily living. Nevertheless, the future of computer-based therapies in aphasia is promising. Software can offer the possibility of delivering a wide range of personally tailored treatment to people with aphasia. More research is needed to assess the real-world impact of this type of intervention and how patients' characteristics influence their responses to computer-based therapies.

1.5. Transcranial direct current stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive technique. It delivers low-intensity current to the brain to modulate cortical activity. The practical operation of tDCS is simple: it includes 1) a battery that delivers current and 2) two or more electrodes (depending on the montage) that are attached to the scalp of the subject (see Figure 7). Using this tool two main types of stimulation can be given: a) anodal stimulation (a-tDCS) which is excitatory; and b) cathodal stimulation (c-tDCS) which is inhibitory (Nitsche & Paulus, 2000). Moreover, tDCS devices can be set up to deliver sham stimulation (s-tDCS) in which anodal current is delivered for only a few seconds. This provides the subject with a sensation of stimulation but with no effects on the brain. Sham stimulation is useful in studies to test tDCS efficacy while controlling for any placebo effects (Gandiga, Hummel, & Cohen, 2006).

In recent years, researchers have investigated the mechanisms of tDCS and its potential to treat or boost treatments in patients with psychiatric conditions (Boggio et al., 2008; Brunoni, Schestatsky, Lotufo, Bensenor, & Fregni, 2014) motor disabilities (Scheffler, Williams, Mon-Williams, & Sinani, 2010; X. Zheng & Schlaug, 2015) or cognitive impairments (Convento, Russo, Zigiotto, & Bolognini, 2016; Crinion, 2016; Ferrucci et al., 2016; Nienow, Lim, & MacDonald, 2016; Vannorsdall et al., 2015). It has been demonstrated that this technique produces a modulatory effect in brain activity (Nitsche & Paulus, 2011; Stagg & Nitsche, 2011) that might persist up to one hour after stimulation (depending on the stimulation parameters) (Brunoni et al., 2012). Extensive research has attempted

to clarify the physiological changes induced by tDCS during both 1) the stimulation period and 2) the later persistent effect:

1) Shift in the resting potential of the neuronal membrane is the primary mechanism of action (Stagg & Nitsche, 2011). Electrical current affects the membrane polarisation by modulating calcium (Ca^{2+}) and sodium (Na^{+}) flow through the cellular membrane. This modulation might increase or decrease neuronal firing. For instance, Liebetanz, Nitsche, Tergau, and Paulus (2002) showed that blocking voltage-gated Ca^{2+} and Na^{+} channels reduces anodal stimulation effects. a-tDCS works by facilitating membrane depolarisation, hence it leads the cellular membrane from resting or inactivity to excitation, thus facilitating neuronal firing. In contrast, c-tDCS increases the membrane hyperpolarisation, producing a larger neuronal inhibition.
2) The effect of tDCS may persist even after electrical current delivery has finished. One possible explanation of this phenomenon is that the cellular membrane potential requires time to shift and equally requires time to return to baseline. This explanation is derived from studies where stimulation duration is considered. de Aguiar, Paolazzi & Miceli (2015) reviewed studies in healthy volunteers and aphasic post-stroke patients where stimulation time was examined. Most studies deliver current for 20 minutes with positive effects. However, they established that studies in which current is delivered for 10 minutes or 50 minutes have not found effects of a-tDCS. They interpreted these findings as being due to neurophysiological homeostasis. This means that cellular membranes require long stimulation to change their functioning to the new condition, but prolonged stimulation may also produce membrane

adaptation, hence membrane stability and neuronal firing return to baseline condition. From a different perspective, it has been argued that persistent effect of a-tDCS is associated with long-term potentiation (LTP) in which synapses strengthen for long periods (supporting learning processes) (Fritsch et al., 2010; Nitsche et al., 2008). Contrary to this, c-tDCS is associated with long-term depression where weakness in the connections eliminates synapses. In favour of this argument, Nitsche et al. (2004) studied the effects of blocking NMDA receptors on tDCS, as NMDA receptors are largely linked to LTP. They found that neuronal activity during a-tDCS is significantly reduced when glutamatergic channels are blocked. In contrast, enhancing the efficacy of NMDA receptors increased the effect of a-tDCS. They conclude that a-tDCS is associated with LTP because it increases the density of NMDA and glutamatergic receptors, hence it increases the neuronal response to afferent stimuli in the synapse.

1.5.1. tDCS safety

Studies of direct cortical stimulation in animals and transcranial stimulation in healthy subjects - and patients - have shown that the risk of adverse effects with this technique is very low (Nyffeler & Muri, 2010). Reported side effects are: headache, skin irritation, itching, nausea, phosphenes (flashes of light), seizure, and dizziness. Additionally, delivering current has the potential of damage the brain tissue. Direct stimulation of cortical regions in animals has shown that tissue damage is produced after a current charge of 216 A/cm² (Rossi et al., 2009). 20 minutes of tDCS produces a current charge of 0.09 A/cm² approximately, hence

tDCS following standard protocols is far beneath the level that would risk inducing tissue damage.

1.5.2. tDCS in speech and language therapy (SLT)

There has been increasing interest in the investigation of whether tDCS enhances treatment effects in aphasic patients (for review see De Aguiar, Paolazzi & Miceli, 2015). Using neurostimulation for SLT in aphasia assumes that practising linguistic tasks activates spared or compensatory language-specific networks. Concurrent tDCS might modulate the synaptic activity (i.e. shift in the membrane polarisation) of these neuronal networks to optimise the connectivity and facilitate patients' re-learning and language recovery. This hypothesis has been confirmed with two fMRI studies (Holland et al., 2011; Meinzer et al., 2012) in which simultaneous SLT and tDCS showed therapeutic improvement concomitant with reduced BOLD response in task-specific brain regions. These results can be interpreted as effective engagement of neuronal circuits, hence improving activation and efficiency in connections of stimulated areas.

Nevertheless, the mechanisms of tDCS in SLT are still matter of debate. For instance, extensive reviews of the literature (Crinion, 2016; de Aguiar, Paolazzi & Miceli, 2015; Stagg & Nitsche, 2011) have shown that multiple variables, such as electrode size and position, current strength, shape of the brain (gyri and sulcus) or duration and frequency of stimulation, may influence aphasic patients' response to tDCS. These studies have tried to clarify the effects of tDCS by comparing aphasic treatment results in different stimulation conditions:

1) Online/Offline tDCS: stimulation can be delivered when patients are receiving treatment (online tDCS) or before practising a task (offline tDCS). LTP requires an optimal microenvironment to strengthen neuronal connections during learning; therefore determining whether tDCS should be delivered online or offline is essential to enhance patients' outcomes to SLT. These two approaches have been examined by Monti et al. (2008). They compared online versus offline tDCS in anomia treatment finding that only left c-tDCS produced improvement in naming retrieval accuracy during the offline condition. This was interpreted as a reduction of neuronal inhibition in perilesional regions. However, it is difficult to conclude whether therapeutic results improve offline as most studies that found positive results applied online tDCS (Crinion, 2016; De Aguiar, Paolazzi & Miceli, 2015).

2) Stimulation of perilesional and contralateral homologous regions: Much of the current literature on aphasia has focused on lesion-site and prognosis of language recovery (Seghier et al., 2016). Sparing of left perilesional regions is associated with a better response to SLT (Fridriksson, Bonilha, Baker, Moser, & Rorden, 2010; Saur et al., 2005). Likewise, other studies have shown that the right hemisphere might play a role in language recovery (Forkel et al., 2014; Saur et al., 2006). Nevertheless, recent studies have found that disruptive TMS on contralateral regions in the right hemisphere improved language recovery in aphasic patients (Naeser et al., 2005; Naeser et al., 2011). These controversial findings have led to hypotheses that lesions in the left language-related regions reduce transcallosal inhibition of contralateral language-homologous regions, and

the resulting uncontrolled activation of the right hemisphere restricts reactivation of spared perilesional language networks. Three different approaches using tDCS have been used to determine where tDCS would be delivered: a-tDCS of perilesional regions; a-tDCS of contralateral regions; and c-tDCS of contralateral regions. Crinion (2016) extensively reviewed the literature finding that better results are obtained in studies that delivered a-tDCS in left perilesional regions and contralateral homologous. Additionally, she found that therapeutic gains do not increase with c-tDCS in the right hemisphere.

3) Acute versus chronic aphasia: most studies have only investigated the effect of tDCS in chronic post-stroke aphasia. This is due in part to acute post-stroke patients being more likely to have an increased risk of seizures. Additionally, aphasic patients in acute stroke usually have a phase of 'spontaneous recovery' of language abilities; a rapidly changing baseline is a challenge to early interventional studies. There are only few studies using tDCS in sub-acute stroke that have showed patients' improvement associated with stimulation (Crinion, 2016). However, more studies are needed to reach solid conclusions.

In summary, existing research on tDCS and SLT has shown that the 'ideal' combination of behavioural treatment and neurostimulation is: a-tDCS in perilesional regions, for 20 minutes, while practicing linguistic tasks (online). Additionally, tDCS seems more suitable for use in chronic patients as their brain activity is more stable and they are less likely to have tDCS-provoked seizures.

1.6. Factors that predict language recovery and therapy-driven recovery in post-stroke aphasia

Prognosis of language recovery is a major area of interest within aphasic studies. However, examination of aphasia recovery is challenging because it involves different phases (i.e. acute/subacute versus chronic stroke) and several potential factors that could influence patients' outcomes. In general, studies in this area have tried to determine what individual, neurological, social, and therapeutic-related conditions impact patients' language recovery (Lazar & Antoniello, 2008; Plowman, Hentz, & Ellis, 2012). This section attempts to provide a brief overview of the literature regarding relevant factors that may influence patients' language recovery and their response to SLT. This is divided in two major parts: (i) factors that influence aphasia recovery and therapy-driven recovery in acute/subacute stroke (between first hours and six months after stroke); and (ii) factors that influence aphasia recovery and therapy-driven recovery in chronic stroke (between six months and years after stroke). This time-related division is important in aphasia recovery because acute stroke is generally driven by neurological interventions (delivered at the hospital) and spontaneous biological recovery that occurs in the next hours and days after the stroke occurs (Cramer, 2008). These factors could make conclusions less clear in the early phase but is unlikely to be a problem in the chronic phase.

Only few prospective studies have investigated what factors predict patients' language recovery in acute stroke (i). However, these studies vary in terms of methodological approaches (i.e. instruments used for language assessment, time post-onset at which patients were tested, type of stroke, etc.). Pedersen,

Jorgensen, Nakayama, Raaschou & Olsen (1995) conducted a prospective study in a big sample (*n*=881) of acute post-stroke patients. They found that 38% of the patients (i.e. 334) had aphasic symptoms at hospital admission. Only 30% of these patients had complete aphasia recovery at six months. The remaining patients with aphasic symptoms reached a plateau of spontaneous recovery on average two weeks later, but this depended on initial aphasia severity. They concluded that only initial aphasia severity predicts patients' language recovery in acute stroke. Lazar, Speizer, Festa, Krakauer & Marshall (2008) performed a study in acute stroke (ranging from 24 to 72 hours of stroke onset) including only patients with a single event. They followed up patients for three months. Regression analyses showed that no single measure predicted language recovery. However, a combination of age, initial aphasia severity, and lesion size together significantly correlated with language recovery at 3 months follow-up. Maas et al. (2012) conducted a study in patients within the hyperacute time-window (after 12 hours of symptoms appearance). They found that initial aphasia severity, age, lesion size, lesion site (left perisylvian and subcortical regions), history of multiple strokes, and level of sedentariness correlated with language recovery at six months.

In terms of factors that influence patients' responses to aphasic therapy in acute/subacute stroke, Bhogal et al. (2003) reviewed the literature to investigate whether therapy length and intensity correlate with therapeutic gain. They found that intensive therapy in a short period of time (nine hours per week in average for eleven weeks) correlated with improvement of patients' outcomes. In line with this study, Godecke et al. (2013) analysed therapeutic results in two different

trials. They found that number of therapeutic sessions starting few days after stroke (before day 14), initial aphasia severity and a measure of disability in daily life activities (modified Rankin Scale) predicted patients' therapy gains calculated as proportion of the potential maximal gain (Lambon Ralph et al., 2010). Using the same population, these authors conducted a secondary study following patients up to six months (Godecke et al., 2014). They corroborated that early initiation of aphasia therapy predicts patients' outcomes in SLT.

Several studies have tried to identify predictors of aphasia recovery in chronic stroke (ii). Different methodological approaches have been conducted but results may differ along studies. Lazar and Antoniello (2008) examined whether aphasia type is an important predictor of recovery. They found that diagnosis initially given (at acute stage) changes over time: in the long-term and once spontaneous recovery have reach the plateau, anomic aphasia is the most frequent syndrome exhibit by patients. In terms of prognosis of recovery, they established that anomia, transcortical and conduction aphasia are less severe, hence recover better than Broca's, Wernicke's, and global aphasia. Moreover, in the same review, they found that lesion location is an important predictor of recovery. Patients that spared key language-related perisylvian regions recover better than patients with damage in those regions. Likewise, Plowman et al. (2012) conducted a review of the literature. They found that lesion location and lesion size together and aphasia severity predict long-term language recovery. In a study conducted by Wang, Marchina, Norton, Wan, & Schlaug (2013), they found that the site and size of lesions of the arcuate fasciculus predict patients' outcome in speech production and naming tasks. In other study, using MRI and

behavioural data, Hope, Seghier, Leff & Price (2013) analysed a large sample of chronic stroke patients and found that combination of time since stroke, lesion volume and primarily lesion location accurately predicts chronic patients' recovery even several years after stroke onset. Lastly, Forkel et al. (2014) in a volumetric study in aphasic patients found that spared WM volume in the right arcuate fasciculus predicts aphasia severity at six months after stroke onset.

In terms of factors that influence aphasic patients' response to SLT in chronic stroke, Breier, Maher, Novak & Papanicolaou (2006) studied patients' outcomes to constraint-induced language therapy (i.e. practice and repetition on a mass basis). They used magnetoencephalography in a group of five patients with Broca's aphasia and one with conduction aphasia. Results showed that pre-treatment bilateral activation of posterior temporo-parietal regions predicted therapeutic improvement. Good responders showed bigger activation in those regions than non-responders. Marcotte et al. (2012) conducted an intervention study in chronic patients with anomia (n=9). Patients were tested and scanned (structural MRI and fMRI) before and after therapy. They found that patients' outcomes were predicted by: 1) integrity of Broca's area; 2) baseline activation of left premotor cortex in naming tasks; and, 3) baseline scores in naming, verbal comprehension, and repetition. Patients with less severe impairments responded better to this therapy. Bonilha, Gleichgerrcht, Nesland, Rorden & Fridriksson (2016) conducted a study with anomic patients (n=24) that undertook intensive treatment (three hours per day for two weeks). Results showed that preservation of left temporal regions and aphasia severity predicted patients' outcomes.

Finally, some studies have tried to identify cognitive predictors of patients' response to therapy. For instance, Lambon Ralph et al. (2010) used factor

analysis to identify groups of linguistic and cognitive tasks that significantly predicted therapy gain in chronic anomic post-stroke patients. The factors included phonological abilities and a non-linguistic dimension that loaded onto attention, visuospatial memory, and executive functioning tasks.

In summary, initial aphasia severity and early aphasia therapy appear to be solid predictors of aphasia recovery in acute/subacute stroke. In chronic stroke, a variety of studies have indicated several variables associated with recovery: the most important are lesion location, preservation of key left hemisphere language regions, reorganisation of the language network (activation of both left perilesional and right hemisphere regions), WM volume of language homologues right hemisphere regions, aphasia severity, and aphasia type.

Background - Summary

This background section has reviewed the key aspects of this study: Reading and its cerebral underpinning, the triangle model of reading, central alexia and its characteristics, executive functions in aphasia, computerised therapies for aphasia treatment, tDCS in SLT, and prognosis of language recovery. Nevertheless, more information is needed about neurological, linguistic and non-linguistic/cognitive factors involved in aphasic patients' recovery after stroke.

1.7. Main aims and research questions

My research aimed to study both neurological and cognitive factors that predict which patients with CA respond to a computer-based reading therapy (iReadMore). The results are presented in three experimental chapters. They investigate three main aims:

(1) to characterise chronic CA patients' neuropsychological profile.

Specifically, this thesis will explore which cognitive abilities and brain regions are associated with reading impairments in CA: do CA patients exhibit impairments in non-linguistic/executive functions tasks? Which executive abilities are impaired? Are executive impairments in CA linked to their linguistic impairments? Which brain regions correlate with patients' reading impairments and their remaining reading abilities?

As stated previously (outline of this thesis), these questions are addressed in Chapter three in which baseline patients' abilities are analysed and compared to controls and normative data. Moreover, PCA and VBM analyses are conducted to answer these questions. Based on the current literature, one hypothesis was that reading impairments in CA are associated with executive functions. Another hypothesis was that GM and WM regions within the dorsal and ventral visual streams would be associated with different dimensions of reading abilities in CA identified by PCA.

(2) to determine whether cognitive abilities and brain lesion-site predict patients' outcomes in response to a computerised reading therapy.

My research aimed to study which individual (demographic and behaviour profile) and neurological (brain-based) variables influenced CA patients' response to iReadMore therapy. Studies of chronic aphasia suggest that cognitive/non-linguistic abilities significantly influence the effectiveness of SLT (e.g. Brownsett et al., 2014): Chapter four attempts to answer: is patients' response to iReadMore predictable? Which neuropsychological abilities are required for a positive response to iReadMore? Do patients with poor executive abilities have a poor response to reading therapy? Do CA patients require domain-general cognitive treatment to respond better to SLT? Is patients' response to iReadMore related to lesion site?

Based on the hypothesis that patients' response to a specific reading therapy will be predicted by their performance on a battery of cognitive measures and the distribution of their brain lesion, an important contribution in the understanding of factors that predict patients' recovery is expected.

(3) to explore if chronic CA patients present macrostructural and/or microstructural brain changes in response to iReadMore therapy.

Finally, using a quantitative MRI protocol called multiparameter mapping (Callaghan et al., 2014) longitudinal analyses are conducted in chapter five to determine whether changes in the patients' brain structure are associated with therapy-driven recovery. Based on the current literature it was expected that brain changes in response to iReadMore will occur in perilesional language/reading related regions or in contralateral homologues.

The following chapter moves on to describe in greater detail the iReadMore therapy, therapeutic outcomes in my sample of CA patients, and the methods used in this study.

2. METHODS

In this thesis I have implemented different methods to investigate which cognitive variables predict patients' recovery responses to therapy and what structural changes the therapy may induce. This chapter aims to describe how the iReadMore trial was conducted and what analyses were performed to produce this thesis. This chapter is divided into two parts. The first part describes the treatments that the study participants received (iReadMore computerised-therapy and tDCS) followed by a discussion of the patients' outcomes to these interventions. The second part describes data collection at each time point (behavioural and brain data) and the methods used to analyse these data. The order I discuss my methodology mirrors the structure of the experimental chapters that follow, so: description of the interventions (iReadMore and tDCS); how the effects of the two interventions were measured; baseline behavioural data collection and analysis (including data reduction techniques such as PCA); analyses aimed at explaining the therapeutic effects; analyses aimed at predicting the therapeutic effects; analyses aimed at identifying structural brain changes associated with the therapeutic effects.

2.1. Materials and methods

2.1.1. Study design

The data reported in this thesis is a subset of a larger repeated-measures study with six time points (T1-T6. See Figure 3) designed and implemented by Professor Alexander Leff and Dr Zoe Woodhead to assess the effectiveness and

interactions of two interventions: 1) iReadMore therapy; and 2) anodal transcranial direct current stimulation (a-tDCS).

The data I helped collect and analyse in this thesis are from time points T1-T4 only, when behavioural (T1-T4) and brain-based (T3 and T4) data was collected over the course of 3 months (green dotted line in figure 3). The main outcome measure (single-word reading test: SWR) was collected at every time point. This task contained a selection of 90 trained and 90 untrained words, matched for psycholinguistic variables. Both reading accuracy and reaction times were assessed. Brain outcome data was acquired with a quantitative MRI protocol that is explained in a later section.

Baseline sessions were spread across T1 and T2, spaced by 2-4 weeks, where patients were assessed using a comprehensive battery of cognitive tests (linguistic and non-linguistic tests described later in the instruments section) in the absence of any treatment. T3 was an additional pre-treatment assessment session, 4 weeks after T2, aiming to identify the amount of change caused by spontaneous recovery or test-retest effect on the outcome measures. As well as SWR assessment, a structural MRI scan was acquired at T3. Between T3 and T4, patients were trained for 4 weeks with a computer-based therapy called “iReadMore” and concurrent tDCS stimulation. The last time point (T4) involved post-treatment SWR assessment and a second structural MRI scan.

The larger study (described in a publication currently under review) used a crossover design with a second 4 week block of iReadMore therapy between T4-

T5. The crossover design was used to test the effects of real (a-tDCS) versus sham (s-tDCS). Each patient received either a-tDCS or s-tDCS in the first block, then crossed-over to the other stimulation condition in the second block. Post-treatment assessment at T6 (3 months after T5) only included the SWR assessment.

During each block of iReadMore therapy, patients completed at least 35 hours of training over 4 weeks. They practiced at home plus in face-to-face sessions with a specific list of 150 words. In the second block, participants were trained with a new list of 150 words (selection of therapeutic items is explained later in the iReadMore intervention section). Moreover, participants came to our laboratory 3 times per week to receive 40 minutes of face-to-face iReadMore therapy concurrent with 20 minutes of a-tDCS or s-tDCS.

The required sample size was calculated based on data collected from the pilot study performed by Dr Woodhead et al. (2013). Power analysis using G*Power software (Faul, Erdfelder, Buchner, & Lang, 2009) with power (1 - β) set at 0.90 and $\alpha = 0.05$ (two-tailed) indicated that a sample of at least 18 participants would be needed to detect a similarly-sized effect of around 10% improvement in reading ability.

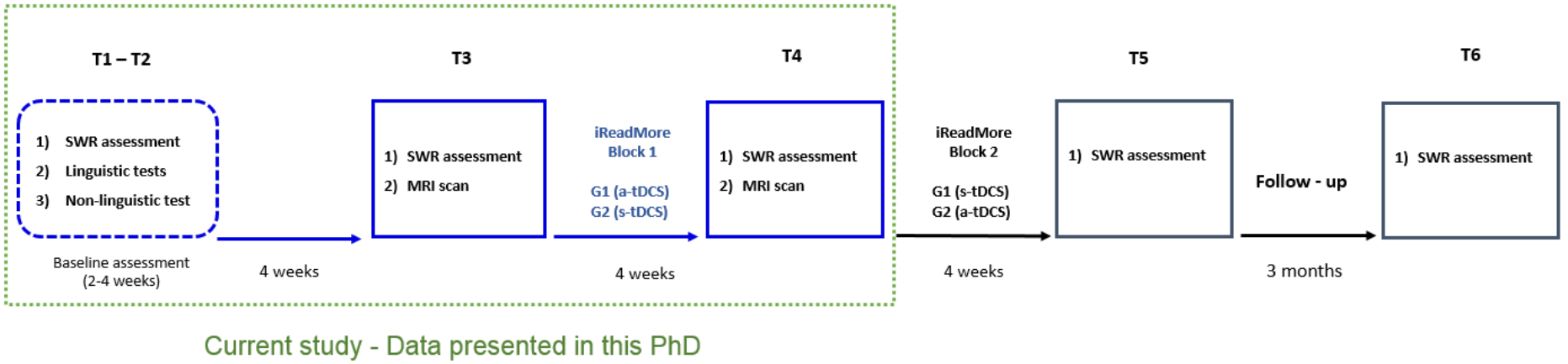

Figure 3. Study design. The current study (T1 - T4, within the green dotted line) is a subset of a larger longitudinal study (T1 – T6). It involved baseline behavioural testing (T1 – T2), and pre-treatment and post-treatment (T3-T4) reading testing and MRI scan. In the first block of therapy, participants received behavioural training (iReadMore) and tDCS for 4 weeks. For tDCS, patients were randomly allocated in two groups to receive real or sham tDCS. The larger study (outside green dotted line) included a second block of therapy and tDCS. In this block, for tDCS patients received the opposite stimulation to the received in block 1. SWR= single-word reading task; MRI= structural magnetic resonance imaging; G= group; tDCS: transcranial direct current stimulation; a-tDCS: anodal tDCS; s-tDCS: sham tDCS.

2.1.2. Participants

23 patients with chronic post-stroke aphasia (15 males, mean age 54.4 years, range 25 – 78 years; see Table 1 for demographic details) were recruited from the PLORAS database (Seghier et al., 2016) or out-patient speech and language therapy services at the National Hospital for Neurology and Neurosurgery, University College London Hospitals.

The inclusion criteria in this study were:

(i) Left hemisphere stroke with preserved or partially preserved left IFG. This was a specific requirement of the tDCS therapy.

(ii) At least one year post-stroke.

(iii) English as their first language.

(iv) In the aphasic range on either the naming or the spoken picture description subtests of the Comprehensive Aphasia Test (CAT) (Swinburn, Porter, & Howard, 2004). According to the normative data, the non-aphasic range for the Naming objects subtest is 42-48 (inclusion criterion <42); for the Naming actions subtest is 8-10 (inclusion criterion <8); and, for the Spoken picture description is 33-87 (inclusion criterion <33).

(v) Impaired on the Single word reading subtest of the CAT. In this test, the non-aphasic range is= 44–48 (inclusion criterion <44).

(vi) Normal or corrected to normal vision and audition.

The exclusion criteria were:

(i) A history of other neurological or psychiatric condition.

(ii) A history of developmental dyslexia.

(iii) Any contraindications for MRI scanning.

(iv) Any contraindications for tDCS.

(v) Severe impairment in speech production. This requirement was defined using the word repetition subtest of the CAT with a cut-off based on the PLORAS database where a severe impairment is indicated as a T-score <44.

The CONSORT diagram flow ("CONSORT Transparent reporting of trials,") (Figure 4) shows the number of participants recruited, allocated, and analysed. The diagram includes only the first block of therapy (n=23) which is the focus of this thesis. Analyses corresponding to chapter three and four were conducted on 23 participants. However, in the MRI data presented in chapter five, data from six participants were excluded (n=17, excluding participants 10, 15, 16, 18, 19, and 22) as they had contraindications for the MRI protocol required for the analyses presented in those chapters. For safety reasons those six patients were scanned instead at the Birkbeck-UCL Centre for Neuroimaging (BUCNI) in a 1.5T scanner. Chapter three involved voxel-based morphometry (VBM) analysis using modulated segmented images with voxel values between 0 and 1 for each tissue class. These images always sum to 1 if the values are added up for each tissue class at that voxel. Hence, there would be no reason to assume that images used for VBM analysis would differ between scanners. Chapter four involved analyses of binary lesion images (0, 1) to calculate percentage damage of parcellated regions. Again, there should be no difference across the scanners for acquisition of these images. In chapter five the focus of analyses were on quantitative imaging data in which voxel's values depend on the magnetic field strength of the scanner. Hence data from the two scanners could not be combined for this analysis.

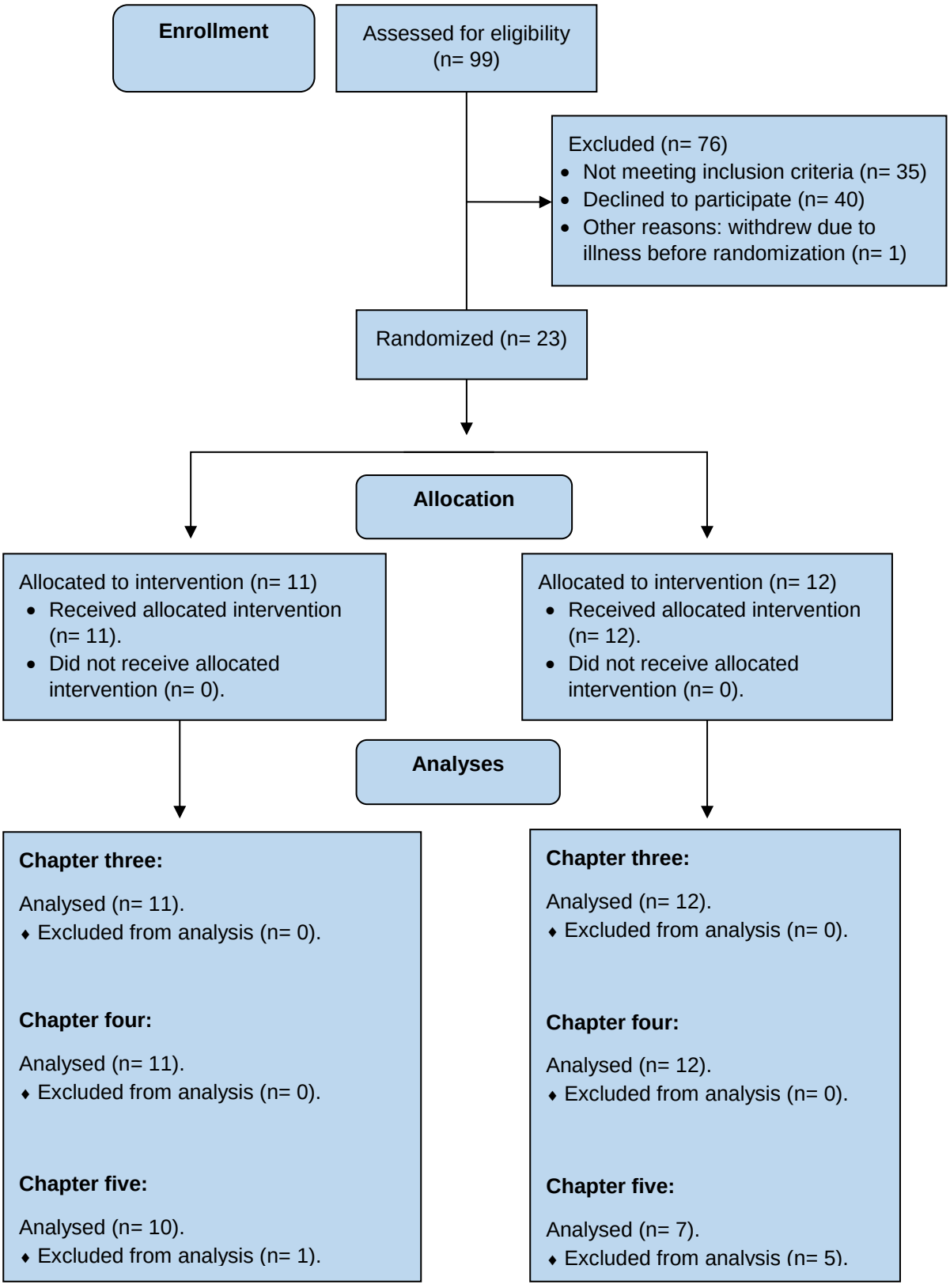

Figure 4. CONSORT flow. This diagram shows participant enrolment, allocation, and analyses in the therapeutic trial. Allocation is divided according to tDCS group in the block 1 of iReadMore therapy.

Participants were recruited on the basis of the above criteria and not on alexia subtype. However, along with the patients' demographic information, Table 1 includes details of their reading profiles according to dyslexia subtypes. The patients were categorised as having phonological (P), deep (D) or surface (S) dyslexia using definitions from Whitworth et al. (2014). These authors define alexia subtypes based on patients' reading errors and lexicality, regularity and imageability effects during reading of single words and non-words/pseudowords.

In this classification reading errors include:

1) Phonological errors: regularisation of the written word - irregularisation of the word is also possible but frequency of this phenomenon is very low.
2) Visual/phonological errors: at least 50% of letters or phonemes in the target word are present (in the same order) in the inaccurate response.
3) Semantic errors: the response is semantically related but visually different to the target word.
4) Visual/semantic errors: the response is semantically and visually related to the written word.
5) Morphological errors: the response shares the root of the word but with addition, deletion or substitution of a morpheme.

The reading effects are defined as follow:

1) Lexicality effect: characterised by worse accuracy reading non-words than real words. This reflects impaired sublexical (O-P) processing.
2) Regularity effect: better accuracy reading regular than irregular words.

3) Imageability effect: better accuracy reading high- imageability words than low imageability words. This indicates that reading is mediated by semantic processing (O-S-P route) and that the sublexical (O-P) route is impaired.

Regularity and imageability effects were determined using binary logistic regression on word reading accuracy data from the baseline testing sessions (T1 and T2), including the psycholinguistic variables of word length, frequency, regularity and N-size.

Based on these conditions, phonological dyslexia (P) was defined according to the presence of a lexicality and imageability effect with no regularity effect or semantic errors in word reading. Deep dyslexia (D) was defined according to a lexicality and imageability effect, no regularity effect, but with evidence of some semantic errors. Surface dyslexia (S) was defined according to a regularity effect, no lexicality effect, but phonological errors (Whitworth et al., 2014).

Patient ID	Age (in years)	Gender	TPS (in months)	LV (in cm^3)	Handedness R/L	CA subtype
1	44	Male	94	240.9	R	D
2	50	Male	82	304.5	R	D
3	64	Male	25	102.7	R	P
4	52	Male	66	122.7	R	P
5	56	Female	93	149.8	R	S
6	55	Female	75	151.2	R	P
7	33	Female	59	181	R	P
8	67	Male	107	11.7	R	D
9	43	Female	55	399.2	R	D
10	61	Male	19	195.6	R	D
11	52	Male	12	31.2	R	P
12	50	Female	14	59.4	R	P
13	54	Male	24	149.3	R	P
14	56	Male	23	45.1	R	P
15	54	Male	39	189.7	R	P
16	73	Male	158	205.2	R	D
17	60	Male	16	102.6	R	D
18	78	Male	22	128.5	L	P
19	50	Female	72	141.3	R	P
20	72	Male	101	243.3	R	D
21	58	Female	41	297.7	R	P
22	42	Male	13	43.7	L	P
23	26	Female	81	161.9	R	D

Table 1. Demographic and clinical information on each patient. TPS= time post-stroke; LV= lesion volume; R= right; L= left; CA= central alexia; P= phonological alexia; S= surface alexia; D= deep alexia; CA= central alexia.

23 age- and gender-matched healthy controls (15 males, mean age 54.4, range 23 – 76 years) were assessed to acquire normative data for all tasks that did not have published norms. These tasks (explained in a latter section) were: single-word reading (SWR), pseudoword reading, written semantic matching, written sentence to picture matching, the Neale Analysis of Reading Ability test, subtests 1 and 2 of the Cattell Culture Fair test, Digit span of the Wechsler Adult Intelligence Scale IV, the Two-Armed Bandit Task, a non-verbal version of the Sustained Attention to Response Task (SART), and a visuo-spatial short-term memory task. Controls completed all baseline tasks in one session of approximately 2 hours. An independent samples t-test showed no significant difference in age between groups ($t(44)=.012$, $p=.991$).

Additionally, a dataset of 29 healthy subjects' quantitative MRI scans previously collected by Dr Jenny Crinion was used as control group to identify patients' brain lesions (the quantitative MRI protocol and the brain lesion identification procedure are explained in the structural MRI section). This group was age-matched to the patient group (18 males, mean age 54.6, range 20 – 72 years; $t(50)=-.050$, $p=.960$). All participants in the current study gave written informed consent.

2.2. Therapeutic interventions

2.2.1. iReadMore - Training stimuli

iReadMore includes a set of 590 words selected from the SUBTLEX lexical database (Brysbaert & New, 2009). Words are distributed in three lists (i.e. list A, B, and C) made up of 180 words each, and 50 core words with very high

frequency. Lists are counterbalanced as follows: 1) all words are between three and six letters in length; 2) words have high written frequency (SUBTLEXWF > 50); and, 3) words across lists are matched by imageability, regularity, number of phonemes and syllables.

At each time points of the therapeutic trial words are pseudo-randomized across all subjects to be the therapeutic items trained in block 1 and block 2 of iReadMore or untrained words (to investigate generalisation of the therapeutic effect). Finally, the core words are tested at each time points and trained at each therapy block.

2.2.2. iReadMore therapy

iReadMore is a computer-based single word reading therapy developed in our laboratory ("Neurotherapeutics group, Institute of Cognitive Neuroscience - UCL"). This therapy was based on a previous app created by Woodhead et al. (2013). The current iReadMore trial investigated whether this therapy was effective in improving reading accuracy and speed in patients with CA. iReadMore involves adaptive multimodal treatment based on pairing the written word with the corresponding spoken word and picture (See Figure 5). The assumption behind this design implies bootstrapping of reading by activation of phonological (i.e. spoken words) and visual semantic representations (i.e. picture) of the word.

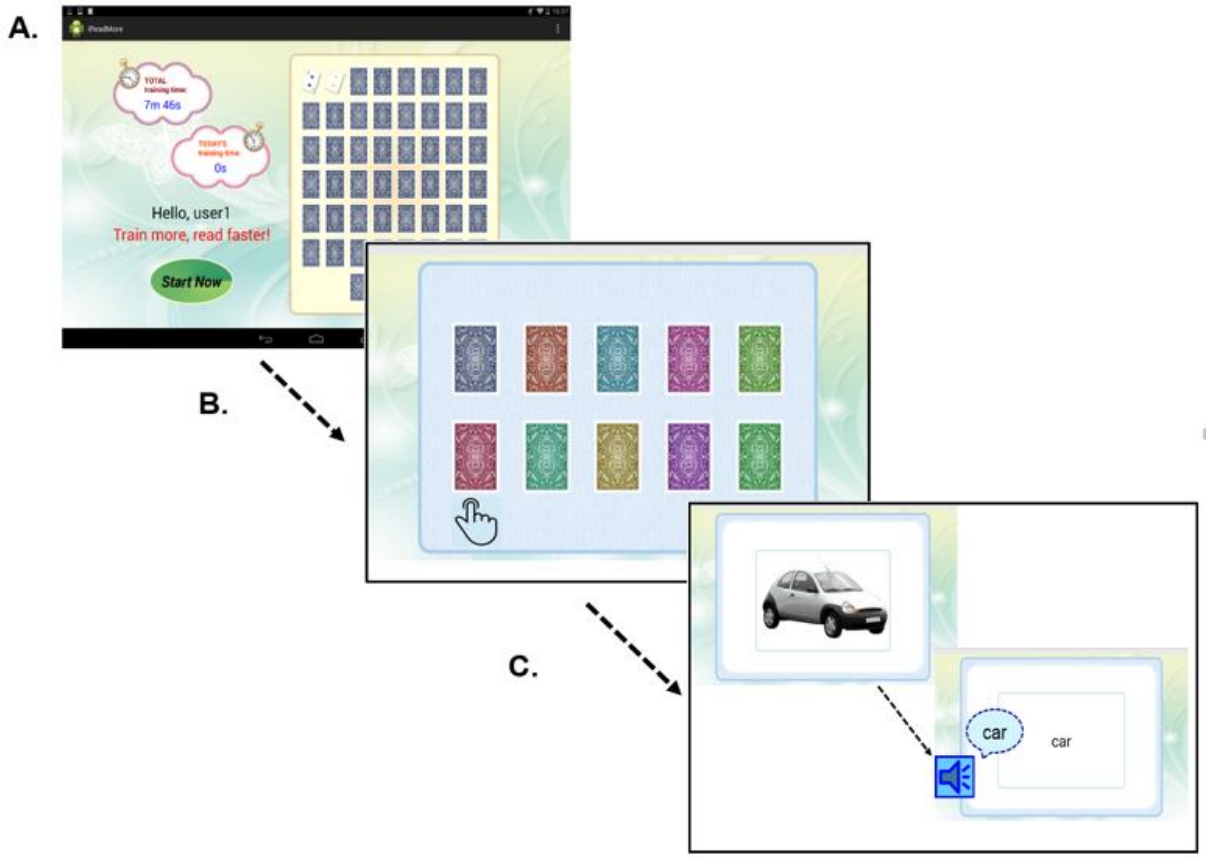

Figure 5. iReadMore training trials. Panel A: Initial screenshot displaying participant's name and overall time of training. Deck of cards in the right side represents each training trial (B). Panels B and C: iReadMore training: the participant touches any of the cards (B) and a visual, a written, and a spoken representation of the word are presented simultaneously (C).

iReadMore encompasses both training and testing blocks. Each training block includes presentations of 10 written words (Figure 5 - A and B). For each word, a picture is presented followed by its corresponding written and spoken word, presented simultaneously (Figure 5 - C). These pairings are always congruent.

Then, patients enter a testing block (Figure 6) comprising up to 30 trials of a matching task. In each trial, a written word from the training block is presented simultaneously with a spoken word. For 50% of the trials the written and spoken words match (e.g. *car,* "car") and for 50% of the trials they do not match (e.g. *car,*

“cat”). The subjects have to make a two-alternative forced choice decision by button press for each trial. Reading accuracy is scored: 2 points for a correct response that is faster than the ‘fast threshold’ (ranging from 4 to 2 seconds, adapted to task performance); 1 point for a correct response that is slower than the ‘fast threshold’; and, -1 point for an incorrect response or if no response is received after 10 seconds. Patients received immediate feedback for each trial, with positive or negative sounds and an onscreen indication of their score changing. Patients are able to visually track their performance: at the top of the screen there is a gender-personalised avatar which moves forward or backward according to the participant’s accuracy and speed. If they score enough points in the testing block, they win a card as the avatar reaches it.

Task difficulty in each level is defined using an adaptive algorithm that increases or decreases according to patient’s accuracy. If the patient reached the criterion score within the level (up to 30 trials), difficulty increases in the following training and testing blocks. Difficulty is determined by two parameters:

1) The duration of written words presentation in the training and testing blocks: initially written word duration is matched to the patient’s baseline word reading speed (T1-T2). Then, speed may increase or decrease according to patient’s accuracy in each level of the testing blocks.
2) Matching task difficulty is adapted independently for each word by making the written and spoken words in different trials progressively more similar. For each ‘different’ trial the target spoken word is paired with a written distractor. The written distractor may be ‘easy’ (shares only the first letter in common with the target word), ‘medium’ (shares the first letter and at

least one other letter) or ‘hard’ (shares the first letter and at least two other letters).

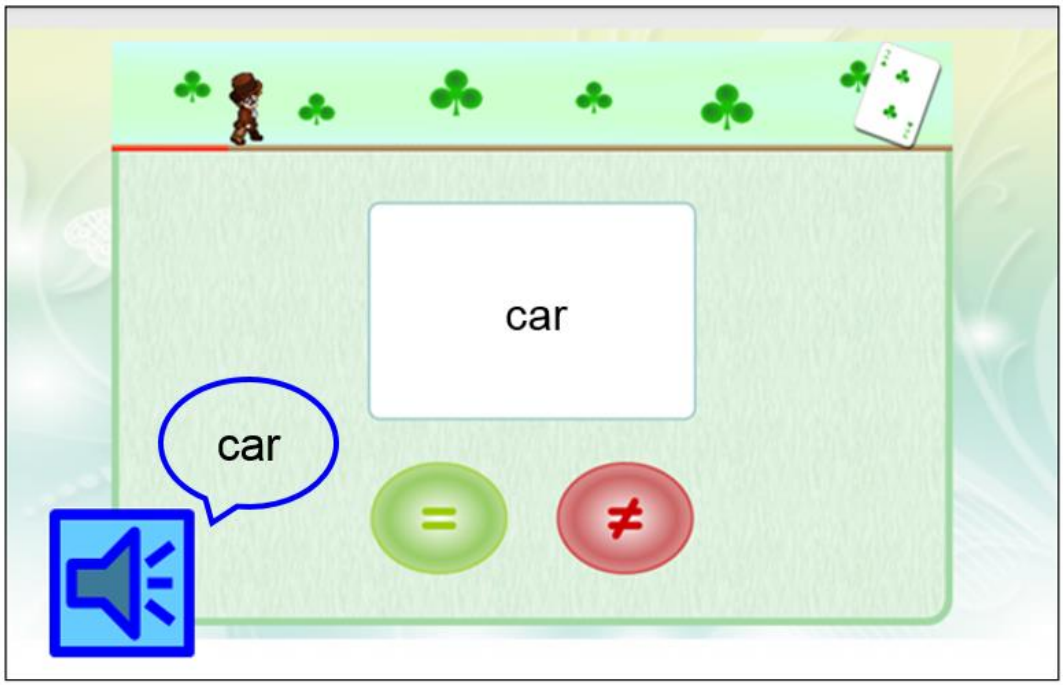

Figure 6. iReadMore testing trial. Once patients have completed training of a set of the words, they are tested for reading accuracy and speed. The written word is presented simultaneously with a spoken word. Patients answer whether both stimuli matched or not.

2.2.3. Transcranial direct current stimulation (tDCS) protocol

In each block of iReadMore (four weeks), participants attended tDCS sessions 3 times per week (Monday, Wednesday and Friday). Each session involved 40 minutes of face-to-face iReadMore therapy with tDCS administered concurrently for the first 20 minutes of training (see Figure 3 - study design). Participants were randomly assigned to Group 1 (a-tDCS in Block 1 and s-tDCS in Block 2) or Group 2 (s-tDCS in Block 1 and a-tDCS in Block 2). The experimenters were blinded to tDCS conditions by using numerical codes to program the tDCS control box in each session. Unblinding of tDCS conditions happened after data

acquisition and data analyses had finished. Hence, a-tDCS was placebo-controlled and double-blind but iReadMore therapy was not.

In this study, the tDCS protocol involved the following parameters:

- Equipment: DC-Stimulator Plus (NeuroCare).
- Electrode size: 25 cm^2.
- Stimulation electrode position: left frontal cortex (10-10 position FC5). (See Figure 7). This area was selected as stimulation target because previous MEG studies have found that left IFG enhances bidirectional brain connectivity with left ventral occipital regions during word reading (Woodhead et al., 2014; Woodhead et al., 2013). Moreover, Holland et al., (2011) found that a-tDCS in this region facilitates speech outputs in linguistic tasks.
- Reference electrode position: right supraorbital region.
- Length of stimulation: 20 minutes.
- Current strength: 2mA (A= ampere).
- Charge applied= 0.05 Coulomb/cm^2 (Coulomb = 1 A/second. Magnitude of electric charge delivered in 1 second by a constant current of 1 ampere).
- Intervals of stimulation: 3 sessions / week.
- Number of sessions: 12 sessions at block 1 and 12 sessions at block 2.
- Anodal stimulations (a-tDCS): 30 second fade-in, 20 minutes of stimulation, and 15 seconds fade-out.
- Sham stimulation (s-tDCS): 30 seconds of current (fade-in). Then, 20 minutes without stimulation, but recording impedance.

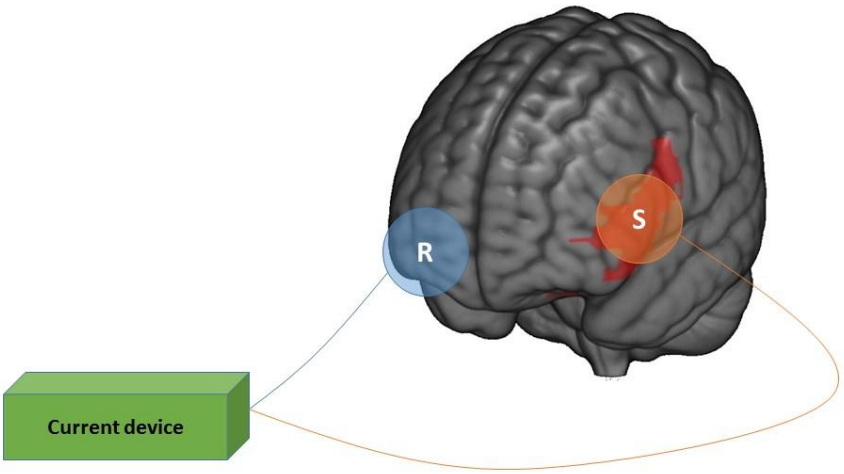

Figure 7. tDCS functioning and electrode positions. tDCS is a very simple tool conformed by two elements: 1) a battery device (in green) which is set up according to the desired parameters; and 2) two electrodes which are attached to the scalp of the subject to deliver the current from the device. One electrode is the stimulator (S) and one is the reference(R). In the iReadMore trial, the anode (S= stimulation electrode) was located over left frontal cortex and the cathode (R= reference electrode) was located over the right supraorbital region.

2.2.4. Behavioural analyses of therapeutic outcomes

A systematic method to study patients' outcomes in SLT is still lacking. Previous published studies have inconsistencies between the outcome measures used to determine SLT effectiveness (Brady et al., 2016; Fillingham, Sage, & Ralph, 2006; Lambon Ralph et al., 2010). In my thesis, the primary outcome measures (dependent variables) were change in reading accuracy and RT between T3 (before therapy) and T4 (after therapy). These measures were calculated from a SWR task (described at the instruments section) containing a word-list of 90 trained and 90 (matched) untrained words. Accuracy and speed were calculated separately for both trained and untrained words. The method chosen to calculate

the therapeutic effect of iReadMore on reading accuracy (Dependent Variable - DV) was the **"percentage of absolute change"** (See Figure 8). It was selected (in preference to change expressed as a percentage of baseline reading accuracy or maximum possible change) on the basis that the sample of patients recruited in this study had variable severity of reading impairments at baseline (see Figure 9); therefore it was used to ensure a consistent measure of improvement at a group level. Additionally, change in reading speed was calculated by subtraction of the averaged RT in words read correctly (T4 - T3).

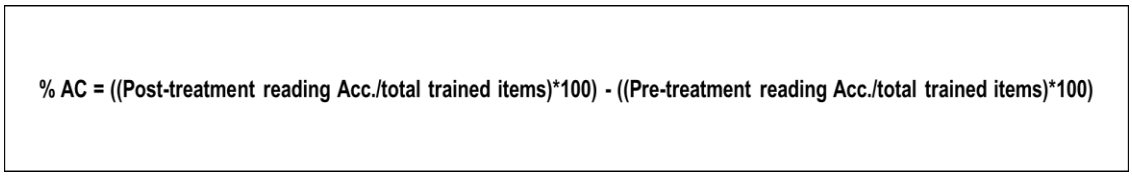

Figure 8. Percentage of absolute change formula. This figure illustrates the formula used to calculate percentage of absolute change (% AC). Acc. = accuracy.

A 2 x 2 repeated measures ANOVA was conducted to compare the effect of iReadMore and tDCS on reading accuracy (i.e. % AC). This analysis involved two factors: 1) within-subjects effect of word list (trained vs untrained words); and 2) between-subjects effect of stimulation (a-tDCS vs s-tDCS). Similarly, these two factors were used to compare the effect of iReadMore and tDCS on reading speed (i.e. average RT change on correctly read items only). Group effect sizes were measured as follows: 1) unstandardised effect sizes were calculated by averaging change across the group in accuracy and RT (as described above); and 2) standardised effect sizes were established by calculating Cohen's d for both reading accuracy and speed. Standardized effect sizes are calculated using a mix of both the change in the outcome measure and the variance associated with this change, while unstandardized effect sizes simply report the magnitude

of the change (Walker, 2007). It is our group's policy to report both where possible.

2.3. iReadMore – Therapeutic results

Because the main aim of this thesis is to understand the behavioural and brain factors that explain and predict responses to the alexia interventions, rather than to understand the mechanism(s) of the interventions themselves; I will report the therapy effects for each participant here, in Table 2. This table contains patients' neurostimulation conditions, reading accuracies, and reading speeds (RT) before (T3) and after (T4) iReadMore therapy. It also includes change in accuracy (% AC) and RT for trained and untrained words. Moreover, for illustrative purposes Figure 9 also shows patients' reading accuracies (A) and speeds (B) before and after therapy.

ID	tDCS a/s	Reading Acc. (%) - T3	Reading Acc. (%) - T4	RT (ms) - T3	RT (ms) - T4	AC (%) - Trained words	AC (%) - Untrained. words	Averaged RT change - Trained words	Averaged RT change - Untrained words
P1	a	31.7	63.3	1377.6	1431.6	31.7	8.4	54.0	66.2
P2	a	26.1	43.3	1367.1	1673.1	17.2	0.0	306.0	454.1
P3	s	99.4	96.7	857.0	867.0	-2.8	-4.4	10.0	36.0
P4	s	65.6	84.4	749.9	706.9	18.9	0.0	-43.0	-22.7
P5	s	52.2	60.6	2189.4	1953.9	8.3	-2.8	-235.6	-30.6
P6	a	88.9	92.8	760.6	687.2	3.9	-2.2	-73.4	-55.5
P7	s	93.3	96.1	944.4	698.2	2.8	-2.2	-246.2	-131.5
P8	a	18.3	30.8	1986.6	1663.0	12.5	-6.7	-323.6	-1228.4
P9	a	75.0	86.7	N/A	N/A	11.7	-1.1	-244.2	-86.0
P10	s	11.7	16.7	1278.5	1034.2	5.0	2.5	N/A	N/A
P11	a	96.1	100.0	754.8	810.5	3.9	3.9	55.7	49.4
P12	s	94.4	96.7	844.4	696.4	2.2	0.0	-148.0	-97.9
P13	a	90.0	94.4	1321.7	1285.6	4.4	7.2	-36.1	4.4
P14	a	86.1	89.4	800.7	816.0	3.3	5.6	15.3	109.9
P15	s	62.2	68.3	1088.7	971.0	6.1	6.1	-117.7	-150.4
P16	s	20.0	25.8	1971.9	1781.1	5.8	-5.0	-190.8	-366.8
P17	a	34.2	44.2	863.6	790.9	10.0	-4.2	-72.7	-49.6
P18	a	77.8	80.0	1160.3	895.7	2.2	-13.3	-264.7	74.3
P19	s	41.1	46.1	800.1	663.2	5.0	7.8	-136.9	-38.6
P20	a	20.0	25.8	1468.9	968.0	5.8	-5.8	-500.9	-148.1
P21	s	67.2	83.3	1199.8	962.8	16.1	5.0	-237.1	-219.4
P22	s	76.7	88.9	705.5	619.9	12.2	1.1	-85.5	-26.3
P23	s	72.2	78.9	1256.4	1155.0	6.7	-2.2	-101.4	0.8

Table 2. Patients' primary outcomes at T3 and T4. It includes percentage of absolute change in reading accuracies and averaged speeds for trained and untrained items. a= a-tDCS; s= sham tDCS; Acc.= accuracy; RT= reaction time in milliseconds; AC= absolute change in percentage; N/A= Not applicable.

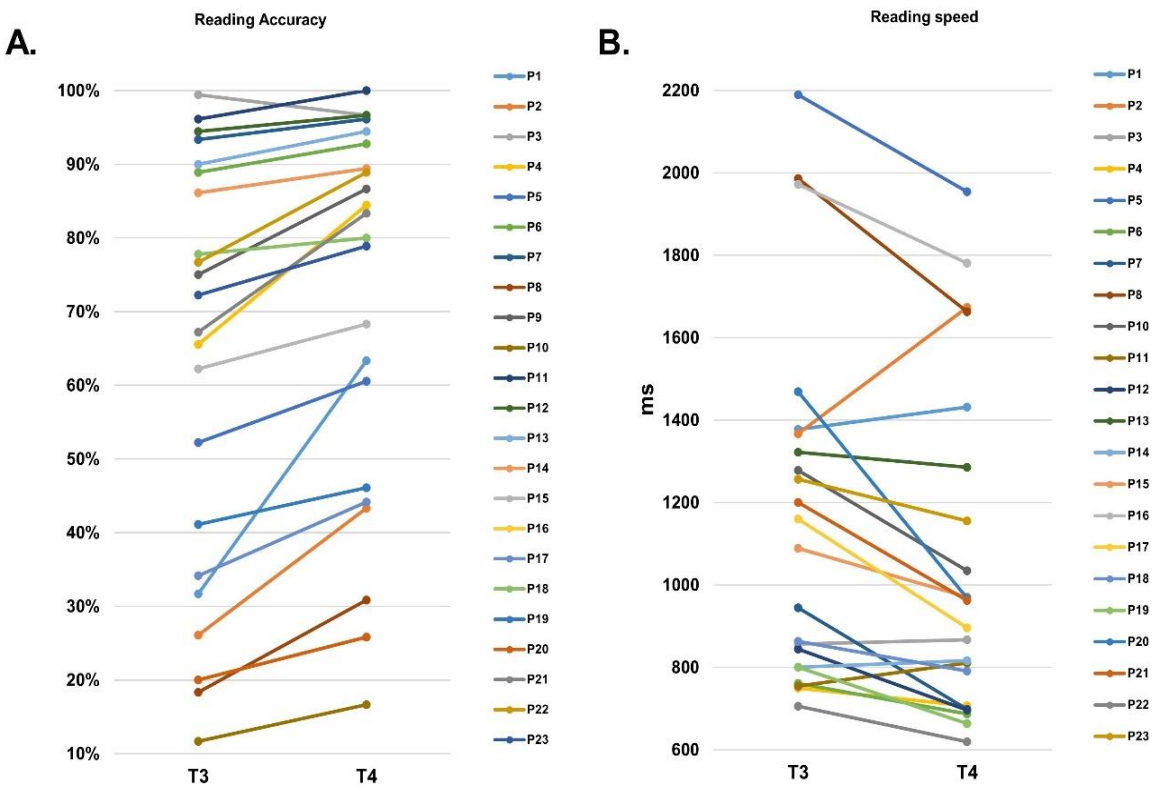

Figure 9. Patients' reading accuracies (A) and speeds (B). These figures illustrate patients' accuracies and speeds before and after iReadMore therapy.

Figure 10 shows the percentage of absolute change at a group level for trained and untrained words after block 1 of iReadMore therapy. This figure also shows the interaction with tDCS. The main effect of word-list showed that there was a larger change for trained than untrained words ($F(1, 21)= 28.93$; $P<.001$; $M=8.4\%$, 95% CI [5.23, 11.67]). The average improvement (i.e. unstandardised effect) in reading accuracy for trained words was 8.4% and the standardised effect (Cohen's *d*) was very large ($d= 1.31$). Average reading accuracy for untrained words decreased by 0.11%. There was no interaction between tDCS group and word-list ($P<.779$).

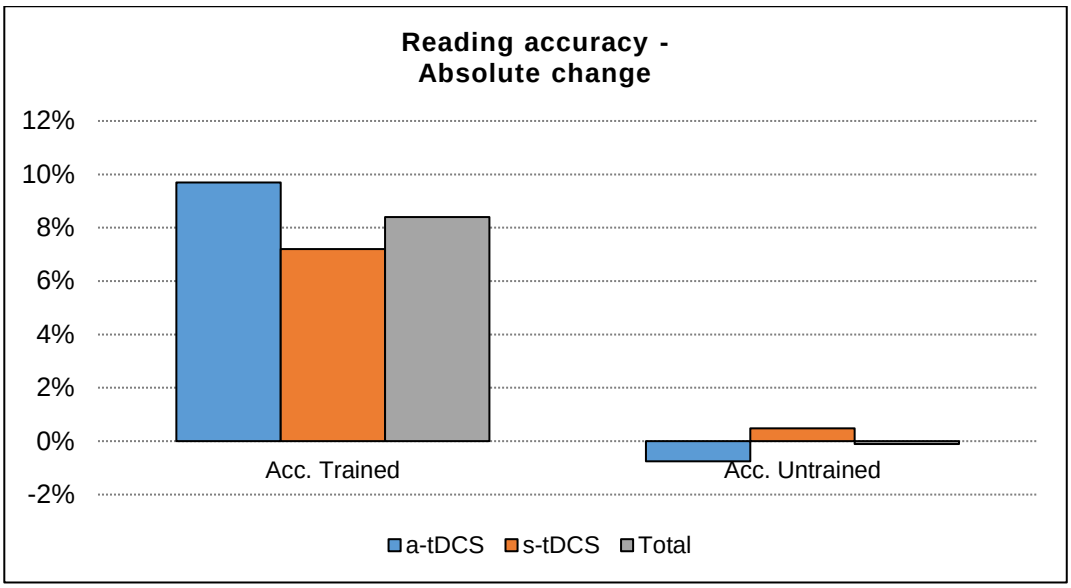

Figure 10. Percentage of absolute change after block 1. This figure illustrates percentage of absolute change at a group level after iReadMore therapy and tDCS. Acc.= accuracy; a-tDCS= anodal tDCS; s-tDCS= sham tDCS

Figure 11 shows the average change in reading speed at a group level for trained and untrained words and their interaction with tDCS group after Block 1 of iReadMore therapy. RT could not be calculated for P9 as his reading accuracy was so low that there were insufficient correct trials available to calculate RT reliably. Hence, results were calculated on 22 patients. There was no significant effect of word-list on RT (p=.516). The average RT for trained words decreased by 119 millisecond while average RT for untrained words decreased by 84 milliseconds. Cohen's *d* for the change in trained word RT was very small (*d*= 0.14). Moreover, there was no main effect of tDCS group on reading speed (p=.735).

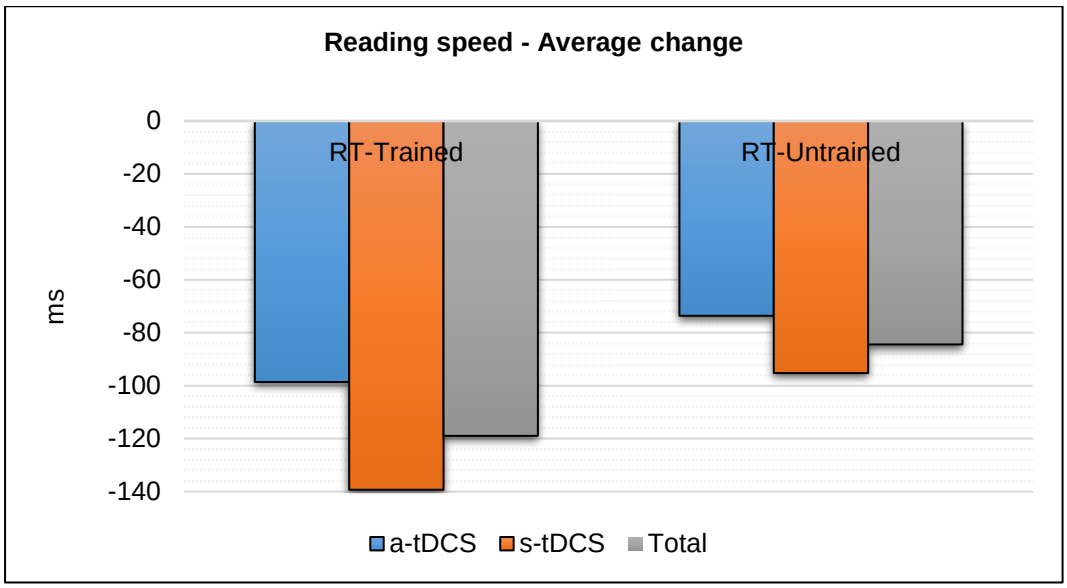

Figure 11. Averaged change in reading speed after block 1. This figure illustrates the averaged change in reading speed at a group level after iReadMore therapy and tDCS. a-tDCS= anodal tDCS; s-tDCS= sham tDCS; RT= reaction time; ms= milliseconds.

In summary, the present study found a positive effect of iReadMore on single-word reading accuracy of trained items. There was no generalisation to untrained words, which is in agreement with previous aphasic intervention studies that have found item-specificity in patients' outcomes (for review see Best et al., (2013)). Although patients at a group level increased their reading speed by 120 ms. in comparison to baseline, there was no significant difference with untrained items (84 ms.). Similarly, a-tDCS did not produce an effect in reading accuracy or speed, a finding that is contrary to previous studies which have suggested a positive effect of a-tDCS in SLT (de Aguiar, Bastiaanse, et al., 2015). However, for the sake of completeness it is important to clarify that results from the full crossover protocol of the iReadMore trial, with two blocks instead of one (Woodhead et al., 2017, under review) have found a positive effect of iReadMore on reading accuracy, reading speed, and a significant beneficial effect of a-tDCS that generalised to untrained words.

2.4. Data acquisition and data analyses

It is important to emphasise that several measures (behavioural and brain) were acquired at each time point of this thesis. Consequently, different analyses were conducted (see Figure 12). Chapter 3 is a cross-sectional study attempting to characterise CA patients' linguistic and cognitive profile. In it I compare patients' baseline scores with controls'. Additionally, I carry out correlations between baseline behavioural measures (including demographic variables). Due to the large amount of data collected at baseline, across multiple tests that assess overlapping or shared cognitive functions, I carried out a principal component analysis (PCA) as a multivariate data reduction technique aiming to identify underlying reading patterns in patients with CA. Later I combined these PCA components with structural MRI data to identify which brain regions support different aspects of reading.

The remaining experimental chapters are centred on predicting patients' response to Block 1 of therapy (T3-T4) in which iReadMore's effect was significant, but the tDCS effect was not. Chapter 4 examines which measures from the patients' pre-treatment data best explains the effect of iReadMore (i.e. reading percentage of absolute change). This was a cross-sectional study using all data collected at baseline (behaviour and brain). To create an explanatory model, regression analysis through automatic linear modelling was carried out. This analysis uses all of the data from all of the patients. Then, I was interested in whether this response to therapy could be predicted in 'new' patients. Hence, I employed a nested cross-validation analysis. Here the model can see all the training data except the primary outcome measure of the therapy (%

improvement in reading ability) from one validation subject, which it has to predict given all of the other subjects' data.

Finally, in chapter 5 I report a longitudinal analysis to study therapy-induced changes in patients' brain structure in response to iReadMore. It includes voxel-based morphometry (VBM) and voxel-based quantification (VBQ) analyses using multivariate parametric mapping MRI data.

In the next section, measures and analyses are described in this order: (1) behavioural data acquisition and statistical analyses; and 2) MRI data acquisition and analyses (see Figure 12).

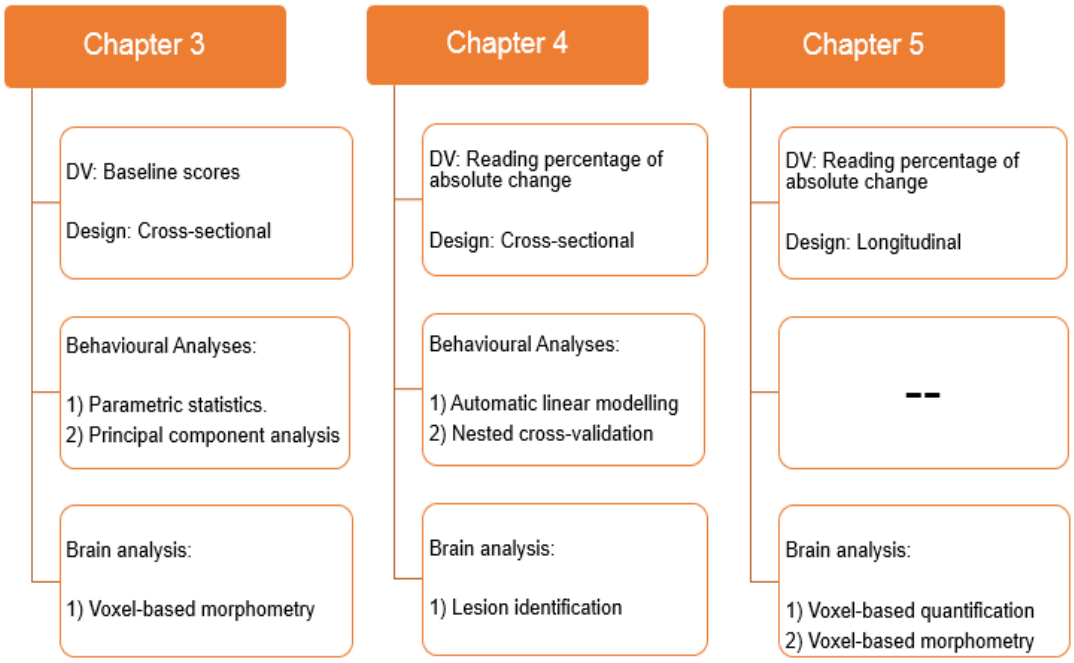

Figure 12. Experimental chapters. This figure shows the structure of each study performed in this thesis. It includes dependent variables (DV), design, and behavioural and brain analyses.

2.4.1. Baseline assessment - Instruments

The behavioural protocol used at baseline (T1 – T2) included a wide range of linguistic and non-linguistic cognitive tasks. In this thesis I wanted to both provide a complete neuropsychological profile of CA patients and explore potential tasks that may predict patients' response to therapy. To achieve these aims, tasks were chosen on the basis that they are broad measures to primarily assess specific cognitive processes. Additionally, I tried to select tasks that would be appropriate for use in aphasic patients, and to avoid tasks that could be performed using a verbal strategy where aphasic patients would be disadvantaged.

In order to test patients' abilities across cognitive domains and considering that patients were aphasic, the behavioural protocol consisted of the linguistic and non-linguistic tasks listed below:

Linguistic tasks*:*

1. Single-word reading (SWR). This task was used at each time point to measure the therapeutic outcomes.
2. Pseudoword reading.
3. Written semantic matching.
4. Written sentence to picture matching.
5. Neale Analysis of Reading Ability test.
6. Communication Disability Profile.
7. Naming objects and naming actions of the Comprehensive Aphasia Test.
8. Auditory discrimination task.

Non-Linguistic tasks / Executive functions:

9. Pyramids and Palm Trees (pictorial version).
10. Subtests 1 and 2 of the Cattell Culture Fair test.
11. Digit span of the Wechsler Adult Intelligence Scale IV.
12. Two-Armed Bandit Task.
13. Sustained Attention to Response Task (SART).
14. Brixton test.
15. Visual short-term memory task.
16. 4-Way Weigl.

1. **Single-word reading (SWR):** this task was designed by Dr Woodhead to assess reading of written single words at each time point. All words from the A, B, C and Core training lists (590 words in total) were tested, across six separate blocks, three at each testing session (T1 and T2). Words were presented in a random order using E-prime software (Schneider, Eschman, & Zuccolotto, 2012). Words were displayed in black, lower case, size 36 Arial font on a grey background.

   Participants were instructed to read the words aloud into a voice-key microphone as quickly and accurately as they could. Participants were given up to four seconds to read the word: responses after this time were scored as incorrect. This time limit was implemented to prevent participant fatigue and to allow the task to be completed within the limited time available for testing. The experimenter controlled the pace of presenting the next trial after a response was received. The experimenter recorded accuracy by button press: 1 for a correct response; 0.5 for a self-correction; and 0 for an incorrect

response or failure to respond. Reaction time (RT) was recorded by the voice-key. The resulting variables were percentage accuracy and mean reaction times. Mean RT was calculated excluding incorrect (or self-corrected) trials; trials where the voice-key did not record the response correctly; and RTs more than two standard deviations away from the subject's mean RT.

After baseline testing (T1-T2), subject-specific training lists were selected, and 90 items from each matched list (A, B and C) and 30 items from the Core list were selected to be tested at all future time-points (270 items in total). Training lists were pseudo-randomized across all subjects. The A, B and C words selected were matched for psycholinguistic variables and baseline performance (accuracy and RT).

2. **Pseudoword reading:** this task was designed by Dr Woodhead to test oral reading of pseudowords. 20 pseudowords were generated using Wuggy software (Keuleers & Brysbaert, 2010). Items were between three and six letters in length and were made up of plausible letter combinations. The style of presentation was identical to the SWR task. Pseudowords were presented in black, lower case, size 36, Arial font on a grey background using E-prime (Schneider et al., 2012). Participants were instructed to read them aloud into a voice-key microphone as quickly and accurately as they could. Unlike the SWR task, there was no time restriction for producing a response. The experimenter set the pace of presenting the next trial after a response was received. The resulting variables (accuracy and RT) were scored and calculated as described for the SWR task.

3. **Written semantic matching (semantic matching):** This task was designed by Dr Woodhead to assess reading for meaning and silent reading speed (access to lexical-semantic information of written words). It consisted of 72 trials presented in E-prime (Schneider et al., 2012). In each trial three words were displayed on the screen. Participants silently read a probe word centre-aligned at the top and displayed in a white box with magenta contour. Below this probe word were two words (a semantically-related target and an unrelated distractor) contained in white boxes with blue contours that were left and right aligned. Participants were instructed to decide which word was semantically related to the probe word as quickly and accurately as they could and to respond using a button press. There was no time restriction for producing a response. A fixation cross was presented for one second between the response and the onset of the next trial. Accuracy and RT of the button presses were recorded automatically (1 point for a correct response; and 0 for an incorrect response). The resulting variables were percentage accuracy and mean RT (for correct trials, excluding trials where RT was more than two standard deviations away from the mean).

4. **Written sentence to picture matching (sentence reading):** This task was created by Dr Woodhead to assess silent reading for meaning. It consisted of 60 trials, presented in E-prime (Schneider et al., 2012), in which patients silently read a sentence of between five and eight words. They were requested to read each sentence as quickly as they could, and to press the space bar once finished. This response was used to determine sentence reading speed. A picture was then displayed on screen and the participant

responded verbally whether the picture was congruent with the sentence or not (50% were congruent). Variables were percentage accuracy on the picture decision task and sentence reading speed in words per minute (WPM, excluding trials where speed was more than two standard deviations away from the subject's mean).

iReadMore therapy uses a crossmodal lexical approach that is highly reliant on mass exposure to be effective. Therapies based on lexical approaches often demonstrate item specific effects (Kurland et al., 2008; Lott, Sample, Oliver, Lacey, & Friedman, 2008; Ska, Garneau-Beaumont, Chesneau, & Damien, 2003). Semantic matching and sentence reading tasks were created for this study because we were interested in measuring the impact of iReadMore on silent reading for meaning but using trained and untrained stimuli in these tests. This allowed us to identify iReadMore therapy effects in reading for meaning and sentence reading, even if the therapy effects were item specific. Existing tests such as the written version of the Pyramids and Palm Trees (Howard & Patterson, 1992) would allowed us to test the effect of iReadMore only on untrained items.

5. **Neale Analysis of Reading Ability test** (Neale, 1997)**:** this test was used to assess reading accuracy, speed, and comprehension of texts. The Neale consists of two parallel forms with eight texts in each, arranged according to length and complexity. In this study only level one and two texts (the easiest texts) were administered. The two parallel forms of the test were counterbalanced between participants. Participants were instructed to read the texts aloud as quickly and accurately as possible. Immediately after

completing the text, comprehension questions were administered. Reading accuracy for each word of the text was recorded as correct (1) or incorrect (0). If they could not read a word within four seconds, the experimenter supplied the word and it was scored as incorrect. Self-corrections were scored as correct. The resulting variables were percentage reading accuracy, mean reading speed in WPM and total score on the comprehension questions.

6. **Communication Disability Profile (CDP)** (Chue, Rose, & Swinburn, 2010)**:** this is a patient-reported questionnaire for aphasic patients focused on activities of daily life. The reading section of the CDP was tested before therapy started to provide a self-report measure of reading ability. The test consists of four questions asking for the patient's self-assessment of their abilities in the last week for silent reading of: 1) a single words; 2) a headline; 3) a whole story in a paper; and, 4) a letter. Patients were instructed to answer the questions by pointing to a scale of five different facial expressions ranging from bad (0) to good (4). The resulting variable was overall score (maximum score = 16).

7. **Naming objects and naming action:** these subtests from the CAT (Swinburn et al., 2004) were used to test word retrieval by confrontation. In this study, both subtests were combined and used as a measure of aphasia severity. Naming objects and naming actions include respectively 24 and 5 black and white drawn pictures. Participants were instructed to retrieve the name of the picture or find the word to describe the action. If the participant named the picture within four seconds, 2 points were awarded. If the

participant named the picture after a delay longer than four seconds, or produced a self-corrected error, 1 point was awarded. If they could not name the picture, they received 0 points. The resulting variable was total score from both tests (maximum score = 58).

8. **Auditory discrimination task:** this task was designed by Robson, Keidel, Ralph & Sage (2012) to test acoustic-phonological perception. It was used to provide a measure of the participant's ability to discriminate phonemes. The task consisted of three auditory non-words (A - B - C) displayed in E-prime (Schneider et al., 2012). In each trial the first (A) or last stimulus (C) is identical to the stimulus in the middle (B). Participants were instructed to identify the odd-one-out (A or C) by button press. There were 14 levels of difficulty according to phonological similarity between the stimuli in each trial. The difficulty level changed according to performance using an adaptive staircase model: difficulty increased after 3 correct consecutive responses, and decreased after one incorrect response. The task started at the easiest level (14) and finished after succeeding at the hardest level (1); after 8 level reversals; or after 8 errors at level 14. The resulting variable was the final score, calculated by averaging the difficulty levels of the last 4 incorrect trials.

9. **Pyramids and Palm Trees (PPT)** (Howard & Patterson, 1992)**:** the visual picture version of the Pyramids and Palm Trees test was used to test access to visual semantic information .The task consists of 52 trials. In each trial three pictures are shown: a probe picture, centred at the top, and two pictures below located at the left and right side. One picture is a semantically-related target and the other an unrelated distractor. Participants were asked to select

which of the two pictures below are semantically-related to the target picture. There was no time restriction for producing a response. 1 point was given for correct responses and 0 for incorrect responses. The resulting variable was total response accuracy (maximum score = 52).

10. **Subtests 1 and 2 of the Cattell Culture Fair test** (Cattell & Cattell, 1949): these subtests were used to examine fluid intelligence and reasoning. In this context, fluid intelligence is understood as a group of abilities that allow solution of novel and complex problems (Conway, Cowan, Bunting, Therriault, & Minkoff, 2002; Kvist & Gustafsson, 2008).

    Subtest 1 is a pattern completion task. In each of 12 trials, three black and white drawings were presented (following a pattern). Participants had to choose which drawing out of five options, completed the pattern. Participants were given up to 3 minutes to complete the task.

    Subtest 2 is an odd-one-out task. In each of 14 trials, five black and white drawings were presented. 4 out of the 5 drawings follow a pattern, and participants had to identify the odd-one-out. Participants were given up to 4 minutes to finish the task.

    In both subtests correct responses were scored with 1 point and incorrect responses with 0. The resulting variable was total score from subtest 1 and 2 (maximum score = 26).

11. **Digit span subtest (from the Wechsler Adult Intelligence Scale IV):** This task was used to test attentional span and verbal working memory. This subtest involves repetition of number strings forward and backward. Initially,

participants were instructed to repeat strings of up to 9 numbers in the same order as the experimenter (forward). The second part of the tasks involves backward repetition of up to 8 numbers. Before testing, participants were asked to count numbers from 1 to 9 to confirm they were able to verbally produce numbers. Correct responses were scored with 1 point and incorrect responses with 0. The resulting variable was total score from both tests transformed into a scaled score.

12. **Two-armed bandit Task (TAB):** this task is a modified version of a decision making task used to assess environmental and reinforcement learning abilities created by Chowdhury et al.,(2013). The task consisted of 220 trials presented in Matlab (The MathWorks, 2014). Trials were presented in two blocks (110 trials each) separated by a short break. Participants were instructed to select one of two boxes (red or blue), and to try and judge which box had the highest probability of producing a reward. The probability associated with each box changed trial by trial according to Gaussian random walk. If participants chose the correct box a pound symbol and a rewarding sound indicated a win. Otherwise, a black cross and a punishment sound indicated the absence of a win. The resulting variable was the percentage of trials where the patient selected the box with the highest probability (optimal choice).

13. **Non-verbal version of the Sustained Attention to Response Task (NV-SART)** (Manly, Davison, Heutink, Galloway, & Robertson, 2000)**:** This is a Go/No go task used to test sustained attention, RT and response inhibition. It involves 215 trials presented in E-Prime (Schneider et al., 2012). In each

trial one of two pictures of different men is displayed on the screen (one man represents the ‘go’ trial and the other represents the ‘no-go’ trial). Participants were instructed to press a button each time the go picture was shown, but to withhold their response when the no-go picture was displayed. There were 191 go trials and 24 no-go trials. Five variables were derived from this test: percentage accuracy calculated from go trials (hits); errors of omission on go trials (failing to press on a ‘go’ trial); percentage of rejections calculated from errors of commission on no-go trials (pressing on a ‘no-go’ trial); reaction times to correct ‘go’ trials; and, post-error slowing.

Post-error slowing is considered a measure of cognitive control (Dutilh et al., 2012; Jonker, Seli, Cheyne, & Smilek, 2013). It was calculated from the mean RT of the 3 trials following a commission error trial, divided by the mean RT of all trials except those 3 trials before and after a commission error.

14. **Brixton spatial anticipation test** (Burgess & Shallice, 1997)**:** This test assesses executive functions including reasoning, anticipation, cognitive control, solving problems, cognitive flexibility, adaptation in response to changes in the environment, response inhibition, working memory and attention. This task consists of 55 trials. Each trial contains the same template formed of ten circles with one coloured blue. In each trial the blue circle changes its position according to specific patterns. Participants were instructed to point to where the blue position would be in the next trial, according to the pattern. Raw score (out of 55) was calculated based on number of errors and was transformed in a scaled score.

15. **Visual-spatial short-term memory task (VSSTM):** I created this task to test visual short-term and visual working memory – it is a non-verbal, visuospatial version of the digit span task. It consists of 14 trials presented in E-prime (Schneider et al., 2012). On the screen participants saw five grey squares located horizontally. In each trial, some of the squares were lit up in a particular order. Participants were instructed to remember and reproduce the sequence by button press. There were 7 levels of difficulty, each of them including two trials. The first level started with a sequence of two squares and difficulty increased by adding one square to the sequence in each difficulty level up to a maximum of eight. The task was discontinued after two consecutive fails to reproduce the sequence within a level. The resulting variable was the total number of sequences correctly reproduced (1 point each).

16. **4-Way Weigl:** this is an alternative version of the WCST (Beglinger, Unverzagt, Beristain, & Kareken, 2008) used to test executive functions such as solving problems, cognitive flexibility, behaviour to achieving a goal, and response inhibition. Participants were presented with 12 coloured plastic tokens. They were instructed to figure out and sort the tokens in one of up to four options (colour, shape, symbol and texture). If the sort was completed within 45 second, the participant was instructed to arrange the tokens in a new sort. Otherwise, additional instructions (stepdown A and B) were given to complete the groups. The resulting variable was total score (out of 12) counted as follows: unassisted sorts with 45 seconds were scored with 3 points; step down A (i.e. first group within a sort was completed by the experimenter, then the participant finished the sort) was scored with 2 points;

step down B (i.e. spoken instruction given from the experimenter to complete the sort) was scored with 1 point. Moreover, secondary variables were also calculated: 1) the number of failures to complete the sort (less than 2 tokens are left unsorted); and 2) perseverations (type A and B). Perseveration type was the repetition of a previous sort. Type B involved the interruption of a correct sort to reverse the tokens to a previous sort.

The section above has described the linguistic and non-linguistic tasks that conformed the behavioural protocol used at baseline (T1-T2). To conclude this section, the resulting variables that were calculated from the behavioural protocol are listed in table 3.

Linguistic variables		Non-linguistic variables	
1. SWR - Acc.	11. NEALE - Comprehension	17. PPT	27. VSSTM - Acc.
2. SWR – RT	12. CDP - Score	18. Cattell - Total	28. Weigl - Score
3. Pseudoword - Acc.	13. Naming - Total	19. DS – Total	29. Weigl - StepdownA
4. Pseudoword – RT	14. Auditory discrimination	20. TAB - Optimal choice	30. Weigl - StepdownB
5. Semantic Matching - Acc.	15. Naming objects	21. NV-SART - Acc.	31. Weigl - FCS
6. Semantic. Matching - RT	16. Naming actions	22. NV-SART – Omissions	32. Weigl - Pers. A
7. Sentence reading - Acc.		23. NV-SART - Rejections.	33. Weigl - Pers. B
8. Sentence reading - Speed		24. NV-SART - RT.	34. Weigl- Pers.Total
9. NEALE - Acc.		25. NV-SART - PES.	35. DS - Forward
10. NEALE - Speed		26. Brixton - Errors	36. DS - Backward

Table 3. List of resulting variables. This table lists the resulting linguistic and non-linguistic variables from the behavioural protocol tested at baseline (T1-T2). Variables 15-16 and 29-36 (in Italic) are secondary variables calculated from tasks. SWR= single-word reading; Neale = Neale Analysis of Reading Ability test; CDP= communication disability profile. PPT= Pyramids and palm trees test; DS= digit span; TAB= Two-armed bandit; NV-SART= Non-verbal version of the Sustained Attention to Response Task; VSSTM= visual-spatial short-term memory task; Acc.= accuracy; RT= reaction time; FCS= failure to complete the sort; Pers.= perseveration.

2.5. Behavioural analyses

2.5.1. Principal component analysis (PCA)

Reading deficits in aphasic patients can be classified according to which grammatical class of words or 'part of speech' patients struggle with. While the canonical forms of acquired alexia were described using detailed case studies with specific deficits (phonological, surface and deep dyslexia; for review see Leff and Starrfelt (2014)), examination of larger groups of less well selected patients suggests that these disorders (particularly phonological and deep dyslexia) may exist on a continuum (Crisp & Lambon Ralph, 2006). CA is a broader definition

which includes any mix of these main forms of reading impairments where other language modalities (such as speaking and writing) are also affected to some degree (Leff & Starrfelt, 2014). In this thesis I have used a multitude of reading and non-reading linguistic tests to characterise the patients. Performance on some of these tests is highly correlated (see Chapter three) suggesting that they capture overlapping aspects of reading and cognitive abilities. One way to try and identify the underlying components of performance that may be affect scores on a range of tests is to use a form of data reduction known as principal component analysis (PCA).

Recent studies used PCA to study key aspects of aphasic patients' language abilities (Butler, Lambon Ralph, & Woollams, 2014; Halai, Woollams, & Lambon Ralph, 2017; Lambon Ralph et al., 2010). It is a multivariate technique suitable to reduce large data sets with large numbers of variables while preserving as much as possible of the variance from the original data. PCA aims to identify patterns in the data by transforming correlated variables into the minimum number of linear components (Field, 2013; Jolliffe, 2002). As a result, PCA produces a matrix that transforms the general structure of the data into a reduced number of components. PCA has multiple advantages: 1) PCA produces data-driven models; 2) it combines data from several dependent variables, hence it increases the power of the analysis; and 3) PCA circumvent the multicollinearity problem by merging groups of variables that are highly correlated. The results of PCA can be combined with volumetric neuroimaging methods (Butler et al., 2014), to identify brain regions or neural networks where tissue integrity correlates significantly with particular components.

All reading scores from baseline tasks (i.e. accuracy and speed) were entered into the PCA to investigate independent cognitive patterns underlying reading performance in patients with CA (see Chapter 3 for the results). PCA parameters were established as follows:

1) Multicollinearity: even though PCA analyses circumvent the multicollinearity problem by grouping variables, very strong associations can bias the PCA (Field, 2013). Therefore, it is a good practice to exclude strongly correlated variables. Only variables with correlations lower than 0.9 were included in the PCA.
2) Bartlett's test of sphericity: this measure determines whether PCA is adequate for analysis. It tests the null hypothesis that variables are uncorrelated. This measure is centred on the relationship between variables: highly correlated variables produce only one component, but uncorrelated variables (less than 0.3) cannot be grouped into components, hence PCA is not useful. The likelihood of significance in this measure is high because it depends on the sample size and correlations between variables (Field, 2013). Hence, only PCA with Bartlett's test of sphericity <.001 was considered as adequate.
3) Kaiser-Meyer Olkin Measure (KMO): This is a measure of sample size adequacy. KMO values above 0.5 are considered as acceptable power to draw clear conclusions. Complementary to KMO, a subject-to-variable ratio was calculated. MacCallum, Widaman, Zhang, & Hong (1999) determined that a ratio above 1.2 is satisfactory to consider a sample as appropriate. These two values are used in the PCA in this thesis.
4) Orthogonal rotation: this is a means to distribute variables' weights along components. It generates independent and uncorrelated components. This

method guarantees that components are unique, therefore results are easily interpretable (Butler et al., 2014; Halai et al., 2017). Varimax rotation was used as it attempts to only load variables which significantly contribute to the component.

5) Components with eigenvalues above 1 were retained: an eigenvalue is considered an indicator of the importance of each component (Field, 2013). As a rule, components with the highest weights have the highest eigenvalues. However, PCA can generate several components with low significance (i.e. low eigenvalues) that are difficult to interpret. In this study PCA was configured to retain only components with large eigenvalues (>1) (Lambon Ralph et al., 2010).
6) Relationship between variables within a component: PCA produces a component matrix with information describing to what extent a particular variable contributes to a component. The cut-off to determine that a variable gives a substantive contribution within the component was established as 0.6 (Field, 2013), therefore, only scores above this threshold were considered significant.

2.5.2. Automatic linear modelling (ALM) - explanatory modelling

Automatic linear modelling (ALM) is a tool recently implemented in SPSS (IBM) to perform linear regression analysis using multiple predictor variables. Manual selection of the best subset of variables in a big data set might be time consuming and problematic because bias selection increases type I and Type II errors. Conversely, ALM generates an optimal model from data in which several independent variables (IV) are potential predictors of the dependent variable

(DV). This procedure is optimised automatically with two steps of the regression process: 1) data preparation and 2) variable selection.

1) Data is prepared by identifying missing values, types of variables (i.e. continuous, ordinal or categorical) and outliers. To deal with this procedure ALM replaces missing values, transforms categorical variables in dummy variables, and calculates a Cook's distance value in cases that are three standard deviations (SD) away from the mean. Cook's distance measure is useful in estimating the influence of each case in the fitted model. This is given under the basis that an estimation of each variable's impact in the model is necessary, as in some cases outliers do not necessarily influence the fitted model (contrary to cases in which non-outliers strongly bias the model). As a rule, if Cook's distance value is close to 1 it can be considered problematic and a decision concerning inclusion/exclusion of these cases needs to be made (Field, 2013).
2) Variables selection: ALM in SPSS includes two options to generate a model: best subsets and stepwise selection. Best subsets considers all possible models, but it is recommended for data with less than 20 variables (Yang, 2013). Stepwise selection creates one single model by testing the contribution of each variable, while controlling for other variables. Once the first predictor is included into the model, this procedure adds and removes single variables to assess whether a specific predictor contributes to improve the model. Analyses in this thesis were conducted with stepwise selection.

Moreover, ALM provides additional parameters to estimate model adequacy:

- Adjusted R^2: this parameter estimates how much of the variance in the data is explained by the model. This measure is called “adjusted” because it depends on the number of variables included in the model.
- Akaike’s information criterion (AIC): a measure to compare models (Field, 2013). The AIC for a single model does not provide meaningful information, but the relative AIC values for multiple models are meaningful. The AIC represents the distance between a model and the original data (i.e. how much data is lost in a model) and penalises complex models. The model with the lowest AIC is the preferred one.
- Overfit prevention criterion: SPSS uses the average squared error to prevent model overfitting.
- F-test: compares models to estimate the model that best fits the data.

Chapter 4 involved analyses of pre-treatment data (demographic, behaviour and parcellation of brain lesions) to predict patients’ reading’s percentage of absolute change in response to iReadMore. An in-sample analyses using ALM was performed to create an explanatory model. This model was created through forward stepwise variables selection and involved analysis of 110 predictor variables. Other analyses were conducted with the default parameters.

2.5.3. Predictive modelling - Nested cross-validation (N-CV)

The previous section explained why ALM is suitable for generating models to predict therapeutic outcome with multiple predictor variables. However, regression models are in-sample analyses. This means that models have satisfactory power to predict outcomes within the data collected, but model

generalisation (how well out-of-sample data is predicted) is low, and risk of model overfitting in new participants is high.

Cross-validation (CV) is a suitable means to assess out-of-sample model accuracy (Hope et al., 2017; Price, Ramsden, Hope, Friston, & Seghier, 2013). The assumption behind CV is that a model's accuracy from collected and new data would be similar (i.e. generalisation). CV tests model accuracy in an independent dataset by using the data both as a training set and as a test set. This allows to estimate whether a model generalises to new data. The key characteristic of CV analysis is that it estimates the error rate in out-of-sample data (best fit model). To achieve this objective CV splits the data in two groups and in some cases in three groups (see Figure 13):

1) Training set: the data (predictors and outcomes) used to create a model.
2) Test set: the independent data to estimate the accuracy (error rate) of the training data set. The test set is used only once and cannot be used to build the model.
3) Validation set: this set depends on the type of cross-validation method. It is used to adjust parameters to increase model accuracy.

There are four types of CV:

1) Holdout CV, which randomly divides the data into a training set (the bigger part of the data) and a test set (a smaller portion of the data).
2) K-fold CV, in which the data is divided in K sub-samples. Each sample has the role of test set; hence there are K error rates. Then, the average of the error rate is used to evaluate the accuracy of the model.

3) Random subsampling CV which randomly creates N data sets (test sets) from the training set. Error rate is calculated from the average error rate of the N data sets (Arlot & Celisse, 2010).
4) Leave-one-out CV that creates the test set by removing one data point from the data set. The remaining data (N-1) conforms the training data. Leave-one-out CV repeats this process N times (the folds) according of the amount of data points (sample), therefore each data is test set of a training set in some part of the process. The average error rate is calculated to evaluate the model.

In Chapter 4 I was interested in examining whether the explanatory model obtained with ALM analysis was able to predict new patients' response to iReadMore (out-of-sample). To test this hypothesis nested cross-validation (N-CV) was conducted. N-CV is a variant of leave-one-out CV. This method create N training (1) and test (2) sets (outer loop) depending on the N sample, but in each fold (i.e. each iteration) it generates an extra step (inner loop) to create a validation test (3) that optimises parameters of the training set before it is evaluated with the test set (see Figure 13). This extra-step reduces the model's error rate in each fold, hence improving model accuracy (Baumann & Baumann, 2014). Moreover, boosting was used to improve predictive accuracy, creating a set of 10 models per fold.

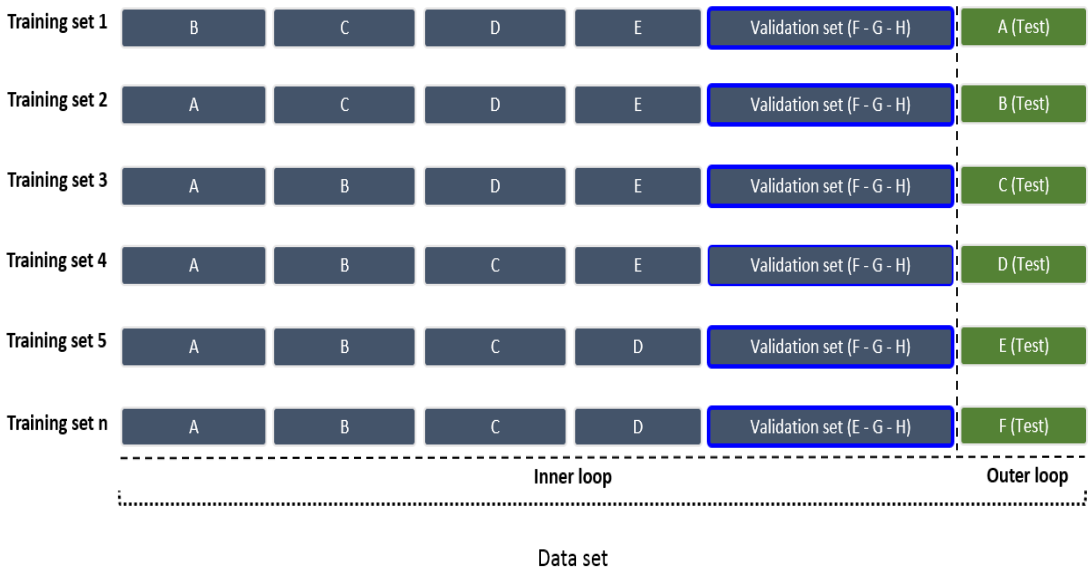

Figure 13. Nested cross-validation (N-CV) method. It represents data partion in a sample of N participants. N-CV creates a training and validation set to optimise parameters, before the validation set is assessed with the test set.

2.6. Principles of structural MRI

In this thesis patients had an MRI scan at T3 and T4 (see Figure 3). The following section presents a brief introduction to the Magnetic Resonance Imaging (MRI) principles and explains the procedures implemented for imaging analysis.

Magnetic resonance imaging (MRI) is a technique used to produce images of the body. To acquire images a person is positioned inside an MRI scanner (see Figure 14) that consists of: 1) a static electromagnet that produces a strong magnetic field (B0); 2) radiofrequency (RF) transmit and receive coils, which emit RF pulses and detect the reflected RF signal, and 3) magnetic field gradients, which localise the source of the reflected signal by generating short-term spatial variations of the magnetic field strength across the person.

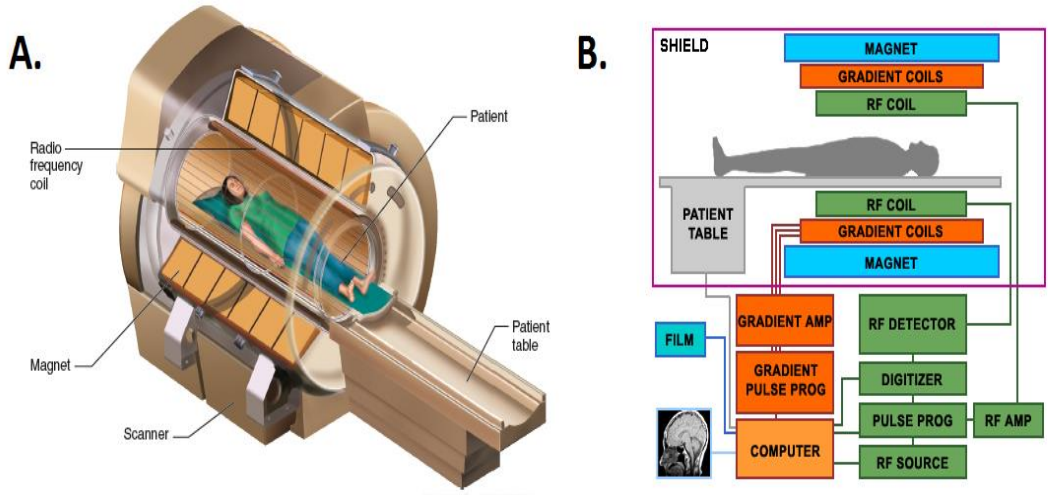

Figure 14. Structural MRI. A. MRI scanner and its main components. B. schematic view of the MRI components ("Mri Block Diagram," 2016).

The principles of MRI scanning rely on detecting the presence of hydrogen protons (H+), which are abundant in the human body because 70-80% of most tissues are composed of water. Protons have two fundamental properties: 1) they spin around in random directions and 2) have a positive electrical charge. These two properties are essential for a phenomenon known as “magnetic moment”, which causes the proton to align the magnetic field created by its own spinning electrical charge with the much stronger magnetic field inside the MRI scanner (Westbrook, Roth, & Talbot, 2011).

When the strong external magnetic field (B0) is applied, some of the magnetic moments of the protons align in the same direction of the magnetic field (i.e. parallel) and, others in the opposite direction (i.e. anti-parallel). Additionally, the protons “precess”, i.e. the axis of their magnetic moments oscillate around the magnetic field. The RF fields are applied at the same frequency as the frequency that the protons precess. The application of RF causes resonance that perturbs or excites the nucleus as it absorbs the energy. Once the RF is removed, two

things occur: 1) the hydrogen nucleus loses the energy obtained from the resonance (T1 recovery); and, 2) the nucleus exchanges energy with surrounding nucleus, resulting in loss of magnetization (T2 decay). T2 decay is also known as “Relaxation” and it reflects how long tissues take to return to the equilibrium after application of RF (i.e. free induction decay).

The recovery and relaxation properties of different tissue types (i.e. water or fat) create contrasts that allow us to view anatomical structures. Different types of images are obtained by varying the parameters of the acquisition protocol (i.e. T1, T2 contrast and proton density). In T1-weighting (T1w) images, fat loses longitudinal magnetization faster than water, therefore the T1 time for fat is shorter and its level of magnetization is higher after RF pulse. This results in high signal intensity from fat, showing bright fat (e.g. white matter) and dark water. For T2-weighting images (T2w), fat loses transverse magnetization faster than water and its level of magnetization is lower, therefore fat produces low signal intensity, showing dark fat and bright water. Finally, proton density weighting images (PDw) depend on the contrast in the tissue signal intensity according to the relative numbers of hydrogen atoms in different volumes (e.g. CSF or blood). For this contrast, high PD (such as brain tissue) produces high signal intensity (Westbrook et al., 2011).

2.6.1. Quantitative imaging (qMRI) and multiparameter mapping (MPM)

Traditionally, morphometric MRI studies have used T1w and T2w images to examine the brain macrostructure and its changes associated to events such as learning (Maguire, Woollett, & Spiers, 2006) or aging (Hutton, Draganski,

Ashburner, & Weiskopf, 2009). Similarly, other studies have focused on understanding changes in the brain volume in clinical populations with psychiatric (Rametti et al., 2010) or neurological conditions (Seghier et al., 2016). These studies have provided understanding of how the brain works and how behaviours are associated with spared functioning of specific brain structures. However, clear mechanistic interpretations of structural changes observed in longitudinal studies are difficult to achieve because cellular processes underlying results may vary according to multiple factors. For instance, neuroplastic changes in the brain structure might be explained by different cellular mechanisms such as neurogenesis, gliogenesis, myelination, angiogenesis, etc. (Zatorre, Fields, & Johansen-Berg, 2012). Furthermore, previous research has drawn attention to some issues associated with methodological procedures, data acquisition and inter-site variability: 1) factors such as brain normalisation and smoothing may affect the spatial resolution (Thomas & Baker, 2013); 2) head size, head motion, heart rate and breathing may induce artefacts in the MR signal, hence in the acquired image; and, 3) conventional scans (e.g. T1w) are not specific to MRI parameters. These images have arbitrary units and signal intensities that depend on the whole scanner system, therefore conventional images provide unstandardized measures that cannot be compared with other images (Weiskopf, Mohammadi, Lutti, & Callaghan, 2015).

Quantitative imaging (qMRI) is a group of methods that complement conventional volumetric studies. qMRI allows in-vivo examination of the brain microstructure at a tissue and cellular level. Whereas conventional scans (e.g. T1w) have arbitrary units and signal intensities that depend on the whole scanner system (Weiskopf et al., 2015), qMRI permits the extraction of standardised measures of

biomarkers specific to particular MRI microstructural tissue properties (e.g. relaxation time), therefore providing unbiased measures of cellular mechanisms (Weiskopf et al., 2013). For instance, R1 is the longitudinal recovery rate or inverse T1. This measure depends specifically on how much water and what macromolecules are in the tissue. High macromolecule content such as in myelin and iron produces a shorter T1 relaxation, then relaxation time in WM regions happens more rapidly and values are higher than other regions with low macromolecules content. In this case, R1 provides a standardised measure which can be used as a biomarker of WM myelination. Additionally, as qMRI measures are standardized, acquired MRI scans can be compared across different imaging sites, provided the MRI field strength is the same.

Multiparameter Mapping (MPM) is a qMRI protocol developed to study the microstructural properties of brain tissue (Callaghan et al., 2014; Draganski et al., 2011). The key characteristic of the MPM protocol is the acquisition of several biological measurements from the analyses of four maps called: effective proton density (PD*), magnetization transfer (MT), longitudinal relaxation rate (R1), and effective transverse relaxation rate (R2*) (Figure 15).

1) PD* is a measure of water content in the tissue (how many protons are contributing to the signal). PD* signal is lower in WM, higher in GM and very high in CSF. PD* is measured in percentage units (p.u.).
2) R1 (the inverse of T1) is a measure of iron, water, and macromolecule content in the tissue. R1 signal is high in WM. R1 is measured in milliseconds (s^{-1}).
3) MT reflects macromolecular content, mainly myelin. Values are higher in WM. MT is measured in percentage units.

4) R2* (the inverse of T2*) signal is created when magnetization is disturbed and then decays. Areas with high content of iron such as the basal ganglia show rapid decay (Weiskopf et al., 2015). R2* is measured in milliseconds (s^{-1}).

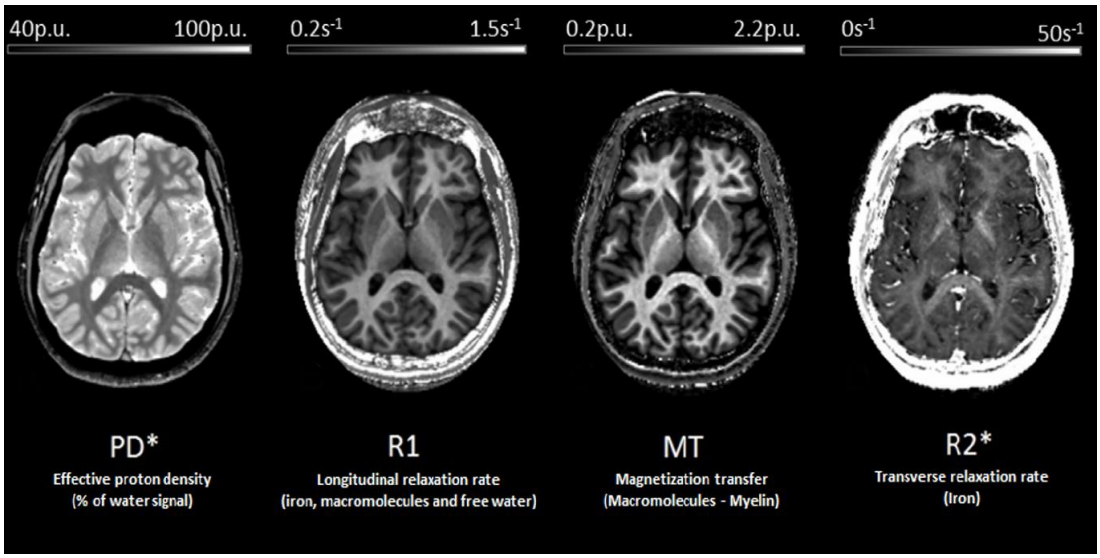

Figure 15. Multiparameter mapping protocol. This figure shows maps acquired with the multi-parameter protocol. PD* and MT maps are semi-quantitative. R1 and R2* are quantitative. p.u.= percentage units. s^{-1}=milliseconds (Callaghan et al., 2014).

2.6.2. MRI data acquisition and pre-processing

At T3 and T4 each patient underwent a quantitative MPM protocol (Weiskopf et al., 2013) at 3T (Magnetom TIM Trio, Siemens Healthcare, Erlangen, Germany) using a standard 32 channel head coil for signal reception and RF body coil for transmission (see Figure 16). The sequence parameters were as described by Callaghan et al. (2015) with the exceptions that the FLASH (fast low angle shot) data were acquired with 1mm isotropic resolution using a field of view of 256 mm head-foot, 240 mm anterior-posterior, and 176 mm right-left. To accelerate the sequence, partially parallel imaging with an acceleration factor of 2 was used in each of the phase-encoded direction. The GRAPPA algorithm was used with 44

and 40 integrated reference lines in the first and second phase-encoded directions.

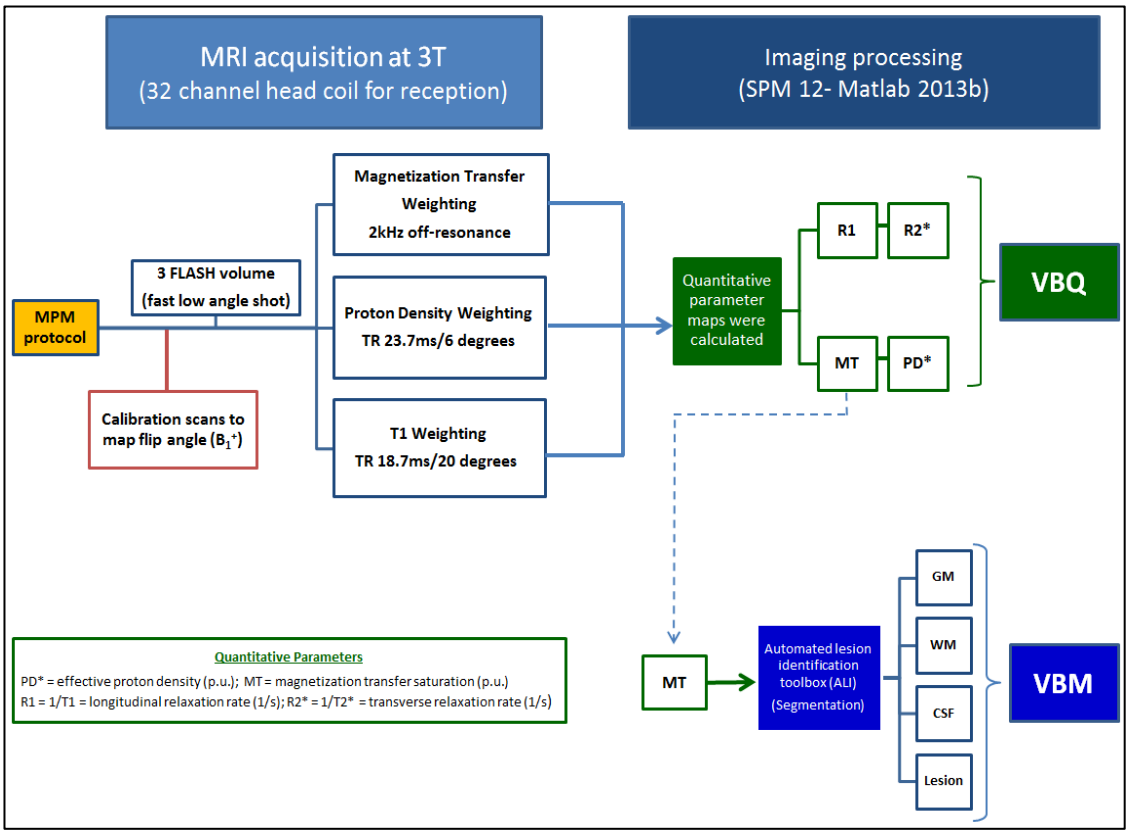

Figure 16. Multi-parameter mapping MRI protocol acquisition and processing. 3 FLASH volumes at 1mm isotropic resolution were acquired to calculate quantitative maps (VBQ). Voxel-based morphometry analysis was conducted from the Magnetization transfer map and using the Automated lesion identification toolbox- ALI.

2.6.3. Voxel-based morphometry (VBM) – Pre-processing

VBM is a morphometric method to study volumetric differences in the shape of brain regions at a macroscopic and mesoscopic level (Ashburner, 2010). In this study VBM analyses were performed with MT images acquired with the MPM protocol. The MT image has high quality with better contrast in subcortical region (in comparison for instance to T1w images) (Weiskopf et al., 2015). Hence, MT images improve the brain tissue segmentation. To obtain the MT maps, the MPM images were preprocessed in Statistical Parametrical Mapping 12 ("SPM12," 2014), using the Voxel Based Quantification (VBQ) toolbox ("Quantitative MRI

and Voxel-Based Quantification (VBQ),") and Matlab 2014a (The MathWorks, 2014). Preprocessing of MT images involved four processes:

1) Spatial normalization, where all images were matched in the same stereotaxic space removing spatial and positional differences between subjects. The template image was the canonical MNI space image incorporated in SPM 12. Images were normalised so that the values in each voxel were modulated to reflect tissue density, thereby preserving information about the amount of tissue from the original image.
2) Tissue segmentation: In this study, the segmentation-normalization procedures were performed using the Automated Lesion Identification algorithm (ALI), which is optimized for patients with focal brain lesions and creates a new tissue class or space “lesion” for the abnormal tissue to occupy (Seghier, Ramlackhansingh, Crinion, Leff, & Price, 2008). Hence, the resulting images were segmented into GM, WM, CSF and lesion according to the most likely tissue class at each voxel.
3) Smoothing of GM and WM images: this step involved blurring the segmented image, and replacing each voxel by the weighted average of the surrounding voxels. Images were smoothed with an isotropic Gaussian kernel of 8 mm full width at half maximum.
4) The statistical parametrical map (SPM): finally, a voxel-wise statistical test was performed using the general linear model (GLM) to identify voxels where GM and WM densities were significantly related to explanatory variables in the GLM (Ashburner & Friston, 2005).

Particularly, ALI toolbox is optimised to identify focal lesions (Figure 17). In this thesis lesions were detected by comparing patients’ segmented MT maps to

comparable MT maps from a previously collected dataset of 29 healthy controls. Controls' scans were pre-processed following the same procedure as patients' scans.

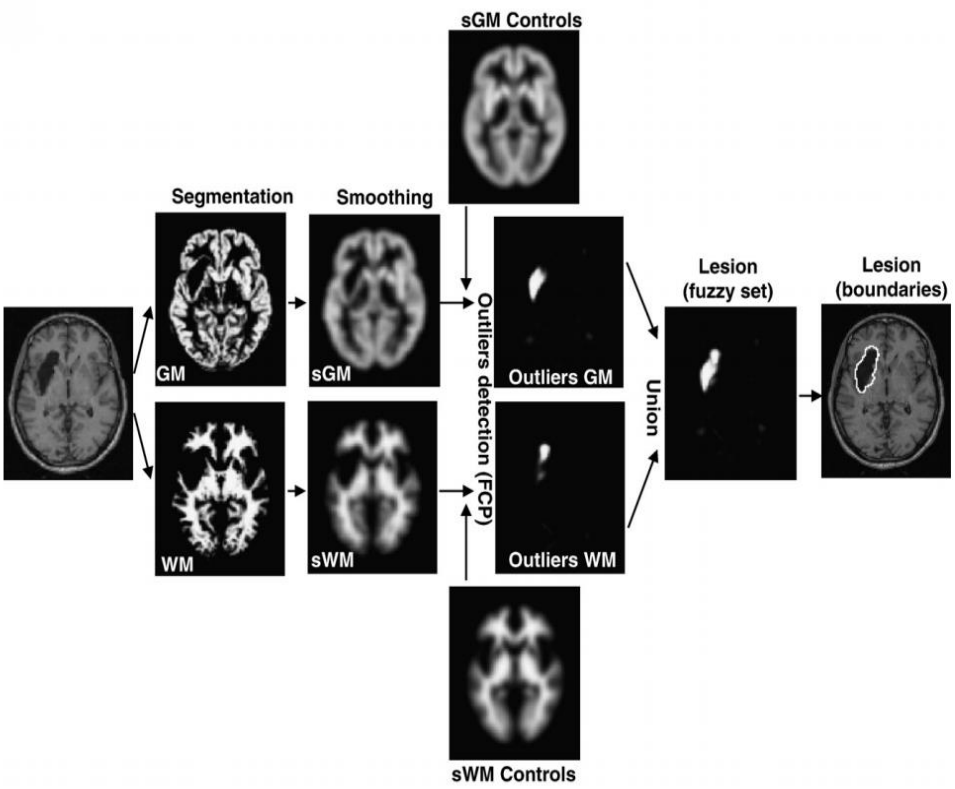

Figure 17. Brain segmentation. This figure illustrates the brain segmentation process using ALI toolbox (Seghier et al., 2008). ALI is optimised to identify focal lesions. In this thesis, MT images from the MPM protocol were used to performed VBM analysis.

Next, a binary lesion image was calculated for each patient. Three processes were performed using this image:

1) Lesion volume was calculated for each patient (see Table 1).
2) Binary images were encoded by lesion load in a series of anatomically defined regions of the brain. Each loading represented percentage of damage calculated over a total of 398 regions covering the whole brain: 0% if the region is completely preserved by a patient's lesion(s), rising to 100% when the region is completely damaged. Analyses in chapter 4 were conducted using these lesion loads. Regions were extracted from the

Anatomy Toolbox (Eickhoff et al., 2005), the Automatic Anatomical Labelling toolbox (Tzourio-Mazoyer et al., 2002), the ICBM-DTI-81 white-matter labels atlas (Oishi, 2011) and the JHU white-matter tractography atlas (Hua et al., 2008). The aim here was to cover the whole brain (GM and WM) in as flexible a manner as possible, so that patients' lesions could be encoded with minimal a priori assumptions concerning what parts of their lesions might be most relevant to their treatment responses.

3) Binary images were overlapped and thresholded to obtain a lesion overlay map (LOM). In the patient group the overlay covered perisylvian regions in the left hemisphere corresponding to the anatomical distribution of the MCA (see Figure 18). The brain region where the maximum number of patients had damage (n=20) was the WM of the superior longitudinal fasciculus deep to the left supramarginal gyrus (SMG) (x, y, z= -40, -34, 30). Moreover, the LOM was used to mask results and see whether significant clusters were in intact or damaged cortex.

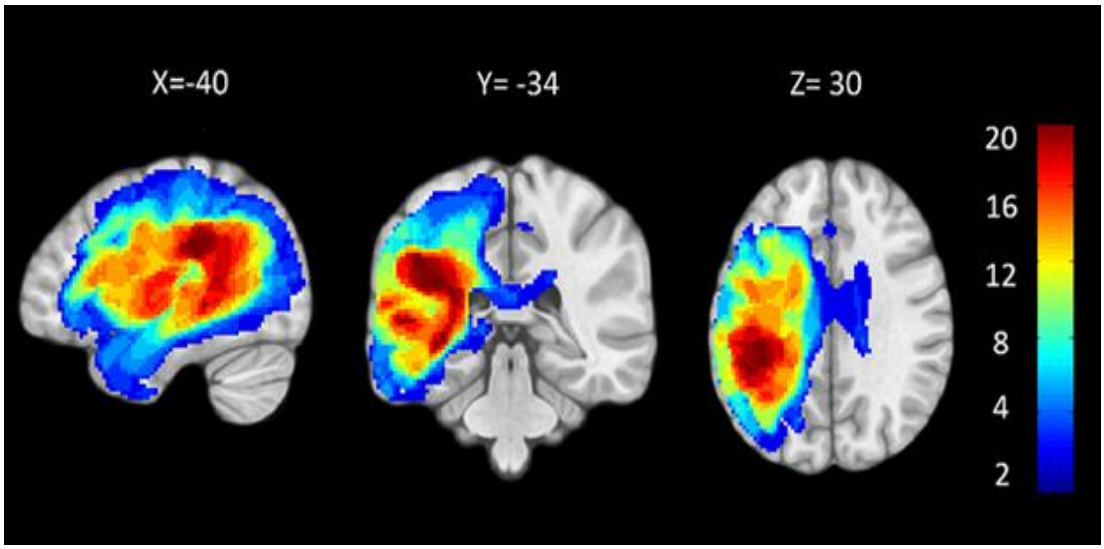

Figure 18. Lesion overlay map (LOM). LOM showing the spatial distribution of the lesion across patients. This image was thresholded to show voxels where two patients or more had damage.

2.6.4. Voxel-based Quantification (VBQ) – Pre-processing

Chapter 5 involved longitudinal VBQ analyses. VBQ was done to identify GM and WM microstructural changes associated with reading change due to therapy. VBQ is a method developed to perform statistical analyses at individual and group level with data acquired using the MPM protocol (Weiskopf et al., 2013). This toolbox normalises quantitative maps into MNI space (Montreal Neurological Institute space) preserving the quantitative values within tissues, and minimising partial volume effects.

Analyses were carry out using unmodulated GM and WM images from MT, PD*, R1, and R2* maps. Initially, for each participant post-treatment MPM images (T4) were co-registered into the pre-treatment MT scan (T3). This MT scan was used as reference because it has the highest resolution, hence the best contrast. The co-registration toolbox embedded in SPM12 was used. Images were both co-registered and re-sliced with default parameters except for interpolation in which 5^{th} degree B-Spline was chosen. Then, MPM scans were subtracted (post-treatment – pre-treatment) to obtained one scan for each map (MT, PD*, R1, and R2*) representing brain differences between T3 and T4. To normalise these quantitative maps to MNI space, a subject-specific deformation field was created using ALI and then, these maps were smoothed at 6mm FWHM. Finally, a voxel-wise statistical test (SPM) was performed to identify voxels where GM and WM values were significantly related to explanatory variables in the GLM

Methods - Summary

This methods chapter provided a detailed description of the data acquired along the iReadMore project and the analyses conducted in this thesis. As this was a therapeutic study, the first part described the study design, patients' characteristics, the iReadMore computerised therapy, tDCS parameters, and therapeutics results (for block one of therapy that is the focus on this thesis). The second part described the behavioural protocol tested at baseline (T1-T2), the MRI protocol (MPM), and the behavioural and brain methods used to analyse these data. Description of these methods was done in the same order as the experimental chapters that follow in this thesis.

3. INVESTIGATING THE COGNITIVE PROFILE OF PATIENTS WITH CENTRAL ALEXIA AND THE BRAIN REGIONS UNDERLYING THEIR BASELINE READING ABILITIES

Introduction

Aphasic patients with CA present with diverse reading impairments along with deficits in other linguistic modalities such as speech production, verbal comprehension and writing (Leff & Starrfelt, 2014). However, recent studies have showed that executive functioning in aphasic patients is associated with their proficiency in linguistic tasks and is also possibly related to language recovery (Brownsett et al., 2014; Lambon Ralph et al., 2010). In this thesis, the pre-treatment assessment included a wide range of cognitive tasks to measure patients' reading, wider linguistic and executive function abilities (see chapter 2). The aim was to characterise patients' baseline neuropsychological profile and also to examine whether these data might predict patients' responses to iReadMore (this hypothesis is tested in chapter four).

This chapter describes the baseline cognitive profile of CA patients (i.e. preserved/impaired cognitive abilities) and identifies independent brain regions associated with PCA derived components of reading tasks (see Figure 19). In order to achieve these aims, this study was divided in two sections: 1) An exploratory analysis of baseline scores (T1 - T2), including a comparison with

control data; and 2) PCA analysis to identify the components that underlie performance across all reading tasks with a VBM analysis using those components as explanatory variables. Results for each section are presented and discussed separately.

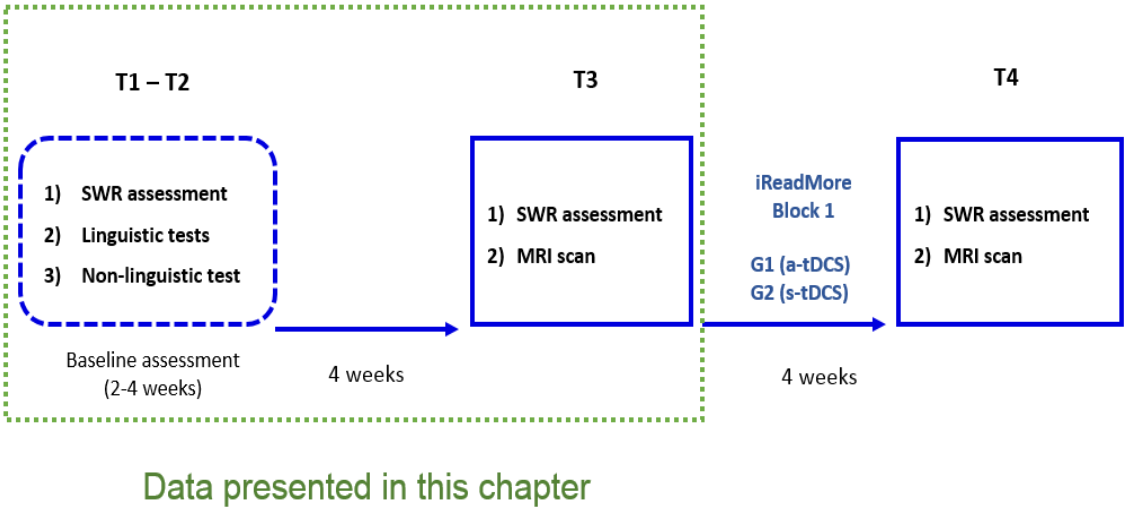

Figure 19. Study design – Experimental chapter one. In this study analyses were performed with behavioural data collected at T1 - T2 and pre–treatment MRI data collected at T3 (green dotted line). SWR= single-word reading task; MRI= structural magnetic resonance imaging; G= group; a-tDCS: anodal tDCS; s-tDCS: sham tDCS.

The aims of the study presented in this Chapter were:

1) To characterise the cognitive profile of patients with chronic CA.
2) To identify associations between baseline behavioural variables in CA patients.
3) To identify independent behavioural patterns underlying remaining reading abilities in patients with CA.
4) To study which brain regions correlate with PCA components of reading tasks in CA.

Hypotheses:

1) Patients with chronic CA will have impairments in non-linguistic executive function tasks compared to healthy, age-matched controls.
2) Baseline reading performance of patients with chronic CA will be associated with their executive function capacities.
3) Volume of GM and WM in temporal and parietal regions of patients with CA will correlate with unique reading components identified by PCA.

It is important to clarify that VBM analysis allows to infer cognitive deficits from damaged brain regions. Although left frontal, temporal and parietal regions are thought to underpin reading abilities (Brambati et al., 2009; Ripamonti et al., 2014), patients recruited for the iReadMore trial were selected if they preserved cortex in the left inferior frontal gyrus (for tDCS), hence the left frontal regions were omitted from the pre-defined search area.

3.1. Results

3.1.1. Preliminary analysis - Descriptive statistics

Analyses were conducted in SPSS 22 (IBM, Released 2013). In the patient group, descriptive statistics were calculated for demographic data (i.e. age, gender and time post-stroke) and lesion volume. For controls, only age and gender were calculated. Results are summarised in table 4.

	N	Mean	*SD*	MIN	MAX
Patients					
Age	23	54.4	12.2	25	78
Time post-stroke (in months)	23	56.13	38.8	12	158
Lesion volume (cm^3)	23	159.1	95.4	11.7	399.2
Controls					
Age	23	54.4	12.4	23	76

Table 4. Demographic information for patient and control groups.

In both the patient and control group, the mean age was 54.4 years (*SD*= 12.2 years for patients and 12.4 years for controls). There was no significant differences in age ($t(44)=-.012$, $p=.991$). The groups were also matched by gender: in each group, 15 of the participants were male and 8 were female. All subjects in the patient group had chronic stroke, and were at least 12 months post-stroke (*M*= 56.1 months, *SD*= 38.8 months). Lesion volume range was between 12 cm^3 and 399 cm^3 (*M*= 159 cm^3, *SD*= 95.4 cm^3) (Figure 20).

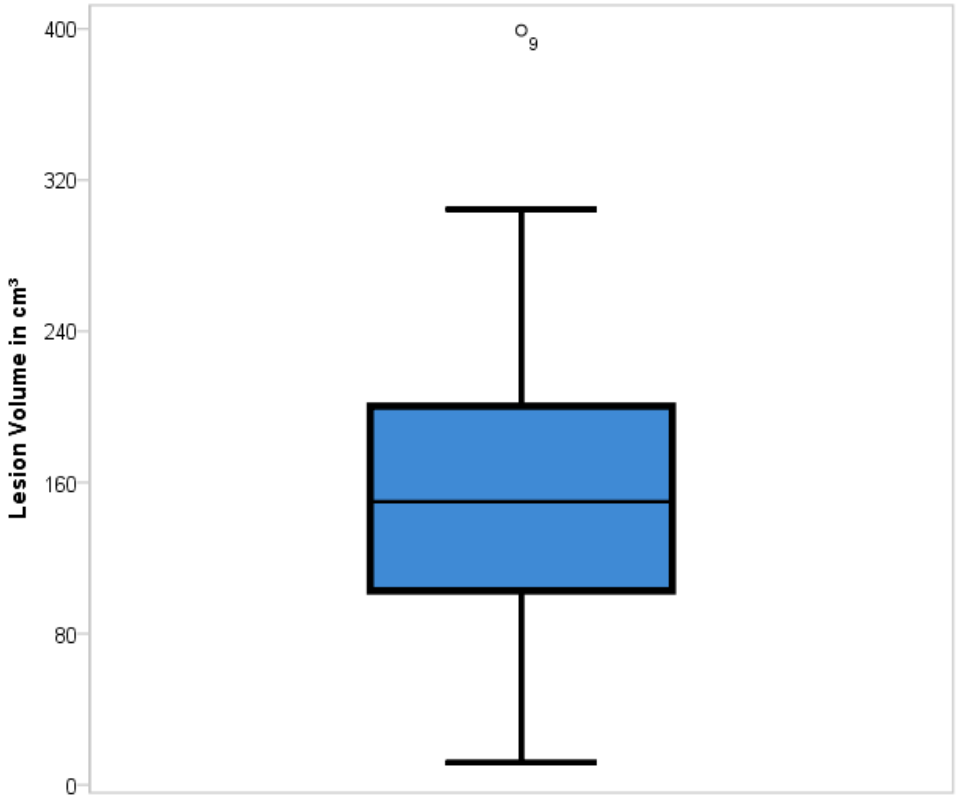

Figure 20. Lesion Volume average. This boxplot summarises lesion volume range (12-399 cm^3) and mean (M= 159 cm^3, SD= 95.4 cm^3) in the patient group.

3.1.2. Behavioural analyses of cognitive tasks

Comparison of patient and control groups

Statistical analyses between mean values in each group were conducted using independent-samples t-tests or one-sample t-tests when normative data were available. Results were divided into linguistic and non-linguistic/executive function tasks (See Table 5 and Table 6 respectively). Results from the digit span subtest were presented within the non-linguistic/executive function tasks because it is mostly considered a measure of verbal working memory (Baddeley, 2003).

	Patient	Control/ Reported norms	
	Mean (*SD*)	**Mean (*SD*)**	***t (df)***
SWR - Accuracy (%)	59.8 (30)	99.5 (.6)	-6.5 (22)**
SWR - speed (ms)	1125.7 (336)	533.3 (104)	7.6(22.2)**
Pseudoword Reading – Accuracy (%)	19 (27)	93.5 (11)	-12 (27.5)**
Pseudoword Reading – speed (ms)	1689 (715)	697.5 (249)	4.07 (8.8) **
Written Semantic matching- Acc. (%)	90 (14)	99 (1.4)	-3.1 (22.4)**
Written Semantic matching speed (ms)	5017 (3949)	1310 (390)	4.4 (21.4)**
Sentence Reading - Acc. (%)	81.2 (16)	98 (2.3)	-4.7 (23)**
Sentence Reading - wpm	73.3 (35.3)	309.1 (119)	-9.1 (26.2)**
Neale - Acc. (%)	50 (37.3)	99 (2.6)	-6.2 (43)**
Neale – wpm	30 (18)	168.7 (30)	-19 (43)**
Naming objects score	30.61 (13.3)	46.37 (1.6)	-5.7 (22)**
Naming actions score	5 (3.4)	9.88 (0.43)	-6.9 (22)**
Auditory discrimination task	3.16 (3.1)	1.05 (0.15)	3.1 (20)*

Table 5. **Comparisons of the mean scores for linguistic tasks.** This table shows reading and naming scores differences (t-test) between patient and control group. SWR = single-word reading task; Neale = Neale Analysis of Reading Ability test; Acc. = accuracy; ms = milliseconds; wpm = words per minute; * p<0.05; ** p<0.01.

As can be seen from table 5, patients' performance was significantly worse than the age-matched controls across all reading tests; they were also significantly worse than published norms on confrontation naming and auditory discrimination. This simply confirms what we already knew clinically: that the patients were both aphasic and had a significant reading disorder (CA).

Results in the non-linguistic/executive function tasks varied across tasks. There were significant differences between patients and controls in the: Pyramids and palm trees (PPT); Cattell's subtests 1 and 2; digit span, forward and backward; visual-spatial short-term memory task (VSSTM); 4-Way Weigl; and reaction times in the Sustained Attention to Response Task (NV-SART). However, there were no differences between groups' performances in the: Two-arm bandit task (TAB);

Brixton test; and accuracy, omissions, commission errors, and post error slowing in the NV-SART.

	Patient	Control/ Reported norms	
	Mean (SD)	Mean (SD)	*t* (df)
PPT	49.17 (2.31)	51.2 (1.4)	-3.8 (22)**
Cattell - subtest 1	7.52 (1.7)	9.04 (2.1)	-2.7 (44)**
Cattell - subtest 2	6.61 (2.1)	8 (2.3)	-2.02 (44)*
Digit span - forward	3.48 (1.93)	11 (2.3)	-12.0 (44)**
Digit span - backward	1.70 (1.7)	7.17 (2.44)	-8.9 (44)**
Digit span – total	5.36 (3)	18.2 (4.3)	-11.9 (44)**
Two-arm bandit (raw score)	127.7 (6.4)	129 (6.5)	-.43 (43)
Two-arm bandit % optimal choice	56.3 (6.5)	57 (7.5)	-.34 (43)
NV-SART % of hits	97 (3.8)	98.3 (1.9)	-1.5 (44)
NV-SART - omissions	5.7 (7.3)	3.2 (3.6)	-1.5 (44)
NV-SART - RT(ms)	441 (179)	340 (111.4)	2.3 (37)*
NV-SART - Errors	8.5 (6.7)	9.4 (5.72)	-.52 (44)
NV-SART – PES	15.5 (321)	58.1 (231.2)	-.52 (44)
Brixton test – errors	19.1 (9.0)	16 (5.7)	1.64 (22)
VSSTM – score	4.91 (2.1)	7.04 (1.8)	-3.7 (44)**
4- way Weigl (raw score)	8.70 (3.1)	11.3 (1.2)	-4.03 (22)**

Table 6. Comparisons of the mean scores for non-linguistic tasks. This table shows executive functions scores (t-test) between patient and control groups. PPT = Pyramids and palm trees test; NV-SART= Non-verbal version of the Sustained Attention to Response Task; VSSTM= Visual-spatial short-term memory task; RT= reaction time; ms = milliseconds; WPM = words per minute; PES= post-error slowing; * p<0.05; ** p<0.01.

Discussion - Comparison of patient and control groups

In terms of the cognitive profile in CA, comparison between groups showed that patients have significantly worse performance than controls in reading and naming tasks. These results further confirm that patients were aphasic and had central alexia. On the question of patients' impairments in non-linguistic executive functions tasks, results were rather heterogeneous with both preserved and

impaired abilities. There were no differences compared with controls on abilities such as environmental learning and adaptation to novel situations (tested with the TAB); rule change detection, anticipation, cognitive control, and inhibition (tested with the Brixton test); or sustained attention and error awareness (tested with the NV-SART). In contrast, they showed difficulties in: verbal and visual working memory (digit span and VSSTM tests); access to semantic knowledge (PPT); reasoning and solving complex problems particularly in tasks demanding cognitive flexibility (Cattell and Weigl tasks).

Patients' results in the NV-SART require a larger discussion. This finding is contrary to studies which suggest that aphasic patients have poor performance on tasks that assess different forms of attention (including sustained attention. e.g.:(Murray, 2012)).The NV-SART assesses sustained attention, which demands cognitive control and inhibition. In this task participants respond continuously and as quickly as they can. However, a stimulus that demands that the response is withheld is presented in a pseudo-random manner. This implies that subjects who respond quickly are more likely to have commission errors (i.e. respond with a button-press to a No-go trial) when an inhibitory response (withhold button press) is required. Group comparison showed no difference in any of the variables in the NV-SART (i.e. accuracy, errors of omission (not pressing for a 'go' trial), errors of commission (not withholding a button press), and post-error slowing) except for reaction time, which was significantly slower for patients. Contrary to other tasks, reduced speed in this task might be interpreted as a measure of cautiousness, which means that participants who respond more slowly are actually demonstrating more cognitive control; hence

they are less likely to produce an error. Although there were no significant differences between groups, controls were quicker but had more errors than patients. In other words it is hard to know if the patients are just slower than controls and this causes them to do relatively well in the test, or whether their sustained attention is truly unaffected by their stroke.

Executive functioning is a multidimensional construct that is most commonly affected in patients with frontal lobe damage (Alvarez & Emory, 2006; Stuss, 2011; Stuss & Alexander, 2000). However, several studies have shown that many abilities linked to executive functions depend mainly on spared frontal regions as well as temporal, parietal and subcortical areas (Jeneson & Squire, 2012; Raine & Yang, 2006; Wagner, Shannon, Kahn, & Buckner, 2005). In this study, patients were selected on the basis of preserved or partially preserved brain tissue in the left IFG, so participants tended to have damage to more posterior MCA areas such as the perisylvian regions (see Figure 18).

Different approaches to characterising executive functions have been suggested. For instance, Miyake et al. (2000) in an effort to arrange executive functions in terms of abilities and task demands, grouped them in three domains: 1) “shifting of mental sets” in which the key demand involves engagement/disengagement of task; 2) “monitoring and updating of working memory representations”, that fundamentally includes working memory tasks; and 3) inhibition of dominant responses. Although not all tasks in the behavioural protocol fit these categories, and in some cases a task can be linked to any of those categories (e.g. Two-armed bandit task), it might be concluded that in terms of this classification CA

patients have impairments mainly in tasks demanding 1) shifting of mental sets as evidenced by poor performance on the Cattell subtest and the 4-way Weigl, and 2) monitoring of working memory representation as evidenced by poor performance on digit span and the VSSMT.

3.1.3. Correlations between behavioural variables

In order to examine the associations between primary behavioural variables (26), scores were first transformed into Z scores to produce normally distributed variables. Three demographic variables (age, lesion volume, and time post-stroke) were also included in the analysis to explore whether patients' characteristics are associated with patients' performances. Bivariate correlations were conducted between variables (29 in total). For illustrative purposes, the results are presented in a color-coded correlation matrix in the figure 21. Moreover, the whole group of correlations are reported in the appendices.

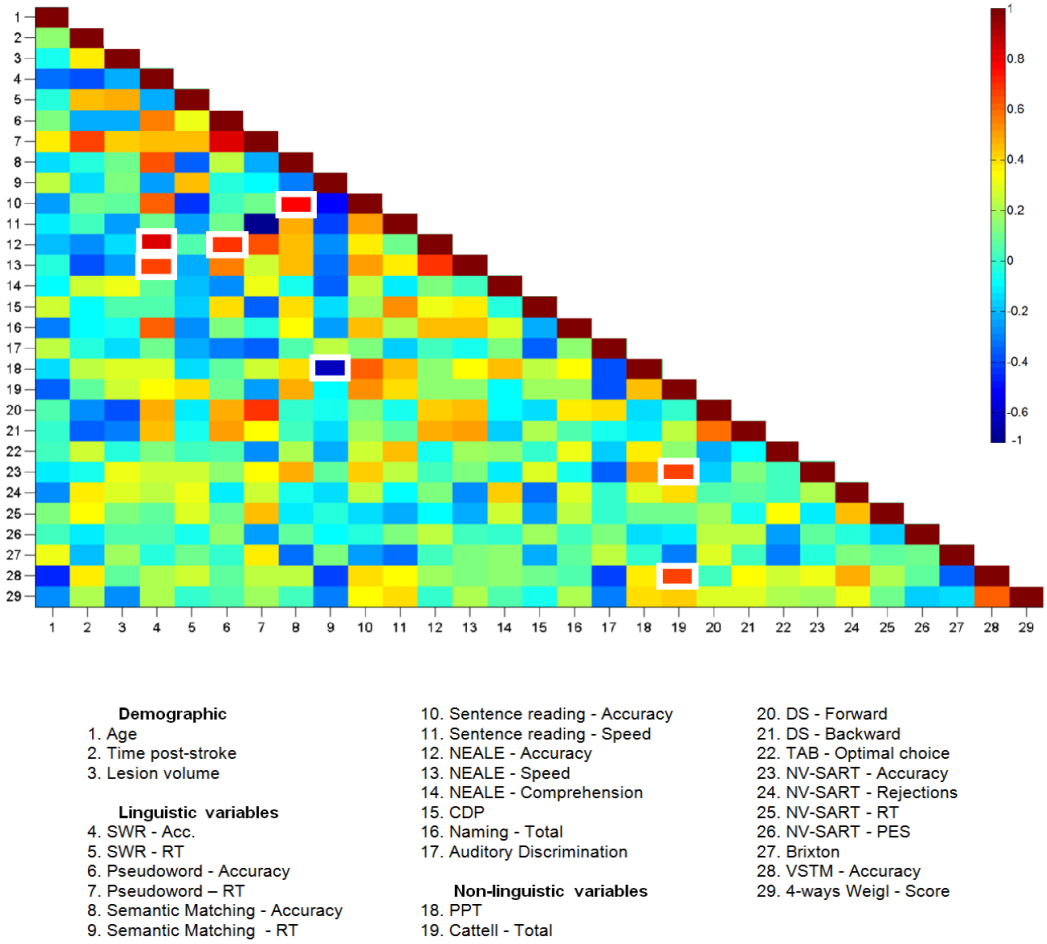

Figure 21. Correlation Matrix. Colour-code matrix showing positive and negative correlations (*r*) between primary variables tested at baseline. Significant variables after Bonferroni correction for multiple comparisons are highlighted in white. These results are reported in more detail in Table 7 below. SWR= single-word reading; RT= reaction time; Neale = Neale Analysis of Reading Ability test; CDP= communication disability profile. PPT= Pyramids and palm trees test; TAB= Two-armed bandit; NV-SART= Non-verbal version of the Sustained Attention to Response Task; VSSTM= visuo-spatial short-term memory task.

To test the hypotheses that reading patients' performances are associated to their executive function abilities, correction for multiple comparisons was conducted using Bonferroni adjusted alpha levels of .001 per test (.05/29). Significant results are reported in the table 7.

Pair of variables	*r*	*p*
1. Correlations between linguistic variables		
SWR Acc. / Neale Acc.	.808	<.001
SWR Acc. / Neale speed (wpm)	.647	.001
Pseudoword reading Acc. / Neale Acc.	.673	.001
Semantic matching Acc. / Sentence reading Acc.	.747	<.001
2. Correlations between non-linguistic variables		
Cattell's total score / VSSTM accuracy	.648	.001
Cattell's total score / NV-SART accuracy (%)	.633	.001
3. Correlation between linguistic and non-linguistic variables		
Semantic matching RT (ms) / PPT score	-.717	<.001

Table 7. Significant correlations between baseline variables. SWR= single-word reading; SWR = single-word reading task; Neale = Neale Analysis of Reading Ability test; Acc. = accuracy; wpm = words per minute; ms = milliseconds; VSSTM= visual short-term memory task; NV-SART = Non-verbal version of the Sustained Attention to Response Task.

Discussion - Behavioural analyses of cognitive tasks

There is some evidence indicating that executive functions such as working memory, cognitive control or mental flexibility are linked to aphasic patients' proficiency in linguistic tasks and possibly in language recovery (Brownsett et al., 2014; Kuzmina & Weekes, 2016; Lambon Ralph & Fillingham, 2007; Nicholas et al., 2005; Penn et al., 2010). This analysis explored associations between reading ability and executive function in patients with central alexia. Whilst some correlations were observed within domain (i.e. between linguistic variables or between non-linguistic variables), only one correlation between domains survived correction for multiple comparisons (between semantic matching and PPT tasks).

No correlations between linguistic and non-linguistic variables was an unexpected finding because it contradicts the hypothesis that reading performance in CA is associated with patients' executive abilities.

The discussion will concentrate on the main findings: (i) associations between variables from the same cognitive domains; and (ii) association between variables from different cognitive domains.

(i) Six significant correlations were found between variables from the same cognitive domain. Four of these correlations were between reading variables: The Neale is a standardised test used to assess oral text reading and text comprehension in children (Neale, 1997; Spooner, Baddeley, & Gathercole, 2004), although it has also been used in adult stroke populations (Spitzyna et al., 2007). Accuracy in the Neale was significantly related to 1) accuracy in SWR and 2) accuracy in pseudoword reading. These three tasks share oral reading; therefore the most likely explanation is all three tap into conversion from orthography to phonology. Furthermore, this correlation shows that even though the SWR and pseudoword reading tasks were created for this therapeutic trial, they have convergent validity and consistency with a standardised test; hence they are measuring the same construct. The association between accuracy in the SWR and the Neale requires further discussion. This result might indicate that single words can be conceived of as the building blocks of text reading. This association is important for the iReadMore therapy as it only trains single-word reading, yet the therapeutic aim is to improve real-world reading, which is dominated by text. Often, patients refer to difficulties in reading long texts, such as letters, news, or books. This limitation impacts upon their daily activities

resulting in frustration and loss of independence (Darrigrand et al., 2011). This suggests that there is a window of hope for generalisation of the iReadMore in oral reading accuracy of texts, even if the effects are item-specific.

Another correlation was between 3) SWR accuracy and speed in the Neale (measured in words per minutes). This association clearly shows that good performance reading single-words leads to high efficiency in reading texts. The last correlation between linguistic tasks was 4) semantic matching accuracy and sentence reading accuracy: these two tasks demand silent reading and reading comprehension. Similarly to the oral reading tasks discussed previously, one task requires silent reading of single words (semantic matching) and the other demands silent reading of sentences. This suggests that good performance on reading comprehension involves preserved access to semantic knowledge and appropriate abilities to link words within contexts.

There were two significant correlations between non-linguistic variables: the behavioural protocol included subtest 1 and subtest 2 of the Cattell Culture Fair test (Cattell & Cattell, 1949) which measures fluid intelligence. A total score combining both measures was produced. Correlation 5) was between the Cattell total score and accuracy in the VSSTM task. Both tasks demand mental manipulation of visual information in space. This correlation might support the assumption that fluid intelligence is associated with visual working memory. This is in agreement with evidence from studies in children and adults that have found associations between fluid intelligence and tasks that assess working memory (Conway et al., 2002; de Abreu, Conway, & Gathercole, 2010). The other

correlation involved 6) total score in the Cattell and accuracy in the NV-SART. The NV-SART is a measure of cognitive control (Manly et al., 2000). Accuracy in this test is determined by a sustained response along time. This result indicates that tests of fluid intelligence perhaps rely on or similarly stress cognitive control and sustained attention systems.

(ii) Turning now to associations between variables from different cognitive domains, only one correlation was found: 7) RT in the semantic matching task was related to score in the Pyramids and palm trees test (PPT). The correlation was negative indicating that patients who have difficulties accessing visual semantic knowledge are also slow (high RTs) on tasks of reading comprehension. This shows that although the tasks differ in their use of linguistic versus pictorial stimuli, they both rely on shared semantic knowledge.

The fact that no correlations were found between linguistic and executive function tasks is surprising and it might suggest that while both linguistic and non-linguistic test performance is affected in this patient group, they are not correlated so are perhaps damaged separately. In other words, severity of damage in one system does not predict severity of damage to the other and vice-versa. For instance, impairments in verbal comprehension might affect participants' performance only in executive tasks with verbal demands. Results in this chapter are in line with those obtained by Sesma, Mahone, Levine, Eason & Cutting (2009) that studied the influence of executive functions in reading in a group of children. They found that verbal working memory and planning are important for reading comprehension, but not for recognition and reading of written words. Similarly, Fedorenko (2014) reviewed the contribution of executive functions, grouped as

the “multiple demands” system, in aphasic patients’ language comprehension. She concluded that executive functions participated in but are not crucial for comprehension. She also showed that key brain regions involved in verbal comprehension are distant to regions associated to the multiple demands system.

3.1.4. PCA of reading abilities and VBM analysis

The second section of this chapter aims to identify brain regions within the left temporal and parietal lobes where grey matter or white matter density correlated with independent reading components of residual ability in patients with CA. In order to achieve this aim, first a PCA analysis of the reading variables was conducted. Then, a VBM analysis was carried out to identify independent GM and WM regions related to the resulting reading components.

Five participants had incomplete baseline data (see Table 4) in reading tasks, representing 4% of the values. SWR - RT could not be calculated for four participants (P8, P10, P16 and P20) due to the low number of correctly read words (<20%). Participant 20 was unable to attempt the pseudoword and text reading tasks. Participant 8 was unable to attempt the semantic matching task, and both participants 8 and 17 were unable to attempt the sentence reading task: due to the 2-alternative forced-choice nature of these tests the missing accuracy values were replaced with chance level (50%). All other missing values were addressed using multiple imputation in SPSS by creating ten imputed datasets. Averaged scores of the imputed datasets were used in the PCA. Moreover, pseudoword reading speed was excluded from the PCA because there were no

correct trials to calculate reaction times from in 9 out of 23 participants (this was a task the CA patients really struggled with).

PCA Results

Very strong correlations have the potential to bias the PCA (Field, 2013), hence a good approach to PCA should exclude these variables. Bivariate Pearson's correlations showed that no pair of measures (reading accuracy and speed variables) had correlations stronger than r = 0.9 (see appendices), hence all variables met this inclusion criteria for PCA.

PCA of reading variables

The Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy was .645, and Bartlett's test of sphericity was significant ($X^2(36) = 103.9$, $p<.001$). Both tests indicated that the data were suitable for PCA. In addition to the KMO coefficient, sample adequacy was calculated based on subject to variable ratio ≥ 1.2 (Butler et al., 2014; Halai et al., 2017; MacCallum et al., 1999). In this study, 23 patients were assessed and 9 variables were used in the PCA giving a ratio = 2.6, which is also indicative of an adequate sample size.

The PCA created a model with two components with eigenvalues (e) > 1 (see Table 8). This model accounted for 67% of the variance in the original data. The first component (e= 4.1) explained 46% of the variance in the data and had a high loading on tasks that involved reading words aloud (text reading accuracy, pseudoword reading accuracy, and word reading accuracy); hence this component was labelled "reading aloud". The second component (e= 1.9)

explained 21% of the variance and loaded high on tasks involving silent reading for meaning (sentence reading and semantic matching tasks), hence this component was labelled “reading for meaning”. As longer reaction times reflect worse reading ability, reaction times measured in milliseconds (for word reading and semantic matching tasks) have an inverse association with reading ability. Conversely, reading speed on sentence and text reading tasks were measured in words per minute (WPM) and so load positively onto the PCA components. Table 9 summarises patients’ scores on the reading tasks and the PCA components.

	Component Matrix	
	Reading aloud (e=4.1)	**Reading for meaning (e=1.9)**
Neale – accuracy	**.914**	.126
Pseudoword reading accuracy	**.860**	-.232
SWR - accuracy	**.768**	.370
Neale - speed (wpm)	**.733**	.386
Sentence reading – accuracy	.271	**.846**
Sentence reading - speed (wpm)	.040	**.654**
Semantic matching – accuracy	.455	**.622**
SWR - speed (ms)	.114	**-.729**
Semantic matching - speed (ms)	-.257	**-.708**

Table 8. PCA components matrix. Loading of reading tasks on components extracted from the varimax rotated PCA. In bold high loads. e= eigenvalue; WPM = words per minute; ms = milliseconds. Neale = Neale Analysis of Reading Ability test; SWR = single-word reading task; wpm = words per minute; ms = milliseconds.

Patient ID	PWR – Acc. (%)	WRT – Acc. (%)	WRT- RT (ms)	SM – Acc. (%)	SM - RT (ms)	SR – Acc. (%)	SR - wpm	TR – Acc. (%)	TR - wpm	Nam-O (Max=48)	Nam – A (Max=10)	Reading aloud	Reading for meaning
1	0	58.35	1377.32	97.22	3708.28	90	84.66	45.33	21.15	35	5	-0.67	0.40
2	0	40.31	1373.07	80.56	4976.5	76.67	73.8	52.56	18.8	28	3	-0.77	-0.28
3	70	96.69	981.88	97.22	1707.83	66.67	35.58	94.66	29.25	38	9	1.39	-0.55
4	0	71.11	791.55	91.67	3431.48	93.33	75.33	34.66	14.45	32	6	-1.00	0.96
5	75	63.82	1956.91	80.56	10854.86	60	28.32	93.58	15	3	0	1.42	-2.65
6	30	91.94	803.76	97.22	3127.52	96.67	61.23	87.17	32.31	46	8	0.66	0.62
7	2.5	90.05	979.44	94.44	5088.54	93.33	37.12	93.58	38.35	46	9	0.51	0.26
8	2.5	12.48	NA	50	NA	50	NA	52	16.63	32	10	-1.22	-1.16
9	20	58.24	1350.99	93.06	1927.03	76.67	50.08	90.67	27.5	42	5	0.44	-0.34
10	0	3.39	NA	51.39	9040.91	41.67	35.74	28	12.39	22	1	-1.43	-1.68
11	75	96.28	872.16	98.61	2072.25	90	91.41	97.44	83.9	41	10	2.00	0.50
12	25	90.59	852.94	95.83	2895.54	90	92.92	94.67	53.84	42	6	0.80	0.78
13	65	91.53	1503.9	97.22	4760.29	96.67	114	98.72	58.28	41	9	1.78	-0.07
14	0	80.37	937.72	97.22	6496.44	86.67	56.42	81.33	20.45	34	8	-0.18	0.32
15	2.5	47.29	1101.92	73.61	4530.96	83.33	32.81	64.1	20.83	6	2	-0.71	-0.26
16	0	19.97	NA	98.61	2161.51	93.33	89.56	11.54	14.66	35	6	-1.22	0.80
17	10	28.14	1256.9	91.67	16336.42	50	NA	30.77	13.29	19	0	-0.86	-1.45
18	7.5	75.42	864.19	98.61	3994.54	93.33	62.21	75.64	48.8	21	4	0.33	0.71
19	5	35.85	757.18	95.83	2251.88	93.33	104.4	67.95	31.01	16	0	-0.82	1.24
20	NA	13.39	NA	95.83	3229.88	76.67	95.61	NA	NA	5	0	-0.04	0.04
21	0	59.49	1138.73	93.06	13351.56	86.67	46.99	70.51	21.19	41	6	-0.48	-0.41
22	27.5	74.92	700.81	95.83	2328.57	90	176.11	86.67	31.89	38	4	-0.01	1.54
23	0	75.51	1249.59	100	2111.24	93.33	94.89	88.46	27.06	41	5	0.08	0.69

Table 9. Patients' scores on the linguistic assessment and PCA components. Abbreviations: PWR= pseudoword reading; WRT= Word reading test; SM= Semantic matching; SR= Sentence reading; TR= Text reading; Nam-O= Naming objects (CAT); Nam-A= Naming actions (CAT); Acc. = Accuracy; RT= Reaction time; ms=milliseconds; wpm= words per minute; Max= maximum score; Comp= component. NA= not applicable.

3.1.5. Neuroimaging results

Voxel-based morphometry (VBM) analysis

Analyses to test the third hypothesis aimed to identify which areas of MCA territory show significant brain-behaviour relationships with the reading components using VBM. My search area comprised temporal and parietal lobes of the left hemisphere as these encompass the dorsal and ventral streams (Dehaene et al., 2010) thought to underpin sublexical reading (orthography to phonology; dorsal stream) and lexical reading (orthography to semantics to phonology; ventral stream). Although the inferior frontal lobe is important for reading, patients in this study were recruited for the iReadMore trial involving tDCS, which selectively required intact cortex in the IFG. As these criteria meant that I could not make lesion-deficit inferences about the role of frontal regions in CA it was omitted from the pre-defined search area.

The WFU PickAtlas (Maldjian, Laurienti, Kraft, & Burdette, 2003) was used to create a left temporal and parietal lobe mask. This mask had 2mm 3D dilation to be as inclusive as possible of effects at the edges of the area of interest. For each analysis, a multiple regression model was created (see Figure 22) with segmented GM or WM images as the data, the PCA reading component scores as explanatory variables, plus nuisance variables including: subjects' age, lesion volume, time post-stroke, and naming score (total) as a measure of aphasia severity. The SPM results were interrogated by first selecting a liberal uncorrected voxel threshold of $p<0.01$. Then the left temporal and parietal mask was applied for small volume correction, and only clusters within the mask that survived a conservative significance threshold of $p<0.05$ FWE corrected for

multiple comparisons were reported. The anatomical locations of the resulting clusters were labelled using the Harvard-Oxford atlas and the JHU White-Matter tractography atlas (Hua et al., 2008) distributed with FSL (http://www.fmrib.ox.ac.uk/fsl/).

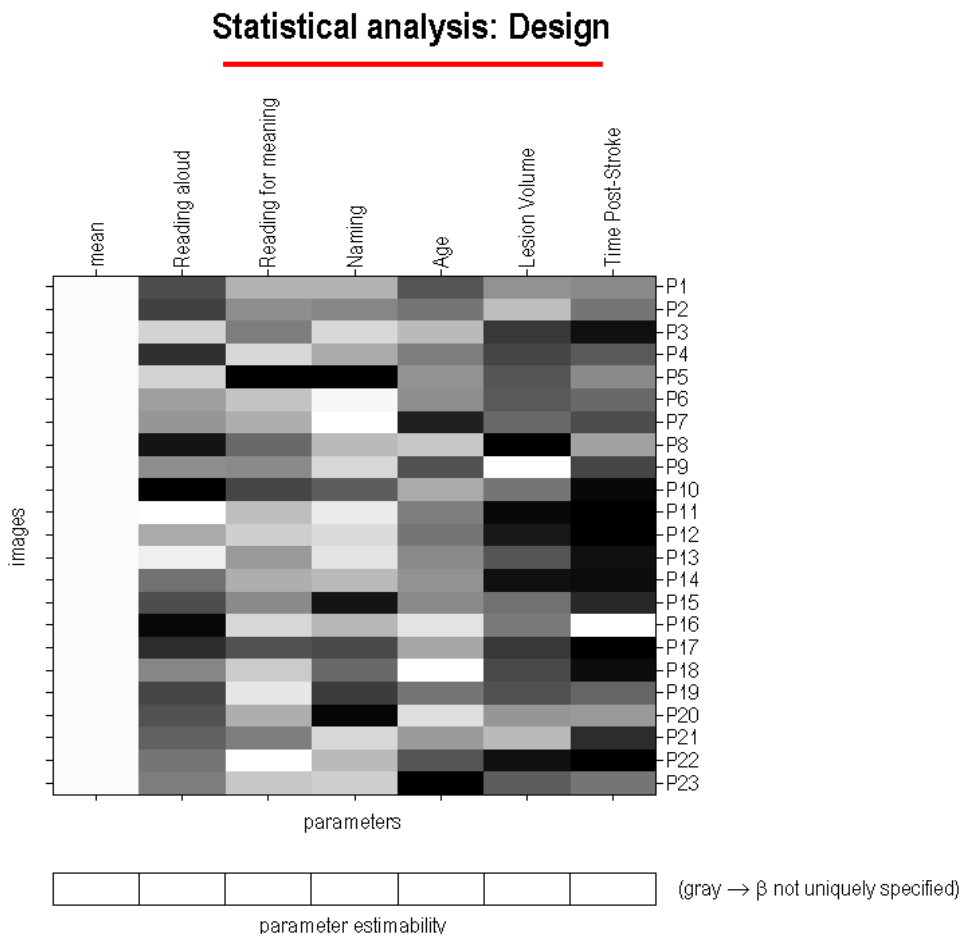

Figure 22. VBM-Design matrix. Design matrix used in the VBM - multiple regression – analysis. Segmented images were entered to identify unique regions associated to PCA reading components while controlling for demographic data and aphasia. Analyses included GM or WM images (separately) with each component from PCA analysis.

The VBM results (Figure 23) showed positive correlations between the PCA components and tissue volume, controlling for the effects of age, lesion volume, time post-stroke and naming ability. Significant clusters are reported in Table 10.

Component	Cluster size (voxels)	Cluster -level *p* (FWE)	Peak co-ordinate (x, y, z)	Peak location	*Z*
1. Reading aloud - GM [red region in Fig 23]	533	.05	-44, -44, 36	Supramarginal Gyrus	3.79
2. Reading for meaning-GM [anterior yellow region in Fig 23]	580	.038	-50, 6, -46	Temporal Pole	3.53
3. Reading for meaning (GM) [posterior yellow region in Fig 23]	777	.011	-52, -52, -10	Inferior Temporal Gyrus	3.33
4. Reading for meaning (WM) [lateral blue region in Figure 23]	1060	.009	-38, -14, -28	Temporal Fusiform Cortex, anterior division	3.90
5. Reading for meaning (WM) [medial blue region in Figure 23]	3316	<.001	-26, -50, -8	WM deep to the collateral sulcus	4.33

Table 10. Anatomical location of brain regions associated to PCA reading components. Regions were determined with the Harvard – Oxford cortical and subcortical structural atlases and JHU White-Matter tractography atlas. GM= grey matter; WM= white matter; FWE= family-wise error correction.

Reading aloud component

Patients' performance on this component was correlated with a cluster of 533 contiguous voxels in the GM of the left SMG (Table 10) extending anteriorly into the parietal operculum. This cluster was wholly contained within the lesion overlay map (green contour in Figure 23, thresholded to voxels where ≥ 2 patients had damage); 18/23 patients had damage to the peak voxel and 21 had damage to any voxels within this region. No significant correlations were found between the reading aloud component and WM volume.

Reading for meaning component

Patients' performance on this component was correlated with two GM and two WM clusters. In the GM, the first cluster included 777 contiguous voxels encompassing the posterior part of the left middle temporal gyrus (MTG) and inferior temporal gyrus (ITG) (see Table 10). In this region 14 patients had

damage to the peak voxel and 15 had damage within the area. The second cluster included 580 contiguous voxels and it was located in the ventrolateral anterior temporal pole. In this region no patients had damage to the peak voxel and only 4 had damage within the area. Both of these clusters were located on the boundary of the lesion overlay map.

In the WM, the first cluster was very large and included 3316 contiguous voxels. This cluster covered the WM extending from left occipital cortex to left medial temporal cortex. No patients had damage to the peak voxel of the cluster, and as shown in Figure 23 (in blue) the cluster largely fell outside of the lesion overlay area. However, 20/23 patients had damage to some part of this extensive cluster. The second cluster included 1060 voxels and it was in WM underlying more anterior portions of the anterior parahippocampal and fusiform gyri. Only two participants had lesioned tissue at the peak voxel of this cluster and 7 had damage within the area.

Post-hoc tests

The GM region that correlated with the reading aloud (figure 23-A) component was clearly within the bounds of the group LOM (green contour in the figure) as was the first GM cluster in the reading for meaning analysis. Two of the other clusters identified by this analysis were near or outside the borders of the group LOM (Figure 23-B and C). Post-hoc analyses were performed to investigate whether findings outside the LOM were driven by damage to these regions, either primary damage or secondary to Wallarian degeneration (in which case the patients as a group should have more damage here compared with controls) or whether the region was not affected either directly or indirectly by stroke (in which

case the patients as a group should not differ to controls). To do this GM and WM density values were extracted in the two peak co-ordinates from the patients' images and compared them to the control group's images (see Figure 23-D).

A post-hoc unpaired t-test revealed that tissue density in the GM of the anterior temporal lobe was significantly lower in the patient group ($t(50)=-2.3$, $p=.024$). However, the null hypothesis for the WM region of the posterior and medial temporal lobe was not rejected ($t(50)=-1.4$, $p=.167$).

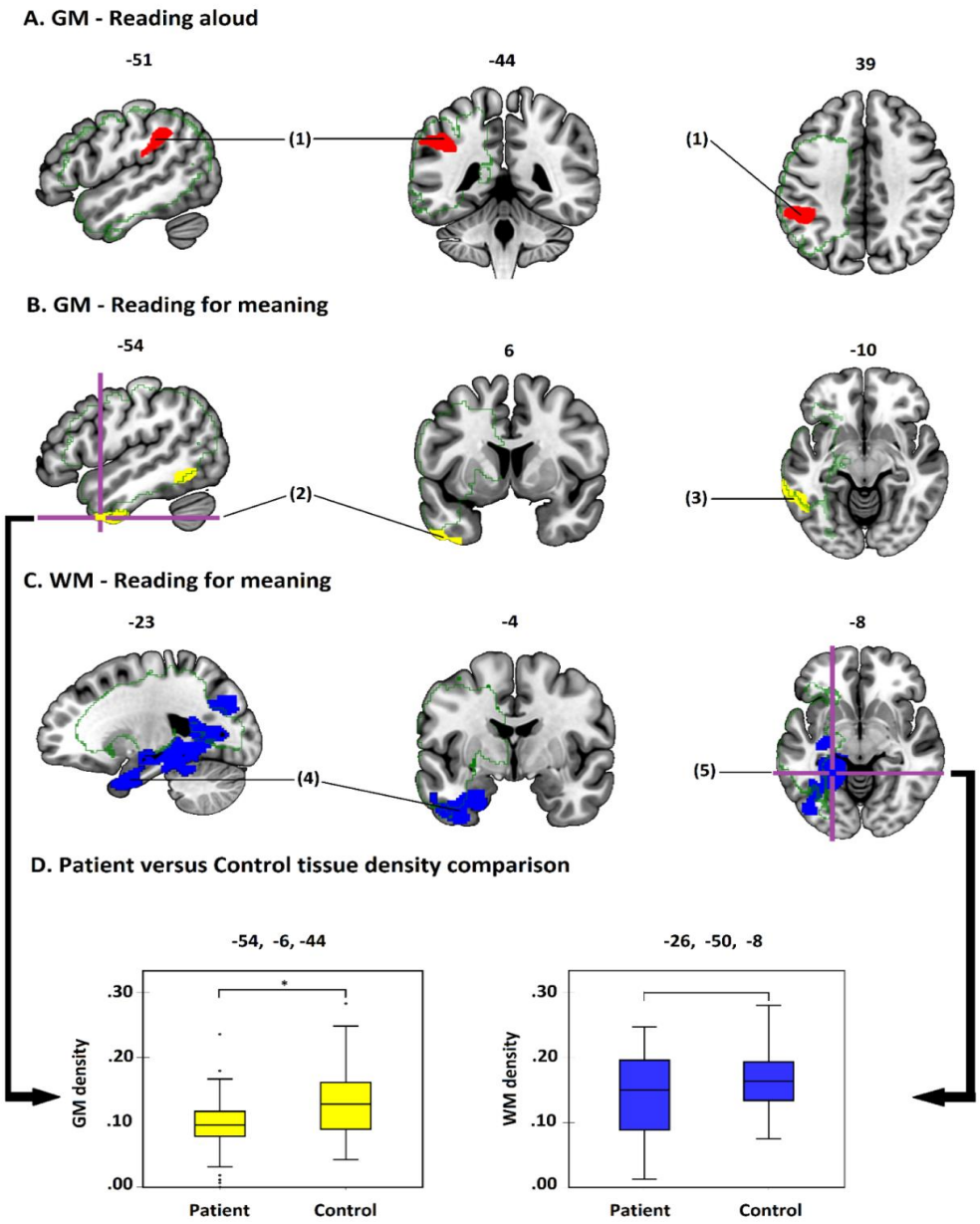

Figure 23. VBM results of PCA components. VBM results show positive correlations between behavioural PCA and tissue volume in grey (GM) and white matter (WM) of the patient group. Results are presented at P<.01 voxel-level, P<0.05 FWE-corrected cluster-level. A: The reading aloud component correlated with a cluster in (1) the left supramarginal gyrus (SMG). B: The reading for meaning component correlated with two GM clusters. One cluster in (2) the left anterior temporal lobe (ATL) and other in (3) the left posterior MTG and ITG. C: The reading for meaning component also correlated with two WM clusters. One cluster covers (4) WM of the middle and posterior left fusiform gyrus. Other cluster encompassing (5) posterior and medial WM deep to the lingual gyrus. Contour of the lesion overlay map (LOM) is shown in green to illustrate clusters within or outside the lesioned areas. *Crosshairs in magenta indicates peak co-ordinates at the boarder of/outside the lesioned areas.* D: post-hoc analysis of group mean GM and WM densities at these two co-ordinates. Co-ordinates are displayed in X, Y, Z. GM = grey matter; WM = white matter. *= p<.05.

Discussion - PCA and VBM analyses

VBM and voxel-lesioned symptom mapping (VLSM) analyses have been extensively performed on aphasic patients. In a general view, most of these studies aim to correlate tissue density of brain regions with patients' performance in cognitive tasks. As patients' scores reflect impaired abilities (compared to controls), these volumetric methods allow us to infer which regions are critical in supporting a specific cognitive function (which is represented by a task). However, results and conclusions from VBM and VLSM analyses are often limited because cognitive tasks are mostly unidimensional, while cognitive processes are multidimensional.

In this study the aim was to identify brain regions within the left temporal and parietal lobes that correlate with residual reading ability in patients with central alexia. Like other researchers investigating post-stroke aphasia, PCA was chosen as a multivariate approach to the behavioural data (reading variables) combined with a VBM (mass univariate) analysis of the brain imaging data to identify brain-behaviour correlations (Butler et al., 2014; Halai et al., 2017; Lambon Ralph et al., 2010; Mirman et al., 2015). While mass univariate approaches have been criticized recently as being prone to spatial bias (Mah, Husain, Rees, & Nachev, 2014), the large spatial extent of the regions identified hopefully mitigate these concerns to some extent. The discussion of these results will be concentrated on the three main findings: (i) PCA analysis of reading behaviour; (ii) VBM results likely related to tissue damage (regions in and at the border of the group lesion overlap map); (iii) VBM results in brain regions where

tissue density was largely preserved (regions outside the border of the group lesion overlap map).

(i) The behavioural PCA identified two components, which were labelled as ‘reading aloud’ and ‘reading for meaning’. The first component, reading aloud, explained the largest variance in the data and had high loadings on accuracy of pseudoword reading, word reading, and text reading. This means that patients presented a profile characterized by speech production (grapheme to phoneme conversion) and phonological difficulties; this is in keeping with the majority of the patients having a profile consistent with the phonological dyslexia subtype of central alexia (see Table 1 in Chapter two). In contrast, the ‘reading for meaning’ component had a high loading on accuracy of written sentence-to-picture matching and written semantic matching tasks. These variables relate to conceptual knowledge, understanding of written words, and text comprehension during silent reading. Furthermore, sentence reading speed in WPM also loaded onto this component showing an association between speed and accuracy in the reading for meaning tasks. It is worth noting that although most patients had a phonological dyslexia profile, the second PCA component shows that they also showed substantial variation in reading for meaning, which might ordinarily be associated with surface dyslexia.

(ii) The brain-behaviour VBM analysis within left temporal and parietal lobes revealed that reading aloud correlated independently with one GM region, while reading for meaning correlated with two GM and two WM regions. The first four regions were all within or at the edge of the patients’ LOM (green contour in Figure 23) while the last region was mostly outside it; the relationship between the identified regions and the LOM affects the inferences that can be drawn. Regions

inside the LOM probably support reading behaviour in the undamaged brain, and the degree to which they are spared correlates with residual reading ability. The WM region outside the LOM clearly supports reading but it is probably unaffected, either directly or indirectly by the stroke damage. Each region associated with PCA results will be discussed in turn.

The reading aloud component identified the GM of the left SMG, region (1). This result supports the idea that the left SMG is crucial in the neural system of reading aloud, linking orthography to phonology. Evidence from lesion-behaviour studies of stroke patients with phonological and deep dyslexia (Woollams, 2014) and central alexia (Ripamonti et al., 2014) both identified the left SMG. A VBM study in patients with primary progressive aphasia (Brambati et al., 2009) also identified a positive relationship between sparing of the left SMG and phonological reading ability. Studies in controls using fMRI tasks (Graves et al., 2010; McDermott, Petersen, Watson, & Ojemann, 2003; Oberhuber et al., 2016; Price, 2012), VBM (Carreiras et al., 2009) and transcranial magnetic stimulation (Sliwinska, Khadilkar, Campbell-Ratcliffe, Quevenco, & Devlin, 2012), also strongly support the role of the SMG in phonological processing of written words.

The remaining four clusters are all associated with the ability to read for meaning and are located in different parts of the dominant temporal lobe. The first GM cluster (2) is in the ventral anterior temporal pole (aTL) while the second (3) covers the left posterior MTG and ITG. The anterior temporal pole region has been postulated as a hub that integrates multimodal semantic information for quite some time now (Dilkina, McClelland, & Plaut, 2008; Guo et al., 2013; Hoffman et al., 2015; Lambon Ralph et al., 2010; Patterson, Nestor, & Rogers, 2007; Rice et al., 2015). Again, previous VLSM and VBM studies of stroke

patients and those with PPA, respectively, have identified both regions as supporting visual semantic processing (Binder et al., 2016; Brambati et al., 2009; Guo et al., 2013; Ripamonti et al., 2014; Wilson et al., 2012). fMRI studies of reading have also shown stronger activation of the left anterior ventral occipitotemporal cortex and posterior part of the middle temporal gyrus in tasks involving the lexico-semantic route (reading irregular words > pseudowords, irregular > regular words, and familiar words > pseudowords) (Price, 2012) and text comprehension (Ferstl, Neumann, Bogler, & von Cramon, 2008).

Two WM regions were identified in the reading for meaning analysis (Figure 23-C). The more anterior and lateral cluster (within the LOM, (4)) is large (over 1000 voxels) and covers much of the middle and posterior parts of the left fusiform gyrus, the latter of which consistently demonstrates task-specific activation in many functional imaging studies of single word and pseudoword reading (Price, 2012; Taylor et al., 2013; Vigneau et al., 2005; Woodhead et al., 2011). The posterior fusiform is usually supplied by the posterior cerebral artery, while the middle and more anterior parts are more likely to receive some contributions from the MCA supply. Given that all patients had MCA territory strokes, it is most likely that the WM of the fusiform features heavily in the LOM because of secondary damage from the initial stroke. Two possible mechanisms may explain indirect tissue damage: 1) inadequate collateral flow that increases lesion extension (Campbell et al., 2013); or 2) Wallerian degeneration that causes deafferentation of regions outside the original stroke area over time. This effect has been observed after large MCA strokes in humans (Gupta et al., 2006).

Perhaps the most interesting finding relates to the final, posterior and medial WM region deep to the lingual gyrus and medial to the fusiform (region 5 in Figure 23-C). An association of this region with reading for meaning has been demonstrated by studies on typically developing children (compared with those with developmental dyslexia), where a semantic category judgment task on visually presented words activated the lingual gyrus (Shaywitz et al., 2002); although meta-analyses of functional imaging studies of reading in normal adults associate this area with lower level visual analysis of written words (Jobard et al., 2003). This region is clearly outside the boundary of the LOM and was the only region that had similar tissue density to age-matched control subjects (Figure 23-D). The identification of this region cannot therefore be easily explained by any of the mechanisms discussed so far. Two main possibilities arise, both equally compatible with the data presented here: 1) pre-morbid reading ability is related to WM density in this region, so those who have high values here will be less severely affected by their stroke than those who have low values; 2) as the patients are all in the chronic phase (>1 year post-stroke, M=4.7 years) plastic changes in this region (presumably experience-dependent) have occurred since the stroke and support residual reading ability. The first possibility, essentially relating to pre-morbid, inter-individual differences in brain structure that may be driven by genetic or environmental factors, is supported by studies where behaviour in an unselected population correlates with measures of white matter integrity e.g.: fractional anisotropy of posterior white matter correlating with reaction times on a test of visuo-spatial perception (Tuch et al., 2005). The second possibility is supported by evidence from the human expert performance literature where measures of white matter structure correlate with practice-based expertise. In the case of learning to read, this was demonstrated nicely by a study

that identified posterior WM tract changes in the splenium of the corpus callosum, after adult illiterates had learnt to read (Carreiras et al., 2009). Hence, the association with reading here may reflect re-modelling of perilesional tracts as a form of post-stroke compensatory plasticity. This hypothesis will be studied further with longitudinal data collected in this cohort.

Finally, it is important to note that these findings were biased towards the anatomical area of interest (the left temporal and parietal lobes), chosen because so many other studies had identified these regions as being involved in supporting both reading aloud and reading for meaning. The analysis was not blind to effects in other brain regions but the statistical threshold was higher (FWE corrected for the whole brain volume) and significant regions outside the pre-defined anatomical mask that survived this correction were not found.

In conclusion, PCA of reading abilities in patients with CA has shown a clear dissociation of phonological (reading aloud) and semantic (reading for meaning) dimensions in reading tasks. Additionally, VBM analysis of GM and WM in parietal and temporal regions demonstrated the association of phonological processing with the dorsal stream (the left supramarginal gyrus) and semantic processing with the ventral stream (the left ventral temporal lobe). This is in agreement with cognitive and anatomical models of reading (Plaut, 2008). Particularly, WM findings highlighted a possible compensatory role of undamaged ventromedial temporal regions in supporting reading ability after stroke, which has not been previous reported.

Summary and Conclusions - Experimental chapter one

A detailed neuropsychological characterisation (preserved/affected cognitive abilities and their neuroanatomical association) of reading impairments in CA is useful in clinic and research. It could help to create more accurate behavioural models as well as having the potential to guide new therapies aiming to improve cognitive impairments of aphasic patients. The purpose of this chapter was to investigate the baseline cognitive profile of patients with reading impairments and the neural basis associated to their difficulties. In order to take an inclusive view of the profiles of reading impairment that occur in post-stroke aphasia, I examined a heterogeneous group of patients with CA rather than dividing them categorically into sub-groups according to dyslexia subtype (i.e. phonological, surface or deep dyslexia) or aphasia type. Moreover, I was interested in determining whether non-linguistic abilities (mostly executive functions) are related to patients' reading impairments. Hence, a behavioural protocol including a broad range of linguistic and non-linguistic/executive functions tests was used. To answer those questions, behavioural data and structural MRI data were analysed. Different approaches to analyse the data were implemented: 1) comparison between CA patients' performances and controls; 2) correlations between patients' demographic and behavioural variables; and, 3) combination of a multivariate method (PCA) with neuroimaging volumetric analysis (VBM) focused on left parietal and temporal regions.

The group analysis showed that CA patients do have difficulties with some executive function tasks. A few studies have argued that executive functions might play a role in patients' responses to therapy (Brownsett et al., 2014;

Lambon Ralph et al., 2010). This hypothesis is tested in chapter 4. Results showed significant associations between variables of the same cognitive domain (reading or executive functions variables). Only one association was found between variables from different domains (score in the PPT and RT of the semantic matching task), however, no associations relating reading with executive functions variables were found. Although analyses were exploratory, this finding is not clear. It might be related to the characteristics of the executive function tasks used in this study which were selected to avoid verbal demands in our sample of aphasic patients. Furthermore, it is possible that executive tasks do not cover executive abilities that might be related to patients' reading abilities

The PCA analysis of reading tasks identified two main components encompassing 'reading aloud' and 'reading for meaning'. VBM analysis of PCA components showed a positive association of: 1) phonological processing (reading aloud) with GM in the left SMG which is part of the language dorsal stream; and 2) semantic processing (reading for meaning) with GM and WM along the temporal lobe in the language ventral stream. Findings associating reading for meaning ability and WM volume in posterior regions of the temporal lobe (lingual gyrus and posterior fusiform gyrus) have not been reported previously. Tissue density comparison with healthy controls revealed no difference in the WM volume of this WM region. This result suggested a possible compensatory role of undamaged ventromedial temporal regions in supporting reading ability after stroke.

4. INVESTIGATING NEUROLOGICAL AND COGNITIVE FACTORS THAT PREDICT CENTRAL ALEXIA PATIENTS' RESPONSES TO A COMPUTERISED READING THERAPY

Introduction

In the previous chapter, patients' baseline data were analysed to investigate which brain regions were associated with preserved and affected reading abilities in CA. From a clinical point of view, understanding the relationship between patients' impairments and their lesioned brain regions is important because it might be used as a biomarker for identifying patients who would benefit from one type of treatment rather than another. Although several effective therapies to treat aphasia are available (Brady et al., 2016), very little is known about what factors are associated with patients' responses to SLT. Prognosis of language recovery centred on demographic, cognitive, brain and social factors have been a central issue in aphasia studies (for review see: (Maas et al., 2012; Plowman et al., 2012; Seghier et al., 2016)). However, few studies have investigated the response to therapy-driven language recovery (Bonilha et al., 2016; Crinion & Leff, 2007; Lambon Ralph et al., 2010; Naeser et al., 1998). One of the main challenges facing therapeutic studies in aphasia is that patients' responses are variable. Improving our understanding of the relationship between patients' characteristics and their responses to therapy would allow us to personalise or tailor therapeutic strategies for specific patients according to their demographic, brain lesions and cognitive profile.

In recent years, computerised interventions have gained in popularity to support language treatments; however, there is no information about neuropsychological factors that predict patients' outcomes to this (or indeed standard face-to-face) type of therapy.

In this chapter I investigate what pre-treatment cognitive variables (T1-T2) as well as lesioned brain regions (from pre-treatment MRI scans at T3) might explain the variability in response to iReadMore therapy (T3-T4. See Figure 24). This study attempted to determine what variables are associated with the therapeutic effect of iReadMore (DV) calculated as **percentage of absolute change in single-word reading accuracy between T3 and T4** (see Figure 9 and Table 2 in Chapter two). Furthermore, I tested whether therapeutic outcomes in *new* patients can be predicted (generalisation) using the explanatory model obtained from my data. It is important to clarify that prediction in "new patients" does not mean different patients from the 23 participants that took part of this study. Here, "new" means that the percentage of change in response to therapy for each participant is withheld from the explanatory model (in-sample analysis), which then has to estimate patients' responses from all other available data using out-of-sample analysis (i.e. using the nested cross-validation method described in chapter two).

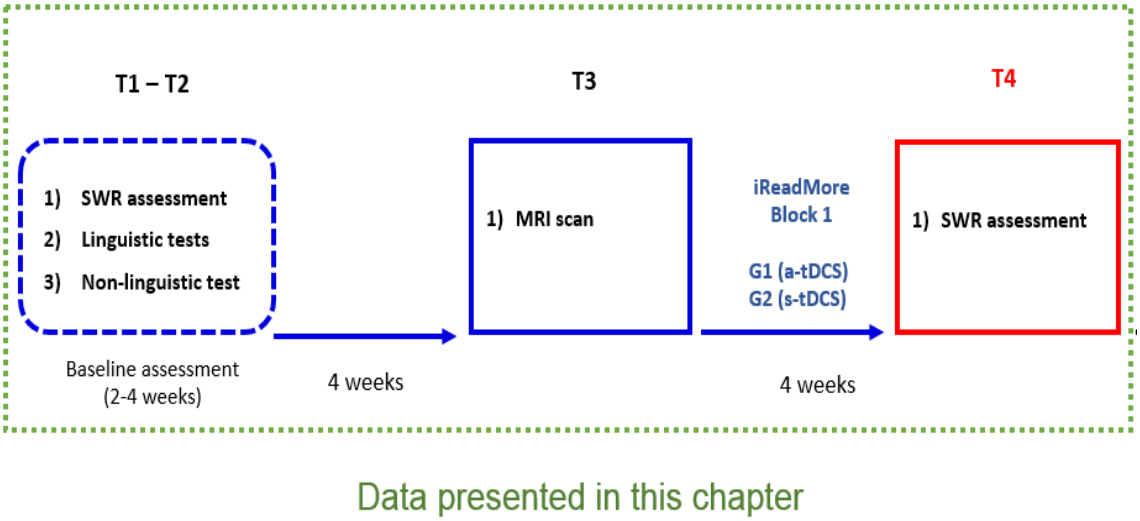

Figure 24. Study design - Experimental chapter two. In this study analyses attempted to explain patients' responses to iReadMore therapy between T3 and T4 (reading change after training was calculated at T4 – highlighted in red). The explanatory variables were taken from behavioural data collected at T1 - T2 and pre–treatment MRI data collected at T3. *Note that for illustrative purposes the SWR assessment performed at T3 and the MRI scan at T4 were no included in this figure.* SWR= single-word reading task; MRI= structural magnetic resonance imaging; G= group; a-tDCS: anodal tDCS; s-tDCS: sham tDCS.

The aims of this study were:

1) To examine whether pre-treatment behavioural data contributes to understanding patients' response to iReadMore therapy.
2) To investigate which lesioned brain regions contribute to understanding patients' response to iReadMore therapy.
3) To test whether the therapeutic effect of iReadMore in "*new*" patients can be predicted.

Hypotheses:

1) Patients' responses to iReadMore therapy can be explained by pre-treatment demographic, behavioural and neuroimaging data.

2) Responses to iReadMore therapy in *new* patients can be predicted from their pre-treatment data.

The principal focus here was on the changes observed in the patients' scores (*n*=23) in single-word reading accuracy between T3 and T4: i.e. these changes are the dependent variable in both of the analyses reported. The independent data were the patients' scores (primary and secondary variables) in the pre-treatment behavioural tasks (36 variables) and the proportions that each patient's lesions had appeared to destroy of a series of anatomically defined regions. Also, other variables were included: (a) age at therapy onset; (b) time since stroke had occurred; (c) gender (male or female); (d) total lesion volume; and (e) tDCS group (see Table 1 and Table 2 in Chapter two).

4.1. Results

Parcellation of binary lesion images

Pre-treatment binary lesion images of all patients were encoded by lesion load in anatomically defined regions of the brain (see Chapter two). Each loading represented percentage of damage: 0% if a region was completely preserved up to 100% when a region was completely lesioned. Only those regions where at least 10 patients had lesion loads of at least 10% were included. From a total of 398 regions covering the whole brain, 69 regions in the left hemisphere that met the criteria were included in the analyses (see the appendices).

4.1.1. Analysis 1: explaining treatment responses from pre-treatment data (in-sample)

In order to produce explanatory models of patients' responses to iReadMore, analyses were conducted used the automatic linear modelling tool in SPSS 22 (see methods in chapter 2). Overall, 110 independent variables per patient were available for analyses (5 demographic variables, 36 behavioural variables and 69 brain regions). In order to examine the accuracy of patients' variables to explain their responses to iReadMore treatment, three separate models were produced:

1) A model from behavioural and demographic data alone (including 41 variables).
2) A model from neuroimaging data alone (including 69 variables representing lesioned brain regions)
3) A model from all of the available data together (110 variables).

Significant variables in each model are listed in order of their predictor importance (most important first):

1) The 'behaviour and demographics model' included: (i) accuracy in the Neale reading test (β = -0.39, p = 0.001); (ii) age at therapy onset (β = -0.24, p = 0.018); and (iii) reaction time in the Non-verbal version of the Sustained Attention to Response Task (NV-SART) (β = 0.14, p = 0.038). See Figure 25. The adjusted R^2 for this model was 0.50, and its Akaike information criterion (AIC) was 81.75. In this model, accuracy in the Neale and age showed a negative association with reading change, whereas RT in the NV-SART showed a positive association. The resulting model

indicates that patients who were younger, with worse accuracy in the Neale, and slow in our attentional task improved more after therapy.

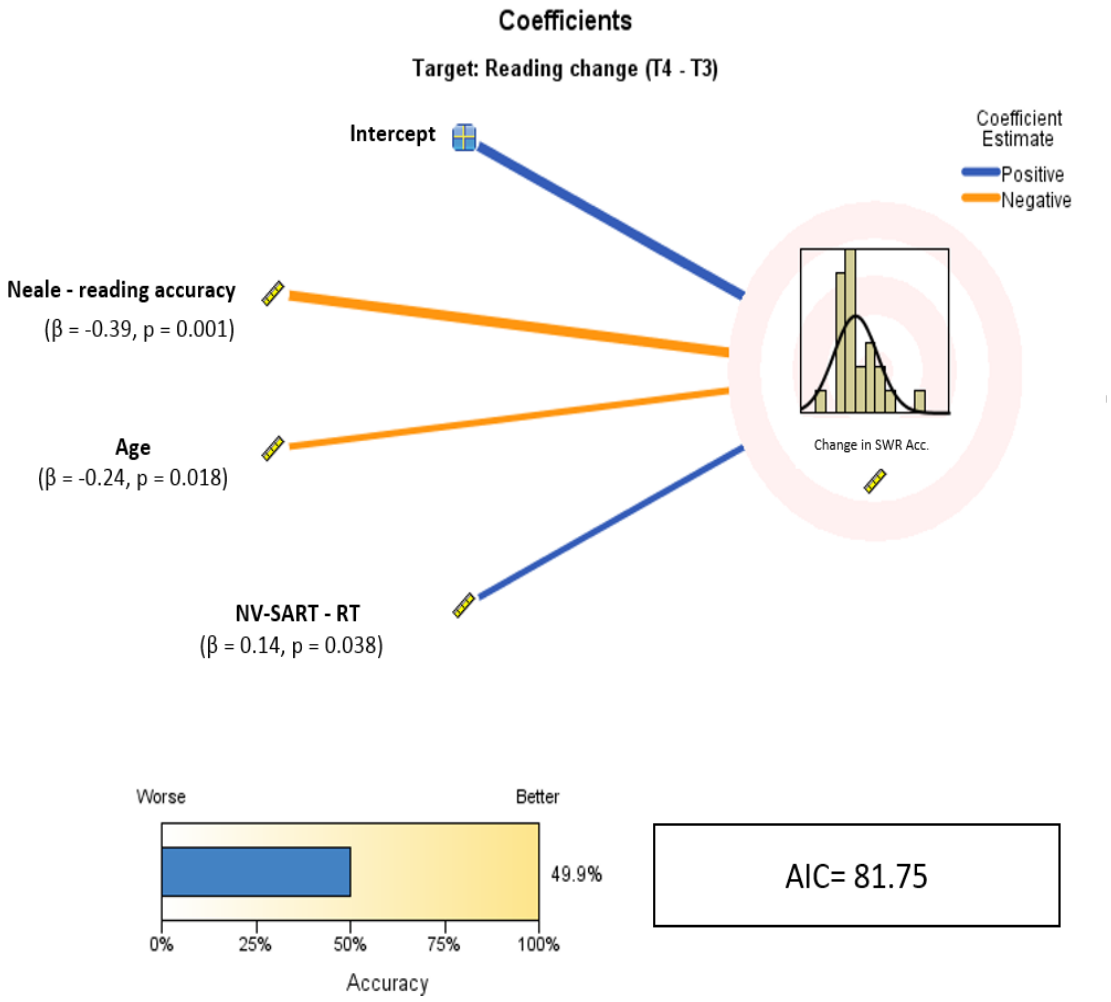

Figure 25. Behavioural and demographic data model. Plot produced in SPSS 22 representing significant variables in model 1 (behavioural plus demographic variables). It indicates that patients who were younger, severely affected at baseline, and slow in the SART improved more. Variables are displayed in order of significance. Positive correlations in blue and negative correlations in orange. Horizontal bar at the bottom (in blue) represents the model accuracy (adjusted R^2). NV-SART= Non-verbal version of the Sustained Attention to Response Task; SWR= single-word reading; Acc. = accuracy; AIC= Akaike information criterion.

2) The 'neuroimaging model' included only damage in left hemisphere regions: (i) the white matter connecting the thalamus to the parietal cortex (β = 23.32; p < 0.001); (ii) the inferior longitudinal fasciculus (ILF) (β = -27.97; p < 0.001); (iii) auditory cortex area TE10 (β = 9.63; p = 0.002); (iv)

Broca's area (β = -10.94; p = 0.003); and (v) the intraparietal sulcus (β = 5.37; p=.039). See Figure 26. The adjusted R^2 for this model was 0.76, and its AIC was 69.35. In this model, correlations were positive except for damage in the inferior longitudinal fasciculus and Broca's area. Interpretation of positive correlations (i.e. greater damage results in better improvement) is discussed further. However, the resulting model might indicate that patients are more likely to respond to therapy if left ILF and Broca's area are spared, as well as they are more likely to respond to therapy if they have lesions of the left WM connecting the thalamus and parietal lobe, in the left intraparietal sulcus, and auditory cortex.

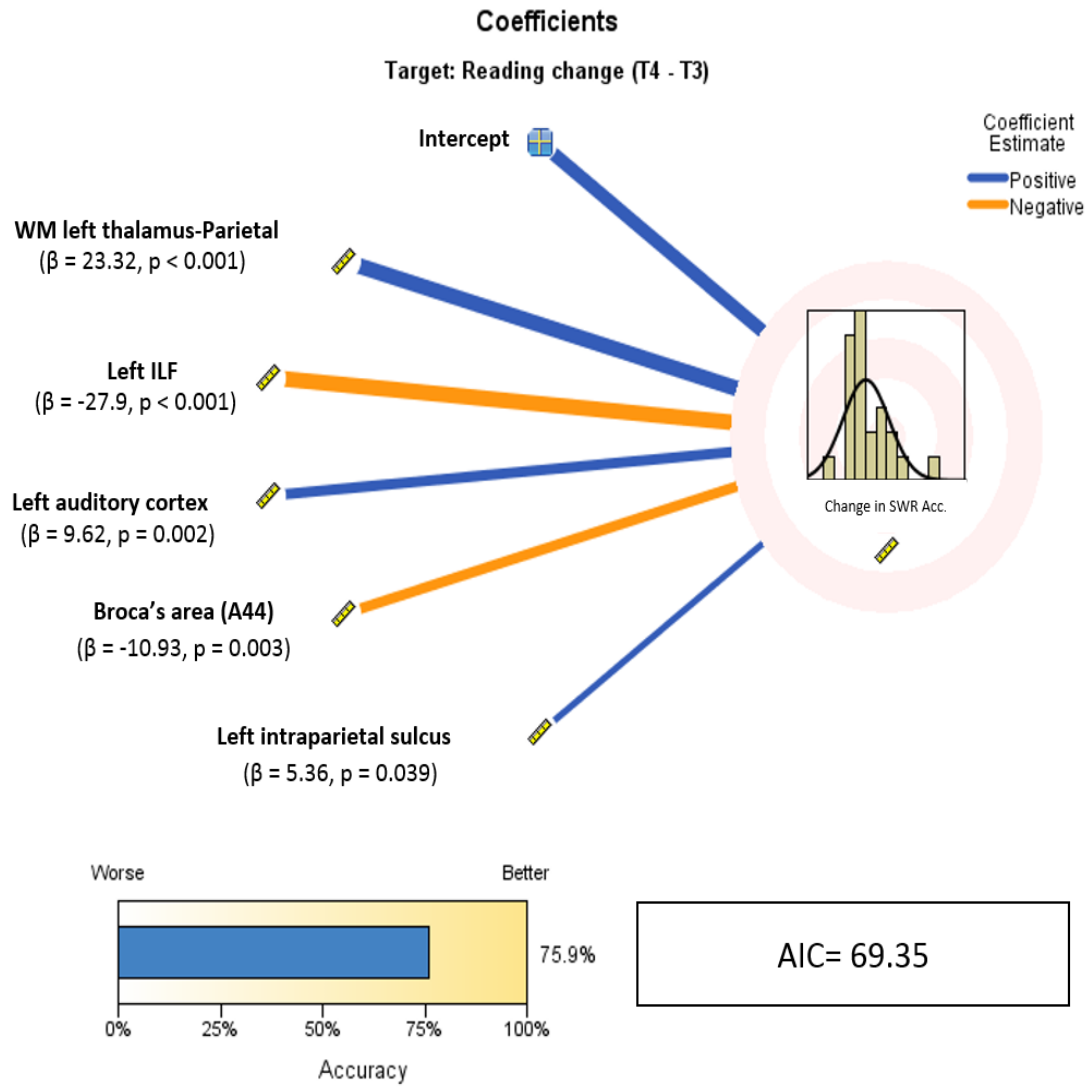

Figure 26. Neuroimaging model. Plot produced in SPSS 22 representing significant variables in the model 2 (neuroimaging variables). It indicates that patients are more likely to respond to therapy if spared left ILF and Broca's area. Positive response is also likely if lesions are located in posterior regions. Variables are displayed in order of significance. Positive correlations in blue and negative correlations in orange. Horizontal bar at the bottom (in blue) represents the model accuracy (adjusted R^2). WM= white matter; ILF: inferior longitudinal fasciculi; SWR= single-word reading; Acc. = accuracy; AIC= Akaike Information Criterion.

3) The combined model (all of the available data) included: (i) accuracy in the Neale reading test (β = -0.42, p < 0.001); (ii) damage to the white matter connecting the thalamus to the parietal cortex (β = 27.14; p < 0.001); (iii) damage to left Broca's area (β = -10.94; p < 0.001); (iv) age at therapy onset (β= -0. 15; p = 0.001); (v) comprehension in the Neale reading test

(β = 0.68; p = 0.001); (vi) accuracy in the written semantic matching task (β = 0.123; p = 0.005); and (vii) damage to the left insula (β = -3.68; p = 0.043). See Figure 27. The adjusted R^2 for this model was 0.94, and its AIC was 47.98. Both positive and negative correlations resulting in this model are discussed and interpreted further.

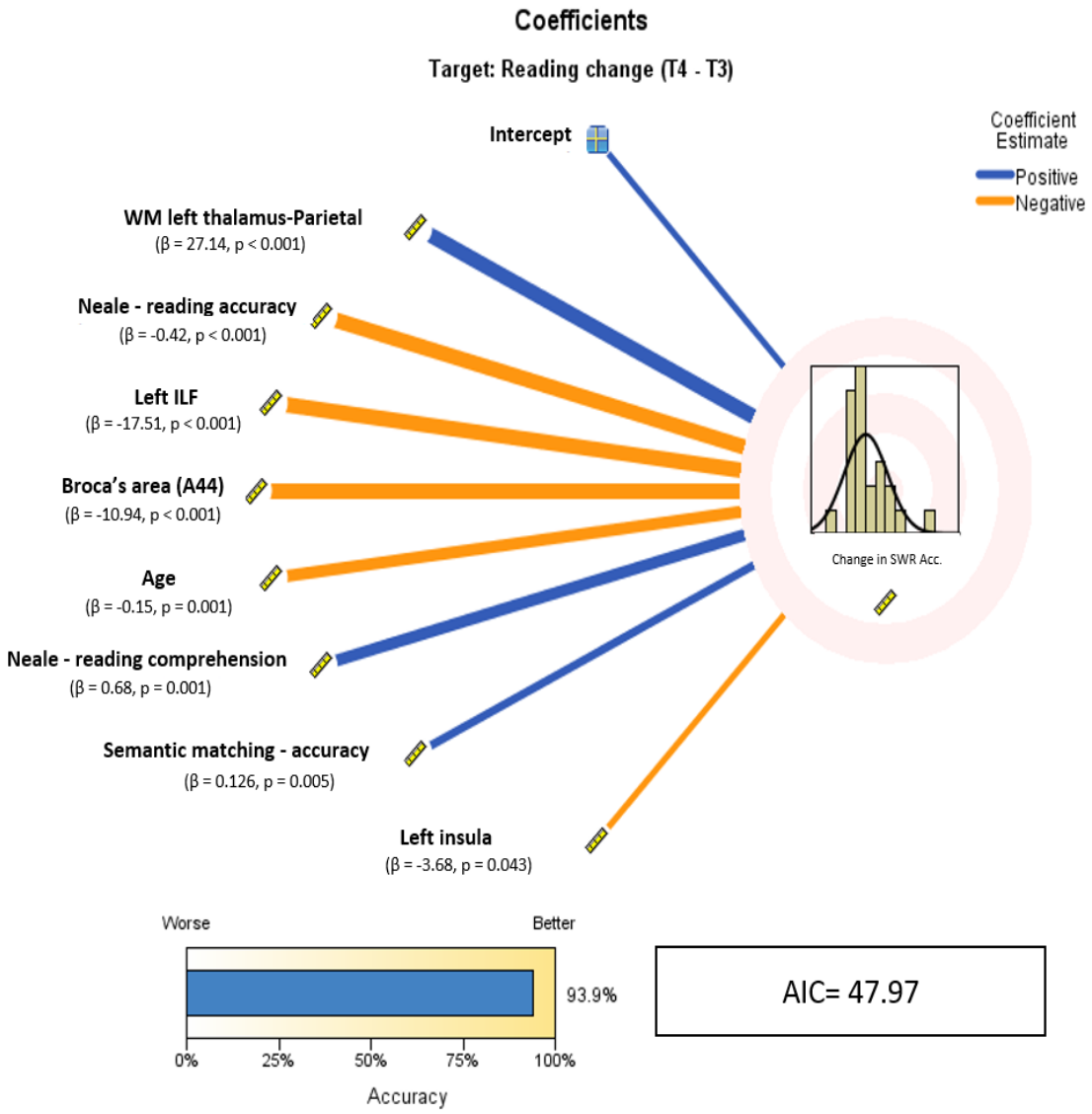

Figure 27. Demographic, behavioural and neuroimaging model. Plot produced in SPSS 22 representing significant variables in the model 3 (all variables together). Variables are displayed in order of significance. Positive correlations in blue and negative correlations in orange. Horizontal bar at the bottom (in blue) represents the model accuracy (adjusted R^2). WM= white matter; ILF: inferior longitudinal fasciculi; SWR= single-word reading; Acc. = accuracy; AIC= Akaike Information Criterion.

The Akaike Information Criterion (AIC) can be used to compare each of these models to the others: the 'neuroimaging only' model has a lower (better) value than the 'behavioural plus demographics' model (69.35 vs 81.75), and the combined model's AIC is lower still (47.98). Given these figures, the relative evidence for these models can be quantified as Bayes Factors: BF = exp ((AIC1 - AIC2) / 2), where AIC2 is the smaller (better) of the pair.

The Bayes Factor for the neuroimaging model versus the behavioural and demographics model is 493: i.e. the evidence that the neuroimaging model is better than the behavioural plus demographics model is 493 times greater than the evidence against. This is either 'decisive' (Jeffreys, 1961), or 'very strong' (Kass & Raftery, 1995) evidence, depending on the preferred heuristic for interpreting Bayes Factors. And the comparison yields still stronger evidence in favour of the combined model versus the neuroimaging model (69.35 vs 47.98): BF = 44. Using the same classifications for interpreting Bayes factors, this evidence is 'strong' in favour of the combined model (see Table 11) (Jeffreys, 1961; Kass & Raftery, 1995).

Bayes factor interpretation (Jeffreys, 1961)		Bayes factor interpretation (Kass & Raftery, 1995)	
B10	**Evidence against model 1**	**B10**	**Evidence against model 1**
1 to 3.2	Not worth more than a bare mention	1 to 3	Not worth more than a bare mention
3.2 to 10	Substantial	3 to 20	Positive
10 to 100	Strong	20 to 150	Strong
> 100	Decisive	> 150	Very strong

Table 11. Bayes factor. This table shows two interpretations of the Bayes factor evidence against model one (or in favour of model two). This information was taken and adapted from Kass & Raftery (1995).

The best explanation of these treatment responses depends on access to demographic, behavioural, and structural neuroimaging data together. Figure 28 displays the brain regions where damage was most strongly associated with treatment responses in that third, combined model.

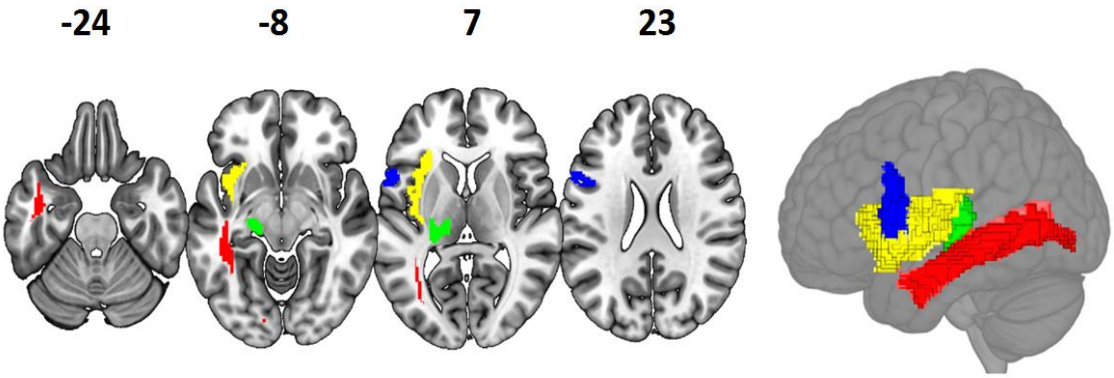

Figure 28. Significant brain regions in the combined model. The brain regions implicated in the combined model (demographics, behavioural, and lesioned brain regions) displayed both at the left of the figure on axial slices of the brain (Z) and on a rendered whole brain (right). The regions are: (a) the white matter connecting the thalamus to the parietal cortex (green); (b) the inferior longitudinal fasciculus (red); (c) Broca's area (blue); and (d) the left insula (yellow). In this model all regions were negatively associated with reading change, except for (a).

4.1.2. Analysis 2: predicting treatment responses from pre-treatment data (out-of-sample)

To test whether treatment responses could be predicted in *new* patients nested cross validation (N-CV) was performed on the data. In each fold of the analysis, a single patient (the 'test patient') was removed from the original set of 23, to leave a 'training set' of 22 patients. Linear models were then fit to this training set, as in the 'explanatory modelling' analysis. In this case, boosting was used to improve predictive accuracy, creating a set of 10 models per fold. This ensemble was then used to predict the treatment response for the test patient. The process

was then repeated 23 times, so that each patient's treatment response could be predicted given models identified only from the other patients.

The results from analysis 1 (in-sample) suggested that patients' treatment responses can be expressed as a linear function of demographic and pre-treatment behavioural data, combined with lesion location information. In this section, I asked whether these associations were consistent enough to predict treatment responses in *new* patients. This analysis was run using N-CV, as described in the methods chapter, and the results showed that predicted treatment responses from this analysis are significantly correlated with the patients' empirical treatment responses ($r = 0.48$, 95% CI lower = 0.08, upper = 0.75, $p = 0.02$); see Figure 29. The implication is that new patients' responses to the iReadMore treatment are in principle predictable, given access to demographic, behavioural and structural neuroimaging data available before the treatment begins.

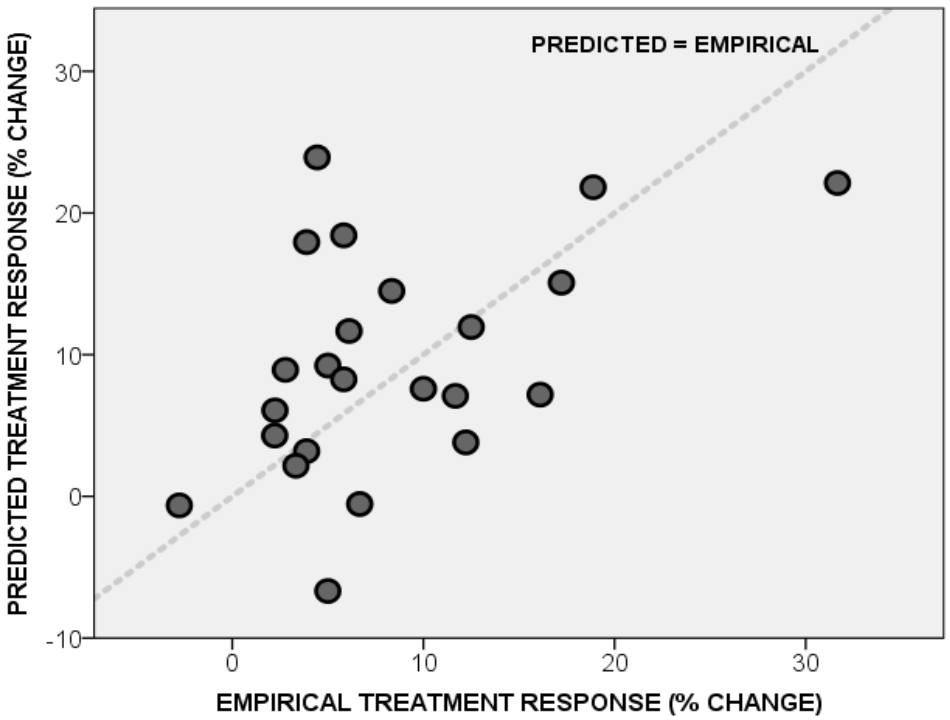

Figure 29. Out-of-sample analysis. Predicted treatment responses, derived via nested cross-validation, versus the individual patients' empirical treatment responses to the iReadMore therapy. The dashed line is at y = x: perfect predictions would fall along this line.

Discussion

Stroke survivors with aphasia are famously variable: some recover much more quickly and fully than others, and some respond much better to the same speech and language therapies than others. Prior studies have shown that much of the variability in language outcomes can be explained and predicted by reference to the details of the lesion damage that individual patients have suffered (Hope et al., 2015; Hope, Seghier, Leff & Price, 2013; Hope, Seghier, Prejawa, Leff, & Price, 2015). Here, results have shown that at least some of the variability in responses to a particular speech and language therapy – driven by the iReadMore application – can be explained and predicted in much the same way. As far as I know, this is the first demonstration that structural neuroimaging data can be used (in combination with demographic and pre-treatment behavioural

data) to predict responses to speech and language therapy for patients with any acquired disorder of language.

In-sample analyses suggested that much of the variance in the patients' responses to treatment can be explained by reference to data available before the treatment commenced. More surprising, however, was the unique contribution conveyed by their lesions' locations, as measured via pre-treatment structural MRI: the model evidence for the neuroimaging model (2) was 493 times better than that for the 'behaviour and demographics' model. The implication is that responses to iReadMore therapy are lesion-site-dependent: that patients with different lesions will respond differently to this treatment, even when pre-treatment symptom severity is taken into account – as it is, explicitly, in the combined model (3), which is driven by demographics, pre-treatment language skills, and lesion location information together. If responses to the iReadMore therapy are lesion-site-dependent, then responses to other speech and language therapies might be lesion-site-dependent too. The implication here is that speech and language therapy might be applied more efficiently if treatment decisions are made with reference to the lesions that patients have suffered as well as their baseline language performance.

The only demographic variable that appears in the combined model is 'age': patients who were older appeared to respond less well to the iReadMore therapy. There is no good consensus in the prior literature on the role of age in recovery from aphasia: Pickersgill & Lincoln (1983) found a similar association, though only for those patients with 'severe' initial symptoms, but others have found no

relationship at all (Lendrem & Lincoln, 1985; Plowman et al., 2012, Watila & Balarabe, 2015). Indeed, studies disagree as to whether age is even relevant to patients' natural language outcomes after stroke, irrespective of therapeutic interventions (Kertesz & McCabe, 1977; Pedersen et al., 1995): results include a role for age in responses to the computerised therapeutic intervention, but possibly this cannot resolve the wider debate on its own. Three behavioural variables also appeared in the combined model: (i) initial reading accuracy; (ii) reading comprehension accuracy; and (iii) semantic matching skills. The weight on the first of these three predictors was negative meaning that patients with poorer pre-treatment reading skills tended to improve more during treatment. Superficially, this might seem to be inconsistent with the well-known association between greater initial symptom severity and poorer long-term language outcomes after stroke (e.g. (Swinburn, Porter & Howard, 2004)). However, this could be interpreted as a ceiling effect: patients with worse pre-treatment skills have more room for improvement. The latter two behavioural variables had positive weights. These might indicate that semantic abilities help to compensate for patients' reading impairments. Patients with better or more preserved semantic skills pre-treatment responded better to the iReadMore treatment – consistent with the finding that semantic processing skills contribute to language outcomes after stroke, even when the initial severity of aphasia is taken into account (Fucetola et al., 2006).

The combined model also referred to damage in four left-hemisphere brain regions: (iv) the inferior longitudinal fasciculus, (v) the insula, (vi) Broca's area (BA44 or pars opercularis), and (vii) the WM connecting the thalamus to the parietal lobe. This finding suggests that these regions are important either for

reading *per se*, relearning *per se* or relearning of reading. The first three of these show the expected, negative weight, implying that greater damage in those regions is associated with poorer responses to treatment. All of these regions have been associated with reading performance in previous studies. Broca's area has long been associated both with speech production (Broca, 1861; Flinker et al., 2015; Mohr et al., 1978; Smith, 1971; Stark, 2010) and with reading (Klein et al., 2015). The left pars opercularis which corresponds to the posterior region of Broca's area, receives connections from inferior parietal regions and motor cortex. Particularly, fMRI studies have shown important activation of this region during reading aloud of pseudowords and irregular words (Price & Mechelli, 2005). The insula was implicated as a key locus for the coordination of speech articulation by Dronkers (1996) (though see also (Hillis et al., 2004), for an alternative account), and damage to the insula was implicated in phonological dyslexia in a recent study using voxel-based lesion symptom mapping (Ripamonti et al., 2014). Damage to the inferior longitudinal fasciculus has been associated with language impairments typical of semantic dementia (Agosta et al., 2010a), including impaired word perception, and also specifically with reading impairments (Epelbaum et al., 2008). The last region in the combined model (the WM connecting the thalamus and parietal lobe) is more mysterious, principally because it has a positive weight: greater damage here is associated with better responses to the iReadMore treatment. Since more damage is presumably not 'better' in itself, anywhere in the brain, this finding might be interpreted as a marker for patients whose lesions leave other critical regions preserved or as a marker for a lesion that produces a reading deficit that responds best to iReadMore.

Out-of-sample analysis goes beyond the in-sample analysis by demonstrating, for the first time, that the associations between pre-treatment patient data and eventual treatment responses are strong and consistent enough to drive reasonable predictions, at the individual level, for incoming patients. While reasonably large by the standards of therapeutic intervention studies, the sample size in this study is still too small to measure the quality of those predictions with any great confidence. This is evident in the breadth of the 95% confidence interval (lower = 0.08; upper = 0.74). More confident estimates, and hopefully better predictions, should flow from analyses with larger samples of patients. But even in a sample of 23, this study has the power to distinguish signal from noise: predicted treatment responses are significantly correlated with the patients' empirical treatment responses, which is at least preliminary evidence that *new* patients' responses to this treatment can be predicted.

Summary and Conclusions – Experimental chapter two

Better understanding of patients' characteristics that impact therapeutic outcomes is essential if we are to create more personalised therapies. This study began with the recognition that responses to speech and language therapy are variable: some patients respond much better to the same treatment than others, even when pre-treatment symptom severity is taken into account. This variability has made it difficult to validate these interventions, both singly and in general (Kelly, Brady, & Enderby, 2010). My hypotheses were that some of this variability can be 1) explained and 2) predicted by reference to patients' pre-treatment data (i.e. demographic information, behavioural scores, and the details of the lesions that patients have suffered). The results support these hypotheses. I have only

considered a computerised reading therapy here (iReadMore), focused on a specific aphasic deficit (central alexia), but if responses to this therapy depend on patients' pre-treatment data, then the implication is that responses to other therapies might also depend on them too. I hope these results encourage further attempts to characterise other treatment effects, hence it will drive the development of personalised medicine for stroke survivors with aphasia.

5. INVESTIGATING CEREBRAL STRUCTURE CHANGES INDUCED BY A COMPUTER-BASED READING THERAPY IN CHRONIC APHASIC PATIENTS

Introduction

Neural correlates of aphasia recovery have been the subject of intense study over the years. The literature indicates at least two general patterns of brain reorganization, which are not mutually exclusive: 1) recruitment of spared perilesional sylvian regions in the left hemisphere when lesions are reasonably small (Fridriksson et al., 2010; Heiss, Kessler, Thiel, Ghaemi & Karbe, 1999; van Oers et al., 2010; Warburton, Price, Swinburn & Wise, 1999); and 2) recruitment of right hemisphere language homologue regions in patients with extensive left hemisphere damage (Forkel et al., 2014; Hope et al., 2017; Wan, Zheng, Marchina, Norton & Schlaug, 2014; Xing et al., 2016). These studies have used mainly both functional neuroimaging (fMRI and PET) and diffusion tensor imaging techniques. Although volumetric studies using VBM have shown cortical changes associated with learning (Draganski & May, 2008), very little is known about volumetric (macrostructural) changes associated with therapy-driven recovery in aphasia and its underlying biological mechanisms (microstructural changes).

This chapter aims to explore if any detectable changes occurred in the brain structure of chronic CA patients in response to iReadMore therapy. In this study patients had an MRI scan before and after the first block of therapy (T3 and T4, see Figure 30). They were scanned using the multiparameter mapping protocol

(MPM) (Callaghan et al., 2014) which provides quantitative measures associated with microstructural properties of the brain tissue (see chapter two). Here, VBM and voxel-based quantification (VBQ) analyses were conducted to investigate macrostructural and microstructural changes associated with patients' response to the therapy. Similar to the previous chapter, the effect that I am modelling (DV) is the reading accuracy after iReadMore therapy (T4) calculated in **percentage of absolute change in single- word reading between T3 and T4** (see Table 2 in chapter two).

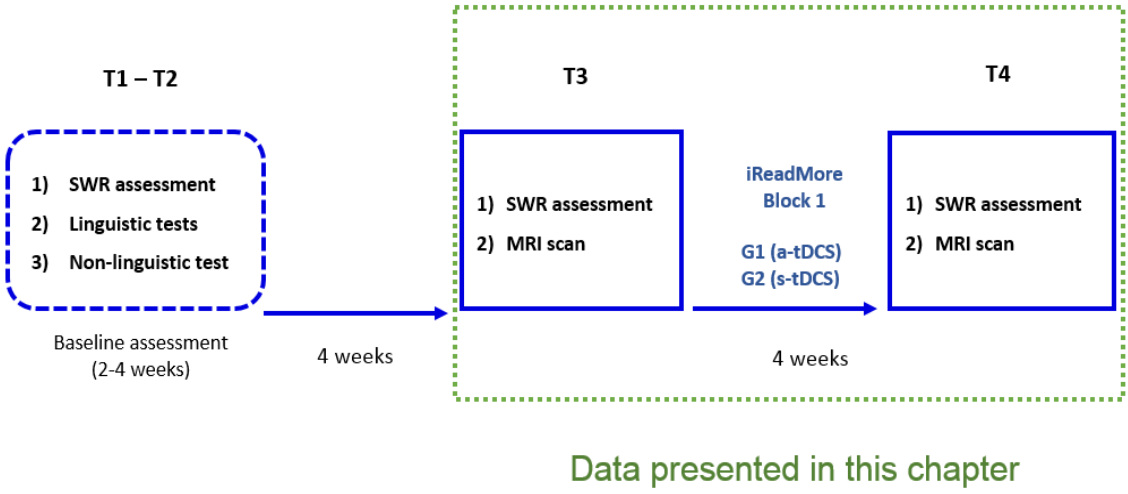

Figure 30. Study design - Experimental chapter three. Longitudinal analyses of MRI scans were conducted to investigate structural changes associated with patients' responses to iReadMore therapy between T3 and T4. SWR= single-word reading task; MRI= structural magnetic resonance imaging; G= group; a-tDCS: anodal tDCS; s-tDCS: sham tDCS.

The aims of this study were:

1) To explore which GM and WM regions show macrostructural and microstructural changes in response to iReadMore Therapy.

2) To study whether brain regions supporting therapy-driven recovery in central alexia are ipsilateral/perilesional or contralateral to the lesioned tissue.
3) To investigate what biological mechanisms support brain plasticity associated with therapy response in central alexia.

Hypotheses*:*

1) Central alexia patients' response to iReadMore therapy will significantly correlate with increases in GM and/or WM density in preserved left hemisphere reading-related regions and/or right hemisphere homologues (VBM analysis).

2) Central alexia patients' response to iReadMore therapy will significantly correlate with increases in macromolecules, iron, and/or myelin content in GM and/or WM regions of preserved left hemisphere reading-related regions and/or right hemisphere homologues (VBQ analysis).

It is important to clarify that analyses in this study were conducted only on 17/23 patients. For this thesis, 17 patients were scanned at the Wellcome Trust Centre for Neuroimaging (UCL) in a 3T scan. However, for safety reason (i.e. body implants) participants 10, 15, 16, 18, 19, and 22 were scanned at Birkbeck-UCL Centre for Neuroimaging (BUCNI) which is a 1.5T scanner. VBQ analysis compares quantitative images in which voxels' values are in physical units (e.g. milliseconds. See Chapter two for details) that depend on specific MRI tissue

properties. It is possible to compare these quantitative images between scanners, but only for scanners with the same magnetic field strength. For this reason, these six participants could not be included in the VBQ analysis.

Images for VBM analysis (i.e. modulated segmented images) contain voxel values between 0 and 1 that represent the probability of the voxel belonging to the tissue class. In these images, voxel values are not dependent on the magnetic field strength. Although there would be no reason to assume that images used for VBM differ between scanners, testing of my hypotheses with different sample sizes (and therefore power) would be difficult to interpret. Therefore, data from those six patients were not included for the VBM analyses either.

5.1. Results

5.1.1. Voxel-based morphometry (VBM) analysis

Analyses for GM and WM images were conducted separately. For each analysis, a multiple regression model was created including the subtracted GM or WM images (i.e. post-treatment image – pre-treatment image, representing brain differences between T3 and T4), absolute reading change (percentage), plus nuisance variables including: subjects' age, lesion volume, time post-stroke, and tDCS group (Figure 31). The SPM results were thresholded in the same way as the PCA analysis in Chapter three, at $p < .01$ voxel-level, $p < .05$ (FWE) corrected at cluster-level.

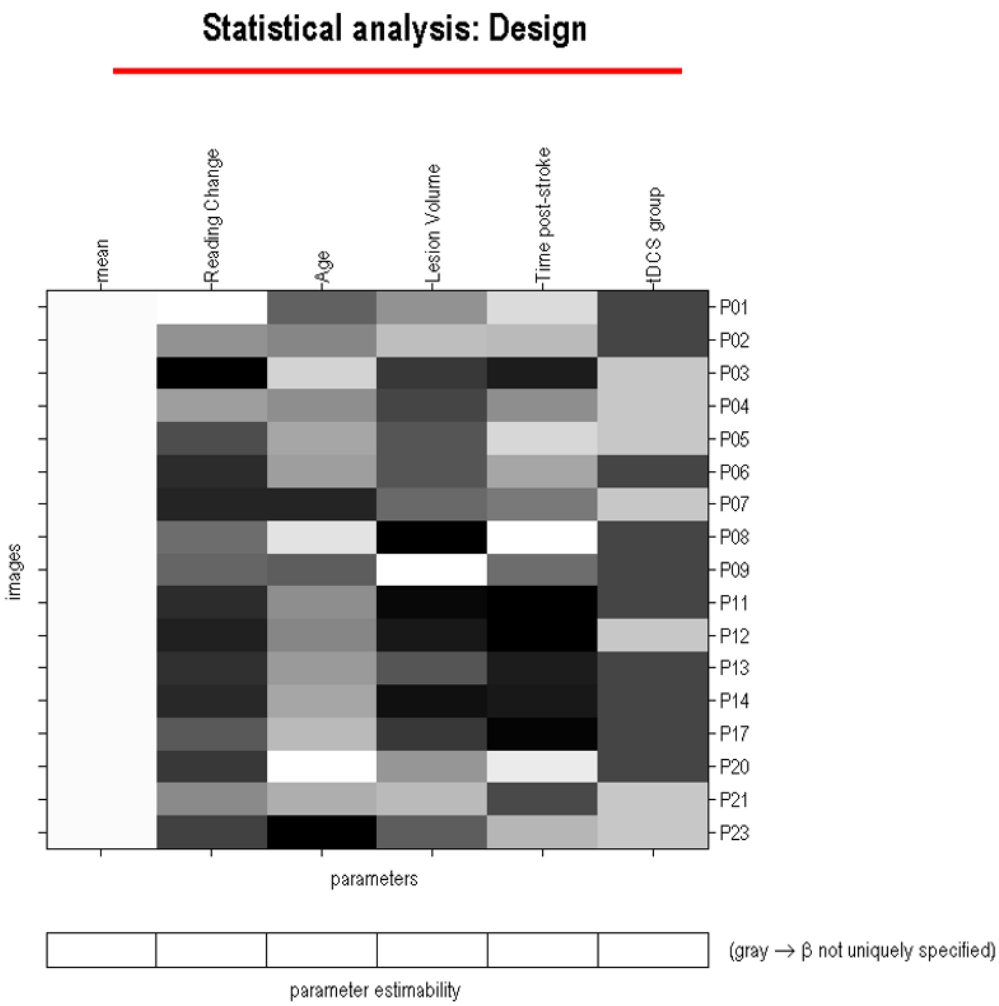

Figure 31. VBQ-Design matrix. Design matrix used in the VBM and VBQ analyses. GM and WM were entered into a multiple regression model to identify brain regions associated with absolute change in reading accuracy (DV) while controlling for demographic data and tDCS group. Analyses included GM or WM images (separately).

VBM results of GM and WM volume

No GM or WM regions showed significant volume change associated with change in reading accuracy after iReadMore.

5.1.2. Voxel-based quantification (VBQ) analysis

For each VBQ analysis (PD*, MT, R1, R2*), a multiple regression model was created including the subtracted GM or WM images, absolute reading change, plus nuisance variables including: subjects' age, lesion volume, time post-stroke, and tDCS group. The SPM results were thresholded in the same way as the VBM analysis above and in the PCA analysis in Chapter three, at p< .01 voxel-level, p<.05 (FWE) corrected at cluster-level.

VBQ results of the multiparameter mapping (MPM) images

The VBQ results showed significant positive correlations between the R2* GM and patients' reading change. This was an extensive cluster of 792 contiguous voxels encompassing the left superior frontal gyrus and the supplementary motor cortex (SMC) bilaterally (Figure 32). For illustrative purposes average of values across voxels in this cluster was calculated for each participant and plotted. See Figure 33. Cluster and coordinates are reported in table 12. No significant correlations were found between reading change and other MPM images.

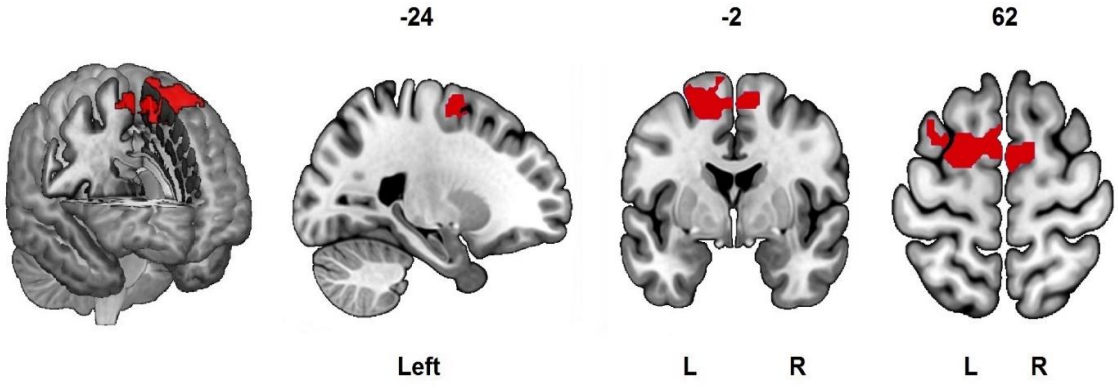

Figure 32. Longitudinal VBQ analysis. VBQ result showing positive correlations between change in reading accuracy after treatment and R2* values in a grey matter region encompassing the left superior frontal gyrus and the supplementary motor area bilaterally. Results are presented at P<.01 voxel-level, P<0.05 FWE-corrected cluster-level. L= left; R= right.

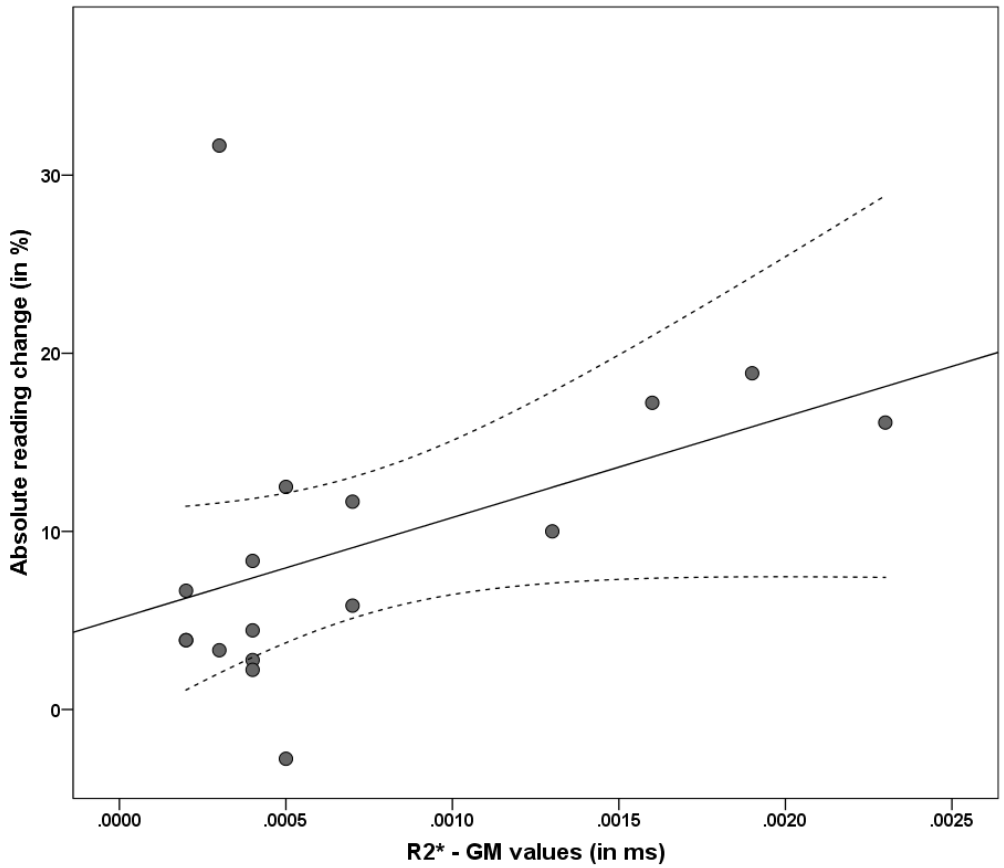

Figure 33. GM - R2* longitudinal change. This plot shows the relationship between patients' percentage of reading change after iReadMore therapy and averaged R2* values (expressed in milliseconds) in the GM cluster after VBQ analysis. R^2= 0.195; Y= 5.12 + 5.66E3*x; Dotted lines indicates 95% confidence interval. R2*= effective transverse relaxation rate; ms= milliseconds.

MPM map	Cluster size (voxels)	Cluster-level *p* (FWE)	Peak co-ordinates (x, y, z)	Peak location	*Z*
1. Effective transverse relaxation rate (R2*) [red region in Fig 32]	792	.009	-26, -2, 66	Left SFG	3.84
			-2, 2, 62	Left SMA	3.09
			6, -4, 64	Right SMA	2.92

Table 12. R2* result - Cluster location. Anatomical location of R2* - GM brain region associated with reading change after iReadMore therapy. Regions were determined with the Harvard – Oxford cortical structural atlas. SFG= superior frontal gyrus; SMA= supplementary motor area; FWE= family-wise error correction.

Discussion

To my knowledge, this is the first time that the MPM protocol has been implemented to investigate both macrostructural and microstructural changes after therapy in chronic post-stroke aphasic patients. The MPM protocol consists of four quantitative maps (PD*, MT, R1, and R2*) that provides specific measures of brain plasticity biomarkers in GM and WM. The PD* is a measure of water signal; MT of myelin and macromolecules content; R1 of iron, macromolecules, and myelin content; and R2* of iron content (Callaghan et al., 2014). It is this specificity that allows us to use VBQ analysis of these measures to infer biological mechanisms underlying therapy-dependent brain plasticity. Additionally, the MT map in this protocol is of a sufficiently high image quality for us to conduct VBM analyses in order to explore changes of brain tissues' densities (Weiskopf et al., 2015). Thus, the MPM protocol used in this study is appropriate to investigate both macrostructural and microstructural changes in central alexia associated with reading improvement after iReadMore therapy. In the following, VBM and VBQ results are discussed in relation to three issues: i) GM regions associated with therapeutic reading improvement; ii) perilesional and contralateral regions involved in therapy-driven recovery; and iii) VBM and VBQ results and brain plasticity:

i) VBQ analysis revealed a positive association between change in reading accuracy and effective transverse relaxation rate (R2*) in a GM region encompassing the left superior frontal gyrus (SFG) and the supplementary motor area (SMA) bilaterally. Interestingly, these regions have not been directly associated with reading abilities. The SFG has been linked mainly to executive

functions such as working memory and cognitive control (Brownsett et al., 2014; du Boisgueheneuc et al., 2006; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Meanwhile, SMA has been largely related to planning of motor sequences (Bonini et al., 2014; Nachev, Kennard, & Husain, 2008). Discussion in this section is centred on two possible explanations: 1) that these 'extra-sylvian', hence non-linguistic areas may have a language function; and 2) that these 'non-linguistic' areas may be involved principally in recovery of central alexia: Research in normal readers and patients with brain damage has established which brain regions support reading (see revision in Chapter one). In general, structural and fMRI studies have outlined two perisylvian streams: 1) left temporal and posterior inferior frontal regions (ventral stream); and 2) left ventral temporo-occipital regions, inferior parietal and premotor areas (dorsal stream). Although these two streams do not include either the SFG or the SMA, previous studies have related these regions to linguistic abilities. In a systematic review conducted by Price (2012), the left SFG was found to be involved in speech comprehension and semantic processing. In the case of reading, a meta-analysis of fMRI studies Taylor et al. (2013) found activation of the SFG in the contrast words>pseudowords. Further, Christodoulou et al. (2014) carried out an fMRI study comparing single word reading in normal readers and children with developmental dyslexia. They found that activation of the SFG was linked to reading speed and reading comprehension. Moreover, they observed that normal readers exhibit a greater activation in the SFG compared to dyslexic children when speed rate was increased.

There is also evidence to suggest that the SFG may play a role in aphasia recovery. In a post-mortem DTI study Kinoshita et al. (2012) found association

fibers connecting Broca's area with the SFG. They related this finding to observed speech disturbances in patients after stimulation of the SFG during intraoperative cortical mapping. They suggested that the left SFG could play a role in language reorganisation in patients with brain damage. Abel, Weiller, Huber, Willmes & Specht (2015) carried out a therapeutic study in aphasic patients with naming difficulties. They conducted independent component analysis on fMRI data to explore changes in language reorganization according to lesion site. Results showed that response to therapy and changes in brain activation were related to lesion location: patients with damage in the left IFG did not improve after therapy. They also showed less activation of Broca's area and left SFG. Conversely, patients with spared left IFG had greater rates of therapeutic recovery and showed greater activation in the SFG. The authors attributed these results to disconnection - due to lesion location - between anterior and posterior regions (left IFG and Wernicke's area) and suggested that increased activation of SFG associated with therapy gain reflects an enhancement of brain connectivity. These results are consistent with R2* change in the SFG observed in the current study because here patients spared or partially preserved the left IFG (as inclusion criteria for tDCS stimulation) and R2* increment correlates positively with therapeutic gain, suggesting a compensatory structural change in left SFG.

With regard to the SMA, Price (2012) showed that this region is involved in planning of motor articulatory sequences necessary for speech outputs. GM changes in this region are counterintuitive as iReadMore therapy does not involve speech production (reading aloud). However, this finding might reflect patients' readiness to read aloud (i.e. internal planning of articulatory sequences) or undetectable subvocalisation along training sessions. Moreover, a recent review

conducted by Lima, Krishnan, and Scott (2016) showed that the SMA is anatomically connected to the opercular segment of the IFG via the aslant tract. It has been suggested that this WM tract participates in speech production. Most importantly, they showed that the SMA also participates in auditory perception of speech sounds (including syllables, words, and sentences) as well as in tasks that demand motor representations in response to auditory processing. iReadMore was designed to treat reading by strengthening connections between orthographic, phonological and semantic domains. In each trial of the training phase participants simultaneously read a written word, listened to a spoken word, and observed a matched image (see description in Chapter two). During the testing phase participants had to indicate by button press whether a written word and a spoken word (demanding auditory perception of words) were similar or different. This task involved access to phonological representations of words presented by two different sensorial pathways that involve visual and auditory perception. The increase in iron content (indicated by the increased R2* signal) in the SMA associated with reading improvement endorses this hypothesis. This suggests that SMA supports visual and auditory processing, as implemented in iReadMore, to strengthen orthographic to phonological connections.

Although the studies discussed previously have are in favour of that these two extra-sylvian regions are involved in several language functions rather than these non-linguistic areas support recovery in CA, further work is required to establish which of these two competing accounts is more likely. A new study training non-linguistic (cognitive or sensori-motor) abilities in CA patients, using the same design and imaging protocol as the iReadMore trial would help to disambiguate this question.

ii) Lesion location is a key aspect in prognosis of post-stroke aphasia recovery (Maas et al., 2012; Plowman et al., 2012; Seghier et al., 2016). In the previous chapter I showed that lesion site is an important predictor of aphasic patients' response to iReadMore therapy. However, there is little consensus in the literature regarding the role of spared perilesional and contralateral regions in language recovery. In general, studies have indicated two different mechanisms that are not necessarily irreconcilable: 1) recruitment of preserved left perilesional regions along the Sylvian fissure (Cornelissen et al., 2003; Fridriksson et al., 2010; Heiss et al., 1999; Leger et al., 2002; Miura et al., 1999; van Oers et al., 2010; Warburton et al., 1999); and 2) recruitment of right hemispheric regions homologous to left language areas (Fernandez et al., 2004; Forkel et al., 2014; Gainotti, 1993; Hope et al., 2017; Karbe et al., 1998; Saur et al., 2006; Wan et al., 2014; Xing et al., 2016). The latter occurs mostly when damage in the left hemisphere is extensive. Some studies have outlined a third mechanism, arguing that (3) recruitment of the right hemisphere (RH) is maladaptive because it induces transcallosal inhibition; hence the RH impedes language recovery by constraining recruitment of spared left perilesional regions (Martin et al., 2009; Naeser et al., 2011). In the current study VBQ analysis showed increased R2* signal associated with reading change in a GM cluster localised mostly in perilesional regions (left SFG and SMA), but also encompassing part of a contralateral homologue (right SMA). This finding is in favour of the argument that both preserved left perilesional (1) and RH homologue (2) regions have a supportive role in recovering reading in aphasia; and against a maladaptive role of the right hemisphere (3).

However, findings in the current study do not resolve the dispute in favour of any of these hypotheses: analyses of brains with focal damage have lack of power to detect significant associations to behavioural outcomes if several patients have no tissue in a region. This is a methodological constraint for this study, in which all participants had damage in the territory of the MCA (see lesion overlay image - Figure 18 in Chapter two). Therefore, there is more statistical power to identify associations with therapeutic improvement in regions irrigated by the anterior cerebral artery, as found in this study, which are spared by almost all aphasic strokes. In contrast, most of the studies that have shown recruitment of preserved perilesional regions along the Sylvian fissure have implemented a fMRI paradigm and were case studies (Fernandez et al., 2004; Leger et al., 2002; Miura et al., 1999) or studies with few participants (Cornelissen et al., 2003; Warburton et al., 1999). Further studies to test these hypotheses would combine structural and functional MRI to solve this methodological constraint that may limit detection of therapy-driven structural changes in perilesional regions.

iii) Quantitative maps of the MPM protocol provide measures of the brain microstructure. The VBQ analysis showed a significant positive correlation between R2* in GM and reading change after iReadMore therapy. The R2* measure has shown sensitivity to variations in iron content mostly in GM (Langkammer et al., 2010). Hence, this result can be interpreted as showing that therapy-driven recovery in reading accuracy after iReadMore increased the rate of intracortical iron content in the left SFG and bilateral SMA. At a cellular level, iron plays a crucial role in the synthesis and normal functioning of neurons and microglia: it contributes to oxygen transportation, production of ATP and DNA, and synthesis of neurotransmitters such as dopamine, serotonin, norepinephrine,

and GABA (Gaasch, Lockman, Geldenhuys, Allen, & Van der Schyf, 2007). Particularly in glial cells, iron is essential for lipids and cholesterol synthesis, which are important in the production and maintenance of myelin (Connor & Menzies, 1996; Todorich, Pasquini, Garcia, Paez, & Connor, 2009). The R2* GM result may therefore be indicative of therapy-dependent plasticity, and might reflect neuronal remodelling as a compensatory mechanism.

Although the R2* GM finding in this study reflects brain plasticity associated with therapeutic learning, it is unlikely that only increased iron content can explain structural changes. On the contrary, several factors may influence changes reflected in the MRI signal. VBQ and VBM analyses did not reveal changes in other biomarkers of brain plasticity either in major cortical regions or WM tracts. Hence, this result should be interpreted with caution and understood as a regional finding in a specific group of patients (central alexia) after a particular intervention (iReadMore training). Ideally, VBM results would be supported and complemented by VBQ analysis and vice versa. Although different studies have demonstrated that VBM is suitable to detect GM changes associated with learning conditions (Draganski & May, 2008; Maguire et al., 2006), here analyses did not find changes in GM and WM densities associated with iReadMore therapy. There are two possible explanations for this negative VBM finding. It seems possible that the results relate to differential temporal trajectories of therapy-induced changes. There is support for this from brain plasticity studies in humans and animals that investigate changes that occur in conditions of rapid motor learning (few hours of practice) versus conditions of prolonged training (weeks to months) (Dayan & Cohen, 2011; Karni et al., 1998). A study conducted by Xu et al. (2009) observed local and permanent formation of new dendritic

spines and myelination after rapid training. However, spine density returned to baseline levels two weeks later due to elimination of old spines. In contrast, Dayan & Cohen (2011) reviewed the literature indicating that prolonged training produces local and lasting structural GM and WM changes but in a large time window (up to 3 months). These results suggest that large-scale cortical networks participate in therapeutic learning, but experience-dependent plasticity is constrained to task-conditions, confined to specific brain regions, and might be transient.

The other possible explanation for the lack of findings in VBM and other MPM images is the sample size. This study was conducted only on 17 participants and SPM analyses heavily depend on the difference between sample size and covariates included in each model. The regression model in this study included six covariates (scans, reading change, age, lesion volume, time since stroke occurred and tDCS group) leaving only 11 degrees of freedom for the statistical condition of interest, which directly affects the power to detect therapeutic effects. Despite these interesting preliminary results, further work is required to establish more accurately what compensatory structural changes occur in the brain of aphasic patients in response to reading therapy.

Summary and Conclusions – Experimental chapter three

This longitudinal study investigated whether structural changes occur in the brain of aphasic patients after intervention with a reading therapy; and, if identified, what biological mechanisms might underpin structural changes. Results showed bilateral increases of iron content in left SFG and bilateral SMA. This finding is

significant in at least three aspects: 1) it provides novel evidence for therapy-driven plasticity in chronic central alexia; 2) it supports other studies that have indicated an active role of both perilesional and contralateral homologues regions in aphasia recovery; and, 3) it showed that brain areas traditionally associated with non-linguistic functions play a role in language functions and reading recovery. Further studies might include other language measures, more statistical power (larger sample size), and combined structural and functional MRI in multiple sessions and in a larger time window to corroborate findings of this study, as well as to investigate other mechanisms of brain plasticity in aphasia which is intricate and multidimensional.

6. GENERAL DISCUSSION

The general aim of the present research was to understand the behavioural and brain factors that both explain and predict aphasic patients' responses to a computerised reading therapy called iReadMore. This therapy was designed to improve single-word reading in aphasic patients with central alexia (CA). The iReadMore therapeutic trial (T1-T6) aimed to evaluate the effectiveness of this computerised therapy and its interaction with anodal transcranial direct current stimulation (a-tDCS). However, to address the aim of this thesis, three studies were conducted on a subset of the data (T1-T4) encompassing baseline behavioural data (from T1 and T2), pre-treatment and post-treatment imaging data (from T3 and T4), and patients' outcomes (DV) after block one of iReadMore therapy (between T3 and T4).

Study one (presented in chapter three) involved cross-sectional analyses of behavioural measures collected at baseline and pre-treatment imaging data to characterise the response profile of CA patients. Study two (presented in chapter four) included cross-sectional analyses of the same baseline and pre-treatment data to investigate whether demographic, behavioural and brain data explain and predict patients' outcomes to block one of iReadMore. And, study three (presented in chapter five) included longitudinal analyses of imaging data to investigate structural changes associated with iReadMore therapy.

This final chapter summarises the main aims of this thesis and discusses the major findings of the three experimental studies. Moreover, this chapter considers methodological limitations and suggests future studies.

6.1. Summary of aims

The broad aims of the three studies I have presented in this thesis were:

1) In study one, to characterise the patients' baseline neuropsychological profile. Moreover, to identify independent behavioural patterns underlying patients' reading abilities and their association with brain regions.
2) In study two, to investigate whether pre-treatment behavioural and brain data contribute to explain and predict variability in patients' responses to iReadMore therapy.
3) In study three, to explore whether any detectable changes occur in the brain macrostructure or microstructure of chronic CA patients in response to iReadMore therapy. Furthermore, to investigate what biological mechanisms support structural changes associated with therapy response in CA.

6.2. Overview of key results, possible limitations, and future directions

6.2.1. Chapter three - Investigating the cognitive profile of patients with central alexia and the brain regions underlying their baseline reading abilities

This study aimed first to characterise the neuropsychological profile of aphasic patients with CA. Behavioural analyses demonstrated that our patients exhibited varied performance in non-linguistic executive functions. They preserved abilities such as environmental learning and adaptation to novel situations, rule change detection, anticipation, inhibition, cognitive control, and sustained attention. However, they were impaired in tasks demanding verbal and visual working memory, access to semantic knowledge, fluid intelligence, reasoning, and solving problems. Moreover, results showed significant associations mostly between variables from the same cognitive domain (linguistic–linguistic or executive function–executive function) with only one association between variables from different cognitive domains (linguistic–executive function).

These results differ from other studies that have found that executive functions, particularly cognitive control, play an important role in aphasia recovery (e.g. Brownsett et al., 2014). In contrast, the results in the current study suggested that severity of impairment in executive function does not predict severity of reading impairments in CA, and vice-versa. Instead, these results might indicate that the two abilities are not sufficiently related to think that intervention in one could have a positive impact on the other. In other words, intervention in executive function

before or concurrently with reading therapy might not directly enhance aphasic patients' reading ability. However, the reason for this finding is not clear. It does not seem to fit in with what we know about aphasic patients' characteristics and variability in therapeutic-dependent learning. It seems unlikely that executive abilities play no role in patients' capacities to learn. This discrepancy between my findings and the current knowledge could be attributed to the nature of available executive function tasks which demand several abilities simultaneously. It is possible that this characteristic of the tasks reduces the power of analyses to detect or explain relationships between cognitive domains. Furthermore, it is possible that the tasks in my study do not cover some executive abilities that might be related to patients' response to therapy (e.g. planning/prioritising). It might be also possible that executive functions are important when the patient is responsible for engaging with therapy on their own (i.e. with home practice or apps). In our trial we saw the patients three times per week and were able to monitor and motivate them to continue. Without this they may not have got the therapy dose they required to improve, or may not have understood the task requirements well enough to benefit from the therapy. Another explanation might be related to my inclusion criteria: in this study patients were recruited according to the presence of any word reading impairment. However, reading impairments in post-stroke aphasia are regularly classified as phonological, surface or deep dyslexia. It might be possible that results vary when analyses include patients with a particular aphasic syndrome rather than any aphasic impairments.

Executive function tasks in this thesis were selected to avoid the verbal interference that aphasic impairments may produce in patients' responses. A possible shortcoming of my analyses is that executive function tasks tested in this

study did not involve linguistic responses (except digit span). It is likely that executive tasks with verbal demands have stronger associations with aphasic impairments and patients' responses to therapy. A bigger research programme is needed to provide more evidence in favour or against the impact of general cognitive domain abilities on aphasia recovery. New studies should include other types of patients and testing of both linguistic and non-linguistic executive function tests. For instance, to obtain a more complete explanation about the role of executive functions in language as a cognitive process, it would be interesting to study this association in a sample of patients with pure alexia who should be able to perform most linguistic tasks as well as executive function tasks with both linguistic and non-linguistic demands. Moreover, studies investigating executive function and its impact in aphasia could improve the methodological approach by testing the effect of particular executive abilities on each linguistic skill (naming, repetition, speech comprehension, reading or writing) but testing them with the same task. For instance, the influence of cognitive control (tested with the Brixton task) on naming ability as well as the influence of cognitive control (tested with the same task) on repetition ability. Also, future studies could investigate whether my findings depend on the inclusion criteria by comparing patients with any aphasic impairments against patients with specific aphasia forms. It would indicate if better explanations are given when patients are or are not classified according to aphasic syndromes as occurred in this thesis.

The other aim attempted to identify behavioural dimensions underlying reading abilities in CA and their association with brain regions. To address this I employed a Principal Component Analysis of baseline reading data and associated it with baseline imaging data. This showed a dissociation of phonological (reading

aloud) and semantic (reading for meaning) dimensions in reading tasks. Although the phonological dimension explains most of the variance in the data (consistent with a cognitive profile of phonological dyslexia in most of our patients), the clinical implication of this finding is that CA patients also exhibit semantic deficits during silent reading (for meaning). These impairments are: 1) increased latency of reading; 2) difficulties in accessing semantic knowledge; 3) difficulties in silent sentence reading; and 4) difficulties in reading comprehension (which are more consistent with the surface dyslexia profile). Although PCA was employed to identify independent reading components, this finding suggested that the phonological and semantic dimensions in CA are linked, hence patients' reading impairments fall on a continuum, instead of classical dyslexia syndromes.

Traditionally, VBM studies in aphasia relate behaviour to brain damage. My VBM analysis in CA patients demonstrated the association of the phonological dimension with the left supramarginal gyrus and the semantic dimension with four regions in GM and WM of the left ventral temporal lobe. An important and unexpected finding in these analyses is that two of these regions (GM in the left aTL, and left WM deep to the lingual gyrus) were outside the lesioned overlay area. To the best of my knowledge, WM in the lingual gyrus had never been linked to semantic abilities in reading tasks performed by aphasic patients. Therefore, a post-hoc tissue density comparison with age-matched controls was conducted. Results revealed that patients had significantly lower tissue density in the aTL in comparison to age-matched controls but no differences in the tissue density of the WM in the lingual gyrus. The latter is a major contribution of this study because it provides evidence of a new region that might play a compensatory role in supporting semantic abilities of reading after stroke. This region should be

explored further due to its conceptual and practical implications in aphasia. New studies with other methods such as fractional anisotropy or fMRI would be helpful to determine whether its role in recovery is due to premorbid inter-individual differences in brain structure tissue density or a compensatory mechanisms. Moreover, a TMS study could be conducted in healthy participants to investigate whether transiently disruption of the lingual gyrus would impair the semantic reading abilities.

6.2.2. Chapter four - Investigating neurological and cognitive factors that predict central alexia patients' responses to a computerised reading therapy

This study set out to investigate what available pre-treatment data might explain and predict patients' responses to iReadMore therapy. Demographic data, pre-treatment cognitive variables and brain region lesion loads were analysed independently and together in an effort to explain this variance. The resulting model from in-sample data revealed that a combination of age at therapy onset, symptom severity, accuracy in reading comprehension, accuracy in semantic processing, and, in particular, lesion site, explains most of the patients' variability in response to iReadMore. Then, model generalisation analysis showed evidence that responses from out-of-sample patients to iReadMore can be predicted from the observed patients' treatment responses.

These results have practical and methodological applications. First, it strongly suggests that available pre-treatment data explain patients' variability in

responses to iReadMore; might this also be true for other aphasia therapies? The research group are looking into this with a therapy for aphasic patients with auditory speech comprehension deficits, so we shall soon find out. Second, it showed the importance of lesion location in predicting patients´ outcomes, in comparison with behavioural plus demographic data alone. This result is somewhat surprising because we think of behaviour as a powerful predictor of patients' outcomes, but it turns out that while initial severity is helpful in predicting part of what happens to patients impairments over time (they only get worse in particular neurological conditions), the explanatory model in this study revealed that it is not so helpful in predicting response to therapy (although in my model it does come out as one of the predictors). On the other hand, this finding might be expected for the simple reason that the brain is required to produce language and to respond to any therapeutic interventions, therefore which regions are affected/spared must be important. And third, it clearly supports the idea that we can make individualised predictions and therapies can be applied with better outcomes if treatment decisions are made according to patients' characteristics (demographics, cognitive characteristics, and lesion location).

Regarding future directions, I have employed a novel methodological approach to explain and make individual predictions of effectiveness in a computerised reading intervention. Since this is the first time that these methods have been used in this context (i.e. analyses of responses to aphasia therapy from pre-treatment available data) and the model had a good fit, I suggest that this is an appropriate framework to explain and predict patients´ responses to SLT. This is the major methodological contribution of this thesis**.** What is now needed is a strong programme of research based on the application of these methods in

aphasia and other neuropsychological impairments, aiming to validate and refine the proposed model (used here for the first time) and other models resulting from different interventions. Results of a programme like this would help to tailor therapeutic intervention in aphasia and other neuropsychological conditions.

6.2.3. Chapter five - Investigating cerebral structure changes induced by a computer-based reading therapy in chronic aphasic patients

This study was designed to explore any changes in the brain structure of CA patients after iReadMore therapy. To achieve this aim, multiparameter mapping (MPM) (Callaghan et al., 2014) was implemented. This MRI sequence allows investigation into the macrostructural changes (VBM) and the biological mechanisms underpinning microstructural changes (VBQ). This study found a positive association between improvement in reading accuracy and increased effective transverse relaxation rate (R2*), which is a biomarker of iron content (Langkammer et al., 2010), in a large extra-sylvian region encompassing the left superior frontal gyrus (SFG) and the supplementary motor area (SMA) bilaterally. However, a null result was that no macrostructural changes were detected in GM or WM.

The finding of this study provides a noteworthy contribution because it showed new evidence of therapy-driven plasticity in aphasia recovery. This finding is important because it strengthens the idea that extra-sylvian regions might

participate in language functions and contribute in neural compensatory mechanisms to support post-stroke aphasia recovery. However, it is not surprising that group analyses revealed that extra-sylvian regions in which probably all aphasic patients have tissue (rather than perilesional regions where many patients do not have tissue) are involved in recovery. Moreover, as increased iron content was bilateral, it provided evidence in favour of studies that have found that both perilesional regions and contralateral language homologues are involved in aphasia recovery. Regarding the biological mechanism, iron plays a crucial role in the functioning of neurons and microglia, therefore increased R2* signal in these regions might reflect neuronal remodelling as a possible brain plasticity mechanism. However, it is important to mention that null results in other VBQ analyses and in VBM analyses limit the impact of this study because it is unlikely that only increased iron content in GM underpins patients' responses to iReadMore.

Finally and to conclude, in this chapter I have shown microstructural changes in two GM regions associated with reading recovery. I suggest a confirmatory study with a larger sample to determine whether these results are reproducible and whether better power identifies more regions and other brain biomarkers associated with reading recovery. Studies with larger samples will increase statistical power and that would help to validate the overall results presented in this thesis.

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APPENDICES

3.1.3. Correlations between demographic and behavioural variables

Pair of variables	*r*	*p*
Age / Cattell test 1	-.520	.011
Age / Cattell total score	-.423	.044
Age / VSSTM	-.536	.008
Age / Naming objects	-.421	.045
TPS / DS backward	-.418	.047
TPS / DS total score	-.458	.028
TPS / Single-word reading acc.	-.456	.029
TPS / Neale speed (WPM)	-.462	.030
LV / DS forward	-.469	.024
LV / DS total score	-.494	.016
LV / Weigl – sorts	-.464	.026
LV / Single-word reading RT (ms)	.462	.047

Significant correlations between demographic and behavioural variables. TPS= time post-stroke; LV= lesion volume; DS= digit span; VSSTM= visuo-spatial short-term memory task; SWR= Single-word reading; WPM= words per minute; RT= reaction time; ms= milliseconds.

Pair of variables	*r*	*P*
SWR Acc./ Pseudoword reading Acc.	.530	.011
SWR Acc. / Semantic matching Acc.	.606	.002
SWR Acc. / Neale Acc.	.808	<.001
SWR Acc. / Neale speed (WPM)	.647	.001
SWR Acc./ Sentence reading acc.	.587	.003
SWR RT (ms) / Sentence reading acc.	-.510	.026
Pseudoword reading Acc. / Neale Acc.	.673	.001
Pseudoword reading acc. / Neale speed (WPM)	.543	.009
Semantic matching Acc. / Neale speed (WPM)	.425	.049
Semantic matching Acc. / Sentence reading Acc.	.747	<.001
Semantic matching Acc. / Sentence reading speed (WPM)	.439	.046
Semantic matching RT / Sentence reading Acc.	-.596	.003
Semantic matching RT / Sentence reading speed (WPM)	-.477	.029
Neale speed (WPM) / Sentence reading Acc.	.467	.028
Sentence reading speed (WPM) / CDP	.509	.018
Naming objects / SWR Acc.	.566	.005
Naming objects / Sentence reading Acc.	.420	.046
Naming total score / SWR Acc.	.587	.003
Naming total score / Sentence reading Acc.	.416	.048
Auditory discrimination / CDP	-.439	.046

Significant correlations between linguistic variables. SWR= Single-word reading; WPM= words per minute; Acc. = accuracy; CDP= Communication Disability Profile; RT= reaction time; ms= milliseconds.

Pair of variables	*r*	*P*
DS forward / Naming actions	.583	.003
DS forward / SWR Acc.	.455	.029
DS forward / Pseudoword reading Acc.	.449	.036
DS forward / Neale speed (WPM)	.432	.045
DS backward / SWR Acc.	.420	.046
DS backward / Pseudoword reading Acc.	.486	.022
DS backward / Neale Acc.	.459	.032
DS backward / Neale speed (WPM)	.488	.021
DS total score / Naming actions	.455	.029
DS total score / SWR Acc.	.487	.018
DS total score / Pseudoword reading Acc.	.530	.011
DS total score / Neale Acc.	.502	.017
DS total score / Neale speed (WPM)	.530	.011
Cattell test 1 / Semantic matching Acc.	.499	.015
Cattell test 1 / Sentence reading Acc.	.558	.006
Cattell total score / Auditory discrimination	-.470	.031
Cattell total score / Semantic matching Acc.	.439	.036
Cattell total score / Sentence reading Acc.	.517	.012
PPT / Auditory discrimination	.449	.041
PPT / Semantic matching RT	-.717	<.001
PPT / Neale comprehension Acc.	.430	.046
PPT / Sentence reading Acc.	.602	.002
Weigl - sorts / semantic matching RT	.499	.018
Weigl - unassisted sorts / Sentence reading speed (WPM)	.459	.036
Weigl – Step down B / Auditory discrimination	.485	.026
VSSTM / Auditory discrimination	-.492	.024
VSSTM / Semantic matching RT	-.492	.020
NV-SART hits (%) / Auditory discrimination	-.435	.049
NV-SART hits (%) / Semantic matching Acc.	.437	.037

Significant correlations between executive functions and linguistic variables. SWR= Single-word reading; WPM= words per minute; Acc. = accuracy; DS= digit span; VSSTM= visuo-spatial short-term memory task; PPT= Pyramids and palm trees; NV-SART= Non-verbal version of the Sustained Attention to Response Task; RT= reaction time

Pair of variables	*r*	*P*
DS forward / Weigl – sorts	.491	.017
DS total score / Weigl – sorts	.543	.009
Cattell test 1 / Weigl score	.470	.024
Cattell test 1 / Weigl – sorts	.437	.037
Cattell test 1 / VSSTM	.683	<.001
Cattell test 1 / Brixton (errors)	-.415	.049
Cattell test 1 / NV-SART hits (%)	.491	.017
Cattell test 1 / NV-SART rejections (%)	.427	.042
Cattell test 2 / VSSTM	.426	.042
Cattell test 2 / NV-SART hits (%)	.558	.006
Cattell total score / PPT	.417	.048
Cattell total score / VVSTM	.648	.001
Cattell total score / NV-SART hits (%)	.633	.001
TAB - optimal choice (%) / Weigl - Perseveration A	-.584	.004
TAB - optimal choice (%) / Weigl – Perseverations (total)	-.528	.011
PPT / NV-SART hits (%)	.476	.022
Weigl score / VSTM	.581	.004
Weigl - Perseveration A / Brixton (errors)	.411	.051
Weigl - sorts / VSTM	.522	.011
Weigl - sorts / semantic matching RT (ms)	.499	.018
Weigl - unassisted sorts / VSSTM	.591	.003
VSSTM / Brixton (errors)	-.432	.040
VSSTM / NV-SART rejections (%)	.435	.038

Significant correlations between executive functions variables. DS= digit span; VSSTM= visuo-spatial short-term memory task; PPT= Pyramids and palm trees; NV-SART= Non-verbal version of the Sustained Attention to Response Task; TAB= Two-armed bandit.

3.1.4. PCA of reading abilities and VBM analysis

	Pseudoword reading Acc.	SWR Acc.	SWR speed (ms)	Semantic matching Acc.	Semantic matching speed (ms)	Sentence reading Acc.	Sentence Reading speed (WPM)	Text reading Acc.	Text reading speed (WPM)
Pseudoword reading Acc.	--	**.530*** (.011)	.266 (.271)	.207 (.354)	-.100 (.665)	-.043 (.850)	.043 (.858)	**.673**** (.001)	**.543**** (.009)
SWR Acc.	**.530*** (.011)	--	-.277 (252)	**.683**** (<.001)	-.385 (.085)	**.604**** (.003)	.129 (.588)	**.808**** (<.001)	**.647**** (.001)
SWR reading speed (ms)	.266 (.271)	-.277 (252)	--	-.437 (.061)	.428 (.068)	**-.510*** (.026)	-.326 (.187)	.004 (.987)	-.287 (.233)
Semantic matching Acc.	.207 (.354)	**.683**** (<.001)	-.437 (.061)	--	-.371 (.098)	**.757**** (<.001)	.433 (.056)	.419 (.053)	**.425*** (.049)
Semantic matching speed (ms)	-.100 (.665)	-.385 (.085)	.428 (.068)	-.371 (.098)	--	**-.611**** (.003)	**-.470*** (.036)	-.339 (.133)	-.400 (.072)
Sentence reading Acc.	-.043 (.850)	**.604**** (.003)	**-.510*** (.026)	**.757**** (<.001)	**-.611**** (.003)	--	**.513*** (.021)	.327 (.137)	**.467*** (.028)
Sentence Reading speed (WPM)	.043 (.858)	.129 (.588)	-.326 (.187)	.433 (.056)	**-.470*** (.036)	**.513*** (.021)	--	.057 (.812)	.330 (.155)
Text reading Acc.	**.673**** (.001)	**.808**** (<.001)	.004 (.987)	.419 (.053)	-.339 (.133)	.327 (.137)	057 (.812)	--	**.684**** (<.001)
Text reading speed (WPM)	**.543**** (.009)	**.647**** (.001)	-.287 (.233)	**.425*** (.049)	-.400 (.072)	**.467*** (.028)	.330 (.155)	**.684**** (<.001)	--

Bivariate Pearson's correlations coefficients (r) of reading measures. Significant correlations in bold: *= Correlation is significant at .05 level; **. Correlation is significant at .01 level. Significance in parenthesis. SWR= Single-word reading; WPM= words per minute; Acc. = accuracy; ms= milliseconds; WPM= words per minute.

4.1. Parcellation of binary lesion images

Participant	AG	Frontal Inf. Operc.	Frontal Inf. Tri	Heschl	Ins	Parietal Inf.	Post-central	Pre-central	Putamen	Rolandic Operc.	SMG	Temp. Mid.	Temp.l Sup.	Intrapar. sulcus IP1	Intrapar. sulcus IP2	Broca 44	Inf. parietal - Area PF
P1	0.35	0.67	0.35	1.00	0.83	0.61	0.67	0.40	0.71	0.94	0.99	0.31	0.80	0.92	0.71	0.41	0.84
P2	0.21	0.76	0.46	0.98	0.93	0.31	0.72	0.79	0.87	0.93	0.91	0.44	0.93	0.69	0.36	0.58	0.59
P3	0.97	0.00	0.00	0.01	0.00	0.49	0.00	0.00	0.00	0.03	0.36	0.41	0.32	0.99	0.63	0.00	0.21
P4	0.49	0.52	0.03	0.82	0.51	0.26	0.09	0.12	0.16	0.85	0.61	0.17	0.58	0.72	0.30	0.30	0.28
P5	0.29	0.00	0.00	0.56	0.11	0.09	0.03	0.00	0.09	0.32	0.37	0.81	0.91	0.53	0.04	0.02	0.22
P6	0.44	0.78	0.41	0.92	0.64	0.15	0.12	0.18	0.20	0.67	0.47	0.40	0.69	0.70	0.30	0.52	0.24
P7	0.00	0.66	0.30	0.64	0.85	0.05	0.13	0.24	0.80	0.81	0.17	0.47	0.66	0.05	0.24	0.45	0.10
P8	0.00	0.00	0.00	0.00	0.00	0.00	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P9	0.59	0.84	0.54	1.00	0.69	0.52	0.51	0.48	0.48	0.97	0.85	0.83	0.99	0.93	0.42	0.67	0.56
P10	0.95	0.03	0.00	0.68	0.11	0.83	0.20	0.00	0.00	0.36	0.92	0.64	0.75	1.00	0.93	0.03	0.88
P11	0.35	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.03	0.12	0.01	0.14	0.00	0.00	0.00
P12	0.24	0.03	0.20	0.09	0.18	0.13	0.09	0.15	0.00	0.12	0.92	0.14	0.34	0.38	0.12	0.02	0.55
P13	0.18	0.79	0.31	0.35	0.47	0.30	0.72	0.62	0.16	0.84	0.58	0.01	0.08	0.12	0.30	0.67	0.26
P14	0.00	0.79	0.24	0.16	0.25	0.00	0.08	0.20	0.00	0.53	0.00	0.00	0.04	0.00	0.00	0.66	0.00
P15	0.00	0.70	0.32	0.69	0.84	0.05	0.25	0.18	0.43	0.87	0.45	0.48	0.63	0.02	0.07	0.52	0.07
P16	0.39	0.87	0.30	0.88	0.64	0.44	0.33	0.33	0.18	0.95	0.82	0.30	0.73	0.83	0.84	0.69	0.79
P17	0.78	0.65	0.36	0.44	0.48	0.59	0.08	0.07	0.00	0.62	0.96	0.11	0.31	0.94	0.89	0.61	0.74
P18	0.48	0.14	0.00	0.00	0.03	0.60	0.23	0.00	0.00	0.15	0.80	0.15	0.23	0.93	0.89	0.17	0.70
P19	0.06	0.67	0.19	0.59	0.70	0.05	0.04	0.12	0.17	0.72	0.27	0.64	0.88	0.22	0.12	0.46	0.24
P20	0.40	0.82	0.67	0.95	0.96	0.27	0.38	0.38	0.68	0.96	0.97	0.43	0.72	0.73	0.28	0.68	0.76
P21	0.92	0.16	0.41	0.96	0.41	0.73	0.80	0.57	0.15	0.88	0.99	0.73	0.80	0.96	1.00	0.13	0.84
P22	0.07	0.00	0.00	0.72	0.16	0.24	0.04	0.00	0.00	0.47	0.91	0.05	0.57	0.11	0.14	0.01	0.69
P23	0.55	0.87	0.52	0.70	0.85	0.14	0.21	0.45	0.19	0.85	0.43	0.27	0.67	0.64	0.16	0.69	0.13

Grey matter regions and their proportion of damage in each patient. AG= angular gyrus; Operc = operculum; inf = inferior; tri = triangularis; Ins= insula; Temp= temporal; Intrapar= intraparietal; SMG supramarginal gyrus; sup= superior

Participant	Inf. parietal - Area PFcm	Inf. parietal - Area PFm	Inf. parietal - Area PFop	Inf. parietal - Area PFt	Inf. parietal - Area Pga	Ins Id1	Ins Ig1	Ins Ig2	Audit. cortex - TE10	Audit. cortex - TE11	Audit. cortex - TE12	Somato-sensory cortex - 3a	Somato-sensory cortex - 3b	Parietal operc. 1	Parietal operc. 2	Parietal operc. 3	Parietal operc. 4
P1	1.00	0.83	0.96	0.94	0.56	0.95	1.00	1.00	1.00	1.00	0.22	0.93	0.76	0.96	1.00	1.00	0.76
P2	0.99	0.48	0.96	0.85	0.28	1.00	1.00	1.00	0.97	0.79	0.99	0.98	0.85	0.90	1.00	1.00	0.78
P3	0.29	0.81	0.03	0.03	0.86	0.00	0.00	0.00	0.05	0.01	0.00	0.01	0.00	0.00	0.00	0.00	0.00
P4	0.85	0.71	0.52	0.19	0.59	0.20	0.90	0.95	0.60	0.98	0.09	0.46	0.08	0.63	1.00	0.98	0.22
P5	0.74	0.35	0.29	0.00	0.28	1.00	0.91	0.40	0.81	0.85	0.95	0.00	0.00	0.35	0.52	0.33	0.26
P6	0.88	0.33	0.66	0.25	0.42	0.35	0.95	0.93	0.97	1.00	0.16	0.48	0.13	0.58	0.93	0.86	0.13
P7	0.22	0.03	0.57	0.08	0.00	1.00	0.90	1.00	0.96	0.38	0.99	0.44	0.16	0.61	0.99	0.96	0.39
P8	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.05	0.03	0.00	0.00	0.00	0.00
P9	1.00	0.84	0.95	0.55	0.76	1.00	1.00	1.00	1.00	1.00	0.99	0.93	0.61	0.96	1.00	1.00	0.78
P10	0.97	0.94	0.50	0.57	0.86	0.36	0.09	0.51	0.99	0.63	0.64	0.47	0.23	0.79	0.23	0.12	0.50
P11	0.00	0.02	0.00	0.00	0.09	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
P12	0.98	0.54	0.70	0.45	0.53	0.00	0.09	0.13	0.03	0.14	0.02	0.04	0.14	0.38	0.09	0.02	0.04
P13	0.43	0.21	0.96	0.90	0.06	0.00	0.00	0.38	0.23	0.01	0.16	0.91	0.77	0.83	0.69	1.00	0.73
P14	0.00	0.00	0.06	0.00	0.00	0.00	0.09	0.43	0.11	0.00	0.22	0.13	0.09	0.05	0.03	0.48	0.45
P15	0.50	0.05	0.95	0.46	0.00	0.95	0.19	0.90	1.00	0.61	0.98	0.58	0.28	0.83	0.86	1.00	0.74
P16	1.00	0.36	0.90	0.92	0.20	0.70	1.00	1.00	0.75	0.85	0.69	0.83	0.28	0.93	0.99	1.00	0.61
P17	1.00	0.86	0.58	0.80	0.51	0.00	0.12	0.15	0.18	0.20	0.00	0.07	0.04	0.69	0.30	0.20	0.22
P18	0.88	0.86	0.66	0.53	0.43	0.00	0.00	0.00	0.00	0.00	0.00	0.63	0.33	0.23	0.30	0.12	0.00
P19	0.44	0.17	0.26	0.06	0.17	0.83	0.19	0.83	0.97	0.49	0.95	0.25	0.01	0.38	0.40	0.91	0.36
P20	1.00	0.57	0.96	0.66	0.48	0.61	1.00	1.00	0.70	1.00	0.69	0.71	0.44	0.96	1.00	1.00	0.76
P21	1.00	0.92	0.96	0.94	0.87	0.53	0.86	0.80	0.99	0.99	0.43	0.97	0.91	0.96	0.95	0.98	0.76
P22	0.99	0.74	0.44	0.34	0.36	0.07	0.07	0.82	0.59	0.74	0.37	0.00	0.00	0.89	0.37	0.35	0.23
P23	0.70	0.32	0.70	0.14	0.31	0.39	0.26	0.78	0.97	0.61	0.95	0.42	0.24	0.43	0.56	1.00	0.63

Grey matter regions and their proportion of damage in each patient (continuation). Operc = operculum; inf = inferior; Ins= insula; Audit= auditory.

Participant	T-Pariet.	T.-Visual	Anterior Corona radiata	Ant. limb - internal capsule	Ext. capsule	Fornix	IFOF	ILF	Post. Corona radiata	Post. T-radiation	Retro-lenticular - internal capsule	SF Ang - Occ	SF IFG – Pre-central	SF.Inf Occ Middle - Occ	SF ITG-MTG	SF MFG-IFG	SF MFG-Pre-central
P1	0.89	0.52	0.64	0.83	0.96	0.54	0.65	0.38	0.97	0.59	1.00	0.25	0.97	0.09	0.39	0.84	0.82
P2	0.69	0.29	0.68	0.91	1.00	0.41	0.70	0.46	0.90	0.62	0.97	0.21	1.00	0.12	0.52	0.91	0.99
P3	0.00	0.00	0.00	0.00	0.00	0.01	0.40	0.40	0.59	0.84	0.36	0.89	0.00	0.64	0.32	0.00	0.00
P4	0.33	0.19	0.12	0.28	0.59	0.21	0.23	0.08	0.84	0.39	0.76	0.31	0.86	0.13	0.11	0.45	0.38
P5	0.88	0.94	0.00	0.00	0.18	0.90	0.48	0.89	0.64	0.99	0.98	0.27	0.00	0.34	0.97	0.00	0.00
P6	0.19	0.19	0.50	0.49	0.53	0.16	0.50	0.32	0.77	0.73	0.74	0.58	0.98	0.35	0.49	0.95	0.47
P7	0.30	0.10	0.48	0.93	0.99	0.32	0.49	0.45	0.27	0.00	0.49	0.00	0.94	0.00	0.48	0.77	0.38
P8	0.00	0.00	0.07	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.10
P9	1.00	1.00	0.78	0.93	0.77	0.93	0.75	0.94	0.99	1.00	1.00	0.61	1.00	0.49	0.96	0.96	0.84
P10	0.13	0.29	0.00	0.01	0.01	0.46	0.45	0.71	0.88	0.99	0.68	0.98	0.00	0.75	0.65	0.00	0.00
P11	0.00	0.00	0.00	0.00	0.00	0.00	0.28	0.28	0.19	0.77	0.12	0.58	0.00	0.34	0.35	0.00	0.00
P12	0.00	0.00	0.07	0.02	0.02	0.01	0.24	0.14	0.06	0.31	0.15	0.08	0.30	0.29	0.07	0.17	0.14
P13	0.27	0.39	0.21	0.65	0.40	0.35	0.17	0.07	0.64	0.65	0.39	0.06	0.98	0.02	0.02	0.56	0.73
P14	0.00	0.00	0.03	0.06	0.03	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.72	0.00	0.00	0.45	0.08
P15	0.37	0.16	0.64	0.90	0.78	0.40	0.52	0.62	0.53	0.53	0.66	0.00	0.96	0.00	0.74	0.75	0.47
P16	0.33	0.42	0.28	0.37	0.68	0.34	0.49	0.49	0.96	0.88	0.89	0.48	0.99	0.35	0.49	0.87	0.65
P17	0.15	0.06	0.00	0.00	0.04	0.10	0.22	0.08	0.55	0.46	0.55	0.64	0.43	0.18	0.08	0.22	0.06
P18	0.07	0.00	0.00	0.00	0.00	0.04	0.38	0.45	0.94	0.98	0.39	0.60	0.09	0.77	0.18	0.02	0.01
P19	0.00	0.03	0.29	0.43	0.54	0.13	0.29	0.46	0.20	0.33	0.41	0.01	0.96	0.00	0.75	0.63	0.23
P20	0.51	0.55	0.91	0.86	0.99	0.41	0.85	0.42	0.87	0.77	0.99	0.49	1.00	0.29	0.52	0.97	0.80
P21	0.63	0.74	0.37	0.82	0.40	0.54	0.66	0.76	0.97	1.00	0.90	0.59	0.61	0.86	0.67	0.39	0.75
P22	0.00	0.00	0.00	0.00	0.04	0.02	0.08	0.01	0.08	0.20	0.30	0.00	0.00	0.00	0.03	0.00	0.00
P23	0.06	0.16	0.46	0.35	0.63	0.17	0.62	0.30	0.48	0.57	0.59	0.61	1.00	0.31	0.43	0.92	0.70

White matter regions and their proportion of damage in each patient. T= thalamus; Ant = anterior; inf = inferior; Ext= external; Post= posterior; SF= short fibers; ILF = inferior longitudinal fasciculi; IFOF= inferior frontal-occipital fasciculus; Ang= angular gyrus: Occ = occipital; ITG= inferior temporal gyrus; MTG = medial temporal gyrus; IFG = inferior frontal gyrus; MTG; medial frontal gyrus.

Participant	SF post-central - SMG	SF pre-central - post-central	SF SFG-IFG	SF SPG-AG	SF SPG-middle Occ.	SF SPG-SMG	SF STG-MTG	SF STG-SMG	SLF - FP	SLF-FT	SLF-PT	Sagittal stratum	Sup. corona radiata	Sup. fronto-occipital fasc.	Sup. Long. Fasc.	TH - middle Occ	TH-Sup. Occ.	Tapetum - corpus callosum
P1	1.00	0.73	0.75	0.42	0.16	0.85	0.83	1.00	0.99	0.99	0.90	0.65	0.99	1.00	1.00	0.59	0.62	0.66
P2	0.98	0.97	0.97	0.24	0.06	0.57	0.92	0.99	1.00	0.98	0.80	0.59	1.00	1.00	1.00	0.52	0.52	0.53
P3	0.30	0.00	0.00	0.58	0.62	0.44	0.61	0.83	0.24	0.43	0.96	0.27	0.00	0.00	0.46	0.72	0.68	0.79
P4	0.60	0.23	0.52	0.22	0.17	0.39	0.55	0.97	0.85	0.82	0.78	0.11	0.72	0.99	0.97	0.46	0.49	0.54
P5	0.31	0.03	0.00	0.11	0.05	0.10	0.99	0.96	0.36	0.52	0.86	1.00	0.04	0.00	0.51	0.67	0.65	0.77
P6	0.66	0.23	0.72	0.25	0.25	0.33	0.75	0.97	0.76	0.86	0.89	0.36	0.57	0.75	0.97	0.63	0.58	0.59
P7	0.48	0.24	0.58	0.10	0.01	0.19	0.52	0.25	0.84	0.70	0.07	0.51	0.70	1.00	0.63	0.05	0.04	0.00
P8	0.00	0.01	0.03	0.02	0.06	0.02	0.00	0.00	0.00	0.00	0.00	0.00	0.13	0.06	0.00	0.04	0.08	0.00
P9	0.96	0.75	0.89	0.61	0.30	0.58	1.00	1.00	1.00	1.00	0.97	1.00	1.00	1.00	1.00	0.85	0.83	0.83
P10	0.53	0.23	0.00	0.94	0.87	0.83	0.71	0.97	0.37	0.53	0.95	0.83	0.06	0.01	0.55	0.76	0.77	0.88
P11	0.00	0.00	0.00	0.09	0.22	0.00	0.22	0.15	0.01	0.23	0.51	0.24	0.00	0.00	0.23	0.44	0.37	0.37
P12	0.54	0.03	0.03	0.03	0.00	0.06	0.34	0.87	0.38	0.40	0.58	0.13	0.02	0.00	0.31	0.23	0.14	0.08
P13	0.97	0.86	0.55	0.15	0.02	0.53	0.00	0.40	0.96	0.66	0.14	0.15	0.76	1.00	0.73	0.43	0.43	0.59
P14	0.02	0.12	0.33	0.00	0.00	0.00	0.00	0.00	0.34	0.26	0.00	0.00	0.14	0.66	0.04	0.00	0.00	0.00
P15	0.66	0.33	0.67	0.00	0.00	0.05	0.65	0.55	0.84	0.80	0.24	0.73	0.84	1.00	0.75	0.39	0.42	0.67
P16	0.92	0.39	0.74	0.27	0.25	0.83	0.77	0.98	0.94	0.98	0.76	0.70	0.87	1.00	1.00	0.73	0.68	0.82
P17	0.63	0.05	0.26	0.53	0.23	0.65	0.36	0.91	0.52	0.43	0.64	0.10	0.03	0.00	0.48	0.47	0.47	0.56
P18	0.86	0.30	0.03	0.57	0.42	0.73	0.48	0.90	0.54	0.53	0.75	0.28	0.16	0.00	0.73	0.67	0.64	0.72
P19	0.40	0.14	0.56	0.00	0.00	0.07	0.96	0.84	0.67	0.87	0.62	0.49	0.42	0.93	0.77	0.27	0.26	0.24
P20	0.89	0.47	0.81	0.25	0.18	0.38	0.82	1.00	1.00	1.00	0.92	0.64	0.94	1.00	1.00	0.69	0.63	0.63
P21	1.00	0.80	0.21	0.62	0.33	0.94	0.84	1.00	1.00	1.00	1.00	0.90	0.78	1.00	0.94	0.84	0.84	0.85
P22	0.31	0.02	0.00	0.00	0.00	0.05	0.33	0.93	0.21	0.21	0.46	0.00	0.00	0.00	0.20	0.20	0.20	0.18
P23	0.65	0.29	0.70	0.22	0.27	0.22	0.75	0.94	0.99	1.00	0.81	0.30	0.49	0.63	0.93	0.59	0.57	0.54

White matter regions and their proportion of damage in each patient (continuation). SF= short fiber; SMG= supramarginal gyrus; SFG= superior frontal gyrus; SPG = superior parietal gyrus: SLF = superior longitudinal fasciculi; Sup = super